Juzgado 45 Civil Circuito - Bogotá - Bogotá D.C.

De: Leidy Paola Gonzalez Leguizamo - Grupo de Patología Forense - Dirección Regional Bogotá <lpgonzalez@medicinalegal.gov.co>
Enviado el: lunes, 1 de marzo de 2021 4:32 a. m.
Para: Juzgado 45 Civil Circuito - Bogotá - Bogotá D.C.
Asunto: RESPUESTA CASO BOG-2020-010350 - 11001310301020120025 6
Datos adjuntos: BOG-2020-010350.pdf

Respetada doctora
MONICA TATIANA FONSECA ARDILA
Secretaria
Juzgado 45 Civil del Circuito de Bogotá

De manera atenta adjunto envío respuesta a su oficio 251 de fecha 03 de diciembre de 2020.

Agradezco su atención y confirmación de recibido de este correo.

--
Atentamente,

LEIDY PAOLA GONZALEZ LEGUIZAMO
Asistente Forense
Grupo de Patología - Dirección Regional Bogotá.
Tel. 4069977 Ext. 1322
Instituto Nacional de Medicina Legal y Ciencias Forenses

Servicio Forense Para una Colombia Diversa y en Paz

"Cero Papel ... Mi compromiso con el Planeta"

Grupo Regional de Patología Forense - Dirección Regional Bogotá

BOG-2020-010350

Bogotá, 17- enero-2021

Oficio No. 474495

Doctora
MONICA TATIANA FONSECA ARDILA
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Secretaria
Juzgado 45 Civil del Circuito de Bogotá
Carrera 10 No, 14-30 piso 7
Bogota D. C.

ASUNTO: Oficio No. 251 de Fecha: 2020-12-03
REFERENCIA 11001310301020120256
MARIBELI IVONNE SARMIENTO ARROYO
Caso No. BOG-2020-010350 FECHA 07-diciembre-2020

I. SOLICITUD Y DOCUMENTACIÓN DISPONIBLE:
Se allega con oficio en formato digital enlace https://etbcsj my.sharepoint.com/:f:/g/personal/j45cctobt_cendoj_ramajudicial_gov_co/EsU gyWqnqF5PlmNPhXppS_IBwK2Ho06xMIcYV4gz_0g4mA?e=6P09ym que brinda acceso a la totalidad del expediente que contiene la historia clínica de MARIBELL IVONNE SARMIENTO ARROYO a fin de realizar análisis y experticia con el objeto que se determine el actuar médico e institucional en cuanto a:
- Si se realizó una historia clínica adecuada e idónea.
- Si las valoraciones clínicas fueron adecuadas.
- Si la actuación médica fue prudente, diligente y perita. - O si por el contrario, la actuación médica se ajustó a la Lex Artis.
- Si se faltó a los deberes obligacionales de seguridad, acerca de la infección su causa y tratamiento.

Así mismo solicita una valoración psiquiátrica de CECILIA YOLANDA ARROYO VARGAS y LUIS ALBERTO SARMIENTO TORRES, con el fin de determinar el grado de afectación por el fallecimiento de MARIBELL IVONNE SARMIENTO ARROYO.

II. RESUMEN DE HISTORIA CLÍNICA: Historia clínica contenida en un archivo en formato pdf de 671 páginas nominado 01CuadernoPrincipal, que se encuentra en carpeta titulada CD 1 PRINCIPAL que a su vez está en carpeta principal denominada 110013103010 2012 00256 00. Adulta de 23 años con antecedente de retraso mental por Síndrome de Down y de ductos arterioso resuelto quirúrgicamente en la infancia. Fue llevada en horas de la noche del 16 de agosto de 2009 al servicio de urgencias de la Fundación Abood Shaio con cuadro clínico caracterizado por dolor abdominal asociado a intolerancia a la vía oral, varios episodios de vómitos, fiebre de hasta 39 grados, astenia y adinamia. Al examen de ingreso presentó

saturación de 86%, tensión arterial 97 55, afebril, estable, en regular estado general y abdomen sin signos de irritación peritoneal. Realizan impresión diagnóstica de pancreatitis aguda, administraron metoclopramida IV y solicitaron amilasa y CH. Reporte de amilasa 427 y CH normal. Se mantiene en observación y se solicitan gases arteriales, electrolitos, azoados, FA, TGO, TGP, bilirrubinas y ecografía abdominal. Los gases arteriales reportaron acidosis metabólica compensada, los azoados, fosfatasa alcalina, transaminasas, bilirrubina, electrolitos, PCR, ecografía abdominal, hemograma y parcial de orina reportados normales. Amilasa control 332. Fue valorada por gastroenterología que ordena hospitalizar, sin embargo por falta de camas desocupadas en hospitalización fue remitida en ambulancia básica al Hospital Mayor donde ingresó el 17 de agosto. El hemograma de ingreso mostró leucopenia y trombopenia, gases arteriales con acidosis respiratoria, estable hemodinámicamente sin signos de respuesta inflamatoria sistémica. Medicina interna consideró que los gases arteriales se encontraban en equilibrio ácido-base tomando en cuenta la altura de Bogotá. Persisten los vómitos, de contenido biliar, asociados a dolor abdominal. Realizan ecocardiograma el 18 de agosto por antecedente médico, mostrando insuficiencia pulmonar leve, función sistólica del ventrículo izquierdo conservada y fracción de eyección de 55%. El TAC abdominal total (18 agosto) se halló dentro de límites normales. Iniciaron tolerancia de vía oral con dieta hipograsa y desde el 20 de agosto cursó con tos seca y crépitos finos en base pulmonar izquierda. Fue valorada nuevamente por medicina interna sin encontrar alteraciones a la auscultación pulmonar. La Endoscopia de vías digestivas (21 agosto) mostró evidencia de gastritis antral erosiva y bulbo-duodenitis. Los laboratorios (22 agosto) reportaron amilasa normal 65.27 U/L, potasio bajo 2.90 mmol/L, PCR elevada 16.77 mg/dL, leucopenia, linfopenia y trombocitopenia sin anemia. El 22 de agosto presentó también taquicardia, taquipnea, fue valorada nuevamente por medicina interna cursando con tos seca, con disnea al retiro de oxígeno por cánula, ruidos respiratorios disminuidos en base izquierda, escasos crépitos finos y opacidad en base izquierda a la Rx de tórax, razón por la cual iniciaron manejo con Amoxicilina con diagnóstico de neumonía basal izquierda. Posteriormente ese mismo día, con aumento de la PCR, hipoxemia e inicio de los síntomas luego de más de 48 horas de ingreso consideraron germen probablemente nosocomial y cambiaron antibiótico a Ampicilina Sulbactam y Claritromicina. En horas de la noche presentó dificultad respiratoria, cianosis, patrón moteado y petequias en miembros inferiores por lo que suspenden dipirona y administraron Hidrocortisona y líquidos endovenosos en bolo. Persiste con leucopenia, linfopenia y trombocitopenia sin anemia. Se cambió antibiótico a Piperacilina Tazobactam. El 23 de agosto en horas de la madrugada la trasladan de piso de medicina interna a sala de emergencias (SALEM) por riesgo de falla ventilatoria ya que no había disponibilidad de camas en UCI. Diagnóstico de neumonía con criterios de severidad y sepsis de origen pulmonar a confirmar. Posteriormente el mismo día en horas de la tarde ingresó a UCI en mal estado general, encefalopática, desaturada con piel de aspecto moteado; realizaron intubación orotraqueal y diagnóstico presuntivo de influenza A H1N1 dada la rápida evolución clínica e imagenológica del cuadro pulmonar con probable coagulopatía de consumo. Manejo con Piperacilina Tazobactam, Vancomicina y Oseltamivir además de medidas de sostén. Aspiraron abundante material serohemático de orofaringe. Solicitaron hemocultivos, cultivos de secreción orotraqueal, aislamiento y manejo como caso sospechoso de influenza A H1N1, pronóstico vital reservado. Cursó con desacople del ventilador con parámetros ventilatorios altos y persistió desaturación. Tuvo evolución tórpida con choque séptico refractario y progresión a falla multisistémica, anuria y elevación de azoados. Gases arteriales

con alteración severa de la oxigenación incompatible con la vida. Fallece el 25 de agosto de 2009 a las 21:55 horas.

Reporte de Laboratorio de Salud Pública, diagnóstico de virus respiratorios (fecha de recepción de la muestra 24 agosto, fecha de análisis 27 agosto): POSITIVO PARA VIRUS DE INFLUENZA A, POSITIVO PARA VIRUS NUEVO H1N1.

En servicio de Anatomía Patológica Compensar, realizan necropsia clínica, número del estudio A0033-9, presentando como datos relevantes en la Descripción Macroscópica: hidrotórax bilateral 1000cc; mucosa de laringe, tráquea y bronquios ligeramente eritematosa. Pulmones de 1100 gramos en conjunto con congestión severa y superficie de corte discretamente firme y hemorrágica, vasculatura normal. Ascitis de 450cc. Páncreas de 50 gramos con hemorragia superficial leve en cabeza y bazo de 50 gramos con congestión pasiva aguda. En la Descripción Microscópica: pulmón con material eosinófilo intraalveolar y hemorragia intraalveolar, membranas hialinas extensas, necrosis de neumocitos tipo 1 e inflamación intersticial con linfocitos, plasmocitos y macrófagos. Tráquea y bronquios con inflamación en la pared por linfocitos y plasmocitos, edema y metaplasia escamosa extensa. Hígado con esteatosis macrovesicular extensa. Necrosis parcial de acinos pancreáticos. Bazo con congestión pasiva aguda y necrosis tubular renal aguda extensa. DIAGNÓSTICOS FINALES: DAÑO ALVEOLAR DIFUSO EN FASE EXUDATIVA SECUNDARIO A NEUMONITIS INTERSTICIAL POR VIRUS AH1N1 (INFORME REPORTADO POR DEPARTAMENTO DE EPIDEMIOLOGÍA), TRAQUEOBRONQUITIS CRÓNICA LEVE CON METAPLASIA ESCAMOSA FOCAL. PANCREATITIS AGUDA LEVE. NECROSIS TUBULAR AGUDA EXTENSA. ESTEATOSIS HEPÁTICA MACROVESICULAR EXTENSA.

Enviaron además material de autopsia al Instituto Nacional de Salud al Grupo de Patología, reportando: pulmón con extensa hemorragia reciente intraalveolar sin observar pneumonitis ni neumonía, hay edema y congestión. La vía aérea terminal muestra depósitos fibrinosos con erosión del epitelio e hiperplasia de pneumocitos tipo II. La tráquea muestra erosión del epitelio superficial y mínimo infiltrado inflamatorio linfocitario subepitelial. Diagnóstico: Hemorragia pulmonar reciente y severa, traqueítis aguda leve y depósitos fibrinoides en la vía aérea terminal.

III. CONCLUSIÓN Y OPINIÓN PERICIAL:

Con la información disponible, la muerte se explica de manera natural como consecuencia de DAÑO ALVEOLAR DIFUSO EN FASE EXUDATIVA SECUNDARIO A NEUMONITIS INTERSTICIAL POR VIRUS AH1N1 como consta en el reporte de necropsia clínica emitido por Marco Antonio Bejarano Rodríguez, médico patólogo. Cabe la pena destacar que en dicho reporte se describe además la presencia de pancreatitis aguda leve, compatible con resolución clínica favorable de la misma dado el resultado de la tomografía abdominal reportada normal y el descenso de los valores de amilasa.

Debido a que la solicitud de la Autoridad comprende determinar aspectos relacionados con el diagnóstico y el proceder médico en cuanto a la Lex Artis, respetuosamente el expediente del

caso amerita ser analizado por médico(s) especialista(s) de similares características a los que intervinieron en la atención de la hoy fallecida, contando el Instituto Nacional de Medicina Legal y Ciencias Forenses en la actualidad con asesor especialista en Medicina Interna y Hematología que se encuentra fuera de la ciudad de Bogotá al que se le remitirá la presente historia clínica y quien a su vez la analizará y emitirá respectiva opinión pericial.

Con respecto a la valoración psiquiátrica solicitada a CECILIA YOLANDA ARROYO VARGAS y LUIS ALBERTO SARMIENTO TORRES, se enviará el presente concepto y copia de solicitud al Grupo de Psiquiatría Forense.

Atentamente,

IDANIA CAROLINA LUBO JULIO
Profesional Especializado Forense
Especialista en Anatomía Patológica

Elaboró: Leidy Paola González Leguizamo – Asistente Forense- Grupo de Patología Forense.
Proyectó – revisó – aprobó: Idania carolina Lubo julio- profesional Especializado Forense.

Juzgado 45 Civil Circuito - Bogotá - Bogotá D.C.

De: SHIRLEY LIZETH GONZALEZ LOZANO <SLGONZALEZL@compensarsalud.com>
Enviado el: miércoles, 17 de marzo de 2021 12:34 p. m.
Para: Juzgado 45 Civil Circuito - Bogotá - Bogotá D.C.
CC: notificaciones@mederi.com.co; abogado3@diazgranados.co; Gustavo Castaneda; camargocartagena@gmail.com
Asunto: MEMORIAL 11001310301020120025600 - REMISIÓN DE DICTAMEN PERICIAL MEDICINA INTERNA
Datos adjuntos: REMISIÓN DE DICTAMEN PERICIAL_compressed.pdf

Señor:
JUEZ CUARENTA Y CINCO (45) CIVIL DEL CIRCUITO DE BOGOTA D.C.
Ciudad

REF.: REMISIÓN DE DICTAMEN PERICIAL MEDICINA INTERNA

PROCESO NO.: 11001310301020120025600
NATURALEZA DEL PROCESO: ORDINARIO DE RESPONSABILIDAD EXTRANCONTRACTUAL.
DEMANDANTE: CECILIA YOLANDA ARROYO VARGAS, MÓNICA JANINNI SARMIENTO ARROYO, NATALIA JANINNI DEVIA SARMIENTO, LUIS ALBERTO DEVIA SARMIENTO, LUIS ALBERTO SARMIENTO TORRES, CECILIA VARGAS DE ARROYO Y MARISOL SARMIENTO ARROYO.
DEMANDADO: CAJA DE COMPENSACIÓN FAMILIAR COMPENSAR y otros.

SHIRLEY LIZETH GONZÁLEZ LOZANO, mayor y vecina de esta ciudad, identificada con la cédula de ciudadanía N° 1.018.438.856 expedida en Bogotá D.C., y titular de la T.P. No. 244.256 del Consejo Superior de la Judicatura, actuando en mi condición de apoderada judicial de la Entidad denominada **CAJA DE COMPENSACIÓN FAMILIAR COMPENSAR** en su programa de Entidad Promotora de Salud EPS, en adelante COMPENSAR EPS, por medio del presente escrito y estando dentro del término legal y judicialmente otorgado me permito remitir dictamen pericial emitido por el Dr. Daniel Andres Valencia, médico especializado en MEDICINA INTERNA supraespecializado en gastroenterología con entrenamiento y experiencia profesional en cuidados intensivos.

Así mismo, adjunto al presente escrito se encuentra la hoja de vida, títulos profesionales, certificaciones laborales y literatura médica que acreditan la experticia, experiencia y el soporte técnico que se tuvieron en cuenta para rendir la mencionada experticia.

De la Señora Juez, Atentamente,

Agradeciendo su atención, con altos sentimientos de consideración y respeto,

Respetuosamente,

SHIRLEY LIZETH GONZÁLEZ LOZANO
ABOGADA
Gerencia Jurídica
CAJA DE COMPENSACIÓN FAMILIAR COMPENSAR – COMPENSAR E.P.S

Señor:
JUEZ CUARENTA Y CINCO (45) CIVIL DEL CIRCUITO DE BOGOTA D.C.
Ciudad

REF.: REMISIÓN DE DICTAMEN PERICIAL MEDICINA INTERNA

PROCESO NO.: 11001310301020120025600
NATURALEZA DEL PROCESO: ORDINARIO DE RESPONSABILIDAD EXTRANCONTRACTUAL.
DEMANDANTE: CECILIA YOLANDA ARROYO VARGAS, MÓNICA JANINNI SARMIENTO ARROYO, NATALIA JANINNI DEVIA SARMIENTO, LUIS ALBERTO DEVIA SARMIENTO, LUIS ALBERTO SARMIENTO TORRES, CECILIA VARGAS DE ARROYO Y MARISOL SARMIENTO ARROYO.
DEMANDADO: CAJA DE COMPENSACIÓN FAMILIAR COMPENSAR y otros.

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Así mismo, adjunto al presente escrito se encuentra la hoja de vida, títulos profesionales, certificaciones laborales y literatura médica que acreditan la experticia, experiencia y el soporte técnico que se tuvieron en cuenta para rendir la mencionada experticia.

De la Señora Juez, Atentamente,

Agradeciendo su atención, con altos sentimientos de consideración y respeto,

Respetuosamente,

SHIRLEY GONZÁLEZ LOZANO
C.C. 1.018.438.856 de Bogotá D.C.
T.P. 244.256 del C.S. de la J.

DICTAMEN PERICIAL ESPECIALIDAD DE MEDICINA INTERNA

CASO DE RESPONSABILIDAD MÉDICA – MARIBEL IVONNE SARMIENTO (Q.E.P.D)

Se lleva a cabo el presente dictamen pericial a solicitud de COMPENSAR EPS, para ser aportado dentro del proceso verbal de mayor cuantía adelantado en contra de COMPENSAR E.P.S. y otros bajo el radicado No. 11001310301020120025600 y que cursa en el Juzgado 45 Civil del Circuito de Bogotá D.C.

A. Identificación del Perito.

Nombre: DANIEL ANDRES VALENCIA MORENO
Cédula: 79.796.926 DE BOGOTA
Especialidad: MEDICINA INTERNA
Dirección: CALLE 145 # 13 A 58 APTO 704
Celular: 300-6944062
Email: drvalenciainternista@gmail.com

B. Estudios realizados:

Medicina General: Universidad Militar Nueva Granada.
Especialización en Medicina Interna: Universidad Militar Nueva Granada.
Supra especialización en Gastroenterología: Universidad Militar Nueva Granada.
Especialización en Epidemiología: Universidad de Boyacá.
Especialización en Gerencia de Instituciones de Salud: Universidad de Boyacá.
Formación como Magistrado del Tribunal de Ética Médica
Curso de fundamentación en Cuidado Intensivo (FCCS): Sociedad americana de cuidado crítico.
Diplomado en Ventilación Mecánica y Soporte vital básico y avanzado.

C. Metodología

Para llevar a cabo el presente dictamen pericial se procedió a una lectura y estudio de las historias clínicas de COMPENSAR E.P.S., HOSPITAL DE MEDERI y de la CLINICA SHAIO correspondientes a Maribel Ivonne Sarmiento identificada con cedula de ciudadanía No. 1032371137, sumado a la revisión y conocimiento de artículos científicos, protocolos y guías médicas relacionadas.

D. Respuestas al cuestionario

A continuación, procederé a dar respuesta a las siguientes preguntas formuladas por COMPENSAR EPS:

1. Indíquele al despacho si, de acuerdo a lo registrado en la historia clínica y al protocolo de atención y manejo de casos de infección por AH1N1 y circulares emitidas por el Ministerio de Protección Social en el año 2009, para la atención que recibió la paciente MARIBEL IVONNE SARMIENTO en la Clínica Shaio, existía alguna sintomatología, hallazgos clínicos y/o paraclínicos que hicieran sospechar como primera posibilidad, un compromiso del sistema respiratorio tipo infección por el virus AH1N1?

No, la paciente presenta síntomas gastrointestinales que son poco frecuentes en la Influenza AH1N1 como manifestación inicial

2. Dada la sintomatología que motivó la consulta por el servicio de urgencias a la Clínica Shaio, ¿era adecuado haber considerado como diagnóstico un cuadro de compromiso abdominal con posible pancreatitis aguda?

Si, de hecho, muestra elevación de amilasa

3. De la revisión de la historia clínica. Indíquele al despacho si ¿la paciente MARIBEL IVONNE tenía como antecedente el hallazgo de malformación cardíaca asociada con su Síndrome de Down?

Si, corrección quirúrgica de Ductus Persistente.

4. De acuerdo a lo registrado en la historia clínica de MEDERI y, en el contexto de un paciente síndrome de Down con antecedentes de cierre de ductus arterioso persistente DAP por malformación cardiaca asociada, con vómito, dolor abdominal, amilasa alterada, con leucopenia, trombocitopenia y con equilibrio acido base en gases arteriales y sin otros síntomas asociados, ¿podría sospechársele el curso de una pancreatitis?

La pancreatitis severa se puede comportar como un cuadro de sepsis severa y mostrar todos esos hallazgos, aun cuando inicialmente sea leve puede progresar incluso en pacientes sin comorbilidades.

5. Indíquele al despacho ¿si la toma de gases arteriales está limitada sólo a la presencia de patologías respiratorias o si, por el contrario, se requiere por ejemplo para hacer vigilancia metabólica de un posible compromiso pancreático como el que se le sospechaba a Maribel Ivonne?

No, los gases arteriales son una herramienta muy importante para evaluar la severidad de cualquier enfermedad potencialmente grave de cualquier órgano o sistema (neurológico, gastrointestinal, renal, cardiovascular o respiratorio).

6. Indíquele al despacho si ¿los hallazgos de leucopenia, trombocitopenia y acidosis respiratoria se podían asociar a la sospecha del compromiso pancreático en la paciente Maribel Ivonne?

Si, pueden ser parte de las manifestaciones de progresión a una Pancreatitis severa o las posibles complicaciones infecciosas que se pueden presentar durante el manejo intrahospitalario.

7. De acuerdo a la condición clínica de la paciente y a lo registrado en la historia clínica, ¿considera usted que, para la tarde y noche del 18, 19 y 20 de agosto de 2009 la paciente fue abandonada por la institución hospitalaria, sin que se realizara algún tipo de seguimiento o control por el personal de salud (médicos, personal de enfermería, especialistas) que permitiera establecer su condición a lo largo de este tiempo?

No, considero que según lo revisado en la historia clínica tuvo las condiciones usuales de atención que se prestan en un hospital de III o IV nivel en pisos de hospitalización de cuidado básico.

8. Indíquele al despacho si ¿de acuerdo a revisión de la historia clínica de 18, 19 y 20 de agosto de 2009 e inclusive desde el ingreso de la paciente al servicio de urgencias, se describe algún síntoma o hallazgo clínico a nivel pulmonar?

No, en lo revisado en la historia clínica de los primeros días de hospitalización no hay manifestaciones de enfermedad respiratoria.

9. Teniendo en cuenta la historia clínica de 21 de agosto de 2009 a las 6:00 a.m. se deja anotada la aparición de síntomas respiratorios tales como tos seca, emesis y estertores a nivel de la base pulmonar izquierda para lo cual se ordena radiografía de tórax y endoscopia de vías digestivas altas.

Indicara el perito médico:

a. ¿Fue acertada la sospecha diagnóstica de neumonía y gastritis?

Si, tiene factores de riesgo para las dos enfermedades.

b. ¿Fue adecuada la indicación de esos exámenes paraclínicos para confirmar o descartar las sospechas diagnósticas anteriormente señaladas?

Si, efectivamente se confirmó la sospecha diagnóstica

c. Teniendo en cuenta que los síntomas respiratorios dieron su aparición 4 días después de iniciada la hospitalización en el Hospital Mederi, indicará el perito médico especializado ¿si debía pensarse como **primera** posibilidad que la etiología de la neumonía provenía del virus H1N1?

No necesariamente debía ser la primera sospecha diagnóstica dado el curso de enfermedad que tuvo durante la hospitalización, lo más probable en ese contexto era una infección nosocomial como se sospechó y abordó inicialmente.

10. Indíquele al despacho si ¿una sala de emergencias médicas (SALEM) como las que se encuentran en MEDERI, cuentan con el recurso humano y con la infraestructura para atender y reanimar pacientes en estado crítico, garantizando por ejemplo soporte invasivo de la vía aérea y la administración de medicamentos inotrópicos, para asegurar la estabilidad hemodinámica de un paciente?

Normalmente, en una institución de III y IV nivel, el servicio de Urgencias cuenta con un área de monitorización y atención de pacientes en condiciones críticas con la infraestructura y el personal entrenado para ello, que debe ser homologable con una Unidad de Cuidado Intensivo y un especialista generalmente exclusivo para el área (Medicina Interna y/o Emergenciología)

11. Indicará el perito médico ¿si fue adecuada la conducta médica de intubación orotraqueal en el momento en que se hizo?

De acuerdo con lo descrito en la historia clínica se aseguró la vía aérea cuando se encontraron signos claros de falla ventilatoria.

12. Indicará el perito médico especializado ¿si la hidrocortisona es un medicamento contraindicado para un paciente que cursa con influenza subtipo A H1N1?

Los corticoides no están contraindicados y nunca han estado contraindicados en el tratamiento de infecciones virales, siempre han existido controversias y reportes diferentes en los estudios sobre su riesgo vs. Beneficio, para la época en cuestión se consideraban parte del armamento médico para los casos severos y especialmente en pacientes que progresan a SDRA, donde actualmente continúa la controversia de su uso, siempre basándose en la capacidad de inmunomodulación que tienen para contrarestar los casos de respuesta inflamatoria severa que tienen peor pronóstico.

13. Indicará el perito médico especializado ¿con qué objetivo fue suministrada la hidrocortisona a la paciente Ivonne Maribel y si fue adecuada la indicación médica?

De acuerdo con lo revisado en la historia clínica, su uso inicial fue en el contexto de la sospecha de broncoespasmo, pero posteriormente se usaron frente a la evidencia de progresión a SDRA.

14. Indicará el perito médico especializado ¿si el 21 de agosto de 2009, con la realización de la endoscopia se pudo confirmar la existencia de una patología gástrica denominada gastritis antral erosiva y bulbo duodenitis?

SI

15. Indicará el perito médico si ¿los síntomas presentados por la paciente entre el 17 y 20 de agosto se encontraban explicados por la gastritis antral erosiva, bulbo duodenitis y la pancreatitis aguda en la paciente?

Si, los síntomas pueden ser explicables por estas patologías documentadas.

16. Indicará el perito médico especializado ¿si el virus de la influenza subtipo A -H1N1 se considera de naturaleza nosocomial?

Normalmente es una infección que se adquiere en la comunidad y se disemina rápidamente en el contexto social, pero dentro del contexto de una Epidemia / Pandemia puede ser una infección que se adquiera en el contexto hospitalario, tanto por el personal que labora en la institución como por las visitas que pueda tener un paciente.

17. Una vez debutó el cuadro respiratorio en la paciente, ¿considera usted que el abordaje y manejo médico dado fue el adecuado?

Considerando que la probabilidad más alta era una Neumonía nosocomial, se dio el manejo usual de primera línea de antibiótico y se fue escalonando al ver que no se tenía la respuesta esperada, sospechando gérmenes resistentes del contexto hospitalario usual.

18. Teniendo en cuenta los hallazgos radiográficos de 21 de agosto (neumonía base pulmonar izquierda) y el de 23 de agosto (ocupación alveolar 4 cuadrantes) ¿Considera que se presentó una rápida evolución del cuadro pulmonar y una tórpida respuesta por parte de la paciente, a pesar del manejo médico instaurado? Justifique su respuesta.

Si, el cuadro de presentación inicial es compatible con una neumonía nosocomial bacteriana ya que el patrón de las infecciones virales es diferente, generalmente no hace consolidación, es un compromiso

más difuso en incluso multilobar, por lo que parece haber tenido una presentación inusual o atípica y con una progresión rápida y tórpida que era muy difícil de predecir y controlar.

19. ¿Considera que la virulencia del germen y su agresividad fueron determinantes para la rápida evolución del cuadro pulmonar y la tórpida respuesta por parte de la paciente, a pesar del manejo médico instaurado?

Si, precisamente por eso se busca crear herramientas para identificar cualquier caso potencialmente sospechoso que se pueda manejar lo antes posible para disminuir el riesgo de progresión de la severidad que casi nunca se logra y la probabilidad de diseminación como objetivo principal, sin embargo, en el contexto específico de la paciente en cuestión no cumplía criterios claros de caso sospechoso según la circular 048 de 2009 y por lo tanto no era fácil el abordaje con esos criterios.

20. Considera que ¿existen condiciones propias de la paciente que pudieron haber favorecido el rápido deterioro y la tórpida evolución?

El retraso mental propio del Síndrome de Down puede afectar la capacidad de manifestar los síntomas, el manejo de las secreciones traqueobronquiales y los reflejos de protección de la vía aérea en contexto de vómito con mayor riesgo de broncoaspiración y acumulación de secreciones.
Adicionalmente los estudios han mostrado que los pacientes con síndrome de Down tienen mayor incidencia y prevalencia de infecciones respiratorias y son más severas que en la población general y se atribuye a hipotonía de los músculos orofaríngeos, ERGE, inmunodeficiencia relativa (Ram y Chinen, 2011) o el riesgo de leucopenia (Akin, 1988).

21. Indicará el perito médico especializado ¿Si el fallecimiento de la paciente se le debe atribuir a algún acto médico por acción u omisión?

No, considero que las evaluaciones realizadas y los tratamientos ofrecidos correspondían a lo que el cuadro clínico de la paciente manifestaba y se documentaba, el desafortunado desenlace fatal es propio de la virulencia del germen con efectos pandémicos que hacen difícil la identificación temprana y el tratamiento oportuno por su rápida progresión, especialmente en este caso que tenía manifestaciones clínicas iniciales de otras enfermedades y evoluciona tórpidamente por compromiso pulmonar no esperable y de rápida evolución que presentaba manifestaciones atípicas que dificultaban el abordaje clínico.

22. Si la conducta inicial en MEDERI se hubiera enmarcado desde un principio (esto es desde el inicio mismo de los síntomas respiratorios) como un caso sospechoso de infección por AH1N1, ¿se puede indicar sin duda alguna que la evolución y desenlace hubiera sido diferente al presentado?

No, es muy probable que aun cuando se hubiera sospechado desde el inicio de los síntomas respiratorios una infección por Influenza A H1N1, se hubiera tenido el mismo desenlace fatal, pero con un periodo de intubación y estancia en UCI más prolongado porque la severidad depende de factores propios del paciente y la respuesta de su cuerpo frente a la infección.

E. Conclusiones:

Los pacientes con Síndrome de Down tienen condiciones y características especiales que los predisponen a infecciones respiratorias con mayor frecuencia, severidad y mortalidad que la población general en las diferentes etapas de la vida y aún al día de hoy se encuentran en proceso de estudio, evaluación y construcción de guías especiales de atención.

Los pacientes con Síndrome de Down tienen dificultades comunicativas y de audición que dificultan su evaluación y adecuada orientación médica.

No existen guías en Colombia acerca de la atención de los pacientes con Síndrome de Down

No existen centros especializados de atención para pacientes con Síndrome de Down.

NO existen en los currículos de las facultades de Medicina materias específicas para la adecuada atención de los pacientes con síndrome de Down.

La paciente Maribel Ivonne Sarmiento fue atendida dentro de los tiempos y con los requerimientos propios para las manifestaciones clínicas que presentaba en el curso de la enfermedad durante su hospitalización.

No es posible establecer con absoluta seguridad el tiempo, lugar y mecanismo de infección de la paciente en mención.

La evolución de la enfermedad y la probabilidad de mortalidad por Neumonía multilobar severa viral por Influenza A H1N1, especialmente en el contexto de una Pandemia no es fácilmente determinable ni modificable aún con una alta sospecha diagnóstica y una intubación y manejo temprano en UCI.

F. Bibliografía

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Co-occurring medical conditions in adults with Down syndrome: A systematic review toward the development of health care guidelines. Am J Med Genet. 2018;176A:116–133.

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Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis. Crit Care Med 2009 Vol. 37, No. 5

Principales características de la pandemia por el nuevo virus influenza A (H1N1). J. Vaque Rafart et al. / Med Clin (Barc).2009;133(13):513–521

G. Consideraciones

El suscrito perito declara que el presente dictamen pericial contiene mi opinión independiente y corresponde a mi real convicción profesional y que no me encuentro incurso en ninguna de las causales contenidas en el artículo 50 del C.G.P. para rendir el dictamen pericial.

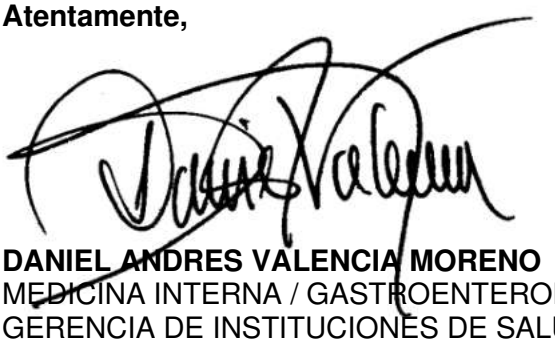
Las publicaciones científicas que he realizado se encuentran relacionadas en la hoja de vida.

En el presente dictamen no se han utilizado métodos, experimentos o investigaciones diferentes a las usadas habitualmente en el desarrollo del ejercicio profesional o de dictámenes periciales rendidos en otras oportunidades.

G. Anexos

Hojas de vida
Diplomas y títulos académicos
Bibliografía

Atentamente,



DANIEL ANDRES VALENCIA MORENO
MEDICINA INTERNA / GASTROENTEROLOGIA
GERENCIA DE INSTITUCIONES DE SALUD / EPIDEMIOLOGIA
CC 79.796.926 DE BOGOTA
RM 63-063/05

HOJA DE VIDA

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PERFIL PROFESIONAL

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ESPECIALISTA EN GERENCIA DE INSTITUCIONES DE SALUD Y EPIDEMIOLOGIA DE LA UNIVERSIDAD DE BOYACA

DIPLOMADOS Y CERTIFICACIONES EN ETLS, BLS, ACLS Y FCCS.

EXPERIENCIA DOCENTE.

EXPERIENCIA ADMINISTRATIVA – DIRECTIVA EN EL SISTEMA DE SALUD Y LA FORMACIÓN PROFESIONAL EN SALUD.

EXPERIENCIA PROFESIONAL EN MEDICINA INTERNA Y CUIDADOS INTENSIVOS.

CARACTERISTICAS PERSONALES Y PROFESIONALES

BUENA TOLERANCIA AL ESTRÉS CON FACILIDAD PARA LA TOMA DE DECISIONES, GUSTO POR EL TRABAJO EN EQUIPO Y EL LIDERAZGO DE PROYECTOS, GRAN SENSIBILIDAD SOCIAL-HUMANA, ALTO NIVEL DE COMPROMISO Y LEALTAD. ABSOLUTO INTERES POR EL APRENDIZAJE, LA ENSEÑANZA Y LA INVESTIGACION CON FACILIDAD PARA EXPONER TEMATICAS EN PÚBLICO Y ESTABLECER RELACIONES INTERPERSONALES. ACTITUD CREATIVA, COLABORADORA Y AMPLIOS CONOCIMIENTOS CLINICOS Y ADMINISTRATIVOS DEL CAMPO DE LA SALUD Y LA FORMACIÓN PROFESIONAL.

DATOS PERSONALES

LUGAR Y FECHA DE NACIMIENTO: Bogotá, septiembre 04 de 1978.
ESTADO CIVIL: Soltero
PROFESION: Médico Internista.

EDUCACIÓN

PRIMARIA Y SECUNDARIA: Instituto Pedagógico Nacional, Bogotá, terminado en 1996.

UNIVERSITARIA PREGRADO: Facultad de medicina, Universidad Militar “Nueva Granada”, Bogotá. Facultad de medicina, Universidad de Antioquia, Medellín (Internado), terminado en 2004.

UNIVERSITARIA POSTGRADO: Facultad de medicina Universidad Militar “Nueva Granada” – Hospital Militar Central, actualmente cursando el último semestre de la subespecialización en Gastroenterología, Facultad de medicina Universidad Militar “Nueva Granada” – Hospital Militar Central, especialización en Medicina Interna (junio de 2015) y Universidad de Boyacá, Gerencia de Instituciones de salud (2008) y Epidemiología (2009).

OTROS: Inglés, 5 semestres, UMNG, certificado de aprobación, The Pet Test (The British Council - Embajada de Inglaterra), Bogotá.

Certificado de aprobación Windows XP e Internet, UMNG, Diplomados certificados en ETLS, BLS, ACLS, FCCS. Violencia Sexual y Donación-Trasplante de órganos.

CONGRESOS / SIMPOSIOS / SEMINARIOS

Curso Formación Magistrados Seccionales de ética médica, Tribunal Nacional de ética Médica, Bogotá, Julio de 2017.

Seminario Accesos Vasculares guiados por ultrasonido, Universidad del Rosario, abril 2017.

II Curso Internacional de Medicina Crítica y Cuidado Intensivo, Fundación Santa Fe de Bogotá, noviembre de 2016.

IX Curso Taller de Ventilación Mecánica (SORBA), Fundación Santa Fe de Bogotá, septiembre de 2016.

Soporte Vital Básico y Cardiopulmonar Avanzado (BLS - ACLS), American Heart Association, Centro de estudios en Medicina de Urgencias y Emergencias – Universidad Nacional, 07, 08 y 09 de septiembre de 2018.

Curso de Violencia Sexual y de Género, INFORTE, agosto 08 de 2018.

Curso de Gestión Operativa de la Donación con Fines de Trasplante, FUNDONAR Colombia, abril 17 de 2019.

Fundamental Critical Care Support (FCCS), Society of Critical Care Medicine, noviembre 24 de 2019. Bogotá.

EXPERIENCIA

SERVICIO SOCIAL OBLIGATORIO

Hospital “La Misericordia” II Nivel, Calarcá, Quindío, enero 22 a 31 de julio de 2004 y Hospital de Barcelona I Nivel, Calarcá , Quindío, agosto 01 de 2004 a enero 22 de 2005.

LABORAL

Médico hospitalario Urgencias y Sala de Partos, Hospital “La Misericordia”, II Nivel, Calarcá (Quindío).

Médico hospitalario Urgencias y Sala de Partos, Hospital Sagrado Corazón de Jesús, I Nivel, Quimbaya (Quindío).

Médico Servicio de Urgencias, Hospital Militar Central, III-IV Nivel, Bogotá.

Médico hospitalario, Hospital Central Policía Nacional, III – IV Nivel, Bogotá.

Médico Ambulancia de alta complejidad, Servicio de Ambulancias del Oriente Aéreas y Terrestre, Tunja y Yopal 2009.

Médico Bienestar Universitario, Universidad de Boyacá 2009.

Docente Formación Integral I y II, Correlación Clínica y patología, Universidad de Boyacá 2009.

Director Programa de Medicina, Universidad de Boyacá 2009-2010.

Coordinador Médico Departamental, SOLSALUD EPS S.A 2010-2011.

Gerente Departamental, SOLSALUD EPS S.A. 2010-2011.

Auditor Médico de concurrencia, calidad y cuentas médicas, CLINICA MEDILASER, Tunja – Boyacá 2011.

Médico Internista - Coordinador Unidad de Cuidados Intensivos Adultos, CLINICA MEDILASER, Tunja – Boyacá 2015-2017.

Médico Internista Urgencias y pisos, CLINICA MEDILASER, Tunja – Boyacá 2015-Actualmente.

Médico Internista, consulta externa, IPS FAMILY MEDICAL CARE, IPS Salud Vital Integral, IPS Punto de Vida; Colmédica Medicina Prepagada y Clínica Medilaser Tunja – Boyacá. 2016-2017.

Coordinador Medicina Interna Urgencias, Clínica San Rafael – Dumian III Nivel, Girardot – Cundinamarca. 2017- Actualidad.

Médico Internista Unidad de Cuidado Intensivo, Clínica de Marly, Bogotá de abril 2019 a julio 2020.

Médico Internista Unidad de Cuidado Intensivo, Asociación Médicos Cuidado Crítico (AMECRI) para Hospital Militar Central, Bogotá diciembre 2019 - Actualmente.

LOGROS Y/O DISTINCIONES OBTENIDAS

Primer puesto (pregrado), Primer concurso de investigación, Facultad de Medicina UMNG-NOVARTIS, Proyecto: ¿Alcoholismo en médicos?

Monitor de Microbiología, Facultad de medicina (UMNG).

Representante de los estudiantes, Comité de Investigaciones de la facultad de medicina de V a IX semestres.

Integrante “Club de Investigadores”, facultad de medicina, UMNG.

Mejor promedio general acumulado (PGA) del curso (35 estudiantes), durante la carrera (X semestres).

Campeón de Volley-ball, 2001 y 2002, torneo mixto Inter-facultades UMNG (capitán de equipo).

Presidente Tribunal de Ética Médica de Boyacá, período 2016-2017.

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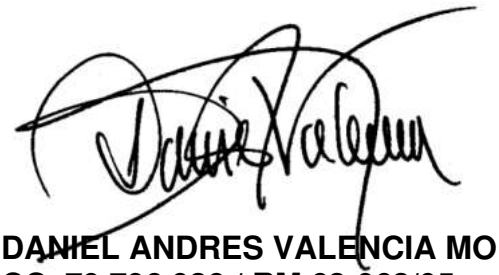
Teléfono: 320-8386700



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CERTIFICACIONES LABORALES

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UNIVERSIDAD MILITAR
NUEVA GRANADA

Creación Decreto 84 de 23 de enero de 1980, reconocimiento institucional Resolución 12975 de 23 de julio de 1982 del Ministerio de Educación Nacional, personería jurídica Ley 805 de 11 de abril de 2003

ACTA DE POSGRADO 918 UMNG
Hospital Militar Central H.M.C

En Bogotá, D.C., a los nueve (09) días del mes de junio de 2015, se reunieron los siguientes funcionarios: Por parte de la Universidad: Señor **Mayor General EDUARDO ANTONIO HERRERA BERBEL,** Rector; **Doctora MARTHA LUCIA BAHAMON JARA,** Vicerrectora Académica; **Coronel Médico JORGE ENRIQUE LUQUE SUAREZ,** Decano de la Facultad de Medicina y Ciencias de la Salud. Por parte del Hospital Militar Central: **Mayor General LUIS EDUARDO PEREZ ARANGO,** Director del Hospital Militar Central y el **Doctor LUIS ANTONIO CASTRO GOMEZ,** Subdirector de Docencia e Investigación Científica, con el objeto de estudiar los resultados académicos de un(a) Residente que adelanto sus estudios de Educación Avanzada y otorgar al mismo el título de **ESPECIALISTA**.

FUNDAMENTOS LEGALES

Artículos 10, 24, 25 y 28 de la Ley 30 de 1992, artículo 2º y literal g) del artículo 3º del Decreto 2725 de 1980; artículo 2º de la Ley 805 de 2003; Resolución 12975 de 1982 y Decreto 2376 de 2010 del Ministerio de Educación Nacional y Acuerdo 06 de 2012 de la Universidad Militar Nueva Granada.

OTORGAMIENTO DE TÍTULOS

La Rectoría de la **Universidad Militar Nueva Granada** teniendo en cuenta que la Facultad de Medicina y Ciencias de la Salud por intermedio de su Decano, la División de Registro y Control Académico por intermedio de su Jefe y el Hospital Militar Central por intermedio de su Director, han informado que el(la) Profesional **DANIEL ANDRES VALENCIA MORENO,** identificado(a) con la cédula de ciudadanía Nº 79796926 de BOGOTA D.C., ha cumplido satisfactoriamente con los requisitos académicos y las exigencias establecidas en los Reglamentos Internos de la Universidad Militar Nueva Granada y del Hospital Militar Central y las normas legales pertinentes, resuelve en nombre de la **República de Colombia** y por autorización del **Ministerio de Educación Nacional** otorgarle el título de **ESPECIALISTA EN MEDICINA INTERNA,** quedando registrado su diploma y acta de grado con el número de registro **918**

Para constancia de lo anterior y en cumplimiento de lo establecido en el artículo 7º del Decreto Nº 2725 del 10 de octubre de 1980 firman al respaldo los que en ella intervinieron.

Doctor LUIS ANTONIO CASTRO GOMEZ
Subdirector de Docencia e Investigación Científica

Siguen firmas al respaldo...

Mayor General LUIS EDUARDO PEREZ ARANGO
Director del Hospital Militar Central

Coronel Médico JORGE ENRIQUE LUQUE SUAREZ
Decano de la Facultad de Medicina y Ciencias de la Salud

Doctora MARTHA LUCIA BAHAMON JARA
Vicerrectora Académica

Mayor General EDUARDO ANTONIO HERRERA BERBEL
Rector

ACTA DE POSGRADO 918

Ingeniera DIANA MAYERLLY CAVIEDES CASTRO
Jefe División de Registro y Control Académico

UNIVERSIDAD MILITAR NUEVA GRANADA

Creación Decreto 84 de 23 de enero de 1980, reconocimiento institucional Resolución 12975 de 23 de julio de 1982 del Ministerio de Educación Nacional, personería jurídica Ley 805 de 11 de abril de 2003

0040380

ACTA DE GRADO Nº 3019

En Bogotá, D.C., a los Diez y Nueve (19) días del mes de Diciembre del año Dos Mil Tres (2003), se reunieron en la Rectoría de la **Universidad Militar Nueva Granada**, los siguientes funcionarios: el Brigadier General **ADOLFO CLAVIJO ARDILA,** Rector; el Brigadier General **CARLOS LEONGOMEZ MATEUS**, Vicerrector (encargado) y el Doctor **JOHNNY NEISSA GUIZA,** Decano (encargado) de la Facultad de Medicina y Ciencias de la Salud, con el objeto de estudiar los resultados académicos de un egresado de la Universidad Militar "Nueva Granada" y otorgarle el título en la forma que más adelante se indica:

FUNDAMENTOS LEGALES

Artículos 8, 9, 24, 28 y 137 de la ley 30 de 1992, Artículos 2º y literal g) del artículo 3º del Decreto 2725 de 1980; Artículo 1º del Decreto 2273 de 1985; Resolución 12.975 del 23 de julio de 1982 del Ministerio de Educación Nacional; Resolución 418/92 del Instituto Colombiano para el Fomento de la Educación Superior (**ICFES**).

OTORGAMIENTO DEL TITULO

La Rectoría de la **Universidad Militar Nueva Granada**, teniendo en cuenta que la Facultad de Medicina y Ciencias de la Salud por intermedio de su Decano y la División de Registro Académico han informado que el señor **DANIEL ANDRES VALENCIA MORENO,** identificado con la cédula de ciudadanía Nº 79.796.926 de Santafé de Bogotá D.C., ha cumplido satisfactoriamente con los requisitos académicos, las exigencias establecidas en los reglamentos internos de la Institución y las normas legales pertinentes resuelve, en nombre de la **República de Colombia** y por autorización del **Ministerio de Educación Nacional**, otorgarle el título de **MEDICO Y CIRUJANO,** quedando registrado su diploma y acta de grado en el libro de registro, bajo el número **4733.**

Para constancia de lo anterior y en cumplimiento de lo establecido en el artículo 7º del Decreto Nº 2725 del 10 de octubre de 1980 firman los que en ella intervinieron.

La presenta Acta es fiel copia de su original.

Dada en Bogotá, D.C. a los diez (10) días del mes de Enero de dos mil ocho (2008).

REFRENDA ACTA Nº 3019.

WILLIAM A. CASAS GOMEZ
Jefe División de Registro Académico

ACTA DE POSESIÓN DE CARGOS DE MAGISTRADOS DEL TRIBUNAL SECCIONAL DE ÉTICA MÉDICA DE BOYACÁ

07 DE AGOSTO DE 2017

Siendo las 09:10 a.m. del día lunes, 07 de agosto de 2017, en el Salón de la Constitución del Palacio de la Torre de la Gobernación de Boyacá en la ciudad de Tunja, se reunieron los miembros del Tribunal Seccional de Ética Médica de Boyacá, los doctores: Daniel Andrés Valencia Moreno, Saulo Flaviano Guarín Cortés, Tito Gregorio Francisco Mojica Rodríguez, Carlos Manuel Mojica Walteros y Wilma Inés Castilla Puentes, ante el Gobernador de Boyacá, Ingeniero Carlos Andrés Amaya Rodríguez, como primera autoridad política del Departamento, quien a través de acto solemne y en cumplimiento del artículo 70 de la Ley 23 de 1981 y de lo dispuesto por el Tribunal Nacional de Ética Médica, realizó el juramento y la posesión de los cargos de Magistrados del Tribunal Seccional de Ética Médica de Boyacá por parte de los doctores que resultaron electos por el Tribunal Nacional de Ética Médica en Sesión N° 1350 del 17 de enero de 2017 para el período 2017-2019.

Los magistrados que asumen sus funciones, juran cumplir con la Constitución, la Ley y las normas de Ética Médica, entendiendo las responsabilidades y dignidades con las que son investidos y comprometiéndose con el bienestar de la salud y la Medicina en Boyacá.

Como Constancia de lo anterior, firman los honorables magistrados del Tribunal Seccional de Ética Médica de Boyacá y el señor Gobernador del Departamento de Boyacá.

DANIEL ANDRÉS VALENCIA MORENO
Magistrado T.S.E.M. Boyacá

SAULO FLAVIANO GUARÍN CORTÉS
Magistrado T.S.E.M. Boyacá

CARLOS MANUEL MOJICA WALTEROS
Magistrado T.S.E.M. Boyacá

TITO GREGORIO FRANCISCO MOJICA R.
Magistrado T.S.E.M. Boyacá

WILMA INÉS CASTILLA PUENTES
Magistrada T.S.E.M. Boyacá

CARLOS ANDRÉS AMAYA RODRÍGUEZ
Gobernador de Boyacá

CURSO SOPORTE VITAL AVANZADO

SVCA/ACLS

REPUBLICA DE COLOMBIA

REPUBLIC OF COLOMBIA

ICARO APH S.A.S.

NIT: 900594014-6

Res. 2149 – 6 de Diciembre de 2013

CERTIFICA QUE

CERTIFIES THAT

DANIEL ANDRES VALENCIA

Identificación *I.D. Card No* **79.796.926**

Aprobó satisfactoriamente todos los objetivos del

CURSO SOPORTE VITAL AVANZADO SVA

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JESUS IGNACIO TOBAR ERASO
Instructor AHA - NAEMNT

CRISTIAN FERNEY HEREDIA ALBA
Gerente ICARO APH S.A.S

EL PRESENTE CERTIFICADO ES VALIDO SI CONTIENE LOS 2 SELLOS (SECO Y DE TINTA) DE ICARO APH Y LAS FIRMAS EN ORIGINAL

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Apartado 2: DESOBSTRUCCIÓN DE LA VÍA AÉREA.
Apartado 3: DESFIBRILACIÓN AUTOMÁTICA EXTERNA Y MANEJO DEL DESFIBRILADOR MANUAL.
Apartado 4: MANEJO AVANZADO DE LA VÍA AÉREA, TÉCNICAS DE VENTILACIÓN Y OXIGENACIÓN.
Apartado 5: MANIOBRAS BÁSICAS Y AVANZADAS DE REANIMACIÓN EN EL PARO RESIRATORIO.
Apartado 6: MANEJO Y VISUALIZACIÓN DE LAS ARRITMIAS MÁS COMUNES, ANTES Y DESPUÉS DEL PARO CARDÍACO.
Apartado 7: APLICACIÓN DE LA CARDIOVERSIÓN.
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Apartado 10: FARMACOLOGÍA Y USO DE MEDICAMENTOS PARA IMPLEMENTACIÓN DE LA REANIMACIÓN CARDIOPULMONAR.

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UNIVERSIDAD DE BOYACÁ

PERSONERÍA JURÍDICA RESOLUCIÓN No. 6553 DE 1981
RESOLUCIÓN No. 2910 DE 16 DE SEPTIEMBRE DE 2004

En nombre de la República de Colombia y con autorización del Ministerio de Educación Nacional

TENIENDO EN CUENTA QUE

Daniel Andrés Valencia Moreno

C.C. No. 79.796.926 EXPEDIDA EN SANTAFÉ DE BOGOTÁ D.C. – Cundinamarca

CURSÓ TODOS LOS ESTUDIOS Y CUMPLIÓ SATISFACTORIAMENTE LOS REQUISITOS ESTABLECIDOS POR LA UNIVERSIDAD Y POR LAS NORMAS LEGALES LE CONFIERE EL TÍTULO UNIVERSITARIO DE:

ESPECIALISTA EN GERENCIA DE INSTITUCIONES DE SALUD

EN TESTIMONIO DE ELLO LE OTORGA EL PRESENTE

DIPLOMA

DADO EN TUNJA A LOS 26 DEL MES DE JUNIO DE 2009

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DIPLOMA

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Decano Facultad

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UNIVERSIDAD MILITAR NUEVA GRANADA
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C.C. 79.796.926 Expedida en Bogotá D.C.

Ha cumplido en

Hospital Militar Central

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Medicina Interna

Bogotá, D.C., 09 de Junio de 2015.

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DANIEL ANDRES VALENCIA MORENO

C.C o C.E 79796926

Profesión u Ocupación

MEDICO

Especialidad

MEDICINA INTERNA

Institución de Educación

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Ciudad BOGOTA D.C.

Fecha de expedición diploma 19/12/2003

Fecha de inscripción RETHUS 31/01/2005

79796926

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CERTIFICACIONES LABORALES

LA ASOCIACION GREMIAL DE MEDICOS ESPECIALISTAS EN CUIDADO CRITICO

AMECRI

C E R T I F I C A:

Que el señor **DANIEL ANDRES VALENCIA MORENO,** identificado con la cedula de ciudadanía No.79.796.926, expedida en Bogotá, es asociado de nuestra Agremiación Sindical y se desempeña como Médico Especialista, en las unidades de cuidados intensivos posquirúrgica y Médica, del Hospital Militar Central, a través de un contrato de AFILIADO PARTICIPE, desde el 21 de diciembre de 2019, devengado unos ingresos promedios mensuales de **DOS MILLONES OCHOCIENTOS DIEZ MIL PESOS ($2.810.000)** Y unos bonos promedios mensuales en efectivo de **DOS MILLONES CUARENTA Y OCHO MIL PESOS MIL PESOS ($2.048.000).**

Se expide la presente certificación por solicitud del interesado a los veintiocho (28) días del mes de julio de 2020.

Cordialmente,

ADRIANA SALAZAR FERNÁNDEZ
Recursos Humanos

ASG_GAC 080

LA DIRECTORA ADMINISTRATIVA DE ANESMEDIC
SINDICATO DE GREMIO
NIT. 900.459.733-6

CERTIFICA:

Que el Doctor **DANIEL ANDRES VALENCIA MORENO** identificado con Cédula de Ciudadanía número 79.796.926, en virtud del artículo 39 de la Constitución Política de Colombia, está afiliado a este sindicato y mediante convenio de ejecución es afiliado partícipe en la especialidad de Medicina Interna, participa en el desarrollo de diferentes contratos sindicales suscritos entre Anesmedic y la Clínica Medilaser sede Tunja, desde el 01 de agosto de 2020.

La presente certificación se expide a solicitud del interesado en Neiva (Huila), a los veinticuatro (24) días del febrero de 2021.

ROSA ELENA SALAZAR LONDOÑO
Directora Administrativa

Proyectó: BHBP

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Calle 11 No. 16 - 51
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contactos@anesmedic.com.co

HEALTH & QUALITY S.A.S.
NIT: 901.088.151-0

Tunja, 06 de febrero de 2019

CERTIFICACIÓN LABORAL

La empresa **HEALTH & QUALITY SAS** identificada con NIT: 901.088.151-0 certifica que el señor DR. DANIEL ANDRES VALENCIA MORENO identificado con cedula CC: 79.796.926 de Bogotá D.C. laboró a través de la nuestra empresa, para el Hospital – Clínica San Rafael / DUMIAN, de la ciudad de Girardot como Coordinador del Servicio de Medicina Interna, atendiendo pacientes en los servicios de Urgencias, Consulta Externa y Hospitalización, desde el 01 de septiembre de 2017 y hasta el 31 de enero del presente año, demostrando siempre gran fortaleza académica y profesional, así como un completo compromiso y sentido de pertenencia con la institución y total sentido humano con sus pacientes.

La presente certificación se expide a solicitud del interesado a los 06 días del mes de febrero de 2019.

Cordialmente,

YURI VILLAREAL VERTEL
Administración

CENTRO EMRESARIAL Y DE NEGOCIOS GREEN HILLS
Av. Universitaria N° 75-00 BL-A/ CS 33ª
Tunja – Boyacá
300-6944062

Ocupar.

OCUPAR TEMPORALES S.A.

NIT 800106404-0

CERTIFICA QUE

El(la) señor(a) DANIEL ANDRES VALENCIA MORENO identificado(a) con la cédula de ciudadanía No. 79796926 expedida en BOGOTA D.C. - BOGOTA, se ha vinculado a OCUPAR TEMPORALES S.A., como trabajador(a) en misión, mediante contrato de trabajo por el tiempo que dure la realización de la obra o labor determinada, en los siguientes extremos laborales:

EMPRESA USUARIA	INICIO	TERMINACIÓN	CARGO
MARLY S.A.	29/03/2019	05/06/2020	Médico Internista UCI
MARLY S.A.	6/06/2020	02/07/2020	Médico Internista UCI

En constancia de lo anterior, se firma en la ciudad de BOGOTA, a los 29 días del mes Julio del año 2020.

Personal.

Importante. Esta solicitud solo hace referencia a la información mencionada anteriormente. Si desea verificar la veracidad de esta información, puede comunicarse a la sucursal telefónica más cercana. CALI OCUSERVIS: Calle 15 #22-207 Bodega 19B Terminal Logistico valle del pacifico, Km 6 costado oriental Cali-Yumbo /PBX (2) 3989999 – (2) 6954526 / CALI OCUPAR: Avenida 8 Norte # 23N – 76 /PBX (2) 3989999 – (2) 3908484 / BOGOTA: Cra 15# 97 – 40 / Modelia Cra 72 # 23F-06 / PBX (1) 5921222 MEDELLIN: Cll 32 F # 75B – 52 /PBX (4) 4483935 / PEREIRA: Cll 46 # 10 – 37 / PBX (6) 3364444 / BARRANQUILLA: Cll 98 # 51B – 76 /BPX (5) 3780055 / BUENAVENTURA: Cra 6 # 2 -20 / BPX (2) 2419254 / IBAGUE Cra 5 # 39 – 76 / PBX (8) 2666552 / BUCARAMNGA: Cll 36 # 31 – 39 / PBX (7) 6450751 / BUGA: Cll 7 # 11 – 57 /PBX (2) 2369262 / SANTANDER DE QUILICHAO: Cll 2C # 6 – 38 /PBX (2) 8924058 / VILLAVICENCIO: Cll 34 # 37 – 21 / PBX (8) 6622439.

LITERATURA MÉDICA

BMC Health Services Research

RESEARCH ARTICLE Open Access

Capturing the complexity of healthcare for people with Down syndrome in quality indicators - a Delphi study involving healthcare professionals and patient organisations

Francine A. van den Driessen Mareeuw[1,2], Antonia M. W. Coppus[3,4], Diana M. J. Delnoij[5,6] and Esther de Vries[1,2*]

Abstract

Background: Insight into quality of healthcare for people with Down Syndrome (DS) is limited. Quality indicators (QIs) can provide this insight. This study aims to find consensus among participants regarding QIs for healthcare for people with DS.

Methods: We conducted a four-round Delphi study, in which 33 healthcare professionals involved in healthcare for people with DS and two patient organisations' representatives in the Netherlands participated. Median and 75-percentiles were used to determine consensus among the answers on 5-point Likert-scales. In each round, participants received an overview of participants' answers from the previous round.

Results: Participants agreed (consensus was achieved) that a QI-set should provide insight into available healthcare, enable healthcare improvements, and cover a large diversity of quality domains and healthcare disciplines. However, the number of QIs in the set should be limited in order to prevent registration burden. Participants were concerned that QIs would make quality information about individual healthcare professionals publicly available, which would induce judgement of healthcare professionals and harm quality, instead of improving it.

Conclusions: We unravelled the complexity of capturing healthcare for people with DS in a QI-set. Patients' rights to relevant information have to be carefully balanced against providers' entitlement to a safe environment in which they can learn and improve. A QI-set should be tailored to different healthcare disciplines and information systems, and measurement instruments should be suitable for collecting information from people with DS. Results from this study and two preceding studies, will form the basis for the further development of a QI-set.

Keywords: Down syndrome, Quality indicators, Quality of health care, Netherlands, Delphi technique

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Background

Down syndrome (DS) is the most prevalent genetic cause of intellectual disability (ID) [1, 2]. People with DS suffer from a large variety of health problems and therefore have complex healthcare needs, with many different healthcare providers involved [2–5].

It is widely acknowledged that healthcare for people with DS should be of high quality in order to meet their specific healthcare needs [4, 6, 7]. This is supported by the Convention on the Rights of Persons with Disabilities, advocating high-quality healthcare for people with disabilities, and acknowledging the right for obtaining the highest possible level of health [8]. However, little is known about the quality of DS-specialised healthcare [9, 10].

Quality in healthcare is multidimensional. The World Health Organization formulated six dimensions of healthcare quality: 1) effective (evidence-based and based on needs), 2) efficient (maximising resources, avoiding waste), 3) accessible (timely, geographically reasonable, in a suitable setting), 4) acceptable/patient-centred (taking into account preferences, culture of patient), 5) equitable (same level of quality for everyone) and 6) safe (minimising risk and harm) [11].

Quality indicators (QIs) - also known as quality measures [12] - are an important tool in healthcare quality, as they can improve clinical decisions, guide organisational reform, and structure the development of multidisciplinary teams [13]. Moreover, QIs can provide patients with information that enables them to choose the best suitable care [14]. However, an authors' former study revealed that, up to now, QIs measuring quality of healthcare for people with DS, do not appear to exist [9, 10]. The study found that existing QIs concern people with ID in general (not people with DS in particular), or focus, for instance, on care in assisted living facilities (not specifically on healthcare) [9, 10].

According to Donabedian's (2005) well-known framework for quality in healthcare, a QI-set may include different types of QIs: structure, process, and outcome QIs [13, 15]. Structure refers to the setting in which healthcare is provided (e.g. administrative structure), process to how healthcare is provided (e.g. followed procedures), and outcome to the result of healthcare provided (e.g. recovery, survival) [13]. Generally, QIs are based on quality standards, such as guidelines or protocols [16, 17]. In the Netherlands, a guideline for multidisciplinary healthcare for children with DS [18] is present and is currently being revised. Until now, such a guideline concerning adults with DS has not been present, but is currently being developed.

The present study aims to find consensus among healthcare professionals and patient organisation representatives regarding QIs for healthcare for people with DS in the Netherlands. This healthcare involves, amongst others: a paediatrician, ID physician (in the Netherlands, there is an ID-specialised training for physicians), general practitioner (GP), physiotherapist, speech therapist, psychiatrist, cardiologist, ophthalmologist, and DS-specialised multidisciplinary outpatient clinics, so-called 'Down teams' [3, 5, 7, 19, 20]. There are paediatric and adult 'Down teams' in the Netherlands. Paediatric 'Down teams' typically include a visit to the paediatrician, physiotherapist, ENT (ear-nose-throat)-specialist and others, all on the same day. Adult 'Down teams' are still scarce and have a slightly different composition, due to different needs in adulthood.

The present study is part of a larger project aiming to develop a QI-set for healthcare for people with DS. The project includes a literature review on existing QIs for healthcare for people with DS (indicating the absence of QIs that could serve as a basis for our QI-set) [10], a qualitative exploration of how people with DS, parents and support staff define quality in healthcare [21] (see Table 1), and the current study. In the final project step, findings of the three studies will be combined in order to formulate QIs. In the present study, the following research questions are addressed:

1. *According to healthcare professionals and patient organisations' representatives, how should a QI-set measuring quality in healthcare for people with DS be defined?*
   a. *Which purposes should it serve?*

Table 1 Summary of outcomes of previous study

Outcomes from previous study[a]
Method and participants: Qualitative design including semi-structured interviews with people with DS and with parents, and focus groups with support staff members (of people with DS living in assisted living facilities)
Summary of findings: - Participants mentioned a large variety of healthcare and other services people with DS used. Among others: 'Down team', GP, dentist, psychologist, physiotherapist, speech therapist, ear nose throat physician, ophthalmologist, family support, educational support. - According to participants, good healthcare is: o Person-centred: The person with DS and his/her values and preferences are central; The personal situation and life stage of the person with DS are taken into account and caregivers are involved; Communication between professional and person with DS (and his/her caregivers) is respectful and adapted to the abilities of the person with DS. o Effective, efficient and accessible: Timely recognition of health problems, Healthcare professionals with DS-expertise are nearby; Information about available care is present. o Multidisciplinary, well-coordinated and integrated: It includes actors outside healthcare (e.g. school, work); Information is shared (between professionals); Consultations are planned in a synchronized manner; Transition from paediatric to adult healthcare and services proceeds smoothly.

Abbreviations: *DS* Down syndrome, *GP* General practitioner
[a] Qualitative exploration of opinions and experiences of people with DS, parents, and support staff regarding healthcare quality [21]

b. *Which healthcare disciplines, services and quality domains should it cover?*
c. *Which type of QIs (structure, process, outcome) should it include and how many?*

2. *According to healthcare professionals and patient organisations' representatives, what factors should be taken into account in the further development and implementation of the QI-set?*

Methods

A Delphi technique was used in order to achieve consensus among experts in healthcare for people with DS about relevant items for QIs and related practical issues. Our study is an exploratory inquiry concerning personal opinions of professionals on healthcare quality. According to Dutch legislation [22], ethics approval was deemed unnecessary, since participants in our study were not subject to procedures and were not required to follow rules of behaviour. We obtained a written informed consent statement from all participants prior to the study. This allowed us to use participants' contact details for sending them the questionnaires, or for contacting them in case of problems with receiving or filling out the questionnaires. In this statement, participants also approved the use of their answers to the Delphi-questionnaires in an anonymous manner for the aims of the study.

Participants

We included representatives of all relevant disciplines involved in healthcare for people with DS and patient organisation representatives, all having expertise in healthcare for people with DS. This composition is similar to the composition of the working group developing guidelines for healthcare for people with DS [18]. Recruitment of participants was done by contacting professional organisations from relevant disciplines and two patient organisations (one specific DS organisation and the umbrella organisation of Dutch patient organisations). We explained the purpose of our research and the expected time investment, and asked the organisations to identify members of their organisations with expertise in healthcare for people with DS. When identified members had agreed to participate, contact details were provided to the researchers, who in turn contacted the members. As the Dutch professional organisation of GPs declined to identify eligible GPs because of other priorities, GPs were recruited via the network of the authors and participants, and/or by using publicly available contact details. Table 2 provides an overview of the participant characteristics.

Table 2 Participant characteristics

Characteristic	*n* = 35
Age (y) [mean (stdev) [range]]	50.5 (9.6) [30–73]
Gender [number (%)]	
Female	32 (91.4%)
Male	3 (9.0%)
Profession	
Audiologist	1 (2.9%)
Dentist (ID-specialised)	3 (8.6%)
Dermatologist	1 (2.9%)
Dietician (ID-specialised)	2 (5.7%)
General Practitioner	2 (5.7%)
ID physician	3 (8.6%)
Municipal Health Services doctor	1 (2.9%)
Nurse / coordinating nurse (ID-specialised)	3 (8.6%)
Occupational therapist	2 (5.7%)
Ophthalmologist	1 (2.9%)
Orthoptist	2 (5.7%)
Paediatrician	2 (5.7%)
(child) Physiotherapist	4 (11.4%)
Psychiatrist (child/youth/adult)	1 (2.9%)
Psychologist	1 (2.9%)
Podiatrist	2 (5.7%)
(child) Rehabilitation physician	1 (2.9%)
Representative of patient organisation	2 (5.7%)
Speech therapist	1 (2.9%)
Time working in this profession (y)	
[mean (stdev) [range]]	19.2 (10,2) [0.7–40]
Frequency of contact with people with DS [number (%)]	
(almost) daily	9 (25.7%)
Weekly	14 (40.0%)
Monthly	7 (20.0%)
Half-yearly	3 (8.6%)
Yearly	1 (2.9%)
Less than once a year	1 (2.9%)

Abbreviations: *y* year(s), *stdev* standard deviation, *ID* Intellectual Disability

Four-round Delphi procedure

A Delphi study uses a series of questionnaire-rounds in order to establish consensus among a group of experts about a certain topic [12, 23, 24], and is suitable for the selection of QIs [25]. In such an iterative process, each next round is based on the participants' answers in the previous round. Only items for which no consensus among participants is found, are presented in the next round. Furthermore, participants receive an overview of the overall group response of the previous round, based on which they can reconsider their initial answers [24, 25]. Our study consisted of four consecutive rounds:

– Round 1: Introduction to themes, initial inventory of level of consensus;

- Round 2: Feedback on Round 1 and revisiting themes on which no consensus existed;
- Round 3: Exploration of consensus on sub-domains;
- Round 4: Final consensus building

We used online questionnaires, which were composed using Qualtrics$^{XM®}$. Online questionnaires allow participants to fill out the questionnaires wherever they want, allow anonymous participation of experts across various locations, and prevent one (or a few) expert(s) from dominating the consensus process [12, 23].

Questionnaires and consensus

All questionnaires contained questions with a five point Likert-scale, multiple choice questions and open-ended questions.

Using the Likert-scale questions, participants rated items in terms of relevance for the QI-set (1 'very important', 2 'important', 3 'neutral', 4 'not that important', 5 'not important at all'), or indicated to what extend they agreed with propositions (1 'totally agree', 2 'agree', 3 'neutral', 4 'disagree', 5 'totally disagree'). In round 1 an *'I don't know'*-option was also included. Consensus was defined in advance, as follows: if at least 75% of the participants rated an item as 1 or 2 and the median was ≤2, consensus was achieved among the participants about including the item in the QI-set, or about agreeing with a proposition. If 75% of the participants rated an item 4 or 5 and the median was ≥4, consensus was achieved among the participants about excluding the item from the QI-set, or about disagreeing with a proposition. In all other situations, it was concluded that consensus was not achieved among participants. Although there is no standard for defining consensus in Delphi studies, using a combination of percentages and median for defining consensus is generally accepted [12, 25]. A 75% cut-off is considered adequate in Delphi studies [24]. We decided to present some items to the participants despite the fact that consensus was obtained for these items in the previous round(s), because some participants had not been able to join the first round, or because we thought the items should be presented as a complete set (e.g. all healthcare disciplines possibly involved in healthcare for people with DS). If we deemed more detailed information was needed, more specialised items/propositions, or differently formulated propositions were presented to the participants (e.g. quality domains were presented in round 1 and sub-domains in round 3).

The multiple choice questions and the open ended questions allowed participants to explain their 'rated' answers or add relevant QI-items.

The topics of the questionnaires were largely based on outcomes of the previous study investigating the experiences and opinions of people with DS, parents and support staff regarding quality in healthcare [21] (see Table 1) and on the multidisciplinary guideline for healthcare for children with DS [18]. Additionally, the questionnaires contained topics related to the development, implementation and use of QIs, informed by literature and expertise of the authors. Topics addressed in the questionnaires and number and type of questions are shown in Table 3. An English translation of the questionnaires can be found in Additional file 1.

Delphi in one day

The first questionnaire was sent out on April 25th 2018, the other three on May 30th 2018. This timeframe was chosen because participants preferred to conduct the study (predominantly) on 1 day. This short study duration would thus prevent participant drop-out related to large time intervals between the rounds. It would also limit time investment of both participants and researchers, as participants do not need re-introduction into the topic at the start of each new round, and data collection proceeds quickly. Although the time intervals between the rounds in our study were much shorter than in classic Delphi studies [24], literature does not provide any reason to assume that a shorter study duration affects the results [26]. However, in order to allow for such short time intervals, the rounds required thorough preparation, enabling participants to fill out the questionnaires swiftly, and enabling researchers to perform analyses and adapt the questionnaires accordingly. Therefore, the authors composed most questions beforehand, by anticipating the possible responses of the participants and by using preliminary insights resulting from round 1. Because of this, only a few questions needed to be newly composed between round 2, 3 and 4, and most questions only had to be moved, slightly rephrased, or removed. Additionally, used software was set ready to quickly provide the researchers with information needed to assess consensus (median and 75-percentiles) and with an overview of open-ended question answers. Furthermore, roles of the research team (i.e. obtaining medians and 75-percentiles; extracting open-ended question answers, chairing the discussions (see next paragraph "Analysis"), adapting and sending out the questionnaires) were allocated beforehand.

Analysis

During the study, we used percentages provided by Qualtrics$^{XM®}$ and the median calculated using IBM SPSS Statistics 24, to determine whether the answers of the participants on the Likert-scale questions had resulted in consensus. From the multiple choice questions, only frequencies (percentages) were calculated. Analysis of the answers from open-ended questions included reading and discussing the answers by all authors, which resulted

Table 3 Topics addressed and type of questions per round

Topic addressed	Topic addressed in:			
	Round 1 Introduction to themes, initial inventory of level of consensus	Round 2 Feedback on Round 1 and revisiting themes on which no consensus existed	Round 3 Exploration of consensus on sub-domains	Round 4 Final consensus building
Participant characteristics	6 open ended questions (such as age, gender, frequency of contact with people with DS).	Idem: same questions were presented to participants who had not participated in round 1.		
Purpose of QI-set (e.g. transparency, quality improvement, auditing, insurance)	9 purposes, rate importance	12 propositions[a]	9 propositions[a]	
Quality domains to be included in QI-set (e.g. coordinated care, person-centeredness, clinical outcome)	10 items[b] and 1 proposition for children with DS; 10 items[b] and 1 proposition for adults with DS	7 items[b] for children and adults with DS	28 items[b] (sub-domains)	1 proposition[a]
Healthcare disciplines to be included in QI-set (e.g. Down team, psychological care, physiotherapy)	14 items[b] and 1 close-ended question for children with DS; 14 items[b] and 1 close-ended question for adults with DS	6 propositions; 30 items[b] for children; 30 items[b] for adults with DS	4 open-ended questions	1 proposition[a]
Number and type (structure / process / outcome) of QIs		2 close-ended questions	2 propositions; 1 close-ended question	2 propositions; 3 open-ended questions
Information sources and transparency of QIs and practical issues regarding development	1 close-ended question; 1 open-ended question	1 proposition; 1 close-ended question; 6 open-ended questions	6 propositions; 1 close-ended question; 2 open-ended question	17 propositions
Healthcare quality for people with DS and current use of QIs	3 close-ended questions; 3 open-ended questions	15 propositions		
Aim of the study	1 open-ended question			

Abbreviations: *DS* Down syndrome, *QI* Quality indicator
Empty fields indicate that the topic was not presented to the participants in the concerning round.
[a] Participants indicated to what extent they agreed with propositions (1 'totally agree', 2 'agree', 3 'neutral', 4 'disagree', 5 'totally disagree')
[b] Participants rated items (i.e. healthcare disciplines/services or quality domains) indicating the relevance for the QI-set (1 'very important', 2 'important', 3 'neutral', 4 'not that important', 5 'not important at all')

in identification and structuring of key issues. All authors were involved in all iterations of the study, in an e-mail conversation (first round) and in a face-to-face meeting (rounds 2–4).

Afterwards, in order to structure the data, a dataset containing data from all rounds was created using IBM SPSS Statistics 24, and median and 75-percentile of the Likert-scale questions were calculated again. The calculations were done with and without the patient organisation representatives' answers, in order to discover whether their answers differed from the health care professionals' answers. Differences were indicated together with the concerning findings, in order to interpret the results.

Results

Participants flow

A total of 35 eligible participants was identified. However, one participant could not allocate time for participating in any of the rounds and answered only one question in round two and three. Ten participants could not participate in all rounds. Figure 1 shows a flowchart of the number of participants per round. On average, participants needed 55, 52, 25 and 14 min to complete questionnaires 1, 2, 3 and 4 respectively, with a maximum of 114, 85, 45, and 48 min.

Results Delphi rounds

Distributed across the four rounds, 259 questions were presented to the participants, comprising 20 open-ended questions, 11 closed-ended questions and 228 propositions or items, of which 107 had resulted in consensus among the participants. See Table 4.

Below, the results of the four Delphi rounds are presented in two parts: 1) Defining purposes and identifying QI-topics; and 2) Considerations for further development and implementation of the QI-set. More details about the results can be found in Additional file 2.

Defining purposes and identifying QI-topics

Purposes In the first three rounds, participants indicated the purpose(s) to be served by the QI-set. See Table 5, first row ('Purpose of QIs').

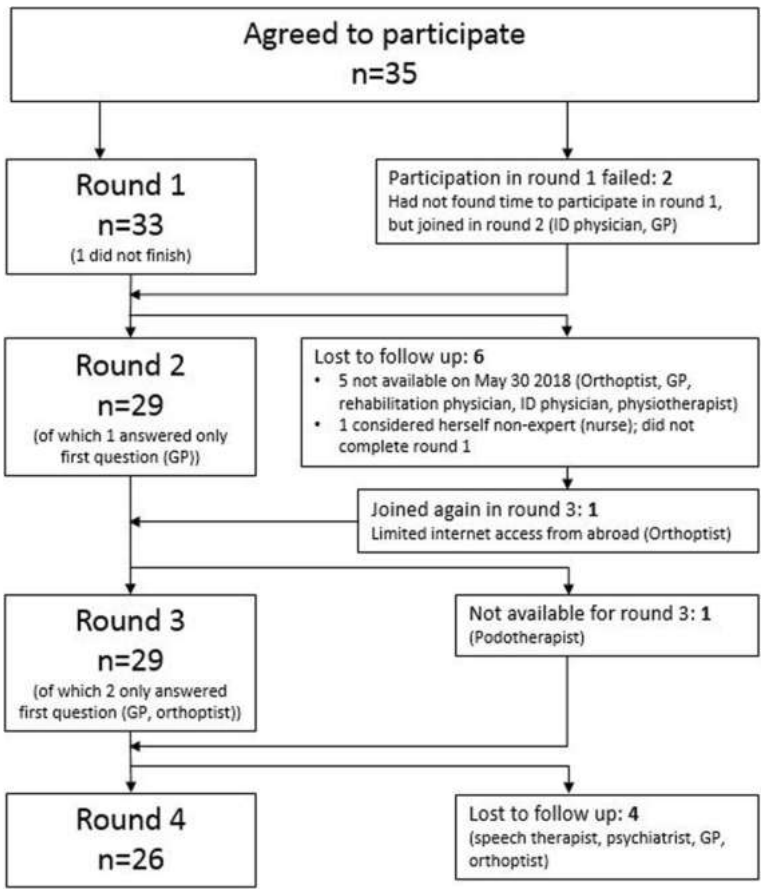

Fig. 1 Flowchart of number of participants for each Delphi round

Related to the purpose "provide healthcare professionals with information on where to find suitable healthcare (providers)", participants explained that providers could use this information for making referrals. Especially for generalists (such as GPs), who cannot reasonably be expected to have much DS-specialised expertise, QIs could be helpful in identifying specialised healthcare professionals to refer to.

Additional to the purposes "improving healthcare on the national level" and "improve healthcare for people with DS delivered by their organisation (e.g. health centre, hospital, department)", participants mentioned that QIs could be part of audits, and could be used to improve processes (logistics, management, ICT etc.). Furthermore, participants explained that QIs should enable benchmarking of one's own functioning as compared to that of colleagues at individual, regional or national level.

About the purpose "using QIs as input for developing guidelines", consensus was achieved in the first round. However, participants commented that QIs should not be used as input for guidelines, but rather the other way around (guidelines should define indicators). We therefore decided to present this purpose to the participants in round two again, which did not result in consensus.

Although there was consensus concerning "QIs should be used to reduce differences in quality of provided healthcare by different providers", some participants argued that differences should exist between providers, because if differences would not exist, this may imply that

Table 4 Number and types of questions per round and consensus among participants on propositions and items

Round	Total number of questions	Open-ended questions	Closed-ended questions	Propositions /Items	Consensus
Round 1	72	5	6	61	37
Round 2	110	6	3	101	31
Round 3	54	6	2	46	28
Round 4	23	3	0	20	11

Table 5 Summary of findings: Defining purposes and identifying QI-topics

Theme	Consensus about (Likert-scale questions) or Majority agreed that (multiple choice / open questions)	Round(s) in which theme was addressed
Purpose of QIs	QIs should: • provide people with DS and their caregivers with information on where to find suitable healthcare (providers); • provide healthcare professionals with information on where to find suitable healthcare (providers); • be used to improve healthcare for people with DS on a national level; • be used to improve healthcare for people with DS delivered by their organisation (e.g. health centre, hospital, department), by using the QIs as input for (interdisciplinary) reflective meetings with colleagues, for short term evaluation of healthcare delivery on the patient level[a], or for adapting protocols; • be used as input for developing guidelines; • be used for inspection and control by national/governmental or intra-organisational authorities; and • be used to reduce differences in quality of provided healthcare by different providers	1,2,3 (more detailed information in Supplementary Table 1, Additional file 1)
Quality domains	The QI-set should cover: • Coordination (both within and between organisations and disciplines) of healthcare for people with DS, including professional collaboration and agreements, and professional-caregiver collaboration; • Transition from paediatric towards adult healthcare; • Effectiveness, including expertise of healthcare professionals and timely detection of health problems; • Person-centeredness, including the social system of a person with DS[a]. • Quality of life, daily functioning, autonomy, and participation in society; • Safety; • Clinical outcomes (e.g. blood screening); and • Adherence to guidelines.	1,2,3 (more detailed information in Supplementary Table 2, Additional file 1)
Healthcare disciplines / services	• Concerning children, the QI-set should include: Down team, paediatrics, physiotherapy, speech therapy, dietetics, psychological/psychiatric care, dental hygiene, specialised dentistry, audiology (screening), and family support[b]; • Concerning adults, the QI-set should include: Down team, ID physician, dietetics, psychological/ psychiatric care, dental hygiene, palliative/geriatric care, general practitioner, audiology, and a case-manager. • QI-set should be sensitive to different healthcare needs in different life phases	1,2 (more detailed information in Supplementary Table 3, Additional file 1)
Number of QIs in set	• QIs should include all disciplines involved in healthcare for people with DS • The QI-set should contain a basic set and additional specialised modules • Each module should contain a maximum of ten QIs • Disciplines are more important to be included in the QI-set if: o more people with DS need them o they contribute more to QoL o there are more doubts about the quality provided by the discipline	2,3,4 (more detailed information in Supplementary Tables 3 and 4, Additional file 1)
Type (structure / process / outcome) of QIs in set	The QI-set should include an (almost) evenly distributed amount of structure, process and outcome QIs.	2,3 (more detailed information in Supplementary Table 4, Additional file 1)

Abbreviations: *DS* Down syndrome, *QI* quality indicator, *ID* Intellectual disability, *QoL* Quality of life
[a] Only consensus if patient organisation representatives were left out of analysis
[b] No consensus if patient organisation representatives were left out of analysis

differences between centres of expertise and other healthcare providers - very much needed for healthcare for people with DS – could not exist.

Quality domains In the first three rounds, participants indicated per quality (sub-)domain how important they considered it to be covered by the QI-set. Table 5, second row ('Quality domains') shows the quality domains that, according to consensus among the participants, should be covered by the QI-set.

Although consensus existed regarding including person-centeredness in the QI-set, this was not reflected in participants' answers regarding sub-domains of person-centeredness, presented to the participants in following rounds. On the one hand, participants explained that QIs should measure whether healthcare is adapted

to the needs of the person with DS, which may also increase effectiveness. On the other hand, no consensus existed about: adapting care to the preferences and desires of the person with DS, self-management, considering experienced burden for parents and other caregivers, and organising multidisciplinary appointments on 1 day.

Furthermore, participants argued that concepts such as quality of life and daily functioning should not appear in the QI-set, because they are too complex to be measured by QIs, too little related to quality of delivered care, or more suitable for inclusion in scientific research, than for being part of a QI-set. Others argued that such concepts should appear in the QI-set, because this would result in increased awareness among healthcare professionals about these important concepts.

Healthcare disciplines/services In round one and two, participants indicated how important they considered each healthcare discipline or service to appear in the QI-set (see Table 5, third row ('Healthcare disciplines / services')). Participants unanimously indicated that the set should contain one or more QIs on Down teams for children. It was even argued that a QI for Down teams could function as an indicator for the quality of all other healthcare for a child with DS, because Down teams are expected to have an overview over the total package of care. However, it was also noted that not all children with DS visit Down teams, implying that a 'Down team QI' would not be able to indicate quality of healthcare for all children with DS. A QI measuring quality of care provided by a paediatrician would therefore be more important. Similarly, a QI measuring healthcare quality of adult Down teams, would not be representative for all healthcare for adults with DS, since the number of adult Down teams is (too) small, as is the number of ID physicians. Participants explained that GPs sometimes provide the healthcare that is not provided by ID physicians / adult Down teams. Therefore, including a QI on healthcare provided by GPs could be important for adults with DS. However, a reason mentioned for *not* including GP-care in the QI-set is that GPs were not expected to have DS-expertise, because they have only a small number of patients with DS.

Furthermore, participants did not agree about coverage of visual functioning and dental care. Monitoring visual functioning was mentioned as a candidate indicator, because visual functioning is apt to change over time. However, no consensus was achieved on including visual screening in the set. Participants' comments about dentistry indicated that some sort of dentistry should be in the QI-set. However, it remains unclear which form of dentistry should be in the QI-set, as some people with DS need a specialised dentist, while for others a general dentist suffices. A mentioned reason for including a QI measuring specialised dental care, was based on the idea that a specialised dentist should always be involved, in order to monitor, recognise and treat DS-specific dental problems.

There was a lot of discussion about including non-medical disciplines/services in the QI-set. For example, consensus about including 'family support' was only achieved when the patient organisations' representatives were included in the analysis, and there was no consensus about including support staff of assisted living facilities in the QI-set. Moreover, the proposition "QIs should also cover non-medical disciplines" did not result in consensus. Some participants argued that including them was especially important because it is too much of a blind spot among healthcare professionals, whereas others explained that non-medical disciplines/services do not belong to a QI-set for quality of healthcare.

Although participants considered adherence to medical guidelines to be an important QI, they also noted that deviation from guidelines may be necessary in order to provide care that answers to the needs of people with DS. Hence, non-adherence to guidelines does not necessarily indicate low quality.

Number and type of QIs Table 5, fourth row ('Number of QIs in set') shows that participants preferred to include all disciplines/services involved in healthcare for people with DS in the QI-set. However, participants also noted that this would result in a QI-set with too many QIs, leading to a too high administrative burden for the users of the QI-set. In round two, participants thought that the total number of QIs in the set should be, or should not exceed, ten. In round three, participants agreed (consensus) that the QI-set should consist of modules: a basic module containing QIs relevant for all people with DS, and additional modules for specific patient groups or healthcare services. In round four, participants thought that each module should contain about ten QIs.

In round two and three, participants indicated that they thought the QI-set should contain structure, process, and outcome QIs (see Table 5, fifth row ('Type of QIs in set')). They also argued that the number of outcome indicators should be the highest, followed by process and structure indicators respectively.

Considerations for further development and implementation of the QI-set

Current and future use of indicators In round one, the majority of the participants indicated that they expected their colleagues (from the same profession) to be willing to register (extra) data for the QI-set. See Table 6, first row ('Willingness to register'). Participants

Table 6 Summary of findings: current and future use of indicators

Theme	Answers to multiple choice / open questions (first 4 rows) and one Likert-scale question (last row)	Number (%) of participants	Round(s) in which theme was addressed
Willingness to register	- My colleagues (from the same profession) will not be willing to register (extra) data for the QI-set	5[a] (16%)	1 ($n = 32$)
	- My colleagues will only be willing to register (extra) data for the QI-set if this would only mean 'clicking a few extra boxes'	14[b] (44%)	
	- My colleagues will be willing to register (extra) data.	13[c] (41%)	
Current collection of data by own organisation	- Information on adherence to guidelines	10 (31%)	1 ($n = 32$)
	- Transition from paediatric to adult healthcare	3 (9%)	
	- Clinical outcomes	10 (31%)	
	- Quality of life / daily functioning / participation	9 (28%)	
	- Coordination within the organisation	5 (16%)	
	- Coordination between organisations/ disciplines	1 (0%)	
	- Whether organisation is findable for potential patients	4 (10%)	
	- Accessibility	6 (19%)	
	- Expertise of healthcare professionals	7 (22%)	
	- Person-centeredness	9 (19%)	
	- Equity	4 (10%)	
	- No quality information collected	13 (41%)	
	- N/A	5 (16%)	
Current use of QIs	- Indicators regarding general internal improvement of healthcare (non DS-specific) or audits,	11 (34%)	1 ($n = 32$)
	- Indicators regarding client satisfaction,	6 (19%)	
	- Indicators regarding discipline/condition-specific (non DS-specific) issues	4[g] (13%)	
	- No indicators	11 (34%)	
	- N/A	2[h] (6%)	
Current use of guidelines	- The multidisciplinary medical guideline for children with DS	13 (38%)	1 ($n = 32$)
	- A general guideline for adults with DS, developed by the organisation I work for	2 (6%)	
	- Discipline-specific guideline(s) for the general population	7[d] (22%)	
	- Discipline-specific guideline(s) for people with ID	4[e] (13%)	
	- Discipline-specific guideline(s) for people with DS	7[f] (22%)	
	- No guidelines	4 (13%)	
Transparency	- QIs should provide quality information on departmental or organisational level (not on individual professionals' level) - Providers should be obliged to publish this quality information on their websites, if they want to be seen as 'DS-specialised'. - QIs should stimulate healthcare improvement, not judge healthcare professionals - Privacy of professionals should be protected just as much as privacy of patients.	Percentages are not applicable: consensus was achieved	3 ($n = 29$), 4 ($n = 26$) (more detailed information in Supplementary Table 5, Additional file 1)

Abbreviations: *DS* Down syndrome, *QI* quality indicator, *ID* Intellectual disability
[a] child physiotherapist, dermatologist, GP, ID physician, psychiatrist
[b] audiologist, 2 podiatrists, ID physician, ID-specialised dentist, municipal health services doctor, 2 occupational therapists, ophthalmologist, 2 orthoptists, paediatrician, rehabilitation specialist, speech therapist
[c] 2 dieticians, 2 ID-specialised dentists, 2 ID-specialised nurses, paediatrician, 3 (child) physiotherapists, psychologist, and the two patient organisation representatives
[d] GP, occupational therapy, dermatology
[e] dentistry, dietetics, dementia
[f] physiotherapy for children, speech therapy for children, municipal health service
[g] dentistry, dermatology, cataract, thyroid
[h] One of the two patient organisation representatives and one retired participant

explained that whether or not healthcare professionals would register data for this QI-set, would be dependent on available time, awareness about the QIs, considered utility of QIs, and frequency of contact with people with DS.

In round one, we also asked participants what kind of quality information they or their organisation currently collected. See Table 6, second row ('Current collection of data by own organisation'). Most participants (41%) indicated that their organisation did not collect any quality information. If information was being collected, it primarily concerned information about adherence to guidelines, clinical outcomes, and findability of the organisation. Furthermore, most participants indicated that they did not use indicators in their work, and if they did use them, it concerned QIs regarding general (not DS-specific) internal improvement of healthcare or audits (see Table 6 third row ('Current use of QIs')). We also asked participants about the guidelines they currently used in their work (see Table 6, fourth row ('Current use of guidelines')). The Dutch multidisciplinary medical guideline for children with DS [18] was the most often mentioned guideline.

Participants were not always in favour of participating in a QI-set that would make quality information publicly available, especially if a QI-set would reveal quality information on the level of individual healthcare professionals. In round one, participants explained that such information would possibly result in long waiting lists for 'good' providers or professionals, which may in turn negatively affect quality. Moreover, once a healthcare provider or professional is labelled as 'not good', this would possibly affect the choice of patients for this provider or professional for a long period of time. Because of these considerations, clarifying propositions were presented to the participants in rounds three and four (see Table 6, last row ('Transparency')). This confirmed the reluctance of participants to publish quality information (provided by the QIs) about individual professionals. It also showed that participants preferred access to this individual information to be limited to healthcare providers, in order to prevent judgement of healthcare professionals by patients or other parties. It should be used for internal improvements instead. Accordingly, participants explained to be reluctant to introduce a quality mark for healthcare providers. However, other participants argued that a QI-set would enable healthcare providers/organisations to profile themselves as 'good' healthcare providers, by 'signing up' for participating in the QIs, on a voluntary basis. Participation in the QI-set would be an indication of DS-expertise, which would also provide insight into available healthcare for people with DS to caregivers and healthcare professionals.

Data source and development of QIs Electronic medical records (EMRs) and patient/parent questionnaires were considered the most important information sources for the QI-set. At the same time, participants underlined that both healthcare professionals and people with DS and their caregivers should not be overcharged with registration burden. See Table 7, first row ('Data source'). Participants suggested to transform (a) patient/parent questionnaire(s) into an easy-to-understand app in order to make it suitable for people with DS. Ideally, such an app should be linked to the information system (EMR) in order to store all information together. However, participants identified the large number of existing information systems, often not mutually communicating, as a potential barrier for implementation of a QI-set.

According to the participants, development of the QIs should be done by researchers (the authors) together with all stakeholders. See Table 7, second row ('Development of QIs'). Participants mentioned representatives of the same diversity of disciplines as mentioned under 'healthcare disciplines/services' to be involved in the development of the QIs. It was also noted that it would be difficult to weigh the different opinions of those involved. The majority of the participants (59%) indicated that whether or not they themselves were willing to participate in development of the QIs depended on the time and effort needed.

Discussion

In this study we aimed to prefigure quality indicators for healthcare for people with Down syndrome. We used a Delphi technique involving healthcare professionals and patient organisations' representatives. The findings of this study, together with findings from two previous studies of the authors (a literature review on existing QIs and a qualitative study involving people with DS and their caregivers [10, 21]), will be used to inform the further development and implementation of the QI-set.

According to the participants in the current study, QIs should be suitable to inform healthcare quality improvement, and should be able to provide an overview of available healthcare to people with DS and their caregivers, and to healthcare professionals. Participants stressed that QIs should not be used to judge healthcare professionals. Furthermore, they opted for an evenly distributed mix of structure, process, and outcome QIs, covering the following quality domains: coordination and continuity of healthcare, effectiveness, safety, person-centeredness, and outcomes concerning health and quality of life. Additionally, participants argued that the QIs should cover all healthcare disciplines involved in healthcare for people with DS. However, they urged to keep the number of QIs low, in order to prevent (administrative) burden for healthcare professionals and people with DS and/or caregivers. Furthermore,

Table 7 Summary of findings: data source and development of QIs

Theme	Answers to multiple choice / open questions (rows 1 & 3) and one Likert-scale question (row 2)	Number (%) of participants	Round(s) in which theme was addressed
Data source	- Data for the QIs should be extracted from the electronic medical records of patients	26 (81%)	1 ($n = 32$)
	- Data for the QIs should be obtained via questionnaires for patients/parents.	25 (78%)	
	- Burden for people with DS and their caregivers should be as low as possible when measuring quality; - People with DS/caregivers as well as healthcare professionals should deliver information for the QIs; - Parents/other caregivers should themselves be responsible for documenting and keeping track of needed healthcare for the person with DS; - When people with DS are not able to provide quality information themselves, their legal representative should decide who is eligible to provide this information. - A dialogue between healthcare professional and person with DS can be used as instrument for measuring customer satisfaction[a]	Percentages are not applicable: consensus was achieved	4 ($n = 26$) (more detailed information in Supplementary Table 5, Additional file 1)
Development of QIs	- With involvement of people with DS	23 (83%)	2 ($n = 28$)
	- With involvement of parents/caregivers	26 (93%)	
	- With involvement of healthcare professionals	27 (97%)	
	- With involvement of health insurers	6 (21%)	
	- I am willing to participate in development	9 (31%)	
	- Whether I am willing to participate depends on the time and effort needed for participation	17 (59%)	
	- I am not willing to participate	3 (10%)	

Abbreviations: *DS* Down syndrome, *QI* quality indicator, *ID* Intellectual disability
[a] There was only consensus among the participants about this proposition if the patient representatives were left out of the analysis

development of QIs should be done with involvement of all relevant stakeholders.

Quality improvement and well-informed choices

According to the participants in our study, two key purposes of a QI-set for healthcare for people with DS are 1) to improve quality in healthcare and 2) to increase insight into available healthcare, enabling people with DS (and their caregivers) to make well-informed healthcare choices, and supporting healthcare professionals to make well-informed referrals. However, participants in the current study argue that the two purposes may conflict with each other. They explained that if quality information was publicly available, especially when it concerned information on the level of individual providers, a "shaming-and-blaming" situation would emerge. They were concerned that this would hamper quality of care, instead of improve it. A study addressing Parkinson's disease, showed a similar reticent attitude amongst healthcare professionals towards sharing quality information with patients [27]. On the other hand, current movements in practice and literature have shown the need for encouraging patients to make well-informed healthcare choices, although the influence of QIs on healthcare choices made by patients has been shown to be limited [27–29]. Hence, patients' rights to relevant information, fostering the choice for the best suitable healthcare, have to be carefully balanced against providers' entitlement to a safe environment in which they can learn and improve.

Capturing complexity

There was much discussion about defining the coverage of the QI-set. Some participants preferred to include only medical QIs, whereas others were convinced that a QI-set should cover disciplines/services outside healthcare, such as support staff of assisted living facilities, in order to reflect the complexity of healthcare for people with DS [5, 30]. However, based on our results (achieved consensus) we conclude that participants prefer to limit the coverage of the QI-set to the medical domain (including psychological care). This medical focus may be a reflection of the specialised focus of healthcare professionals and their training, or of the fragmented care system in the Netherlands [31, 32]. Another explanation for this medical focus may be found in social psychology [33, 34]: healthcare professionals may consider quality improvement or transparency within the medical domain within their control, while they consider other domains beyond their sphere of influence and therefore

less important for a QI-set. The medical focus may however also be a result of the participants' reluctance to face a high registration burden, which participants repeatedly expressed during the study. This confirms the general understanding that QI-sets should be concise to foster their actual use [35, 36].

However, even if the coverage of the QI-set will be limited to the medical domain, it will, due to the multi-morbidity related to DS [5, 30], include a lot of different disciplines, and many quality domains. Hence, developing a concise QI-set will be challenging, even more so as not all quality domains may be applicable to all disciplines and contexts, and the QI-set will have to be compatible with a large variety of data registration systems used by the different healthcare providers involved. In order to limit registration burden, registration of data for a QI-set should be possible together with other currently registered data in the electronic medical record (EMR). This would also prevent registration of the same data in separate registries [37], and facilitate data collection (i.e. extraction from information systems) for the QI-set. Literature shows that automated extraction of indicators from EMRs is possible, however, the structure of information systems and the accuracy of registration by professionals is not always sufficient for enabling automated extraction [38, 39]. Nevertheless, most participants in our study thought that their colleagues (of the same profession) would be willing to register extra QI-data, especially if registration efforts would be kept as small as possible.

Patient reported information

Participants also suggested to use patient reported information (for example from questionnaires) as input for the QI-set, which should ideally be stored within the EMR, together with the data registered by healthcare professionals. Such patient information is often obtained using Patient Reported Outcome Measures (PROMs) and/or Patient Reported Experience Measures (PREMs) [40, 41]. PROMs focus on measuring outcomes of treatments related to patient functioning, while PREMs address patient experiences regarding healthcare processes [36, 39]. PREMs/PROMs are considered robust quality measures [41]. However, due to their cognitive abilities [4], people with DS may not always be able to provide patient reported information, in which case proxies (such as parents) will have to provide this information [42, 43]. Nevertheless, patient involvement in healthcare is considered increasingly important in delivering high quality healthcare in general [44], and concerning people with ID [45]. It may therefore be worthwhile to explore other ways to obtain information from people with DS that could be used for quality improvements. Examples are using narratives for evaluation [46] or apps especially designed for people with DS/ID [47].

Strengths and limitations

The selection of participants reflected the large variety of healthcare providers involved in healthcare for people with DS and included two patient organisations' representatives. Although this presumably led to heterogeneity in answers, which may complicate the formulation of QIs, it can be considered a strength of the study. Participant heterogeneity enriches the results of a Delphi study, which enhances the credibility and acceptance of resulting QIs [12].

Another strength of the study is that consensus was defined in advance [12, 24, 25] (median ≤ 2 in combination with a 75% cut-off).

The fact that the members of the research team (i.e. the authors) have been collaborating before, may have led to some advantageous knowledge of each other's ideas, which may have affected the research team's discussions, and in turn, the content validity of the Delphi-questionnaires. However, we expect this effect to be small because of the heterogeneity of the research team (see "Authors' information") and the limited contact frequency of the team members before the study. Moreover, the fact that consensus was defined in advance, improves reliability of the questionnaire results.

There was variation among the participants regarding the time they had been working in their current position, but they represented ample DS-related experience: 91.4% of the participants had been working in their current position for more than 7 years; 85.7% had at least monthly contact with clients with DS.

Unfortunately, GPs, playing a key role in healthcare for people (especially adults) with DS [48], were underrepresented. Despite extensive attempts, we were only able to include one GP, who could only participate in round one.

The time intervals between the rounds in our study were much smaller than in classic Delphi studies, which have a total study duration of three to twelve months [24]. The short time-intervals were chosen after consulting the participants about their preferences for taking part in the study, in order to limit participant drop-out. Nevertheless, we could not prevent a drop-out of about 25%. However, a response rate of about 75% is considered quite high in Delphi-studies [24]. This relatively high rate was probably achieved by the personal touch we applied in communication with our participants, which is mentioned to be crucial in limiting drop-out [24]. A possible disadvantage of the short time intervals may be that it entails limited time for analysis and preparation of questions for next rounds. We mitigated this possible effect on data collection and results by

preparing a large part of the questions for successive rounds in advance. Another possible disadvantage of short time intervals is related to the fact that participants have less time to reflect on, and adapt, their answers. However, we considered the questionnaires suitable to be completed within short time intervals, as the complexity of the questions presented to the participants was quite low. This is supported by the fact that the participants in our study completed the questionnaires within reasonable time. Moreover, the most complex questions, which may require much reflection time, were placed in the first questionnaire, which participants had to complete within several weeks (instead of within several minutes for the other questionnaires).

Conclusions

Our study showed the complexity of capturing healthcare for people with DS in a QI-set that is relevant for both healthcare providers and people with DS plus their caregivers. We have taken a solid step in unravelling this complexity and its possible impact on developing QIs, thereby making substantial progress in the development of QIs for healthcare for people with DS. Future research can (and will) build further on this foundation.

Since our study involves a large variety of healthcare professionals, with heterogenic view points, our findings may not only be relevant to healthcare for people with DS, but probably to any healthcare discipline. It is even argued that, because of the complexity of healthcare for people with DS, the DS population could be used to assess the quality of the healthcare system in general [2].

Several important lessons from this study should be taken into account in the further development of a QI-set for healthcare for people with DS. First, our findings indicate that a QI-set for healthcare for people with DS has two main purposes: it should be suitable for 1) identifying possibilities for improvement of healthcare for people with DS; and 2) for supporting patients and providers in choosing appropriate healthcare (providers). However, the two purposes need to be carefully balanced, as extensive information transparency fostering patients' healthcare choices, may conflict with ensuring safe and supportive working environments for healthcare professionals, and with fair comparison of providers. Second, capturing healthcare for people with DS in a QI-set requires the set to be suitable for use by all different disciplines involved, and to be compatible with different information systems. At the same time, the set has to be as concise and compact as possible, in order to limit administrative burden. Third, measurement instruments providing information for a QI-set should be suitable for collecting information from people with DS and their caregivers.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12913-020-05492-z.

Additional file 1. (Questionnaires). English translation of the questionnaires of round 1, 2, 3 and 4. This document contains an English translation of the online questionnaires (in Dutch) that were used in the four Delphi-rounds for data collection.

Additional file 2: (Supplementary Tables 1–5). Supplementary Tables 1–5: **Supplementary Table 1.** Extent to which consensus was achieved among participants regarding: Purposes of QIs; **Supplementary Table 2.** Extent to which consensus was achieved among participants regarding: Quality domains; **Supplementary Table 3.** Extent to which consensus was achieved among participants regarding: Healthcare services/disciplines; **Supplementary Table 4.** Preferred number and type of QIs and extent to which consensus was achieved among participants regarding related propositions; **Supplementary Table 5.** Extent to which consensus was achieved among participants regarding: Information sources and transparency of QIs and practical issues regarding development. Tables indicating the extent to which consensus was achieved among participants regarding different aspects of a QI-set for healthcare for people with DS. Results of the study are largely based on these data.

Abbreviations

DS: Down syndrome; EMR: Electronic medical record; ENT: Ear Nose Throat; GP: General practitioner; ID: Intellectual disability; PREM: Patient reported experience measure; PROM: Patient reported outcome measure; QI: Quality indicator; QoL: Quality of life; Stdev: Standard deviation

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Authors' contributions

FDM designed the study, composed the questionnaires in QualtricsXM® (software for online questionnaires), and drafted the manuscript. All authors were involved in data analysis and interpretation. DD, AC and EV contributed to the study design and critically reviewed, revised and edited the manuscript. All authors agreed to be accountable for all aspects of the work and read and approved the final version of the manuscript for publication.

Authors' information

The research team (i.e. the authors) consisted of a paediatrician/professor with expertise in healthcare for people with DS (EV), a professor in health services research and quality measurement (DD), an ID physician/researcher/epidemiologist with expertise in DS (AC), and a health scientist with experience in research involving people with ID (FDM).

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Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request. However, most data generated or analysed during this study are included in this published article and its supplementary information files.

Ethics approval and consent to participate

According to the Dutch Act on Medical Research Involving Human Subjects (1998), ethics approval was deemed unnecessary.
Written informed consent was obtained from all participants prior to the study. The informed consent concerned the use of participants' contact details and answers to Delphi-questionnaires for the aims of the study.

Consent for publication
Not applicable.

Competing interests
No conflict of interest has been declared.

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Publisher's Note

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RESEARCH ARTICLE

Low Rates of Preventive Healthcare Service Utilization Among Adolescents and Adults With Down Syndrome

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Introduction: People with Down syndrome have health risks that require specific lifelong preventive health care. With increasing life expectancy, people with Down syndrome also face health conditions typical of their unaffected peers and thus need coordinated health care. The purpose of this study is to describe rates of age/sex- and Down syndrome–specific preventive healthcare activities among adolescents and adults with Down syndrome.

Methods: Using Medicaid claims (2006–2010) in California, Colorado, Michigan, and Pennsylvania, the cohort was defined as people with Down syndrome aged ≥12 years seen by primary care providers and enrolled in Medicaid for ≥45 of 60 months without dual Medicare enrollment (n=3,501). Age focus–consistent primary care providers were defined as having a focus concordant with a patient's age: 12–17 years, child or mixed-focus; ≥26 years, adult or mixed-focus; 18–25 years, any focus. Differences in healthcare activities were evaluated using Pearson's chi-square, Fisher's exact, and Kruskal–Wallis tests. Analyses were performed in 2015–2017.

Results: Of the cohort, 79% had an age focus–consistent primary care provider. However, 40% of adults aged ≥26 years received care from a child-focused primary care provider. Only 43% with an age focus–consistent provider had ≥1 well examination (age focus–inconsistent primary care provider: 35%, p<0.001). Most preventive activities had poor rates (<50%) regardless of age focus consistency between provider and patient age or whether they were age/sex- or Down syndrome–specific (well examinations; vaccinations; sleep apnea; hearing; and breast, cervical, and colon cancer screenings). Lipids, vision, and thyroid screenings reached moderate levels (50% to <80%).

Conclusions: Rates of age/sex- and Down syndrome–specific preventive recommendations were low among adolescents and adults with Down syndrome, regardless of the age focus consistency of their primary care provider. This represents a significant opportunity to improve primary care in this vulnerable population.

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INTRODUCTION

Down syndrome (DS) is the leading identifiable genetic cause of intellectual disability, occurring in 1:700 to 1:1,000 live births.[1–4] Historically, most children with DS did not survive childhood.[4–8] Thanks to medical advancements, >80% of people with DS now reach adolescence, with a median life expectancy in their mid-50s.[4–6,9–15] Owing to their genetic condition, people with DS have increased risks for multiple

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comorbidities that can present during childhood (e.g., intellectual disability, language difficulties, hypotonia, and congenital heart disease [CHD]) or develop throughout their lives (e.g., hypothyroidism, hearing loss, vision abnormalities, obesity, obstructive sleep apnea, and dementia).[16−23]

There are well-established DS guidelines for preventive care during childhood (age ≤21 years) and clear recommendations during adulthood.[16−22] Previous work by Jensen et al.[24] within a local health system demonstrated suboptimal adherence to most preventive recommendations in adults with DS, regardless of the field of their primary care provider (PCP). Toler[25] documented that preventive care is frequently neglected in women with DS. Similar work by Santoro and colleagues[26,27] within pediatric settings showed poor baseline adherence to most guidelines for children with DS. Yet, people with DS are more engaged in society and reach higher levels of achievement than ever before, incurring risks and developing health issues more typical of their unaffected peers.[28] Consequently, preventive care among adolescents and adults with DS must incorporate both age/sex- and DS-specific preventive healthcare recommendations. However, little is known about national patterns of preventive care within this population.

This retrospective cohort study examines age/sex- and DS-specific preventive healthcare patterns among a cohort of adolescents and adults with DS in 4 U.S. states. Based on prior research[24] and the authors' experiences as PCPs, it is hypothesized that preventive care will be suboptimal for adolescents and adults with DS, but that patients whose PCP's focus was consistent with their age would have higher rates of recommended age/sex-specific care.

METHODS

Study Sample

This study was approved by the Colorado Multiple IRB (13-2072). Data were obtained from the Center for Medicare and Medicaid Services Medicaid Analytic Extract files for all Medicaid beneficiaries in Colorado, California, Michigan, and Pennsylvania from 2006 to 2010 (n=28,752,018). The analysis was restricted to Medicaid beneficiaries with DS who were aged ≥12 years by January 1, 2006. First, patients with DS were identified by ICD-9-CM=758.0[29] within their claims during the study years (n=20,277). Patients whose DS diagnosis only occurred during obstetric visits were not classified as having DS, as this typically reflects DS in their fetus[30] (excluded n=11). Codes used to identify the domains throughout this study are available upon request.[10,16−20,24,31−58]

All medical encounters are not necessarily captured within claims for clients on Medicaid managed care, with restricted benefits, with private insurance, enrolled in a state child health insurance program, or Medicare dual enrolled. The authors therefore restricted cohort selection to patients enrolled in Medicaid fee-for-service (including primary care case management) for ≥75% of the study frame (≥45 of 60 months) to reliably capture encounters (n=9,758). Patients dually enrolled in Medicaid and Medicare were excluded (n=5,807) as investigators could not assess their services billed under Medicare. Each state was impacted differently by the exclusion of dually enrolled patients: Colorado retained 37% of their cohort, Michigan 6%, Pennsylvania 15%, and California 56%. Patients without clinical visits with at least 1 PCP were excluded from analysis (n=450). This led to a final cohort of 3,501 adolescents and adults with DS.

Measures

Patient study age was assigned by age at the study midpoint: July 1, 2008. Age categories were based on study age: 12−17 years, adolescents; 18−25 years, transition aged; ≥26 years, adults. Age-specific preventive healthcare activities were evaluated for all patients meeting the specified age criteria at any time during the 5-year study. Rates of recommended activities were assessed by patient age at each visit, not study age.

PCPs were identified as providers billing ≥10 well examinations in a calendar year. PCPs were identified as (1) child-focused, (2) adult-focused, or (3) mixed-focused, based on the proportion of their well examinations with child- or adult-specific billing codes. PCPs with ≥80% of well examinations billed as well child were categorized as child-focused; providers with ≥80% of well examinations billed as well adult were considered adult-focused. PCPs not meeting either category were assigned the status of mixed-focused. Each patient was attributed to a PCP type (child, adult, or mixed-focus or none) based upon the type of PCP they encountered most frequently. In the case of ties, the PCP type from the most recent well examination was retained. For patients without well examinations, the PCP type from the most recent claim was retained. Age focus−consistent PCPs were defined as having a focus concordant with the patient's age. This includes a child- or mixed-focused PCP for a person aged 12−17 years or an adult- or mixed-focused PCP for a person aged ≥26 years. A person aged 18−25 years would be age focus−consistent if seen by any PCP focus. Although the authors anticipated the training backgrounds of PCPs would be as follows, the poor fidelity of the provider specialty field in Medicaid data did not allow for clear identification of PCP specialty: child-focused, pediatrics; adult-focused, internal medicine or geriatrics; mixed-focused, family medicine or combined internal medicine and pediatrics. The term "age focus−consistent" was used to designate PCP type, as recommendations were in place during the study years making 21 years the upper age limit for patients seen by pediatricians (child-focused PCPs).[59]

The Rural−Urban Commuting Area Codes approximation[60−62] was used to assign patient zoning improvement plan (ZIP) codes as urban or rural. ZIP codes without Rural−Urban Commuting Area Codes were assigned as urban or rural based upon classification of surrounding ZIP codes or the county containing most of the ZIP code.

Identification of comorbidities outside of DS was made by the presence of ≥1 inpatient or ≥2 outpatient claims with the diagnosis code of interest.[63] Patients with DS with only 1 outpatient claim were not excluded as they were found to have similar demographics, diagnoses, and healthcare utilization to those patients with ≥1 claim or with an inpatient claim containing a DS diagnosis code.

This study evaluated age/sex- and DS-specific preventive healthcare activities that were measurable by ICD-9/CPT codes, could occur within 5 years, and had near uniform acceptance during the study years (2006–2010). For each activity, patients received credit if the activity occurred at least once during this 5-year study. Age/sex-specific preventive recommendations included the following: well person examination, influenza vaccination, cholesterol screening (age ≥18 years), cervical cancer screening (women aged 21–65 years), and adolescent vaccinations (age 12–18 years: tetanus, diphtheria, and pertussis; human papillomavirus; and meningococcal).[35,36,58,64] Authors also observed screening activities based on personal risk for osteoporosis (age ≥40 years), breast cancer (women aged ≥40 years), colorectal cancer (age ≥50 years), diabetes, and pneumococcal vaccination. Screening ages for cholesterol, cervical cancer, colorectal cancer, and adolescent vaccinations reflect recommendations from the Agency for Healthcare Research and Quality's National Guideline Clearinghouse during the study years.[35,36] This study followed the more conservative approach to breast cancer screening (age ≥40 years) from the American College of Obstetricians and Gynecologists.[65] Rates of osteoporosis screening were followed starting at age 40 years in this population owing to high rates of low bone mineral density in people with DS of both sexes starting in their 40s.[66,67] This study additionally observed patterns of pneumonia vaccination and diabetic labs in this cohort because of increased risk of complications of respiratory illness and high rates of obesity, respectively, in people with DS.[10,17,68] For DS-specific recommendations, the authors assessed the presence of thyroid, vision, and hearing screening, as well as screening tailored to risk/symptoms for acquired cardiac valve disease and obstructive sleep apnea.[69–71] Rates of each activity were classified as good (≥80%), moderate (50% to <80%), and poor (<50%).[24,69–71]

Statistical Analysis

Patient characteristics and care patterns were compared between patients with DS by PCP focus and age consistency of a PCP's focus using Pearson's chi-square, Fisher's exact, or Kruskal–Wallis tests. Preventive care patterns were additionally stratified by patient study age and compared by age consistency of PCP's focus with patient study age. Analyses were performed in 2015–2017 using SAS, version 9.4.

RESULTS

A total of 3,501 adolescents and adults with DS met inclusion criteria, with a median age of 25 (IQR=19–35) years. Nearly 22% of the cohort were adolescents (aged 12–17 years), 32% were transition aged (18–25 years), and 47% were adults (aged ≥26 years). Of the cohort, 52% was male; 86% resided in urban settings. The cohort was 39% Hispanic, 38% White, 7% Black, 5% Asian, and 4% Native Hawaiian/Pacific Islander, with 6% other/unknown (Table 1). Most of the cohort (83%) resided in California, with 8% in Colorado, 7% in Pennsylvania, and 2% in Michigan. The overwhelming majority was enrolled in Medicaid for the entire study (median=60 months, IQR=60, 60).

A total of 52% of the cohort received care from child-focused PCPs, followed by 24% each from mixed- and adult-focused PCPs. Providers from each PCP type cared for patients in each age category (Table 1, Figure 1). Among adolescents with DS, 88% received care from a PCP whose focus was consistent with their age (74% child focus, 14% mixed-focus). Owing to the definition of age focus consistency, all transition-aged patients received care from an age focus–consistent PCP (54% child-focused, 24% mixed-focused, and 22% adult-focused). The proportion of patients receiving care from adult- or mixed-focused PCPs increased with increasing patient age. However, 40% of adults aged ≥26 years with DS received care from child-focused PCPs.

People in the cohort were medically complex (Table 2) with a median of 5 organ systems chronically affected (IQR=3–7). The most frequent of these are the following: neurologic (76%), mental/behavioral health (74%), respiratory (65%), endocrine (57%), digestive (51%), and dermatologic (50%). A total of 11% had encounters for hypertension, 10% for diabetes, and 23% for hyperlipidemia. Among comorbidities commonly associated with DS, 14% had encounters for CHD, 5% Eisenmenger syndrome, and 2% pulmonary hypertension. A total of 27% had encounters for hypothyroidism and 15% for obstructive sleep apnea.

Using the framework of good (≥80%), moderate (50% to <80%), and poor (<50%) rates for each preventive activity,[24,69–71] the following patterns occurred at least once in the 5-year study period (Figure 2).

All age categories had poor rates (<50%) of well examinations. Only 41% of the cohort had ≥1 well examination (1 well examination, 20%; ≥2 well examinations, 21%). More patients with an age focus–consistent PCP had a well examination (43%) than those with an age focus–inconsistent PCP (35%, $p<0.001$) (Figure 2). More adolescents (aged 12–17 years) receiving care from age focus–consistent PCPs (child- or mixed-focused) had a well examination (49%) than those cared for by age focus–inconsistent PCPs (adult-focused: 25%, $p<0.001$) (Appendix Table 1, available online). Within the transition-aged population (18–25 years), no differences were observed in well examination patterns by PCP type (44% from child- or adult-focused PCPs vs 48% from mixed-focus PCPs, $p=0.253$). Rates of well examinations among adults with DS did not differ by age focus consistency of PCPs (age focus–consistent, 38%; age focus–inconsistent, 36%; $p=0.466$) (Appendix Table 1, available online).

Similarly, there were poor rates (<50%) of all recommended vaccinations (Figure 2). The authors observed no difference in rates of ≥1 influenza vaccination during

Table 1. Patient Characteristics

Characteristic	All patients, % (n) or median (IQR)	Child PCP, % (n) or median (IQR)	Mixed PCP, % (n) or median (IQR)	Adult PCP, % (n) or median (IQR)	*p*-value	Age focus–consistent PCP, % (n) or median (IQR)	Age focus–inconsistent PCP, % (n) or median (IQR)	*p*-value
Total	3,501	51.6% (1,808)	24.4% (854)	24.0% (839)		78.9% (2,763)	21.1% (738)	
Male	52.4% (1,835)	55.8% (1,009)	54.0% (461)	43.5% (365)	**<0.001**	52.4% (1,448)	52.4% (387)	0.988
Study period age, years					**<0.001**			**<0.001**
12–17 (adolescent)[a]	21.5% (754)	30.6% (554)	12.8% (109)	10.8% (91)		24.0% (663)	12.3% (91)	
18–25 (transition)[b]	31.9% (1,117)	33.6% (607)	30.9% (264)	29.3% (246)		40.4% (1,117)	NA	
≥26 (adult)[c]	46.6% (1,630)	35.8% (647)	56.3% (481)	59.8% (502)		35.6% (983)	87.7% (647)	
Median age (IQR) in years	25.0 (18.8–35.4)	21.8 (17.2–30.9)	27.7 (21.3–37.5)	29.6 (22.3–39.8)	**<0.001**	22.8 (18.2–31.8)	33.7 (27.8–41.8)	**<0.001**
Race					**<0.001**			**<0.001**
White	38.2% (1,338)	35.6% (643)	45.9% (392)	36.1% (303)		36.5% (1,009)	44.6% (329)	
Hispanic	39.3% (1,376)	44.4% (802)	31.9% (272)	36.0% (302)		40.9% (1,130)	33.3% (246)	
Black	7.3% (255)	6.6% (119)	8.1% (69)	8.0% (67)		7.4% (205)	6.8% (50)	
Asian	5.1% (179)	3.4% (62)	4.2% (36)	9.7% (81)		5.5% (151)	3.8% (28)	
Native Hawaiian/ Pacific Islander	3.7% (131)	3.8% (69)	3.3% (28)	4.1% (34)		3.8% (105)	3.5% (26)	
Unknown/other	6.3% (222)	6.3% (113)	6.7% (57)	6.2% (52)		5.9% (163)	8.0% (59)	
Urban residence	86.3% (3,023)	86.0% (1,554)	80.1% (684)	93.6% (785)	**<0.001**	86.2% (2,383)	86.7% (640)	0.739
State					**<0.001**			**<0.05**
CA	82.7% (2,896)	80.9% (1,462)	74.2% (634)	95.4% (800)		81.6% (2,254)	87.0% (642)	
CO	8.1% (285)	11.7% (211)	7.1% (61)	1.5% (13)		Non-CA 18.4% (509)[a]	Non-CA 13.0% (96)[a]	
MI	2.3% (79)	2.4% (44)	2.6% (22)	1.5% (13)		Non-CA 18.4% (509)[d]	Non-CA 13.0% (96)[a]	
PA	6.9% (241)	5.0% (91)	16.0% (137)	1.5% (13)		Non-CA 18.4% (509)[a]	Non-CA 13.0% (96)[a]	
Months enrolled in Medicaid (IQR)	60.0 (60.0–60.0)	60.0 (59.0–60.0)	60.0 (60.0–60.0)	60.0 (60.0–60.0)	**0.003**	60.0 (60.0–60.0)	60.0 (60.0–60.0)	0.194

Note: Boldface indicates statistical significance ($p<0.05$) from Pearson's chi-square test, Fisher's exact test, or the Kruskal–Wallis test.
[a]Among adolescents, 73.5% attended child-focused PCPs, 14.4% attended mixed-focus PCPs, and 12.1% attended adult-focused PCPs. Also, 87.9% attended age focus–consistent PCPs, whereas 12.1% attended age focus–inconsistent PCPs.
[b]Among the transition age group, 54.3% attended child-focused PCPs, 23.7% attended mixed-focus PCPs, and 22.0% attended adult-focused PCPs. Also, 100% attended age focus–consistent PCPs.
[c]Among adults, 39.7% attended child-focused PCPs, 29.5% attended mixed-focus PCPs, and 30.8% attended adult-focused PCPs. Also, 60.3% attended age focus–consistent PCPs, whereas 39.7% attended age focus–inconsistent PCPs.
[d]Non-California cell collapsed for age-appropriate/age-inappropriate as at least 1 of the states has $n\leq10$ and cannot be reported per the data use agreement.
NA, not applicable; PCP, primary care provider.

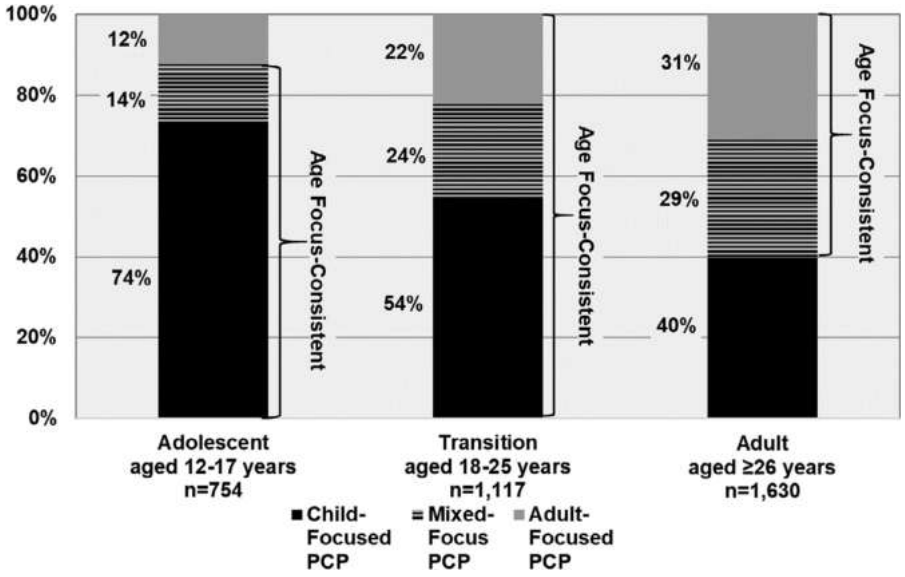


Figure 1. Patterns of PCP focus among adolescents and adults with Down syndrome by patient age.
PCP, primary care provider

the study period (age focus–consistent PCP, 34%; age focus–inconsistent PCP, 37%; p=0.227) (Figure 2). Annual rates of influenza vaccination ranged from 11% (2006–2007) to 16% (2009–2010) (Appendix Table 1, available online). Among those aged 12–18 years, rates of tetanus, diphtheria, and pertussis; human papillomavirus (female patients); and meningococcal vaccination were similarly low with higher rates among patients with age focus–inconsistent (i.e., adult-focused) PCPs (Figure 2). Investigators observed low rates of pneumonia vaccination (2.7%), the decision for which would be prompted by individual risk assessment.

Regarding age/sex-specific activities, moderate (50% to <80%) rates of cholesterol screening were observed for patients aged ≥18 years in most subgroups, increasing to 80% among adults with age focus–consistent PCPs (Figure 2, Appendix Table 1 available online). Diabetic lab studies (HbA1c or blood glucose levels) occurred in 37% of the cohort. All procedure-based services occurred at low rates (<50%) during this 5-year study. Breast cancer screening (female patients aged ≥40 years) was highest at 46%, followed by screening for cervical cancer (female patients aged ≥21 years) at 31%, colorectal cancer (people aged ≥50 years) at 26%, and osteoporosis (people aged ≥40 years) at 7%. The only significant difference by age focus consistency of PCP was in cervical cancer screening (age focus–consistent PCPs, 29%; age focus–inconsistent PCPs, 37%; p=0.014) (Appendix Table 1, available online).

Recommendations for primary care in people with DS include annual screening for thyroid, vision, and hearing abnormalities.[16–20] The authors observed moderate rates of thyroid (72%) and vision (55%) screening, with an inconsistent impact of PCP age focus consistency upon these activities (Figure 2). Poor rates of hearing screenings were observed (18% overall), ranging from 10% (adults with age focus–consistent PCPs) to 44% (adolescents with age focus–inconsistent PCPs) (Appendix Table 1, available online). Among the DS-specific screenings tailored to risk/symptoms, <5% of the cohort had a sleep study to evaluate for sleep apnea. More than 90% of the cohort with both DS and a history of CHD had an echocardiogram during this study period. Only 22% of those with DS but without CHD had an echocardiogram to evaluate for acquired cardiac valve disease (Appendix Table 1, available online).

As California contributed 83% of the cohort, the authors conducted a subgroup analysis to evaluate its impact upon the findings. Without California data, 15 of the 18 domains followed in this study remained within the same categories of good, moderate, and poor rates (Appendix Figure 1, available online). Rates of well person examinations and influenza vaccinations increased into the moderate range at 66% and 52%, respectively, but remained below recommended frequencies. Rates of vision examination decreased to 46%.

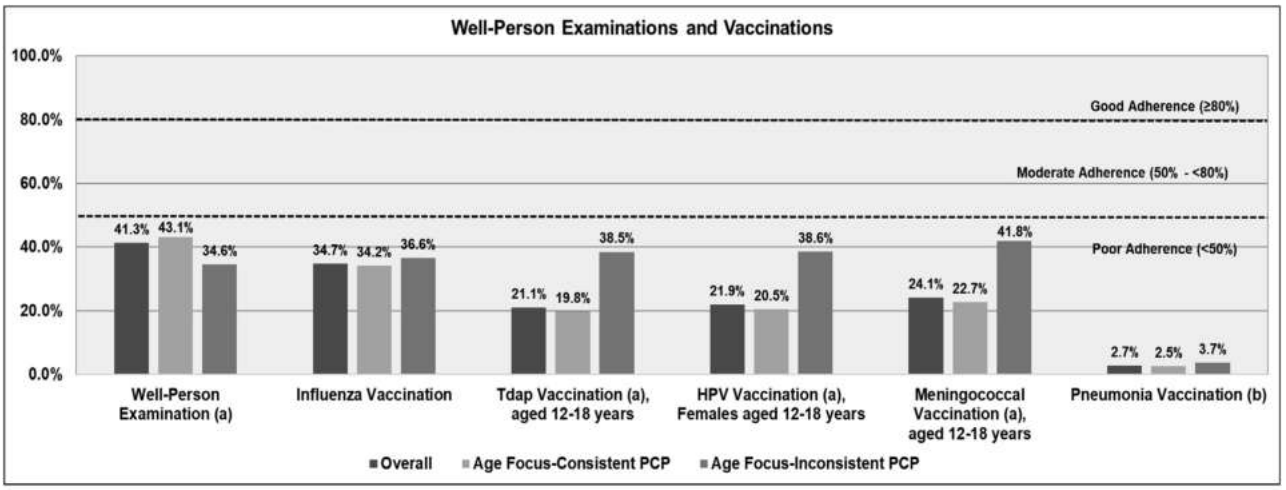
DISCUSSION

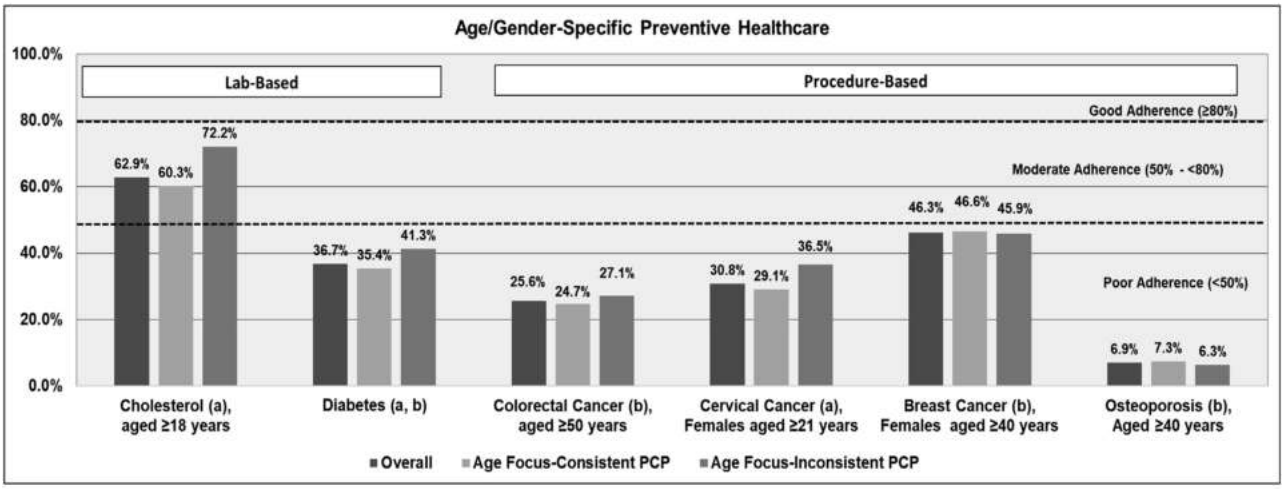
In this cohort of adolescents and adults with DS, child-focused primary care relationships were observed well into adulthood, and poor rates (<50%) of most

Table 2. Medical Complexity of Cohort of Adolescents and Adults With Down Syndrome

Medical complexity	All patients, % (n) or median (IQR), *n*=3,501	Child-focused PCP, % (n) or median (IQR), *n*=1,808	Mixed-focus PCP, % (n) or median (IQR), *n*=854	Adult-focused PCP, % (n) or median (IQR), *n*=839	*p*-value	Age focus—consistent PCP, % (n) or median (IQR), *n*=2,763	Age focus—inconsistent PCP, % (n) or median (IQR), *n*=738	*p*-value
Highlighted comorbidities common either to Down syndrome or adulthood								
Congenital heart disease	13.5% (471)	15.9% (288)	11.6% (99)	10.0% (84)	**<0.001**	13.8% (381)	12.2% (90)	0.26
Eisenmenger syndrome	4.7% (165)	5.9% (106)	3.5% (30)	3.5% (29)	**0.004**	4.6% (127)	5.1% (38)	0.529
Hypothyroidism	27.2% (953)	24.2% (437)	28.7% (245)	32.3% (271)	**<0.001**	26.5% (732)	29.9% (221)	0.061
Hypoxia	4.4% (155)	4.9% (88)	4.8% (41)	3.1% (26)	0.100	4.4% (121)	4.6% (34)	0.789
Obstructive sleep apnea	15.3% (536)	16.3% (294)	15.2% (130)	13.3% (112)	0.153	15.3% (422)	15.4% (114)	0.907
Pulmonary hypertension	1.9% (66)	2.0% (36)	2.0% (17)	1.5% (13)	0.714	1.8% (49)	2.3% (17)	0.347
Dementia	0.9% (33)	—[a]	—[a]	—[a]	NS	0.8% (21)	1.6% (12)	**0.031**
Diabetes	10.2% (356)	9.4% (170)	11.0% (94)	11.0% (92)	0.301	8.9% (247)	14.8% (109)	**<0.001**
Hyperlipidemia	22.7% (796)	17.1% (310)	24.1% (206)	33.4% (280)	**<0.001**	21.1% (584)	28.7% (212)	**<0.001**
Hypertension	10.6% (370)	8.3% (150)	11.1% (95)	14.9% (125)	**<0.001**	9.3% (257)	15.3% (113)	**<0.001**
Chronically affected organ systems								
Number of organ systems chronically affected	5.0 (3.0—7.0)	5.0 (3.0—7.0)	5.0 (3.0—7.0)	5.0 (3.0—7.0)	**<0.001**	5.0 (3.0—7.0)	5.0 (4.0—7.0)	**<0.001**
Neurologic	75.8% (2,653)	77.7% (1,404)	72.0% (615)	75.6% (634)	**0.006**	75.9% (2,096)	75.5% (557)	0.828
Mental/ behavioral health	73.7% (2,580)	73.3% (1,325)	72.4% (618)	75.9% (637)	0.214	72.3% (1,997)	79.0% (583)	**<0.001**
Respiratory	65.0% (2,276)	66.2% (1,197)	63.0% (538)	64.5% (541)	0.252	65.5% (1,811)	63.0% (465)	0.199
Endocrine	57.3% (2,005)	52.2% (943)	60.0% (512)	65.6% (550)	**<0.001**	55.2% (1,525)	65.0% (480)	**<0.001**
Digestive	50.7% (1,776)	52.3% (946)	46.4% (396)	51.7% (434)	**0.013**	49.3% (1,361)	56.2% (415)	**<0.001**
Dermatologic	50.2% (1,758)	49.7% (898)	49.5% (423)	52.1% (437)	0.461	50.1% (1,384)	50.7% (374)	0.777
Musculoskeletal	39.8% (1,393)	37.4% (677)	41.5% (354)	43.1% (362)	**0.011**	38.3% (1,059)	45.3% (334)	**<0.001**
Cardiovascular	38.0% (1,330)	38.3% (692)	35.5% (303)	39.9% (335)	0.158	36.2% (1,000)	44.7% (330)	**<0.001**
Genitourinary	31.0% (1,087)	27.7% (500)	32.8% (280)	36.6% (307)	**<0.001**	30.0% (828)	35.1% (259)	**0.007**
Hematologic	20.0% (699)	17.8% (322)	19.1% (163)	25.5% (214)	**<0.001**	17.7% (490)	28.3% (209)	**<0.001**

Note: Boldface indicates statistical significance ($p<0.05$) from Pearson's chi-square test, Fisher's exact test, or the Kruskal—Wallis test.
[a]Exact cell sizes of 10 or fewer (or their complement) and related statistics are not shown per the data use agreement.
NS, not significant; PCP, primary care provider.





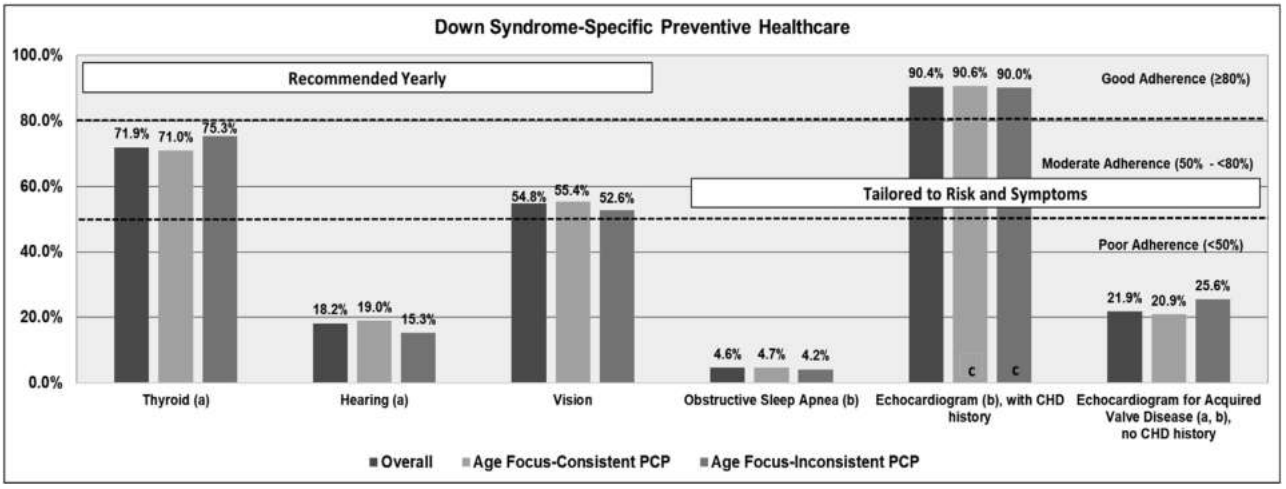


Figure 2. Preventive care patterns by age consistency of PCP focus. All data in this figure represent screening patterns occurring at least once in 2006–2010. Age focus–consistent PCPs are defined as having a focus consistent with a patient's study age: aged ≤18 years, child-focused; aged ≥26 years, adult-focused. Persons aged 18–25 years are considered in transition and therefore can be appropriately seen by child-focused, adult-focused, or mixed-focus PCPs. Overall indicates total cohort.

[a] $p<0.05$ for comparisons between patients seeing age focus–consistent and age focus–inconsistent PCPs.

[b] Personalized screening.

[c] Exact cell sizes of 10 or fewer (or their complement) and related statistics are not shown per the data use agreement.

CHD, congenital heart disease; HPV, human papillomavirus; PCP, primary care provider; Tdap, tetanus, diphtheria, acellular pertussis.

preventive healthcare activities were noted regardless of age focus consistency of PCPs or whether the activity was age/sex- or DS-specific.

In this cohort, 40% of adults with DS (aged ≥26 years) received care from child-focused PCPs. There are several possible explanations for this observation. Pediatric (child-focused) training during our study years contained an explicit focus on the care of people with DS that theoretically increases their comfort in caring for people with DS.[72] Contemporaneous national survey data indicate that only half of general internists feel prepared to care for transition-aged adults with childhood-onset chronic disease.[73] Additionally, longitudinal relationships with PCPs who know their patients with DS well have advantages for provider−patient/caregiver interactions.[59] However, this study observed similar rates of DS-specific activities (both annual and personalized screenings) among providers across age categories, regardless of age focus consistency. Ironically, age focus−inconsistent providers (adult-focused in adolescents, child-focused in adults) demonstrated higher rates of adolescent vaccinations and of cervical cancer screening (Figure 2, Appendix Table 1 available online).

Only 41% of the cohort received at least 1 well examination during these 5 years. Strikingly, all vaccination rates were <50% regardless of PCP age focus consistency. Although 35% of the cohort had ≥1 influenza vaccination during this 5-year study, annual rates were only 11%−16%. By contrast, adult U.S. influenza vaccination rates were 41% (2009−2010).[74] This is particularly important as respiratory infection is the leading cause of death among adults with DS after CHD.[10,68] Additionally, people with DS have immunologic abnormalities that increase their risk for serious infections.[75,76] Thus, many DS-specific recommendations include annual influenza vaccination.[16,17]

This study observed good rates of laboratory-based cholesterol screening (63%). Within procedure-based activities, screening for breast cancer was the most common (46%), followed by cervical cancer (31%), colorectal cancer (26%), and osteoporosis (7%). By comparison, 2010 U.S. screening rates were 72% for breast cancer, 83% for cervical cancer, and 59% for colorectal cancer, with 21% of U.S. women aged 50−64 years receiving osteoporosis screening in the same time period.[77,78] These findings are unexpected as people with DS have a much higher risk of developing osteoporosis (25%−50% prevalence among adult men and women with DS[79−82]) than breast cancer (<1% prevalence[83,84]). In fact, there is ongoing debate regarding the utility of screening mammography in women with DS.[84] Given case reports of individuals with DS and breast cancer, however, the authors argue that family history and clinical presentation should guide breast cancer screening decisions in women with DS.[85]

People with DS are a vulnerable population who benefit from well-supported syndrome-specific recommendations.[16−19,22] Among the activities recommended annually for people with DS, thyroid and vision screening reached moderate rates (50% to <80%), whereas hearing screening occurred in <20% of this cohort. This is particularly concerning as rates of hearing loss in adults with DS range from 73% to 100%.[86] Preventive activities tailored to symptoms among adolescents and adults with DS include screening for obstructive sleep apnea and acquired cardiac valve disease.[17,18] Prevalence estimates for obstructive sleep apnea range from 30% to >90% in DS.[87−94] However, <5% of the cohort had a sleep study. Prevalence estimates for acquired cardiac valve disease in adolescents and adults with DS range from 8% to 46%.[44,48−50,95−97] In this study, >90% of people with DS and CHD had an echocardiogram. However, only 22% of the cohort without CHD underwent an echocardiogram to screen for acquired cardiac valve disease.

Limitations

This retrospective cohort study has several possible limitations. First, the ability to identify conditions and healthcare activities is limited to documentation in claims data and may underestimate conditions or screening practices. Second, the Medicaid population is inherently more complex than commercially insured individuals. However, approximately 80% of people with DS have Medicaid.[98] Thus, these data offer a reasonable estimation of national healthcare patterns in persons with DS. Third, the algorithm attributing PCP focus is based on proxy coding behaviors owing to poor fidelity in the provider specialty code within Medicaid data. Thus, the PCP focus variable may not fully capture the specialties of all providers. Fourth, as discussed, California contributed 83% of the cohort. The subgroup analysis excluding California data showed that the trends identified in this study remained qualitatively within the same categories of poor, moderate, or good rates with the following exceptions: without California patients, the categories for well examinations and influenza vaccinations improved from poor to moderate and decreased for vision screening from moderate to poor (Appendix Figure 1, available online). Given the overall qualitative consistency of the findings and the lack of statistical power to evaluate differences in trends without the California population, the authors retained California patients with DS in this analysis. These limitations notwithstanding, this is among the largest cohort studies of adolescents and adults with DS,

representing healthcare patterns in 4 distinct states. The findings are consistent with previous work[24] and, the authors believe, provide an accurate depiction of trends in preventive health care for adolescents and adults with DS living in the U.S.

CONCLUSIONS

This study of adolescents and adults with DS observed poor rates of most recommended preventive healthcare activities regardless of the age focus consistency of their PCP or whether the activity was age/sex- or DS-specific. This study demonstrates that suboptimal preventive health care is nearly universal among adolescents and adults with DS. Future work should evaluate perspectives regarding primary care delivery to and potential interventions for this population, as enhancing preventive care is essential to improving the health outcomes and well-being of people with DS.

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KMJ contributed to the study design; acquisition, analysis, and interpretation of the data; and drafting the first version of this manuscript and critically revising it. EJC contributed to acquisition, analysis, and interpretation of the data and critical revisions of this manuscript. EJ-C, AVP, and DKR contributed to the study design, interpretation of analysis, and critical revisions of this manuscript.

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SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at https://doi.org/10.1016/j.amepre.2020.06.009.

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RESEARCH REVIEW

Co-occurring medical conditions in adults with Down syndrome: A systematic review toward the development of health care guidelines. Part II

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Abstract

Adults with Down syndrome (DS) represent a unique population who are in need of clinical guidelines to address their medical care. Many of these conditions are of public health importance with the potential to develop screening recommendations to improve clinical care for this population. Our workgroup previously identified and prioritized co-occurring medical conditions in adults with DS. In this study, we again performed detailed literature searches on an additional six medical conditions of clinical importance. A series of key questions (KQ) were formulated a priori to guide the literature search strategy. Our KQs focused on disease prevalence, severity, risk-factors, methodologies for screening/evaluation, impact on morbidity, and potential costs/benefits. The available evidence was extracted, evaluated and graded on quality. The number of participants and the design of clinical studies varied by condition and were often inadequate for answering most of the KQ. Based upon our review, we provide a summary of the findings on hip dysplasia, menopause, acquired cardiac valve disease, type 2 diabetes mellitus, hematologic disorders, and dysphagia. Minimal evidence demonstrates significant gaps in our clinical knowledge that compromises clinical decision-making and management of these medically complex individuals. The creation of evidence-based clinical guidance for this population will not be possible until these gaps are addressed.

KEYWORDS

adult health conditions, clinical practice guidelines, Down syndrome, evidence-based medicine, literature review, trisomy 21

1 | INTRODUCTION

Although the life expectancy of persons with Down syndrome (DS) has increased dramatically in the last half century and now approaches an average of 60 years in many developed countries, consensus-based guidelines for adults with DS over 21 years do not exist (Bittles and Glasson 2004; Glasson et al. 2002). Given this absence of clinical guidance there is concern among health professionals, self-advocates, and caregivers that the medical and mental health needs of this adult population continues to remain underserved (Capone et al. 2018; Carfi et al. 2015; Jensen et al. 2013). Such questions have taken on greater importance as adults with DS are living

Authors listed are in the order of contribution.

longer (Presson et al. 2013) and typically experience an increased burden of chronic medical conditions associated with high morbidity or mortality, some of which may be preventable (Bittles et al. 2007; Esbensen 2010; Glasson et al. 2014; Tenenbaum et al. 2012).

Consensus-derived health supervision guidance for children with DS (birth-21 years) have existed since 1994 (AAP 1994) and continue to be revised on a regular basis based on new or emerging evidence (AAP 2011). There does exist a growing literature in peer-reviewed medical journals addressing screening and/or evaluation for many of the co-occurring medical conditions seen in adults with DS (Capone et al. 2018; Galley 2005; Jensen and Bulova 2014; Malt et al. 2013; Smith 2001; Steingass et al. 2011; Wilson et al. 2015). For the past decade, the Down Syndrome Medical Interest Group in the U.S.A. (DSMIG-USA) has met annually to focus on health care and related topics at their annual symposium, and since 2014 adult health has received special priority (DSMIG-USA 2019). In 2018, a systematic review was published by our workgroup formally reviewing seven high priority medical conditions (congenital heart disease, thyroid disease, cervical spine disease, hearing impairment, overweight/obesity, sleep apnea, and osteopenia/osteoporosis) that often co-occur in adults with DS. This effort serves as both a step toward health care guidelines and in an effort to shape a future research agenda (Capone et al. 2018).

The goal of this review was to build on previous study, with a focus on six additional medical conditions including: hip dysplasia, menopause, acquired cardiac valve disease, type 2 diabetes mellitus, hematologic disorders, and dysphagia. These topics were based on recommendations from the work group to focus on areas that were commonly of clinical concern (see Methods). As described in part I of our previous review, we used the National Library of Medicine (NLM) database PubMed (MEDLINE) to identify review articles from peer-reviewed journals that discuss co-occurring medical conditions and their relative frequency in adults with DS (Capone et al. 2018). Next, we identified original research articles that addressed the prevalence and severity of the conditions and the methodologies used for screening and evaluation. The quality of that evidence was reviewed and implications for the development of practice guidelines were formulated. Finally, critical areas of deficit in clinical knowledge were identified and implications for future research discussed.

A series of key questions were formulated and designed to inform our understanding about the diagnosis and management of these common conditions to further inform clinical decision making.

1 Is the prevalence of (condition) in adults with DS known?
2 Is the severity of (condition) in adults with DS known?
3 Among adults with DS can those at ultra-high risk (for condition) be identified?
4 What are the screening or evaluation methods utilized?
5 Does screening or evaluation lead to reduced morbidity or mortality?
6 What are the financial costs, potential benefits or harms of screening or evaluation?

2 | MATERIALS AND METHODS

2.1 | Survey of resources on health conditions

As previously described in our workgroup's first publication, using the National Library of Medicine (NLM) PubMed database (NCBI 1943–2018) a survey of review articles that discussed the co-occurrence of medical conditions in adults with DS was completed (Capone et al. 2018; Henderson et al. 2007; Jensen et al. 2013; Jones 2009; Maatta et al. 2011; Real de Asua et al. 2015; van Allen et al. 1999; Van Buggenhout et al. 1999). Additional sources of reference not indexed in PubMed included books and book chapters, (Chicoine and McGuire 2010; Pueschel 2006; Pueschel and Pueschel 1992; Rubin and Dwyer 1989) guidance documents prepared for health providers (Cohen and Group 1999; Sullivan et al. 2006; Van Cleve et al. 2006), several journal articles (Kerins et al. 2008; Prasher 1994), and websites (Forster-Gibson and Berg 2011).

2.2 | Topic selection

Seven conditions, congenital heart disease, thyroid disease, cervical spine disease, hearing impairment, overweight/obesity, sleep apnea, and osteopenia/osteoporosis were addressed in our first publication (Capone et al. 2018). In this installment, we identified six additional conditions that are frequently the focus of clinical concern: hip dysplasia, menopause, acquired cardiac valve disease (without CHD), type 2 diabetes mellitus, hematologic disorders, and dysphagia. Three of these topics (menopause, cardiac valve disease, and diabetes) were identified as priority topics in our initial search, but not reviewed in the first manuscript. Three additional topics, (hip dysplasia, dysphagia, and hematologic disorders) are commonly encountered in clinical practice but often overlooked in medical reviews on adults with DS. They were included in this review based upon recommendations by the workgroup itself. Additional medical topics will continue to be reviewed by our workgroup given the availability of published literature to support this endeavor.

2.3 | PubMed literature search

The topical literature searches were conducted between 2017 and 2018 using PubMed to identify original clinical research manuscripts. We used the Medical Subject Headings (MeSH; the NLM controlled vocabulary thesaurus for indexing) to capture related entry terminology in our searches. For example, the MeSH term “Down syndrome” included the search entry terms: Downs syndrome, Down's syndrome, Mongolism, Trisomy 21, and Partial Trisomy 21.

The MESH term “Down syndrome” was combined with one or more main heading MESH terms to identify all of the available articles on that topic (unfiltered search). Then, the limiters *Human* and *≥19 years* were applied to narrow the scope (filtered search). Abstracts were reviewed and excluded according to their relevance as

TABLE 1 PubMed search terms, excluded and included articles by condition

Condition	MeSH search term(s)	Unfiltered search hits	Filtered search hits	Excluded from review	Included in review
Hip dysplasia	Hip dislocation (hip dysplasia, hip displacement)	251	213	209	4
Menopause	Menopause	31	25	20	5
Cardiac valve disease	Heart valve disease, (mitral valve, aortic valve, pulmonic valve) insufficiency; stenosis; prolapse	1,482	589	581	8
Type II DM	Diabetes	734	90	84	6
Hematology	Anemia	175	56	50	6
Dysphagia	Dysphagia, deglutition, swallowing	155	41	36	5

pertaining to the KQs (see below). A majority of articles were excluded at this stage. Whenever an abstract made mention of any KQ, or there was doubt, the full article was procured. The methods and results sections were reviewed to determine which articles met inclusion or exclusion criteria. A single reviewer from our group was chosen to conduct the literature searches, data review and extraction process. All data was reexamined for accuracy by the lead authors. See Table 1 for results of PubMed searches.

2.4 | Inclusion criteria

Study sample includes those ≥19 years (may also include younger subjects who were then removed from data analysis), data addresses at minimum one KQ, supporting data is original (not previously published), any case series or cohort that included >5 participants, any using a case–control research design or a randomized clinical trial.

2.5 | Exclusion criteria

Study sample includes those ≤19 years (exclusively), data does not address at least one KQ, article does not explicitly provide a methodology, the article does not provide original supporting data or uses data that was previously published.

2.6 | Data extraction

Using only the PubMed articles meeting inclusion, data pertaining to KQ was extracted from the abstract, methods, and results sections and entered into a preformatted Excel data template for analysis. See Table 2 for a summary of the articles used for the data extraction.

2.7 | Evidence ratings by condition

Next a critical appraisal of each of the included articles was performed to determine the type of research design used, method of subject ascertainment, total number of study participants, source of control subjects, and the extent of internal and external validity. The grading of *internal validity* considers study design factors such as ascertainment and selection bias, test procedures, and consideration of confounding variables. Using a research design hierarchy studies are graded as poor, fair, or good according to a set of predefined minimal criteria. Criteria differ based upon the type of study being considered (systematic review, case–control, randomized controlled trial, or cohort study). The grading of *external validity* considers the generalizability of findings to a broader, more representative population based upon attributes of the study population, the clinical setting, and qualifications of the personnel conducting the study (USPSTF 2008). See Appendix VII in the USPSTF report for criteria on research design hierarchy, and the grading system used for scoring internal and external validity. See Table 3 for summary of evidence ratings.

3 | RESULTS

3.1 | Hip dysplasia

Of the four articles reviewed, all were small, cross-sectional, and cohort studies (III) (Bennet et al. 1982; Hresko et al. 1993; Roberts et al. 1980; Shaw and Beals 1992). The total number of patients with DS was small (N = 273) and no control subjects were utilized. One study (Bennet et al. 1982) included a single child of under 10 years, another study included subjects from 10 to 70 years. Articles were published between 1982 and 1993, and addressed KQ 1–3, Table 2.

Plain radiographs were used to diagnose hip dysplasia. The prevalence of hip dysplasia across these studies was between 5 and 20%. In children with DS, the estimated prevalence is 1.3–7%, with a peak incidence of frank and recurrent dislocation between 2 and 10 years of age (Abousamra et al. 2016; Kelley and Wedge 2013). Excessive joint mobility and other markers of ligamentous laxity were thought to indicate increased risk. In the series of 18 patients followed for 9 years, two of seven patients with disease at baseline showed progression. Among participants with normal findings at baseline, four out of 11 went on to develop disease. In one study, those with normal hips were more likely to be community ambulators, while those with dysplasia were less likely (Hresko et al. 1993).

TABLE 2 Articles used for data extraction by condition

	Publications (*N*) dates	Subjects (*N*)	Age range[a]	Source of subjects	Methods	Study design
Hip dysplasia	(4) 1982–1993	DS = 273 CTR = 0	10–70 years	Community and residential facility	Plain films, X-rays	Cohort (4)
Menopause	(5) 1997–2010	DS = 651 CTR = 187	21–70 years	Community and residential facility	Behavioral scales, cognitive assessments, record review, structured/semi-structured interviews	Case–control (1), Cohort (4)
Cardiac valve disease	(8) 1986–2010	DS = 619 CTR = 122	9–63 years	Outpatient clinic and residential facility	Cardiac exam, echocardiogram	Case–control (1), Cohort (4), Case series (3)
Type II DM	(6) 1998–2015	DS = 6,714 CTR = 19,276	17–68 years	Outpatient DS clinic, diabetes unit, residential facility, national database	Record review, survey	Case–control (3), cohort (2), case series (1)
Hematology	(6) 1988–2015	DS = 330 CTR = 27	17–66 years	Outpatient clinic, residential facility, day program	CBC	Case–control (2), Cohort (2), Case series (2)
Dysphagia	(5) 2001–2016	DS = 287 CTR = 378	16–68 years	Outpatient clinics, residential facility, daycare centers	Water swallow test, observation, esophogram, manometry	Case–control (3), Cohort (2)

Abbreviations: CTR, participants without Down syndrome (may include typical individuals or those with intellectual disability); DS, participants with Down syndrome.
[a]Age range—those participants <19 years were removed from data analysis.

Two studies received *internal validity ratings* of fair and two of good. Two studies were given *external validity* ratings of poor and two of fair, Table 3. Those receiving a rating of poor generally reflected ascertainment of subjects solely from a long-term institutional setting.

3.2 | Menopause

Of the five articles reviewed, one was a case–control (Schupf et al. 1997) and four were cohort studies (II-2) (Coppus et al. 2010; Cosgrave et al. 1999; Schupf et al. 2003; Seltzer et al. 2001). The number of subjects with DS (*N* = 651) was modestly large and the number of controls (*N* = 187) was small. The age range of participants was 21–70 years. Articles were published between 1997 and 2010, and addressed KQs 1–3, Table 2.

Behavioral scales, cognitive assessment, record review, structured and semi-structured interviews were used to evaluate menopause experience in women with DS. The mean age of menopause was approximately 2 years earlier in women with DS compared to the general population of women and ranged from 44.7 to 47.1 years, and the median age range of menopause was 47.1–49.3 years (Schupf et al. 2003). Earlier age at menopause was associated with an increased risk of dementia in three studies (Coppus et al. 2010; Cosgrave et al. 1999; Schupf et al. 2003) and increased mortality in one study (Coppus et al. 2010). The impact of co-occurring thyroid disease was considered in each of the studies and obesity was considered in two. Three studies received *internal validity ratings* of fair and two of good. One study received an *external validity* rating of fair and four were good, Table 3.

3.3 | Acquired cardiac valve disease

Six of the eight studies on cardiac valve disease (CVD) were done using adult DS cohorts without controls (III) (Barnett et al. 1988; Geggel et al. 1993; Goldhaber et al. 1986, 1987; Pueschel and Werner 1994; Vis et al. 2010). Two studies utilized a case–control design (Goldhaber et al. 1988; Hamada et al. 1998). A single study employed prospective cardiac screening in a subset of participants (Vis et al. 2010). Participants were ascertained through convenience samples including, medical clinics and residential facilities. The cumulative number of subjects with DS (*N* = 619) was modestly large and control subjects without known cardiac disease (*N* = 122) was small. Participants ranged in age from 9 to 63 years. All articles were published between 1986 and 2010, and addressed KQs 1–2, Table 2.

The data reviewed included standard measures of cardiac function—cardiac exam, electrocardiogram (EKG), and echocardiography (ECHO). The subjects studied had no known history of congenital heart disease (CHD). Non-cardiac medical co-morbidities were not considered in any of the studies. Three studies received an *internal validity* rating of fair and five were rated as good. The *external validity* or generalizability of the findings received a rating of fair in five studies and good in three, Table 3.

3.4 | Type 2 diabetes mellitus (T2DM)

Of the six articles reviewed, one used a case–control design (II-2) (Alexander et al. 2016), two used a cohort (II-2) (Real de Asua et al. 2014a, 2014b), and three were case series (III) (Fulcher

TABLE 3 Evidence ratings by condition

	Number of key Qs addressed	Research design hierarchy[a]	Internal validity category	External validity category
Hip dysplasia	3	III	Fair (2), Good (2)	Poor (2), Fair (2)
Menopause	3	II	Fair (3), Good (2)	Fair (1), Good (4)
Cardiac valves	2	III	Fair (3), Good (5)	Fair (5), Good (3)
Type II DM	3	II–III	Poor (1), Fair (2), Good (3)	Poor (1), Fair (4), Good (1)
Hematology	2	II–III	Poor (2) Fair (2), Good (2)	Poor (2) Fair (3), Good (1)
Dysphagia	2	II–III	Fair (2), Poor (3)	Poor (3), Fair (2)

Abbreviations: I, Properly powered and conducted randomized controlled trial (RCT); well conducted systematic review or meta-analysis of homogeneous RCTs; II-1, Well-designed controlled trial without randomization; II-2, Well-designed cohort or case–control analytic study; II-3, Multiple time series with or without the intervention; dramatic results from uncontrolled experiments; III, Opinions of respected authorities, based on clinical experience; descriptive studies or case reports; reports of expert committees.
[a]Research design hierarchy (from USPSTF 2008,p. 36).

et al. 1998; Ohyama et al. 2000; Taggart et al. 2013). In the case–control studies, the number of participants with DS (*N* = 6,714) and healthy controls (*N* = 19,276) were both large. Subjects ranged in age from 17 to 68 years. All articles were published between 1998 and 2015, and addressed KQs 1–3, Table 2.

Most participants were from a single study (Alexander et al. 2016). Subjects in two studies were presumed to substantially overlap based on authorship, timing and description of methods and were only counted once toward total subject number (Real de Asua et al. 2014a, 2014b). Subjects were ascertained from a longitudinal database (96%), outpatient clinic (1%), anonymous survey (1%), a residential living facility (1%), and a diabetes unit (1%). Two studies included laboratory evaluation (Real de Asua et al. 2014a, 2014b); two were from a survey-based dataset (Alexander et al. 2016; Taggart et al. 2013); and two involved retrospective chart review (Fulcher et al. 1998; Ohyama et al. 2000). We assigned *interval validity* ratings of good to three of the articles, fair to two and poor to one of the studies based upon design considerations. One study received *external validity* rating of good, another four were fair while one was rated as poor Table 3.

Various clinical measures were reported including weight, height, BMI, age, waist circumference, waist-to-height ratio, total body fat percentage; and laboratory evaluation included fasting blood glucose, insulin and HbA1C, creatinine, TSH, free T4, cholesterol, HDL, LDL, and triglyceride levels (Real de Asua et al. 2014a, 2014b).

Comorbidities assessed included, family history of early cardiovascular events, presence of arterial hypertension, dyslipidemia, diabetes mellitus, smoking, other conditions (thyroid disorders, obstructive sleep apnea, and Alzheimer's disease), relevant medications (including anti-hypertensive agents, lipid lowering agents, anti-diabetic drugs, anxiolytics, anti-depressants, anti-psychotics, anti-epileptics, non-steroidal anti-inflammatory drugs, levothyroxine, corticosteroids, vitamin B or D supplements, and oral contraceptives/estrogen replacement therapy), and dietary fat, fruit, and fiber intake (Real de Asua et al. 2014a, 2014b). Only a single study focused on the risk for long-term consequences (retinopathy) in those with DS and diabetes (Fulcher et al. 1998).

3.5 | Hematologic disease

Of the six articles reviewed, two used a case–control design (II-2) (Akin 1988; Vergnes et al. 1992), three were cohort studies (II-2) (McLean et al. 2009; Shabayek 2004; Wachtel and Pueschel 1991) and one was a case series (III) (Real de Asua et al. 2015). From the case–control studies, one used participants with intellectual disability at the same educational facility as controls (Akin 1988) while another used an unspecified control group (Vergnes et al. 1992). The cumulative number of participants with DS was small (*N* = 330) who were ascertained from outpatient clinics (44%), educational facilities (32%), a hospital (18%), and a hematology service (3%). Only two studies utilized control subjects (*N* = 27). All articles were published between 1988 and 2015, and addressed KQs 1–2, Table 2.

Four studies included prospective laboratory evaluation (Akin 1988; Shabayek 2004; Vergnes et al. 1992; Wachtel and Pueschel 1991) while two were retrospective (McLean et al. 2009; Real de Asua et al. 2015). Laboratory evaluations included hemoglobin values (Shabayek 2004), complete blood count (CBC) and related investigations in some studies such as serum vitamin B12 or folate levels (Akin 1988; Real de Asua et al. 2015; Wachtel and Pueschel 1991), iron studies (Wachtel and Pueschel 1991), TSH, freeT4, lipid profile, uric acid, and 25-OH-vitamin D levels (Real de Asua et al. 2015). The comorbidities assessed in specific studies included cardiac disease (McLean et al. 2009; Real de Asua et al. 2015) and thyroid disease (Akin 1988; Real de Asua et al. 2015.

The frequency of *anemia* in DS adults as reported in two different studies are quite discrepant at two of 61 (3%) (Wachtel and Pueschel 1991) and 76 of 89 (85%) (Shabayek 2004). These two studies differed in location, population, age of individuals sampled and normative laboratory cut-off values. Some studies showed "no difference" in hemoglobin compared to controls (Akin 1988; Real de Asua et al. 2015). One study analyzed the frequency of anemia by severity with "moderate anemia" observed in 28.6% of the females and 16.1% of the males with DS (Shabayek 2004). The effect of age demonstrated an increasing prevalence of anemia from childhood to early adulthood; as age-specific (19–24 years) hemoglobin values differed by sex with males = 12.5 ± 0.6 and females = 10.9 ± 1.8

TABLE 4 Hematologic laboratory parameters (Mean ± *SD*)

	Akin (Akin 1988)	Wachtel (Wachtel and Pueschel 1991)	Vergnes (Vergnes et al. 1992)	McLean (McLean, McHale, and Enright 2009)	Real de Asua (Real de Asua et al. 2015)
RBC (10^{12}/L)			4.525 ± 0.347		
Hemoglobin (g/dl)		14.8 ± 1.2	14.35 ± 1.14	15.1 ± 2.2	15.2 ± 1.6
Hematocrit (%)		44.5 ± 3.7			
MCV (mm^3)	101	99.1 ± 3.9	94.72 ± 4.38	98.76 ± 5.31	91 ± 11
Leukocytes (×10E3/mm^3)	8.1		6.02 ± 1.7	4.64 ± 1.85	5.8 ± 1.8
Neutrophils			2.92 ± 1.30		
Lymphocytes			2.48 ± 0.78		
Platelets (×10E3/mm^3)				196 ± 71	232 ± 56
Folic acid (ng/ml)		358 ± 151			7.7 ± 3.6
Vitamin B12 (pg/ml)		516.5 ± 221.6			441 ± 156
Fe saturation (%)		29.49 ± 6.7			

(Shabayek 2004). Anemia in DS was also higher in those from lower socioeconomic strata compared to middle and high (Shabayek 2004).

The frequency of *macrocytosis* as reported in one small study was seven of nine (78%) (McLean et al. 2009). A previous report showed that red blood cell (RBC) folate and serum vitamin B12 deficiencies were not related to the macrocytosis (Wachtel and Pueschel 1991). Laboratory values available from each study are summarized; but many did not provide normative values preventing us from calculating a prevalence, Table 4.

A single very small case series reported the frequency of *neutropenia* as (22%) and erythrocytosis (22%) in two of nine participants (McLean et al. 2009). "Benign" neutropenia is a common finding in adults with DS but has not received much research attention.

We assigned *interval validity* ratings of good to 2, fair to 2, and poor to 2 of the studies based upon design considerations. One study received *external validity* rating of good, three were fair while two were rated as poor, Table 3.

Thus, the frequency of mild macrocytosis, mild anemia and mild neutropenia may be common in adults with DS, but prevalence rates are difficult to calculate. The functional consequence of such changes is difficult to predict and likely reflects severity and the specific etiology. Macrocytosis for example, is often clinically benign but could mask the presence of iron deficient anemia which is characterized by microcytosis (Dixon et al. 2010). Similar hematologic findings including neutropenia and macrocytosis have been described in children and adolescents with DS (Dixon et al. 2010).

3.6 | Dysphagia

Two of the five studies on dysphagia used a cohort design (II-2) (Jasien et al. 2016; Smith et al. 2014). Three utilized a case–control design (Hashimoto et al. 2014; Thacker et al. 2008; Zarate et al. 2001) (III). A single study employed prospective screening of their participants (Jasien et al. 2016) but included no controls. Participants were largely ascertained through convenience samples including, medical clinics, community dwelling and residential facilities. The cumulative number of DS participants reviewed was small (*N* = 287) as were the controls (*N* = 378). All articles were published between 2001 and 2016, and addressed KQs 1–2, Table 2.

The data we reviewed was ascertained using a variety of methods including caregiver surveys, direct mealtime observation, water swallow test, esophagram, and tongue pressure measurements. Medical co-morbidities such as poor dental status, tooth loss, known temporomandibular joint dysfunction (TMJ), deglutination disorder, h/o GI surgery were considered reasons for exclusion in some studies. Achalasia, abnormal dentition (missing teeth), were identified as possible risk factors for dysphagia (Smith et al. 2014; Zarate et al. 2001).

Two studies received an *internal validity* rating of fair and three were rated as poor. The *external validity* or generalizability of the findings received a rating of fair in two studies and good in three, Table 3.

Because of differences in methodology and ascertainment it is difficult to compare findings across studies.

4 | DISCUSSION

In this study, we identified six medical conditions that are frequently the focus of clinical concern: hip dysplasia, menopause, acquired cardiac valve disease, type 2 diabetes mellitus, hematologic disorders, and dysphagia. The total number of studies available for review was quite small and the quality of those studies was generally poor to fair. Many studies predated the 1990s before the availability and dissemination of health care guidance for children with DS (AAP 1994). Differences in study sample ascertainment and research design made it difficult to estimate disease prevalence and severity. Further, we were unable to determine the utility of screening asymptomatic individuals for any of the conditions reviewed. It is perhaps of greatest significance that we were unable to identify a single randomized controlled trial from the available literature we searched.

4.1 | Condition specific considerations

4.1.1 | Hip dysplasia

Hip dysplasia is a broadly defined term that encompasses anatomic abnormalities of the ball or socket of the hip joint, congenital or developmental dislocation, and developmental or acetabular dysplasia of the hip. The apparent prevalence of hip dysplasia in adults with DS (5–20%) is higher than in the general adult population (3–4%) (Jacobsen et al. 2005) and higher than in children with DS (Abousamra et al. 2016; Kelley and Wedge 2013). It also has an earlier onset compared to the general population.

Untreated subluxations may become fixed dislocations and the presence of hip disease makes it less likely for an adult with DS to be independently ambulatory. Earlier onset and more rapid progression of disease may lead to the need for total hip arthroplasty (THA) among patients with DS at a younger age. Criteria for THA typically include pain and functional limitations. In the general population, the majority of hip replacements occur in patients older than 65 years, and the need for surgical revision is between 10 and 15% in 10–20 years (Crawford and Murray 1997). In a recent review of adults with DS who underwent THA the surgical revision rate was 7.5% after 5 years, twice that of controls (Sha et al. 2019). The rate of perioperative, medical, and surgical complications in adults with DS is also higher compared to controls (Boylan et al. 2016; Sha et al. 2019).

Currently, screening for hip dysplasia in asymptomatic patients with unchanged gait, may be of little benefit in the absence of interventions to reduce disease progression. Hip dysplasia should be considered in the differential diagnosis of adults with DS presenting with pain or change in activity, such as refusal to walk distances or obvious gait changes (symptomatic). While evaluation with plain radiographs is generally available and sufficient for evaluation, computed tomography (CT) may be needed for both evaluation and surgical planning given differences in the shape of the acetabulum, and differences in the degree of acetabular and femoral ante-version in people with DS. As the life span for people with DS increases and they continue to desire more active lives, intervention using THA is likely to increase (Gross et al. 2013).

Further research regarding the natural history, early detection and prevention of symptomatic hip dislocation in adults with DS appears warranted, and screening protocols for asymptomatic high risk patients should be considered.

4.1.2 | Menopause

Menopause is typically defined as the absence of periods for 12 consecutive months. The average age of menopause for women with DS (late 40s) is approximately 2–3 years earlier than for women in the general population (early 50s) (Schupf et al. 2003). Menopause is associated with a wide range of health effects including, CNS, sleep, metabolic, weight, cardiovascular, musculoskeletal, and urogenital consequences (Monteleone et al. 2018). Some of these symptoms occur in >80% of women (Gracia and Freeman 2018). While some of the studies in this review found an increased risk of dementia associated with an earlier age at menopause transition, the prevalence and severity of related symptoms (hot-flashes, vasomotor changes, cognitive, and mental health), and the risk for associated medical conditions remains underexplored in women with DS (Patel et al. 2001).

None of the studies reported treatment data of menopausal symptoms in women with DS, thus the impact of hormonal replacement therapy (HRT) and non-hormonal treatments on symptoms in this population remains unexplored.

The USPSTF does not presently recommend the use of hormonal replacement therapy (HRT) in post-menopausal women for the prevention of chronic symptoms nor dementia (Gartlehner et al. 2017). However given the >95% risk of early dementia in persons with DS, and the apparent reduced incidence of breast and cervical cancer and hypertension in people with DS, this recommendation should be reconsidered if supportive research evidence is forthcoming (Schupf et al. 2018).

Clinicians may wish to consider menopausal-related symptoms in women with DS >45 years who experience sleep, vasomotor, behavioral, and/or cognitive changes as potentially treatable. Women experiencing severe menopausal symptoms may benefit from the full range of treatment options, for chronic symptoms. These topics require further study prior to making informed recommendations.

4.1.3 | Acquired cardiac valve disease

Approximately 36% of DS subjects had mitral valve disease (prolapse or regurgitation), 10% had tricuspid disease (insufficiency or regurgitation), and 8% had aortic disease (insufficiency or regurgitation). In the single study that employed prospective cardiac screening a subset of participants (N = 138) without known congenital heart defect (CHD), 24 (17%) of these participants were discovered to have previously undiagnosed CHD. Mild to moderate regurgitation was also present in one or more valves (mitral, aortic, pulmonic, and tricuspid) (Vis et al. 2010) and was not associated with age or sex.

The prevalence of adults with DS born with CHD was reviewed by our workgroup previously (Capone et al. 2018). In one of those studies a 75% prevalence of CVD was discovered in those with CHD (Vis et al. 2010). The prevalence rate of CVD in all adults with DS may be up to 50%, which is well above that for the general population (Iung and Vahanian 2014). In children with DS, CVD is associated with CHD such as atrioventricular septal defect, ventricular septal defect and Tetralogy of Fallot (Acar et al. 1999; Tumanyan et al. 2015). Isolated cleft mitral valve can also occur in DS even in the absence of CHD (Hammiri et al. 2016), and its prevalence in DS may be around 6% (Thankavel and Ramaciotti 2016).

Further research to determine the incidence of acquired CVD in adults born with or without CHD could inform the development of screening protocols (Vis et al. 2010).

4.1.4 | Type 2 diabetes mellitus

The prevalence of T2DM in DS as reported in two studies is estimated at 4%–8% (Real de Asua et al. 2014a; Taggart et al. 2013). One study reported an increased risk for developing diabetes in those with DS compared to the general population (Incidence risk ratio = 1.3) but oddly did not specify between type 1 and type 2 diabetes (Alexander et al. 2016). Another study found no patients with DS in their cohort (N = 40) with confirmed T2DM (Ohyama et al. 2000). Regarding comorbidities, the prevalence of diabetic retinopathy is reported in one very small study at one in nine (11%) (Fulcher et al. 1998). Laboratory values available show that those with DS and abdominal obesity were more likely to show signs of insulin resistance (Real de Asua et al. 2014a). A single study found evidence that exercise and diet were useful in preventing diabetes and obesity (Ohyama et al. 2000).

This prevalence rate of T2DM (4–8%) appears to be lower than would be predicted based upon the prevalence of moderate–severe obesity reported in this population (Capone et al. 2018). There is no literature available on the screening or management of T2DM in persons with DS. Future research should focus on development of a standardized screening protocol and assessment tools. Studies in children and adolescents with DS show that insulin resistance is associated with obesity, female gender, and leptin resistance (Yahia et al. 2012; Fonseca et al. 2005). Both leptin levels and leptin resistance has also been shown to be higher in children with DS compared to typical controls (Tenneti et al. 2017). In one study of adults with DS (N = 48) higher levels of fasting insulin, and insulin resistance were reported compared to controls (N = 33) but were non-significant when adjusted for age and gender (Real de Asua et al. 2014a, 2014b). If confirmed by larger studies in adults, this apparent lower prevalence of T2DM could suggest protective factors that modulate the risk for T2DM in this population.

It will be important to expand research to include all known disease risk factors and modifiers such as adiposity distribution, and the role of neuroendocrine and inflammatory mechanisms (Gonzalez et al. 2018). Determining which biomarkers are most useful for understanding physiologic mechanisms and the search for effective biomedical interventions are considered high priority (Bertapelli et al. 2016).

4.1.5 | Hematologic

The frequency of mild macrocytosis, mild anemia, and mild neutropenia may be common in adults with DS, but prevalence rates are difficult to calculate. The functional consequence of such changes is also difficult to predict and likely reflects both clinical severity and specific etiology. Macrocytosis in the absence of vitamin B12 or, is often considered clinically benign but could mask the presence of iron deficient anemia which is characterized by microcytosis (Dixon et al. 2010). Similar hematologic findings including neutropenia and macrocytosis have been described in children and adolescents with DS (Dixon et al. 2010).

Screening parameters and management of hematologic disorders has not been thoroughly considered in adults with DS. Medical comorbidities such as GERD associated esophagitis, celiac disease, liver disease, menorrhagia, and untreated obstructive sleep apnea with nocturnal hypoxemia may affect red blood cell (RBC) indices in the general population. Further research is required to document such changes if present in DS.

A recent metabolomics study of RBCs in subjects with DS (N = 30) and control subjects (N = 67) revealed subtle differences in specific metabolites related to glycolysis, purine catabolism, glutamine/glutamate homeostasis, products of transamination, and other carboxylic acids (Culp-Hill 2017). Widespread dysregulation of RBC metabolism, included intracellular accumulation of lactate, amino acids (except methionine), purine catabolites, glutathione metabolites, carboxylic acids, bile acids (conjugated), and acyl-conjugated carnitines were found. Perhaps such subtle changes reflect a metabolic phenotype.

4.1.6 | Dysphagia

In the studies reviewed, a majority >50% adults with DS may be at increased risk for choking, associated with meals and drinking but a prevalence cannot be calculated.

Co-morbid conditions which place individuals with DS at risk for dysphagia include, oral and dental abnormalities (Faulks et al. 2008; Hennequin et al. 1999) GERD and a variety of esophageal abnormalities (Real de Asua et al. 2015; Wallace 2007; Zarate et al. 1999). Additionally, cervical spine surgery (Siemionow et al. 2017) and achalasia (Zarate et al. 1999) have both been associated with dysphagia and aspiration specifically in adults with DS.

It is unclear what methods should be used when screening for dysphagia or aspiration in this population. In clinical practice, screening questions about mealtime associated symptoms could easily become a part of the routine medical history at annual visits. Direct mealtime observation in conjunction with video-fluoroscopic swallow study (VFSS) probably represents the gold-standard for evaluating dysphagia, however fiber-optic endoscopic evaluation (FEES) is increasingly being used because it can provide information about the effects of dietary modification on swallowing (Wirth et al. 2016).

Because of the high risk for respiratory infections and associated mortality in elderly persons the relationship between dysphagia, aspiration and pneumonia requires extreme clinical vigilance and deserves further study (Bittles et al. 2007; Englund et al. 2013; Lazenby 2008). In elderly adults with DS (>45 years) new-onset seizures, stroke, Parkinsonism, dementia and medications are additional risk-factors which have not been thoroughly investigated (Altman et al. 2013).

Recent lessons learned about dysphagia in children with DS can further our understanding of this condition in adults. High rates of both symptomatic and silent aspiration have been demonstrated in children with DS (Jackson et al. 2016; O'Neill and Richter 2013). Many of these children had cardiac, gastrointestinal, pulmonary, and tracheal malformations requiring surgical repair in early childhood. It is

likely that some of these individuals carry this propensity for dysphagia into adulthood (Kallen et al. 1996; Kohr et al. 2003).

5 | LIMITATIONS

The total number of studies available for review was quite small and the quality of those studies was generally poor to fair. Many studies predated the 1990s before the availability and dissemination of health care guidance for children with DS (AAP 1994). Additional limitations include, the restriction of our review only to that literature written in English and available through the NLM PubMed. The studies available for review were generally poor to fair, especially those relying on data collected retrospectively from chart reviews, or those using convenience samples without controls. Further, the sample size of many studies was quite small and not useful for making statistical comparison across studies. In most rigorous systematic literature reviews, such articles would have been excluded.

The KQ addressed in the literature was very limited indeed, primarily focused on KQ 1, 2 rarely 3 and the quality of this evidence is not very good. We have identified major gaps in our knowledge concerning the preferred, most effective means of screening high-risk individuals, and whether doing so impacts on morbidity or mortality. As such, the financial costs, potential risks and benefits of screening is largely unknown., Many studies were performed in a medical or residential setting because that is where one finds large numbers of adult individuals with DS. Thus, ascertainment bias will result in oversampling the most symptomatic individuals with severe disease. However, individuals with severe disease are probably not uncommon in the primary care setting. Many community-based physicians face the same challenges trying to evaluate and manage complex patients with DS as do specialty centers. It is the community-based primary care providers who will benefit most from having clinical guidance documents to assist in clinical decision making. A single reviewer extracted the data from each article and summarized the findings before it was re-reviewed by a panel of expert practitioners experienced in caring for adults with DS. Inter-rater reliability was not assessed. Despite these limitations, the study represents a coordinated effort by leading medical experts to critically review and synthesize the existing and emerging knowledge to best inform health screening and evaluation practices for adults with DS.

5.1 | The adult population in perspective

The number of persons with DS living in the U.S.A. (2008–2010) is estimated to be between 200,000 and 250,000 (de Graaf et al. 2017; Presson et al. 2013); and the number of adults (>18 years) with DS living in the U.S.A. approaches or exceeds 125,000 individuals.

As longevity continues to increase it is also expected that greater numbers of adults with DS will live to be of advanced-age (>45 years) (Bittles and Glasson 2004). This presents ongoing challenges to the primary care physicians expected to manage an array of congenital, chronic and age-related conditions. Previously, we identified seven conditions that were highly prevalent (>50%) in this population (Capone et al. 2018). In this study, we identified six more conditions that although less prevalent than the original seven, remain the focus of clinical concern: hip dysplasia, menopause, acquired cardiac valve disease, type 2 diabetes mellitus, hematologic disorders, and dysphagia. Differences in how the study samples were ascertained usually from disparate sources (home-community, residential facility, or clinical samples) and the research design (case series, case–control, or cohort design) made it difficult to estimate disease prevalence for any condition.

5.2 | Strategic planning

For planning purposes and informed by this review, we estimate that the number of adults (>18 years) with DS currently living in the U.S.A. with a specific co-occurring health condition can be determined by the following: estimated disease prevalence in the DS population (rounded up to the nearest 5%) × 125,000 estimated individuals (>18 years) living in the U.S.A. = number of individuals with DS affected by the condition. However, these figures represent crude estimates only and are probably unsuitable for public health planning. Thus for hip dysplasia (20%) = 25,000; menopause (50%) = 62,500; cardiac valve disease-independent of CHD- (50%) = 62,500; type 2 diabetes (8%) = 10,000; and dysphagia (50%) = 62,500.

In clinical practice, multiple medical co-morbidities is the rule not the exception, and this entails complex decision-making and management considerations (Evenhuis et al. 2013; Schoufour et al. 2014). Taken together, these factors suggest a modified approach to both diagnosis and treatment in elderly or medically frail adults with DS. In such situations, assessment of the specific risks and potential benefits of diagnostic evaluation and its intended therapeutic purpose needs to be discussed openly with decision-makers. Management strategies for those of advanced-age or nearing end-of-life need to be made available to healthcare providers and family decision makers to use as they see fit in their specific circumstances.

5.3 | Toward guidelines

The biggest challenge for guideline development is their intended scope, breadth and depth. As DS is not a specific disease, but rather a unique human condition associated with a variety of developmental-anatomical differences, acquired (chronic) medical conditions, and precocious aging, such guidelines would potentially involve every major organ system and life-stage. Due to the biologic underpinnings of trisomy 21 some medical conditions may exhibit unique features of etiology-pathogenesis and natural history compared to individuals without this chromosomal condition (Zigman 2013). The best precedent for creating guidance documents has come from the efforts of the American Academy of Pediatrics (AAP 2011). Although guidance beyond 21 years is not within the scope of the AAP document, it

never-the-less serves as an important educational tool about DS that would be of benefit to any health care provider (physicians, nurses, nurse practitioners and physician assistants) who will be providing direct care to adults (Qaseem et al. 2010).

Stakeholder groups including caretakers (parents, siblings, and agency workers) and advocacy organizations (national and regional parent groups) who will use this information to advocate for quality health care locally and nationally (IOM 2011) should also be included in the review process particularly in determining whether an assessment of benefits, harms, and potential alternative options are fully addressed (Diaz Del Campo et al. 2011). Deployment of invested stakeholders will be critical to the prompt dissemination and successful adoption of health guidelines in both the public health and primary care settings (Luke et al. 2013).

5.4 | Realigning clinical research

It is likely that the prevalence rate for most co-occurring conditions is well within the range of rare disease designation (frequency < 200,000) (National Institutes of Health 2017). And so, it remains challenging to plan, organize, and enroll sufficient numbers of adult participants into existing data collection efforts and screening protocols, in part because of their numbers and geographical distribution.

It is not known what percent of the estimated 125,000 adults with DS living in the U.S.A. utilize services at an existing specialty clinic. Those who do almost certainly receive more comprehensive care compared to those who do not (Jensen et al. 2013; Skotko et al. 2013). Although the number of DS clinics serving the needs of adults are few, many are located at large, university-affiliated medical, research and training centers (AUCD 2017; DSMIG-USA 2019). Despite these apparent advantages, clinical research on adults has not kept pace with the need for relevant information. What is required are better efforts to organize and support existing clinical programs to collect and share information on medical screening, diagnostic evaluation and treatment outcomes, as routinely performed at the point of care. Recent efforts to conduct multicenter data collection and sharing using clinician input data are successfully underway (Lavigne et al. 2015, 2017) and may provide the necessary mechanism for further progress if properly funded. Efforts to engage the larger community of families living with DS to participate in clinical research studies is also underway (Peprah et al. 2015). The availability of research funding commensurate with stated long-term goals has only recently been realized (NICHD 2014).

In 2018, the National Institutes of Health (NIH) announced a new trans-NIH initiative to advance the understanding of medical conditions associated with DS. The INvestigation of Co-occurring conditions across the Lifespan to Understand Down syndrome (Project INCLUDE) was announced with three major goals, (a) targeted high-risk, high-reward basic science studies; (b) development of a DS cohort to perform deep-phenotyping and to study co-existing conditions; and (c) to establishing a clinical trials network (National Institutes of Health 2018).

Project INCLUDE will investigate conditions that affect individuals with DS as well as the general population, such as Alzheimer's disease/dementia, autism, cataracts, celiac disease, congenital heart disease, diabetes, and immune dysfunction. The creation of evidence-based guidelines based upon new research and reviews such as ours is the logical next step to "Improving health and well-being of individuals with DS" in line with the NIH INCLUDE initiative.

Presently, the availability of dedicated research personnel and lack of infrastructure support each represent limiting factors in advancing a truly comprehensive data collection effort and person-centered research strategy. While the provision of high quality clinical care to persons with DS is challenging enough, it is yet another matter to capture this experience for the purpose of informing evidence-based care (Murillo et al. 2006). With the necessary support and leadership, it is well within the capacity of existing clinical programs to address this urgent need (Carfi et al. 2015; McCabe et al. 2011; Real de Asua et al. 2015).

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

AUTHOR CONTRIBUTIONS

Each of the authors contributed equally in performing a literature review, data extraction and initial data summation. George Capone, Brian Chicoine, and Peter Bulova established the methodology and procedure for literature review and data acquisition. They also led the work group initiative from its conception and provided mentoring to junior authors. George Capone, Mary Stephens, and Stephanie Santoro wrote and edited the manuscript and tables. All authors participated in reviewing the text prior to submission.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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RESEARCH REVIEW

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Co-occurring medical conditions in adults with Down syndrome: A systematic review toward the development of health care guidelines

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Adults with Down syndrome (DS) represent a unique population who are in need of clinical guidelines to address their medical care. The United States Preventive Service Task Force (USPSTF) has developed criteria for prioritizing conditions of public health importance with the potential for providing screening recommendations to improve clinical care. The quality of existing evidence needed to inform clinical guidelines has not been previously reviewed. Using the National Library of Medicine (NLM) database PubMed, we first identified 18 peer reviewed articles that addressed co-occurring medical conditions in adults with DS. Those conditions discussed in over half of the articles were prioritized for further review. Second, we performed detailed literature searches on these specific conditions. To inform the search strategy and review process a series of key questions were formulated a priori. The quality of available evidence was then graded and knowledge gaps were identified. The number of participating adults and the design of clinical studies varied by condition and were often inadequate for answering all of our key questions. We provide data on thyroid disease, cervical spine disease, hearing impairment, overweight-obesity, sleep apnea, congenital heart disease, and osteopenia-osteoporosis. Minimal evidence demonstrates massive gaps in our clinical knowledge that compromises clinical decision-making and management of these medically complex individuals. The development of evidence-based clinical guidance will require an expanded clinical knowledge-base in order to move forward.

KEYWORDS
adult health conditions, aging, clinical practice guidelines, Down syndrome, evidence-based medicine, literature review, trisomy 21

1 | INTRODUCTION

According to recent estimates, the number of persons with DS living in the United States (2008–2010) is between 200,000 and 250,000 (de Graaf, Buckley, & Skotko, 2017; Presson et al., 2013). A marked increase in the number of persons aged 35–60 years can be explained by the baby boom (1946–1964) and increased life expectancy for older individuals (Presson et al., 2013). The total population prevalence of DS in the United States as of 2010 was estimated to be 6.7/10,000 inhabitants. The age-adjusted prevalence is estimated at 8.6/10,000 for 20- to 24-year-olds; 6.4/10,000 for 30- to 36-year-olds; and 1.9/10,000 for 60- to 69-year olds (de Graaf et al., 2017). Thus, the number of adults (>18 yr) with DS living in the United States approaches or exceeds 125,000 individuals (de Graaf et al., 2017). Further, the life expectancy of persons with DS has increased dramatically in the last half century and now approaches an average of 60 years in many developed countries (Bittles & Glasson, 2004; Glasson et al., 2002).

Consensus-derived health supervision guidelines for children with Down syndrome (DS) (birth-21 yr) have existed since 1994 (AAP, 1994) and continue to be revised on a regular basis based on emerging evidence (AAP, 2011). Consensus-based guidelines for adults with DS over 21 years do not exist. There is, however, a growing literature published in peer-reviewed medical journals addressing screening and/or evaluation for co-occurring medical conditions seen in adults with DS. Many of the reports that highlight co-occurring medical conditions in adults with DS are largely informed by clinical experience and supported by existing literature when available (Chicoine, McGuire, Hebein, & Gilly, 1994; Galley, 2005; Jensen & Bulova, 2014; Malt et al., 2013; Martin, 1997; Pueschel, 1990; Smith, 2001; Steingass, Chicoine, McGuire, & Roizen, 2011; Wilson, Jones, Weedon, & Bilder, 2015). Clinical convenience samples ascertained through specialty clinics focused on DS or intellectual and developmental disabilities (IDD) have also been used to estimate the prevalence and variety of medical conditions in adulthood (Henderson, Lynch, Wilkinson, & Hunter, 2007; Jensen, Taylor, & Davis, 2013; Jones, 2009; Real de Asua, Quero, Moldenhauer, & Suarez, 2015; van Allen et al., 1999; Van Buggenhout et al., 1999). Occasionally IDD population-based databases have been utilized to compile this information using survey methods (Maatta et al., 2011; Wong, 2011).

In a primary care setting, the impetus to initiate screening or evaluation may be based on a person's age, gender, clinical suspicion, existing guidelines, and/or the presence of risk-factors and other co-morbidities. In children with DS the estimated prevalence of certain co-morbidities (e.g., thyroid disease, obstructive sleep apnea) is sufficiently high that routine screening is recommended in asymptomatic individuals (AAP, 2011). In adults questions about the prevalence and severity of co-morbid health conditions and their respective risk-factors has not been fully elucidated. Likewise the efficiency, financial costs, and risk/benefit of routine screening have not been well studied. Nor has the question of whether such screening actually results in measurably improved health outcomes.

The risk of manifesting any particular medical condition varies with the life-stage of an individual (Esbensen, 2010). Several authors have focused on these age-related comorbidities (Glasson, Dye, & Bittles, 2014), reasons for hospitalization (Tenenbaum, Chavkin, Wexler, Korem, & Merrick, 2012), and causes of death (Bittles, Bower, Hussain, & Glasson, 2007). Given the absence of clinical guidance for medical conditions in adults there is sufficient reason to believe that the medical and mental health needs of this adult population also remain largely underserved (Carfi, Brandi, Zampino, Mari, & Onder, 2015; Jensen et al., 2013). Such questions have taken on greater importance as adults with DS are living longer (Presson et al., 2013) and typically experience an increased burden of chronic medical conditions associated with high morbidity or mortality (Bittles et al., 2007; Esbensen, 2010; Glasson et al., 2014; Tenenbaum et al., 2012).

In November 2007, a meeting held at the Centers for Disease Control entitled, "Setting a Public Health Research Agenda for Down Syndrome" was convened to review current knowledge, identify gaps, and develop priorities for future public health research related to Down syndrome (Rasmussen, Whitehead, Collier, & Frias, 2008). Participants from clinical medicine and public health were asked to identify key public health research questions and to discuss potential strategies to address those questions. A subset of topics focused on the provision of health care, including the identification of risk and preventive factors for various health outcomes; understanding of comorbid conditions, including their prevalence, clinical variability, natural history, and optimal means of evaluation and treatment; identification of mental health comorbidities; and improved methods for the diagnosis and treatment of Alzheimer disease.

Since 2010, the Down Syndrome Medical Interest Group in the United States of America (DSMIG-USA) has met annually to focus on health care and related topics at their annual symposium. Beginning in 2014, adult health topics started to receive special priority within DSMIG-USA which in turn has catalyzed interest in further assessing the quality of existing evidence. During this time many of the authors participated in the DSMIG-USA symposia where a portion of this information has been presented. Under the auspices of DSMIG-USA an Adult Health Workgroup was created to present and discuss annually, the emerging evidence in the adult health literature. This article summarizes those efforts and the findings of the Workgroup.

The goals of this review are as follows:

Goal 1: Using the National Library of Medicine (NLM) database PubMed (MEDLINE) identify review articles in peer-reviewed journals that discuss co-occurring medical conditions and their relative frequency in adults with DS

Goal 2: Use PubMed to identify original research articles that address the prevalence, severity and methodologies for screening or evaluation of adults with DS

Goal 3: Guided by key questions formulated a priori determine the quality of the available evidence

Goal 4: Identify critical areas of deficit in our clinical knowledge

Goal 5: Discuss the implication of these findings for the development of practice guidelines and the direction of future clinical research.

2 | MATERIALS AND METHODS

2.1 | Survey of resources on health conditions

Using the National Library of Medicine (NLM) PubMed database (NCBI, 1946–2015), we undertook a survey of review articles that discussed the co-occurrence of medical conditions in adults with DS. Many of the 18 articles contained recommendations for routine screening or evaluation, but only a portion contained original, clinical data in support of their recommendations (Henderson et al., 2007; Jensen et al., 2013; Jones, 2009; Maatta et al., 2011; Real de Asua et al., 2015; van Allen et al., 1999; Van Buggenhout et al., 1999). Additional sources of reference not indexed in PubMed included books and book chapters (Chicoine & McGuire, 2010; Pueschel, 2006; Pueschel & Pueschel, 1992; Rubin & Dwyer, 1989) guidance documents prepared for health providers (Cohen & Group, 1999; Sullivan et al., 2006; Van Cleve et al., 2006), several journal articles (Kerins, Petrovic, Bruder, & Gruman, 2008; Prasher, 1994), and websites (Forster-Gibson & Berg, 2011). See Table 1a for a summary of the resources about general health that were consulted.

2.2 | Survey of review articles

The 18 review articles identified through PubMed were reviewed in detail to determine the types of medical condition that were considered and discussed. Review articles were classified according to study design and the source of patient data as either "literature review/expert opinion," "clinic chart review/original data," "cohort survey/original data." See Table 1b for a summary of data classification.

The frequency at which specific conditions were discussed was totaled across all the articles, and thereby served as a "post hoc consensus" of informed expert-opinion regarding the clinical significance of these conditions in adults with DS. This information was then used to inform the next stage of our review. See Table 2 for the frequency and rank order of medical conditions discussed in the review articles.

The conditions discussed in the publications in rank-order included ophthalmologic-vision, age-related dementia, behavior-mental health, thyroid disease, otolaryngology-hearing, cardiac disease, musculoskeletal-cervical spine, overweight-obesity, respiratory-sleep apnea, dermatologic concerns, seizures, dental concerns, gastrointestinal disorders, vaccination-infectious disease, gynecology-women's health, autoimmune disorders, type II diabetes and various cancers. Fewer, than one-third of articles discussed urologic-renal disorders, hematologic conditions, movement disorders, medication use, hyperlipidemia, gout, chronic pain, and syncope. None of the review articles discussed hospitalizations, end of life care, or cause of death.

2.3 | Topic selection

Our Workgroup agreed that those conditions appearing in greater than 50% of the review articles warranted priority for further review. We prioritized those conditions that met criteria outlined by the United States Preventive Service Task-Force (USPSTF) because of (1) public health importance (i.e., burden of suffering and expected effectiveness of the preventive service to reduce that burden) and (2) the potential for recommendations to impact clinical practice (based on existing controversy or the belief that a gap exists between evidence and practice) (USPSTF, 2008). It was the consensus of the Workgroup to proceed with review of the following medical topics initially, thyroid disease, hearing impairment, congenital heart disease, cervical spine disease, osteopenia-osteoporosis, overweight-obesity, and sleep apnea. The Workgroup continues to evaluate the literature on visual impairment, behavior-mental health, age-related dementia, pulmonary disease, dermatology, gastrointestinal problems, dental problems, infectious disease, and women's health to be included in future manuscripts.

TABLE 1 Health information gathered on adults with Down syndrome by resource type and health information from PubMed review articles

(a) Health information gathered on adults with Down syndrome by resource type

	Review article, *N* = 18	Review article, *N* = 2	Book or chapter, *N* = 4	Medical interest groups, *N* = 3	Website, *N* = 1
Source	PubMed	Not in PubMed	Not in PubMed	Not in PubMed	Not in PubMed
Original data	10 (55%)	2	2	No	No
Guidance provided	13 (72%)	No	3	3	1

(b) Health information from PubMed review articles

	All review articles, *N* = 18	Literature review-expert opinion, *N* = 9	Clinic chart review, *N* = 7	Survey of IDD or DS cohort, *N* = 2
Number of subjects	748 adults	na	554 adults	194 adults
Ages covered	18–70+ years	Adults	18–60+ years	18–70+ years
Original data	10 (55%)	1	7 (100%)	2 (100%)
Guidance provided	13 (72%)	9 (100%)	3 (43%)	1 (50%)

TABLE 2 Frequency and rank-order of co-occurring medical conditions discussed in at least two of the review articles

Topic	Number of articles citing the condition	Frequency (%)	Rank order
Vision/ophthalmology	18	100	1
Thyroid disease	17	94	2
Behavior/mental health	17	94	2
Age related dementia	17	94	2
Hearing/ear-nose-throat	16	88	3
Cardiac	16	88	3
Musculoskeletal/cervical-spine	16	88	3
Overweight-obesity	14	77	4
Respiratory/sleep apnea	14	77	4
Dermatologic	12	67	5
Seizures	11	61	6
Gastrointestinal	10	55	7
Dental	10	55	7
Infectious disease/vaccination	9	50	8
Women's health/gynecology	8	44	9
Metabolism (lipids, glucose)	8	44	9
Autoimmune disorders	8	44	9
Cancer	7	39	10
GU/renal	5	28	11
Hematology	3	17	12
Medication use	2	11	13
Movement disorder/parkinsonism	2	11	13
Lifestyle/activity	2	11	13

Special diets, chronic pain, gout, autonomic dysfunction, syncope, tobacco/alcohol use, sexual activity are each discussed in one article only.

2.4 | Key questions

In accordance with USPSTF practice, we next formulated a series of key questions. The formulation of key questions is an integral part of the approach to conducting systematic literature reviews. Along with the analytic framework, these questions specify the logic and scope of the topic and become critical in guiding the literature search, abstraction, and analysis process (USPSTF, 2008). By consensus, the Workgroup agreed that key questions needed to pertain to the clinical prevalence, severity, risk-factors, screening or evaluation methods, and potential benefits and/or harms in an adult population of persons with DS.

By consensus, the following key questions were formulated:

1. Is the prevalence of (condition) in adults with DS known?
2. Is the clinical severity of (condition) in adults with DS known?
3. Among adults with DS can those at ultra-high risk (for condition) be identified?
4. What are the screening or evaluation methods utilized?
5. Does screening or evaluation lead to reduced morbidity or mortality?
6. What are the financial costs, potential benefits, or harms of screening or evaluation?

2.5 | PubMed literature search

A second phase of topical literature searches were conducted in 2015–2016 also using the National Library of Medicine (NLM) biomedical literature database PubMed (MEDLINE) (NCBI, 1946–2013) to identify original research manuscripts addressing our prioritized topics. We used the Medical Subject Headings (MeSH) (the NLM controlled vocabulary thesaurus for indexing) to capture related entry terminology in our searches. For example, the MeSH term "Down syndrome" included the search entry terms: Downs syndrome, Down's syndrome, Mongolism, Trisomy 21, Partial Trisomy 21.

The MESH term "Down syndrome" was combined with one or more MeSH main heading terms to capture literature (unfiltered) about specific conditions in our search. Then, the limiters "Human," ">19 years" were applied to narrow the scope of the search (filtered). Abstracts from Medline were reviewed and excluded according to their relevance in pertaining to key questions. Whenever an abstract made mention of any key question (or there was doubt) the full article was procured. The sections 2 and 3 were then reviewed to determine which articles met inclusion or exclusion criteria. A single reviewer from our group was chosen to conduct the literature searches then individual reviewers performed the data review and extraction process. See Table 3 for results of PubMed searches.

2.6 | Article inclusion criteria

Study sample includes those >19 years, data addresses at minimum one key question, supporting data are original (not previously published), case series includes >5 participants, or uses a cohort, case-series or case-control research design or randomized clinical trial.

2.7 | Exclusion criteria

Study sample includes those <18 years (exclusively), data do not address at least one key question, study uses an uninterpretable methodology, data have been previously published or does not provide supporting data.

2.8 | Data extraction by condition

Using only the PubMed articles meeting inclusion, data pertaining to key questions were extracted from the Abstract section, sections 2 and 3, and entered into a preformatted Excel data template for analysis. See Table 4 for a summary of the articles used for the data extraction.

TABLE 3 PubMed searches, MeSH terms, article inclusion, and exclusion by condition

Condition	MeSH main heading	Search entry terms included	Unfiltered search hits	Filtered search hits	Excluded from review	Included in review
Thyroid disease	Thyroid disease	Thyroid neoplasms; euthyroid sick syndromes; goiter; hyperthyroidism; hyperthyroxinemia; hypothyroidism; thyroid dysgenesis; thyroiditis	426	175	156	19
Cervical spine disease	Cervical vertebrae; spondylosis	Axis, cervical vertebrae; cervical atlas; cervical spondylosis	120	39	23	16
Hearing impairment	Hearing impairment	Hearing loss; hypoacuisis	134	51	41	10
Overweight-obesity	Obesity	Obesity abdominal; obesity, metabolically benign; obesity, morbid;obesity, pediatric	151	61	56	5
Congenital heart disease	Congenital heart defects	Abnormality, heart; congenital heart defect; congenital heart defects; defects, congenital heart; heart abnormalities; heart defect, congenital; heart defects, congenital heart; malformation of heart	947	234	230	4
Sleep apnea	Sleep apnea syndromes	Apnea, sleep; hypersomnia with periodic respiration; mixed central and obstructive sleep apnea; sleep apnea syndromes; sleep apnea, mixed; sleep apnea, mixed central and obstructive; sleep hypopnea; sleep-disordered breathing	140	33	29	4
Osteopenia-osteoporosis	Osteoporosis	Age-related osteoporosis; bone loss, age-related; osteoporosis; osteoporosis, age-related; osteoporosis, involutional; osteoporosis, post-traumatic; osteoporosis, senile; senile osteoporosis	25	16	8	8

2.9 | Evidence ratings by condition

Next a critical appraisal of each of the included articles was performed by reviewers to determine the type of research design used, subject ascertainment, total number of study subjects, source of control subjects, and the extent of internal validity and external validity. The grading of *internal validity* considers study design factors such as ascertainment and selection bias, test procedures and consideration of confounding variables; while *external validity* considers the generalizability of findings to a broader (more representative) population (USPSTF, 2008). See appendix VII in the USPSTF report for criteria on research design hierarchy, and the grading system used for scoring internal and external validity. See Table 5 for summary of evidence rating.

3 | RESULTS

3.1 | Thyroid disease

Of the nineteen articles reviewed, five used a case-control design (II-2) (Hestnes et al., 1991; Kanavin, Aaseth, & Birketvedt, 2000; Kinnell, Gibbs, Teale, & Smith, 1987; Murdoch, Ratcliffe, McLarty, Rodger, & Ratcliffe, 1977; Percy et al., 1990) while the remaining fourteen were cohort studies (II-2) (Baxter et al., 1975; Dinani & Carpenter, 1990; Kohen & Wise, 1992; Korsager, Chatham, & Ostergaard Kristensen, 1978; Percy et al., 2003; Prasher & Haque, 2005; Van Buggenhout et al., 1999) or case series (III) (Feingold, 2004; Jensen et al., 2013; Mani, 1988; Percy et al., 2003; Prasher, Ninan, & Haque, 2011; Real de Asua et al., 2015; Tenenbaum et al., 2012) focused exclusively on individuals with DS. From the case-control studies, one study used controls with psychiatric disease from a residential facility (Murdoch et al., 1977), two studies used controls with other intellectual disabilities (ID) (Hestnes et al., 1991; Kanavin et al., 2000), and two studies used typically developing controls (Kinnell et al., 1987; Percy et al., 1990). The cumulative number of DS subjects studied appears sufficient ($N = 1426$) having been ascertained from residential institutions (44%), community samples (45%) and clinics or unspecified sources (11%). Eleven of the articles were published prior to the year 2000 (Table 4).

The scope of evaluation included standard thyroid function tests and/or anti-thyroid antibody titers. The medical comorbidities assessed in the studies included treatment with thyroxine (Baxter et al., 1975; Feingold, 2004; Mani, 1988; Prasher et al., 2011), presence of anti-thyroid antibodies, other autoimmune conditions (Real de Asua et al., 2015; Tenenbaum et al., 2012), or dementia (Percy et al., 1990; Tenenbaum et al., 2012; Van Buggenhout et al., 1999).

The prevalence of thyroid disease, including both hypothyroidism and subclinical hypothyroidism, appears to be higher in adults with DS (27% across studies) compared to those in the general population. There is only limited evidence regarding the prevalence of hyperthyroidism (estimated 3% across studies) (Hestnes et al., 1991; Kinnell et al., 1987; Percy et al., 1990; Real de Asua et al., 2015;

TABLE 4 Articles used for data extraction by condition

	Publications (N) dates	Subjects (N)	Age range	Source of subjects	Methods	Study designs
Thyroid dysfunction	(19) 1977–2015	DS = 1,426; ID CTR = 68; PD CTR = 82; CTR = 103	17–76 yr	Community homes, clinics, residential facility	(Thyroid function tests) TBG, thyroid antibodies	Cohort/case series (14), case-control (5)
Cervical spine disease	(16) 1985–2014	DS = 1,561; CTR = 308	18–70 yr	Community and residential	(ADI, disc/bone height); plain films	Cohort/case series (13), case-control (3)
Hearing impairment	(10) 1981–2011	DS = 1,201; CTR = 1,461	15–80 yr+	Clinic or center based	pure tone audiometry, sound field testing, speech audiometry, ABR, tympanogram, bone/air conduction	Cohort/case series (6), case-control (3), epidemiologic (1)
Overweight-obesity	(5) 1992–2011	DS = 1,495; ID CTR = 6,095	15–76 yr	Family or community homes	(BMI) calculated	Cohort/case series (2), case-control (3)
Congenital heart disease	(4) 1999–2013	DS = 10,334; CTR = 69,705	18–68 yr	Residential facilities, hospitals	Echocardiogram	Cohort/case series (3), case-control (1)
Sleep apnea	(4) 2002–2013	DS = 71; CTR = 48	14–56 yr	Clinic	(AHI) Laboratory based PSG	Cohort/case series (3), case-control (1)
Osteopenia-osteoporosis	(8) 1999–2008	DS = 406; CTR = 186	18–60 yr+	Community and clinics	(BMD or BMM) DEXA	Case-control (6), chart review (2)

ABR, auditory brainstem response; ADI, atlas-dens interval; AHI, apnea-hypopnea index; BMD, bone mineral density; BMI, body mass index; BMM, bone mass measurement; CTR, control (typical); DS, Down syndrome; ID, Intellectual disability; PD, Psychiatric disease; PSG, polysomnography; TBG, thyroxine-binding globulin.

Van Buggenhout et al., 1999). Data on severity of thyroid disease in adults with DS are limited, but the case-control studies suggest significant differences in thyroid function test values compared to controls. Overall, a high burden of thyroid disease is evident in this population, and is further supported by the high prevalence of thyroid disease in children with DS (Roizen et al., 2014).

Although conditions such as autoimmune disease are common in people with DS, there is a lack of studies exploring the relationship of these conditions with thyroid disease. One study noted a prevalence of thyroid disease in 74% of a sample of 136 children with diabetes and DS (Aitken et al., 2013), but studies about the co-occurrence of thyroid disease and other autoimmune conditions in adults are limited (Prasher, 1999).

We assigned *internal validity* ratings of good to 15 and fair to 4 of the studies based upon design considerations. Seven studies received *external validity* ratings of good, four were fair while eight were rated as poor. *External validity* was limited in several of the studies whenever participants were recruited from institutional settings which increased the likelihood for more serious comorbid medical conditions (Table 5).

3.2 | Cervical spine

Of the articles reviewed, 15 addressed atlanto-axial instability (AAI) and 5 addressed degenerative disease of the cervical spine. The total number of adults with DS studied was large (*N* = 1,561), but only three studies utilized controls. Thirteen of the studies used a cohort or case series design (III), while three used a case-control design (II-2) (Alvarez & Rubin, 1986; Burke, French, & Roberts, 1985; Cooke & Lansdall-Welfare, 1991; El-Khouri et al., 2014; Elliott, Morton, & Whitelaw, 1988; Ferguson et al., 1997; French, Burke, Roberts, Whitecloud, & Edmunds, 1987; MacLachlan et al., 1993; Miller, Capusten, & Lampard, 1986; Miller, Grace, & Lampard, 1986; Morton, Khan, Murray-Leslie, & Elliott, 1995; Pueschel et al., 1987; Pueschel, Scola, & Pezzullo, 1992; Roy, Baxter, & Roy, 1990; Tangerud, Hestnes, Sand, & Sunndalsfoll, 1990; Van Dyke & Gahagan, 1988) (Table 4).

The scope of evaluation included measurement of the atlanto-dens interval (ADI) or bone height taken from plain films without consideration of co-morbid medical conditions. Although there was some variation in the measures used to define increased ADI, most studies used distances between 4.5 and 5 mm.

The prevalence of AAI in adults with DS (2–20%) appears to be decreased compared to children with DS (15–20%) but higher than typical age-matched controls (Alvarez & Rubin, 1986; Burke et al., 1985; Cooke & Lansdall-Welfare, 1991; El-Khouri et al., 2014; Elliott et al., 1988; Ferguson et al., 1997; French et al., 1987; Miller, Capusten, et al., 1986; Pueschel et al., 1987; Roy et al., 1990; Tangerud et al., 1990). The article with the highest prevalence of AAI (20%) used a cut off of 4 mm which may in part explain the findings (Miller, Capusten, et al., 1986). The presence of os odontoideum and/or ossicles appears to be a marker of high-risk in adults as it is in children (Burke et al., 1985; El-Khouri et al., 2014). Males and females appear to have similar risk; however, periods of inflammation may increase risk (Pueschel et al., 1987).

TABLE 5 Evidence ratings by condition

	Key Qs addressed (maximum = 6)	Research design hierarchy	Internal validity rating	External validity rating
Thyroid dysfunction	3	II-2/III	Fair (4), good(15)	Poor (8), fair (4), good (7)
Cervical spine	3	II-2/III	Fair (3), good (13)	Fair (10), good (6)
Hearing impairment	4	II-2/III	Fair (2), good (8)	Fair (8), good (2)
Overweight-obesity	5	II-2	Fair (1), good (4)	Fair (1), good (4)
Congenital heart disease	6	II-2/III	Poor (1), fair (1), good (2)	Fair (3), good (1)
Sleep apnea	4	II-2/III	Poor (2), fair (2)	Poor (2), fair (2)
Osteopenia-osteoporosis	3	III	Poor (7)	Poor (7)

Research design hierarchy: II-2, well designed cohort or case-control study; III, descriptive studies or case series, expert opinion.

The prevalence of spondylosis or degenerative change of the cervical spine appears to be increased (33–64%) among adults with DS compared to the general population (Burke et al., 1985; MacLachlan et al., 1993; Miller, Capusten, et al., 1986; Tangerud et al., 1990; Van Dyke & Gahagan, 1988). These changes often localize to higher levels of the cervical spine and appear to increase in severity with age (Miller, Capusten, et al., 1986; Tangerud et al., 1990).

Three studies received *internal validity* ratings of fair and thirteen were rated as good based on design considerations. Ten studies received *external validity* ratings of fair, while six received a good rating. These assignments reflect the frequent ascertainment of samples from institutionalized settings (Table 5).

3.3 | Hearing impairment

Four of the articles on hearing loss focused exclusively on persons with DS. Five articles also used non-DS controls with intellectual disability (ID), and one included healthy individuals from the general population. Six articles were cohort studies (II-2) (Lavis, 1997; Evenhuis, van Zanten, Brocaar, & Roerdinkholder, 1992; Keiser, Montague, Wold, Maune, & Pattison, 1981; Maatta et al., 2011; Van Buggenhout et al., 1999; van Schrojenstein Lantman-de Valk et al., 1994), three were case control (II-2) (Buchanan, 1990; Hassmann, Skotnicka, Midro, & Musiatowicz, 1998; Lowe & Temple, 2002), and one was a cross sectional study (III) (Meuwese-Jongejeugd et al., 2006). The cumulative number of DS subjects studied appears large (*N* = 1,201). Seven of the articles were published prior to the year 2000 (Table 4).

The scope of evaluation entailed using standard audiologic methods such as pure tone audiometry or sound field testing (80%), however, various other methods were also used across studies suggesting variability in the approach to screening and evaluation. No consideration was given to other medical comorbidities.

The prevalence of any hearing impairment in adults with DS is up to 73% which is increased compared to both the general population and those with other forms of ID (Lavis, 1997; Meuwese-Jongejeugd et al., 2006). Disease severity appears to increase with age and up to 100% of DS adults experience hearing loss by 60 years, which indicates a high burden of disease in this population. Further support is evident from the high prevalence of middle ear disease and hearing impairment in children with DS (Roizen et al., 2014).

Eight studies received an *internal validity* rating of good and two were rated as fair. Good ratings on *external validity* was assigned to two studies while eight were rated as fair, based largely upon the consistently increased rates of hearing impairment in DS individuals when compared to those without DS across all studies (Table 5).

3.4 | Overweight-obesity

Three of the studies on overweight-obesity were based on a case-control design (II-2), two were case-series studies (II-2). Two of the studies were limited only to persons with DS, while three employed contemporaneous non-DS controls with other forms of ID. All of the studies utilized large study samples (range 183–6,429). The cumulative number of subjects with DS studied was large (*N* = 1,426). Three of the articles were published prior to the year 2000. The scope of evaluation focused exclusively on measures of obesity itself, calculated body mass index (BMI) with no emphasis on comorbid medical conditions. Four studies received an *internal validity* rating of good, and one was rated as fair (Table 4).

Each of the studies utilized BMI as weight (kg)/height (m^2) as the preferred method of evaluation for obesity (Bell & Bhate, 1992; Melville, Cooper, McGrother, Thorp, & Collacott, 2005; Prasher, 1995; Rubin, Rimmer, Chicoine, Braddock, & McGuire, 1998; Stancliffe et al., 2011). In four of the studies, participants were living in their home or community and recruited through a regional hospital or center-based medical clinic. A total of 412 males and 377 females with DS (total = 789), and 201 male and 171 female control subjects (total = 372) with other ID were studied. All subjects were between the ages of 15 and 76 years. Across these four studies 38% of DS subjects were classified as obese and 34% as overweight. Females were more likely than males (43% vs. 33%) to be obese, and about as likely to be overweight (32% vs. 35%). Thus 75% females and 68% males with DS were classified as overweight or obese. In the two studies that utilized ID control subjects (Bell & Bhate, 1992; Melville et al., 2005) 60% of females and 50% of males with ID were classified as overweight or obese. Additionally, in two of the studies a decline in

BMI was noted with advancing age beyond 35 years (Prasher, 1995; Rubin et al., 1998).

In the one study that utilized an existing database of individuals with ID, that included persons with DS (*N* = 706), and those with non-specified ID (*N* = 5,627), 73% of both men and women with DS were classified as overweight or obese, compared to 65% of those with other ID (Stancliffe et al., 2011). Among those with DS women were more likely to be obese than men (48% vs. 41%); which was higher than women and men with non-specified ID (40% vs. 31%).

The *external validity* or generalizability of these findings to the larger population of adults with DS warrants a rating of good in four of the studies; and receives further support from the large number of community-residing persons who participated (Table 5). Additional support for generalizability stems from the consistently high prevalence of overweight-obesity (60–75%) across all studies, and the finding that obesity is often present by adolescence in youth with DS (Tenenbaum et al., 2011).

3.5 | Congenital heart

Three of the studies on adult outcome of CHD were based on chart reviews of a DS cohort without controls (II-2) (Majdalany et al., 2010; van Allen et al., 1999; Vis et al., 2010). The largest study, also retrospective used a case-control design and included a large numbers of participants with CHD both with/without DS (Baraona, Gurvitz, Landzberg, & Opotowsky, 2013). Information about financial costs, hospital LOS, non-cardiac comorbidities, and mortality was presented. A single study employed prospective cardiac screening in a subset of their participants ascertained retrospectively (Vis et al., 2010). Participants were ascertained through convenience samples including, medical clinics, hospitals and residential facilities. The cumulative number of subjects with DS reviewed was large (*N* = 10,472). All articles were published between 1999 and 2013 (Table 4).

The data included standard measures of cardiac function (echocardiography) or in one study morbidity (hospitalization, length of stay, medical conditions, and need for cardiac procedure) and mortality. Non-cardiac medical conditions were considered in only two studies.

Up to 17% of patients residing in a residential setting (the Netherlands) had undiagnosed CHD in addition to the 16% with previously CHD (33%). Regurgitation of the mitral, aortic, and tricuspid valves was present in 75% of subjects (Vis et al., 2010). In patients with AVSD repair left AV valve insufficiency and left ventricle outflow tract obstruction are the most frequently reported long-term complications requiring surgical repair (Martinez-Quintana, Rodriguez-Gonzalez, Medina-Gil, Agredo-Munoz, & Nieto-Lago, 2010). Hospitalized patients with DS and CHD had an increase prevalence of pulmonary hypertension, cyanosis and secondary erythrocytosis compared to those without the condition (Baraona et al., 2013). Among all hospitalized patients with CHD, mortality was higher for those with DS. Bacterial and aspiration pneumonia were exclusively associated with higher mortality in DS. Cardiac procedures, however, were less often performed in patients with DS.

Two studies received an *internal validity* rating of fair one was rated as good and another as poor. The *external validity* or generalizability of the findings received a rating of fair in three studies and one as poor (Table 5). Further support for these findings derives from the large number of participants surveyed, and the known prevalence (40–50%) of CHD in newborns with DS (Roizen et al., 2014).

3.6 | Sleep apnea

Three of the studies of sleep apnea (OSA) focused on persons with DS exclusively, and just a single study employed non-DS (historical) controls also suspected of having OSA. One of the studies used a case-control design (II-2) (Trois et al., 2009), and two were small case series (III) of between 6 and 12 subjects (Andreou, Galanopoulou, & Gourgoulianis, 2002; Resta et al., 2003). Another utilized DS subjects, with/without comorbid depression as a within-syndrome case-control design (Capone, Aidikoff, Taylor, & Rykiel, 2013). The cumulative number of DS subjects studied is quite small (*n* = 71) having been ascertained primarily as clinic convenience samples. All of the articles were published after the year 2000 (Table 4).

The scope of evaluations focused on objective findings (apnea-hypopnea index [AHI], 02% saturation) taken from overnight polysomnogram, with some emphasis on co-occurring medical conditions, such as obesity, thyroid disease and depression. The apparent increased prevalence (85%) and high symptom severity (mean AHI = 25.9/hr) reported across these studies suggests a high disease burden in adults with DS.

Two studies were given an *internal validity* rating of poor and two fair. Because adult persons with DS constitute a special population in the United States, the *external validity* or generalizability of these findings must be made to a larger community-based population of adults with DS. Thus, two studies warrant an *external validity* rating of poor and two are rated as fair. These ratings reflect the small sample sizes and selection bias inherent to clinically ascertained samples (Table 5). However, additional support derives from the high prevalence of OSA in children with DS (Churchill, Kieckhefer, Landis, & Ward, 2012; Hoffmire, Magyar, Connolly, Fernandez, & van Wijngaarden, 2014).

3.7 | Osteopenia-osteoporosis

Six of the articles on bone density utilized a case-control design focusing on adults with DS, and controls with ID (II-2) (Angelopoulou et al., 1999, 2000; Baptista, Varela, & Sardinha, 2005; Guijarro, Valero, Paule, Gonzalez-Macias, & Riancho, 2008; Sakadamis, Angelopoulou, Matziari, Papameletiou, & Souftas, 2002; Tyler et al., 2000). Two studies relied on a retrospective chart review (III) (Schrager, Kloss, & Ju, 2007; van Allen et al., 1999). The cumulative number of DS subjects studied was (*N* = 342). The articles were published between 1999 and 2008 (Table 4).

The prevalence of osteopenia-osteoporosis appears increased among adults with DS compared to adults in the general population

and those with other forms of ID. It is unclear if there is a corresponding increase in bone fracture, but some studies suggest this. Risk factors for low bone-mass density (BMD) were identified in five of the studies and included immobility, inactivity, low calcium and vitamin D, low sunlight exposure, hypogonadism, and seizure disorders. Interestingly males and females appear to be equally affected. Most of the studies measured BMD on dual energy X-ray absorptiometry (DXA) scan as the preferred method of evaluation. The DXA method for screening is widely available and without need of modification in the DS population.

Three studies were retrospective medical clinic chart reviews and the remainder utilized community-based samples. Two studies received an *internal validity* rating of fair and six were rated as poor. The *external validity* or generalizability of the findings was rated as fair in two studies and poor in six of the studies (Table 5).

3.8 | Evidence gaps

There is only limited published evidence available to answer our key questions for each of the co-occurring conditions under review in the adult DS population. Many older studies are descriptive, utilizing small convenience samples and either typical controls or those with IDD as a comparison group for DS. Rarely were persons with DS, without the target condition, used as controls for determining possible risk factors or associated co-morbidities within a larger DS sample. Indeed, there is scant information about risk factors or the direct physiologic impact of other medical co-morbidities on target disease prevalence or severity. No studies have addressed the financial costs or risks/benefits of screening in asymptomatic individuals. A single study addressed morbidity, mortality, and the financial costs associated with the specified medical condition (CHD). Due to the absence of longitudinal, prospective cohort data, we are unable to determine the natural history of disease progression in asymptomatic individuals who eventually become symptomatic, especially those presenting with severe disease. Studies about the use of standard versus alternative methodologies for screening were also generally unavailable.

3.9 | Condition specific considerations and emerging knowledge

3.9.1 | Thyroid disease

An increased frequency of thyroid disease is evident in adults with DS compared to members of the general population (Helfand & Force, 2004). An older USPSTF report reviewed the published evidence on screening for subclinical thyroid disease in typical adults (Helfand & Force, 2004). In the general population subclinical hypothyroidism is considered a risk factor for progression to overt hypothyroidism, Hashimoto's disease, hyperlipidemia, osteoporosis, and mood disturbance; and subclinical hyperthyroidism increases risk for progression to overt hyperthyroidism, thyroid nodules, Grave's disease, atrial fibrillation, osteoporosis, and mood/anxiety disorders. The relationship between thyroid disease and other medical conditions is beginning to be explored in children and adults with DS, with a recent study suggesting a role for both hypothyroidism and oxidative stress in association with osteoporosis (Villani et al., 2016).

Although evaluation methods to screen for thyroid disease are generally available and well established in clinical practice there is a lack of consensus about the frequency and interval of thyroid screening in asymptomatic adults with DS. The true incidence of symptomatic thyroid disease and recommendations for screening has been discussed, with debate focusing on the "normal" reference range for laboratory values (Prasher et al., 2011; Prasher & Haque, 2005).

Identification of individuals at high-risk for thyroid disease includes any individual ever treated with thyroxine, the presence of thyroid auto-antibodies, those with a positive family history of autoimmune thyroid disease or advancing age. The apparent association between autoimmune thyroid disease and other medical comorbidities especially autoimmune conditions deserves further investigation (Aversa et al., 2016; Soderbergh et al., 2006).

Fortunately, hormone replacement therapy makes the treatment of hypothyroidism fairly straightforward and cost-effective for adults with DS; whereas hyperthyroidism often presents a different set of clinical challenges. There is a lack of consensus about the role of thyroidectomy in the treatment of Grave's disease, due to concerns of risk with anesthesia and surgical outcomes in people with DS (Aversa et al., 2015; Goday-Arno et al., 2009).

3.9.2 | Cervical spine

It appears that addressing questions around degenerative disease of the cervical spine is a more urgent priority than screening for AAI per se, although both conditions can co-exist in adults with DS. Cervical spondylosis and cervical spondyolytic myelopathy (CSM) is not seen in childhood, thus clinical suspicion is required throughout adulthood. Because degenerative changes present earlier in adults with DS compared to the general population there needs to be some consensus about screening all adults with DS versus those at high-risk.

The incidence of cervical spondylosis defined as degeneration of vertebral facet joints and intervertebral discs is unknown, but CSM is believed to be the most common spinal cord disorder in typical adults >55 years of age (Young, 2000). Although not demonstrated in adults with DS specifically, typical adults presenting with gait impairment, sensory changes, and neck pain or stiffness are at high risk for disease progression, leading to functionally impairing paraparesis (St. Clair & Bell, 2007; Wang, Hwan, & Hee, 2010).

Evaluation using plain radiographs is generally available and informative regarding sagittal alignment and cervical instability in flexion-extension (Wang et al., 2010). Magnetic resonance imaging (MRI) is required for definitive diagnosis because of its accuracy differentiating neural, osseous, and soft tissue with high resolution and the degree of spinal canal stenosis and associated myelomalacia. If contraindication to MRI exists, computed tomography (CT) may be useful for determining the extent of cervical spondylosis. Although proper imaging can make the diagnosis reasonably straightforward,

treatment often requires surgical decompression-stabilization when severe myelopathy or radiculopathy is present.

Any recommendation to proceed with surgery in symptomatic individuals requires thoughtful consideration, as symptom stabilization rather than complete symptom resolution may be the goal; especially in elderly adults with moderate-severe dementia who are unable to participate in rehabilitation. Surgical outcomes in DS have not been reported as they have for posterior arthrodesis to treat cervical instability (Doyle, Lauerman, Wood, & Krause, 1996).

Putative pathogenic mechanisms include inflammation, collagen sub-types ratio, the integrity of the vascular supply and possibly alteration in bone turnover, none of which have been explored in DS (Nouri, Tetreault, Singh, Karadimas, & Fehlings, 2015; Tetreault et al., 2015).

3.9.3 | Hearing impairment

The prevalence of hearing impairment in adults with DS is >70% and increases dramatically with aging (Lavis, 1997; Meuwese-Jongejeugd et al., 2006). In the general population hearing loss is thought to occur in 25–40% of adults and the prevalence rises to 40–66% in those >75 years, and >80% in those 85 yr and older (Reuben, Walsh, Moore, Damesyn, & Greendale, 1998; Yueh, Shapiro, MacLean, & Shekelle, 2003). In the general population hearing loss is also considered a risk factor for depression, social isolation, poor self-esteem and functional decline (Gates et al., 1996). These same factors deserve further consideration in adults with DS.

Although several screening and evaluation methods are available in clinical practice there is a lack of consensus about the best method or frequency of screening. Current approaches to screening are typically individualized. Routine screening for all adults >40 years which is being incorporated into primary care practice (Patterson & Renaud, 2012) may be especially pertinent to adults with DS who are non-verbal or unable to self-report. The costs, benefits and frequency of repeat screening for all adults with DS versus those at high-risk requires some consideration.

There is a growing recognition about the role of subtle inner ear malformation and temporal bone dysplasia in people with DS discernible by radiologic imaging (Intrapiromkul, Aygun, Tunkel, Carone, & Yousem, 2012; Saliba et al., 2014). The role of risk factors such as childhood history of otitis media or cholesteatoma are also not well investigated (Bacciu et al., 2005). While the evaluation of hearing impairment can be relatively straightforward, newer treatments using amplification or cochlear implants requires further study in adults with DS (Hans, England, Prowse, Young, & Sheehan, 2010; Phelan, Pal, Henderson, Green, & Bruce, 2016; Sheehan & Hans, 2006).

3.9.4 | Overweight-obesity

The consistently high prevalence of overweight-obesity across all studies, and the finding that overweight-obesity is often present by adolescence in people with DS demands greater attention from clinical researchers. Etiology appears to be multifactorial including social, lifestyle, and family variables in addition to an apparent physiologic predisposition (de Winter et al., 2012b).

Recent efforts have confirmed the validity of using body adiposity index (BAI) and dual energy X-ray absorptiometry (DXA) as an alternative to calculated BMI to study obesity in DS (Bandini, Fleming, Scampini, Gleason, & Must, 2013; Nickerson et al., 2015). Obesity itself or its underlying causes appear to contribute to both reduced quality of life (QOL) and high medical complexity especially in the presence of sleep apnea, hepatobiliary disease, musculoskeletal degeneration, cardiopulmonary disease, metabolic disturbance, eating disorders, mood disorders, and reduced physical activity. Some of these relationships are beginning to be explored in youth and adults with DS but their potential interactions require a better understanding (de Winter et al., 2012a; Foerste, Sabin, Reid, & Reddihough, 2016; Galli, Cimolin, Rigoldi, Condoluci, & Albertini, 2015; Ordonez et al., 2012; Ordonez, Rosety, & Rosety-Rodriguez, 2006; Real de Asua, Parra, Costa, Moldenhauer, & Suarez, 2014a, 2014b; Tenenbaum et al., 2011; Wee et al., 2014).

The USPSTF currently recommends that calculated BMI is an acceptable screening modality in the general population, and that waist circumference may be an acceptable alternative in some sub-populations (Moyer, 2012). USPSTF also recommends that typical adults with BMI >30 be referred to an intensive multicomponent behavioral intervention. Adequate evidence indicates that multicomponent behavioral interventions can be effective and that potential benefit outweighs risks. However, evidence for any impact on long-term health outcomes is limited (Moyer, 2012).

Clinical trials focused on weight reduction, long-term management and prevention of obesity in adolescents and adults with DS are needed in conjunction with exploration of predisposing physiologic factors (Bertapelli, Pitetti, Agiovlasitis, & Guerra-Junior, 2016; Fleming et al., 2008).

3.9.5 | Congenital heart

The high prevalence of CHD during infancy and generally good surgical outcomes has in part contributed to the quality of published evidence available on this condition (Fudge et al., 2010; Jacobs et al., 2010). In clinical practice the need for regular follow-up of repaired congenital heart disease (CHD) throughout adulthood is well accepted. Those with previously repaired atrioventricular septal defect (AVSD) appear to have the greatest likelihood of serious long-term complications involving left ventricular outflow obstruction and/or Eisenmenger syndrome, that may require repeat surgical intervention (Martinez-Quintana et al., 2010). In some settings adults with DS alive today may never have had an echocardiogram, and should be screened as the incidence of undiagnosed CHD and valve regurgitation are both high (Baraona et al., 2013). It is perhaps less well appreciated that infants born without CHD can also develop valvular disease as adults (Goldhaber, Brown, & Sutton, 1987; Goldhaber et al., 1986; Pueschel & Werner, 1994). The question of routine cardiac screening for adults without any history of CHD requires clarification.

3.9.6 | Sleep apnea

Both the prevalence and severity of obstructive sleep apnea appears to be higher in the adults with DS ascertained from clinical samples, compared to adults from the general population suspected of sleep disturbance (Jennum & Riha, 2009).

The American Academy of Sleep Medicine (AASM) Adult OSA Task Force provides guidance about high risk individuals in the general population, specific questions and symptoms to consider at the time of evaluation as well as indications for the use of portable monitors (Epstein et al., 2009) Identification of individuals with DS at high-risk for OSA based upon identified symptoms (respiratory pauses, daytime fatigue), risk factors (upper airway anatomy, obesity), or the impact of other co-morbidities (cardiac, mental health) has only recently started to receive attention (Brooks et al., 2015; Fernandez & Edgin, 2013; Konstantinopoulou et al., 2016; Lal, White, Joseph, van Bakergem, & LaRosa, 2015).

The diagnosis and successful treatment of OSA in every person with DS/ID is neither straightforward nor easily achieved. The use of alternative diagnostic methodologies for individuals who cannot tolerate laboratory based PSG is being studied (Maris et al., 2016). In the AASM Task Force article both standard and alternative approaches to therapy are addressed, and supported by the use of clinical decision-making algorithms (Epstein et al., 2009). Practice parameters for surgical modification of the upper airway for OSA in adults has also been addressed by the AASM (Aurora et al., 2010). Evidence is critically reviewed and graded, recommendations made, and commentary regarding values and trade-offs well-articulated.

The pathophysiology of OSA is complex and risk-factors probably differ in children compared to adults with DS. Thus, in adults with DS the previous identification or absence of OSA on PSG during childhood, and role of prior (childhood) surgical interventions (adeno-tonsillectomy, lingual tonsillectomy or midline glossectomy) as putative "protective factors" is probably not justified (Donnelly, Shott, LaRose, Chini, & Amin, 2004; Propst et al., 2016). Newer treatment approaches that address glossoptosis have arrived (Diercks et al., 2016) and are currently undergoing clinical trials in adolescents and young adults with DS (Hartnick, 2017).

A USPSTF report recently reviewed the published evidence on screening, treatment and health outcomes associated with OSA in typical adults (Jonas et al., 2017). The report addresses a series of critical questions including, benefits and harms of screening, diagnostic accuracy and reliability of portable monitors, and potential benefits of various treatments such as continuous positive airway pressure, airway surgery, mandibular advancement, and weight loss. The impact of OSA on several health outcomes such as cardiovascular mortality, stroke, cognitive decline, and dementia were also examined. These same outcomes also deserve further exploration in adults with DS.

Any recommendation to proceed with positive airway pressure (PAP) or airway surgery in symptomatic individuals with DS requires thoughtful consideration for elderly adults with moderate-severe dementia who may be unable to tolerate or benefit from available treatment options.

Mainstream research questions focused on the general population need to be conducted in adults with DS (Lal, Strange, & Bachman, 2012; Macey, Woo, Kumar, Cross, & Harper, 2010; Tsai, 2010; Vgontzas, Bixler, & Chrousos, 2005). For persons with DS the potential costs and benefits of screening all adults versus just those at high-risk require consideration; as do clinical trials examining costs and benefits/harms of both PAP and surgical treatments. The impact of chronic, untreated disease on cognition, mental health, obesity, quality of life (QOL) and mortality also requires further study. The high prevalence and severity of OSA, and decreased resiliency to both the cognitive and mental health consequences requires that we persevere in our efforts to treat these conditions (Capone et al., 2013).

3.9.7 | Osteopenia-osteoporosis

In the DS population, a high prevalence of osteopenia-osteoporosis (>50%) is observed across all studies reviewed, and manifests at an earlier age compared to typical adults. It is unclear if total prevalence of this condition is increased in DS, but it is expected that age-matched prevalence would be higher in DS compared to typical adults. In the general population (50–65%) of women >50 yr, and (30–52%) of men >50 yr have osteopenia-osteoporosis. Interestingly, both males and females with DS may be equally affected. It remains unclear if there is a corresponding increase in bone fracture in DS adults with osteopenia-osteoporosis, some studies suggest this is the case (Schrager et al., 2007).

Dual energy X-ray absorptiometry (DXA), the most widely used and accepted method of screening, is generally available and has been well standardized in typical adults. It is a quick, non-invasive method that uses minimal radiation and does not require modification. The USPSTF recommends that all women >65 yr, or those at high risk for fracture be screened using DXA (Berg, 2003). A review of recommendations from other professional and healthcare organizations has also been conducted (Lim, Hoeksema, Sherin, & Committee, 2009) and recommends that all adults >50 yr be screened for risk-factors, and that DXA screening be implemented in women >65 yr and men >70 yr. Younger post-menopausal women <65 yr undergo screening only when risk factors are present. Thus, the designation of DS individuals as being at high-risk for osteopenia-osteoporosis requires further consideration in clinical practice as DXA screening prior to 45–50 yr of age may be justified in both men and women.

Risk factors such as immobility, physical inactivity, and low sunlight exposure are potentially modifiable risk factors which are not always easily achieved in adults with DS (Hawli, Nasrallah, & El-Hajj Fuleihan, 2009; Matute-Llorente, Gonzalez-Aguero, Gomez-Cabello, Vicente-Rodriguez, & Casajus, 2013). Low calcium and vitamin D intake lend itself to dietary modification (Zubillaga et al., 2006) as does increasing physical activity (Gonzalez-Aguero et al., 2012; Reza, Rasool, Mansour, & Abdollah, 2013) with some degree of success in adolescents with DS having been demonstrated.

The etiology of osteopenia-osteoporosis is likely multifactorial including dietary and environmental factors, but diminished bone formation and low turnover is probably a key factor (McKelvey et al.,

2013). Thus medications which inhibit bone resorption may not be an effective treatment. Research studies addressing bone formation and turnover, hypogonadism, and other endocrine disorders such as low thyroid or parathyroid hormone, oxidative stress, and effects on bone mass are indicated (Fowler et al., 2012; Villani et al., 2016; Zubillaga et al., 2006).

4 | DISCUSSION

4.1 | Limitations of the study

Limitations of this study include the restriction of our review only to that literature written in English and available through the NLM PubMed. Second, the number of studies available for review was limited and the quality of those studies was generally poor to fair, especially for those studies relying on data collected retrospectively from chart reviews, or when using convenience samples without adequate controls. Many studies were performed in a medical or residential setting because that is where one finds large numbers of adult individuals with DS. Thus, any resulting ascertainment bias may tend to oversample symptomatic individuals with severe disease. Perhaps this ascertainment bias reflects a common experience among adult primary care providers who are expected to manage patients with DS and complex symptomatology. It is these providers who will benefit most from having clinical guidance documents to assist in patient care and management. Third, a single reviewer extracted the data from each article and summarized the findings before it was re-reviewed by a panel of expert practitioners experienced in caring for adults with DS. Inter-rater reliability was not assessed. Despite these limitations, the study represents a coordinated effort by leading medical experts to critically review and synthesize the existing and emerging knowledge to best inform health screening and evaluation practices for adults with DS.

4.2 | The adult population in perspective

The number of persons with DS living in the United States (2008–2010) is estimated to be between 200,000 and 250,000 (de Graaf et al., 2017; Presson et al., 2013); and the number of adults (>18 yr) with DS living in the United States approaches or exceeds 125,000 individuals.

As longevity continues to increase it is also expected that greater numbers of adults with DS will live to be of advanced-age (>45 yr) (Bittles & Glasson, 2004). This presents ongoing challenges to the primary care physicians expected to manage an array of congenital, chronic and age-related conditions (Bittles et al., 2007). Of the co-morbid health conditions typically mentioned, visual and hearing impairment, thyroid disease, obesity, sleep apnea, cardio-pulmonary function, cervical and lumbar spondylosis, seizure disorder, and dementia are likely to remain the major considerations (Esbensen, 2010; Glasson et al., 2014). In this regard, guidance around end-of-life and palliative care also remains an area of need (McCallion et al., 2017).

4.3 | Strategic planning

For planning purposes and informed by this review we estimate that the number of adults (>18 yr) with DS currently living in the United States with a specific co-occurring health condition can be determined by the following: estimated disease prevalence in the DS population (rounded up to the nearest 5%) × 125,000 estimated individuals (>18 yr) living in the United States = number of individuals with DS affected by the condition.

Thus, for hearing loss (100%) = 125,000; for sleep apnea (85%) = 106,250 individuals; for overweight-obesity (70%) = 87,500; for cervical spondylosis (60%) = 75,000; for osteopenia-osteoporosis (50%) = 62,500; for previously repaired or uncorrected CHD (35%) = 43,750; for thyroid disease (30%) = 37,500.

Due to the unique biologic underpinnings of trisomy 21 some medical conditions may exhibit unique features of etiology-pathogenesis and natural history compared to individuals without this chromosomal condition (Zigman, 2013). In clinical practice, multiple medical co-morbidities is the rule not the exception, and this requires difficult decision-making and management considerations (Evenhuis, Schoufour, & Echteld, 2013; Schoufour, Evenhuis, & Echteld, 2014). Taken together, these factors suggest a modified approach to both diagnosis and treatment in elderly or medically frail adults with DS. In such situations, assessment of the specific risks and potential benefits of diagnostic evaluation and its intended therapeutic purpose needs to be discussed openly with decision-makers. Management alternatives for those of advanced-age or nearing end-of-life need to be made available to healthcare providers and family decision makers to use as they see fit in their specific circumstances.

4.4 | Toward guidelines

The single biggest challenge for guideline development is based upon their intended scope, breadth and depth. As DS is not a specific disease, but rather a unique human condition associated with a variety of developmental–anatomical differences, acquired (chronic) medical conditions, and precocious aging, such guidelines would potentially involve every major organ-system and life-stage experienced throughout adulthood. The best precedent for creating guidance documents has come from the efforts of the American Academy of Pediatrics (AAP, 2011). Although guidance beyond 21 yr is not within the scope of the AAP document, it never-the-less serves as an important educational tool about DS that would be of benefit to any physician. Much like an airline pilot flying without instrumentation, adult trained providers unfamiliar with DS or the AAP document remain in the unwelcome position of practicing medicine without any guidance whatsoever.

The intended audience for adult guidelines requires thorough consideration throughout the development process. Primary health care providers (physicians, nurses, nurse practitioners, and physician assistants) who will be providing direct care to adults are a primary target group (Qaseem, Snow, Owens, & Shekelle, 2010). The other stakeholder groups include caretakers (parents, siblings, and agency

workers) and advocacy organizations (national and regional parent groups) who will use this information to advocate for quality health care locally and nationally (IOM, 2011). Stakeholders should be included in the review process particularly in determining whether an assessment of benefits, harms and potential alternative options are fully addressed (Diaz Del Campo et al., 2011). Deployment of invested stakeholders will be critical to the prompt dissemination and successful adoption of health guidelines in both the public health and primary care settings (Luke, Wald, Carothers, Bach, & Harris, 2013).

4.5 | Realigning clinical research

Based simply on population prevalence in the United States DS is on the cusp of being considered a rare disease (frequency <200,000) (NIH, 2017). Further, it is likely that the prevalence rate for most co-occurring conditions is well within the range of rare disease designation. And so, it remains challenging to plan, organize, fund and enroll sufficient numbers of adult participants into existing data collection efforts and screening protocols, in part because of their numbers and geographical distribution.

It is not known what percent of the estimated 125,000 adults with DS living in the United States utilize services at an existing specialty clinic. Those who do almost certainly receive more comprehensive care compared to those who do not (Jensen et al., 2013; Skotko, Davidson, & Weintraub, 2013). Although the number of DS clinics serving the needs of adults are few, many are located at large, university-affiliated medical, research and training centers (AUCD, 2017; DSMIG-USA, 2017). Despite such advantages, clinical research on adults has not kept pace with the need for relevant information. What is required are better efforts to organize and support existing clinical DS programs to collect and share information on medical screening, diagnostic evaluation and treatment outcomes, as routinely performed at the point of care. Recent efforts to conduct multicenter data collection and sharing using clinician input data are successfully underway (Lavigne et al., 2015, 2017) and may provide the necessary mechanism for further progress if properly funded. Efforts to engage the larger community of families living with DS to participate in clinical research studies is also underway (Peprah et al., 2015). However, the availability of research funding commensurate with stated long-term goals has never materialized (NICHD, 2014).

Presently, the availability of dedicated research personnel and lack of infrastructure support each represent limiting factors in advancing a truly comprehensive data collection effort and person-centered research strategy. While the provision of high quality clinical care to persons with DS is challenging enough, it is yet another matter to capture this experience for the purpose of informing evidence-based care (Murillo, Reece, Snyderman, & Sung, 2006). With the necessary support and leadership it is well within the capacity of existing clinical programs to step up and address this urgent need (Carfi et al., 2015; McCabe, Hickey, & McCabe, 2011; Real de Asua et al., 2015).

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Pro: The Illegitimate Crusade against Corticosteroids for Severe H1N1 Pneumonia

In this issue of the *Journal*, two groups of authors, one from France (pp. 1200–1206), one from South Korea (pp. 1207–1214), reported increased mortality and increased hospital-acquired infections with the use of corticosteroids in ICU patients with severe H1N1 pneumonia (1, 2). Obviously one's first impression would be to abandon the use of corticosteroids in such patients. We will demonstrate that nothing is wrong with using corticosteroids for treating H1N1-related severe pneumonia.

THERE IS A STRONG BIOLOGICAL RATIONALE SUPPORTING THE USE OF CORTICOSTEROIDS

Acute lung injury following H1N1 influenza infection was characterized by uncontrolled lung and systemic inflammation (3). Autopsy findings demonstrated inflammation-induced damages rather than uncontrolled viral infection (4). Basically, three distinct abnormalities can be found: classic exudative diffuse alveolar damage, severe necrotizing bronchiolitis with extensive and predominantly neutrophilic inflammation of bronchiolar wall and lung parenchyma, and extensive diffuse alveolar damage plus intense alveolar hemorrhage. These lesions are caused by excessive host innate response with exaggerated trafficking of macrophages and neutrophils (5). Subsequently, huge amounts of highly cytotoxic mediators, such as proinflammatory cytokines, superoxide, reactive oxygen species, and reactive nitrogen species, are abundantly released in the lung parenchyma (6). Corticosteroids' transrepression effects occur within a few hours, resulting from physical sequestration in the cytosol of nuclear transcription factors like NF-κB and AP-1, by monomeric glucocorticoid–glucocorticoid receptor α (GGR) complexes, preventing the reading of genes encoding for most if not all proinflammatory mediators. Their transactivation effects require a few days of exposure to a corticosteroid. After conformational changes, the GGRα complex enters the nucleus and up-regulates, via glucocorticoid-responsive elements, genes encoding for regulators of termination of inflammation. Subsequently, key antiinflammatory factors, including phagocytosis, chemokinesis, and antioxidative processes, are activated. Thus, corticosteroids reprogram rather than inhibit immune cells. Corticosteroids induce specific activated, antiinflammatory monocyte subtypes that migrate quickly to the inflamed tissues, and prolong these cells survival via an A3 adenosine receptor–triggered anti-apoptotic effect (7). Obviously, these molecular mechanisms of action of glucocorticoids are appropriate to counteract the uncontrolled inflammation that characterized severe influenza pneumonia (Table 1). Then, unsurprisingly, in a cotton rat model, in combination to neuraminidase inhibitor, corticosteroids dose-dependently inhibited inflammatory cells recruitment to the lung and expression of proinflammatory mediators without affecting viral clearance (8).

CLINICAL EXPERIENCE IS INHOMOGENEOUS AND QUALITY OF CLINICAL DATA AGAINST CORTICOSTEROIDS IS UNRELIABLE

During the 2009 H1N1 pandemic, corticosteroids have been broadly used, and their effects have been variously reported as beneficial (9–11), unfavorable (1, 2), or neutral (12, 13). A recent review has analyzed 22 studies reporting on treatment strategies for patients with H1N1 from the 2009 pandemic (14). There were 0 randomized trials, 15 cohort studies of more than 10 patients, and 7 case series, for a total of 3,020 patients (of whom 1,068 were ICU patients). Corticosteroids were used in 333 patients. There was no evidence for increased mortality with corticosteroids. The two reports from France and South Korea (1, 2) share the same flaws as all previous reports on this topic. Undoubtedly, the only proper method for assessing the efficacy and safety of any drug for any disease is a randomized, double-blind trial. Registries and retrospective cohorts usually aim at describing the natural history of a disease and not at investigating interventions. Indeed, they cannot allow an adequate minimization of selection and confusion biases in the evaluation of drug efficacy or safety, even when based on propensity score analysis. In addition, there are numerous examples of interventions found to be harmful in cohort studies and not in subsequent randomized trials. Among these interventions, the "story" of the pulmonary artery catheter is likely one of the most popular. The provocative increased mortality associated with the use of the Swan Ganz catheter suggested by a large cohort using propensity-matched analysis (15) was subsequently contradicted by several randomized trials (16). Other examples included dopamine, epinephrine, albumin, or synthetic colloids. Amazingly, in the "French" cohort, the authors could also have concluded that the use of vasopressors increased mortality in patients with severe H1N1 pneumonia (1). Indeed, this treatment was also selected as an independent predictor of death. Obviously, this is likely untrue, just as it is for corticosteroids. Sophisticated statistical approaches such as propensity score matching can only take into account measured confounding factors, whereas randomized trials allow controlling for both measured and unmeasured factors (17). Furthermore, in settings with a high correlation between exposure and confounders, as in the case of corticosteroids and H1N1 pneumonia, analyses based on propensity scores usually yielded exaggerated levels of statistical significance (18). Therefore, propensity score–based analysis does not resolve the traditional concern in pharmacoepidemiology that patients who receive a drug differ in disease severity or have other prognostic differences with untreated patients (17). In addition, in the retrospective cohorts reported in this issue of the *Journal* (1, 2) there was no control for the experimental treatment (i.e., corticosteroids). Many patients in these cohorts may have received corticosteroids for other reasons than H1N1-induced acute lung injury or acute respiratory distress syndrome (ARDS). Indeed, initiation of corticosteroids was positively associated with hematologic malignancies, cancer, or chronic obstructive pulmonary disease, and negatively associated with the absence of underlying disease (2). It was not clear which type of corticosteroids was used (2), as the pharmacological properties of different steroids are not equal. Timing of

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TABLE 1. PUTATIVE MECHANISMS OF H1N1-INDUCED LUNG INJURY AND OF CORTICOSTEROIDS COUNTERBALANCING EFFECTS

Exaggerated Innate Immune Response to H1N1	Effects of Corticosteroids
Increased trafficking of neutrophils and activated monocytes to the lung	Decreased neutrophil trafficking, reprogramming of monocytes to produce antiinflammatory subtypes that migrates quickly to the inflamed lung
Promote a Th1-type response	Induce a shift to a Th2 response
Promote Th17-ype cells	Inhibit Th17 cell production of cytokines
Up-regulate expression of TLR-7 and NoD-like receptors/RIG-I	Down-regulate expression of TLR-7 and NoD-like receptors/RIG-I
Overexpression of IL-1, IL-6, IL-8, IL-12p70	Inhibit IL-1, IL-6, IL-8, IL-12p70
Overexpression of IL-15, IL-10	Unaltered regulation of IL-15, IL-10
Overexpression of COX-II	Inhibit COX-II
Promote radical oxygen species and other oxidative processes	Promote antioxidative processes
Induce breakdown of the capillary–alveolar barrier	Protect the capillary–alveolar barrier
Promote cytokine-triggered apoptosis of epithelial cells and pneumocytes I and II	Prevent cytokine-triggered apoptosis of epithelial cells and pneumocytes I and II

Definition of abbreviations: COX = cyclooxygenase; NoD = nucleotide-binding domain–like receptor; RIG-1 = retinoic acid–inducible gene (RIG)-I–like receptors; TLR = Toll-like receptor.

initiation ranged from −2 days to 14 days, and the dose from 200 to 1,600 mg of hydrocortisone or equivalent (1). Finally, neither the duration nor the weaning of corticosteroids was controlled. Of note, after more than half a century of use of corticosteroids for severe infections or ARDS, there is no single randomized trial that has shown increased mortality or increased superinfection. Moreover, in the ARDSnet trial of corticosteroids for persistent ARDS, corticosteroids decreased the risk of superinfection and sepsis (19). Likewise, in a recent multicenter trial in multiple trauma, hydrocortisone therapy was associated with a dramatic reduction in the onset of ventilator-associated pneumonia (20). In sum, it would certainly be a great mistake to change practice on the basis of retrospective data that are so markedly contrasting with the current knowledge of the mechanisms of action of corticosteroids and with their effects demonstrated in randomized trials in patients with all-cause ARDS or sepsis.

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Use of corticosteroids in acute lung injury and acute respiratory distress syndrome: A systematic review and meta-analysis*

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LEARNING OBJECTIVES

On completion of this article, the reader should be able to:

1. Explain outcomes of low dose corticosteroid use in acute lung injury.
2. Describe low dose corticosteroids regimens in acute lung injury.
3. Use this information in a clinical setting.

The authors have disclosed that they have no financial relationships with or interests in any commercial companies pertaining to this educational activity.

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Objective: **Controversy remains as to whether low-dose corticosteroids can reduce the mortality and morbidity of acute lung injury (ALI) or the acute respiratory distress syndrome (ARDS) without increasing the risk of adverse reactions. We aimed to evaluate all studies investigating prolonged corticosteroids in low-to-moderate dose in ALI or ARDS.**

Data Sources: **MEDLINE, EMBASE, Current Content, and Cochrane Central Register of Controlled Trials, and bibliographies of retrieved articles.**

Study Selection: **Randomized controlled trials (RCTs) and observational studies reported in any language that used 0.5–2.5 $mg \cdot kg^{-1} \cdot d^{-1}$ of methylprednisolone or equivalent to treat ALI/ARDS.**

Data Extraction: **Data were extracted independently by two reviewers and included study design, patient characteristics, interventions, and mortality and morbidity outcomes.**

Data Synthesis: **Both cohort studies (five studies, n = 307) and RCTs (four trials, n = 341) showed a similar trend toward mortality reduction (RCTs relative risk 0.51, 95% CI 0.24–1.09; $p = 0.08$; cohort studies relative risk 0.66, 95% CI 0.43–1.02; $p = 0.06$). The overall relative risk was 0.62 (95% CI 0.43–0.91; $p = 0.01$). There was also improvement in length of ventilation-free days, length of intensive care unit stay, Multiple Organ Dysfunction Syndrome Score, Lung Injury Scores, and improvement in Pao_2/Fio_2. There was no increase in infection, neuromyopathy, or any major complications. There was significant heterogeneity in the pooled studies. Subgroup and meta-regression analyses showed that heterogeneity had minimal effect on treatment efficacy; however, these findings were limited by the small number of studies used in the analyses.**

Conclusion: **The use of low-dose corticosteroids was associated with improved mortality and morbidity outcomes without increased adverse reactions. The consistency of results in both study designs and all outcomes suggests that they are an effective treatment for ALI or ARDS. The mortality benefits in early ARDS should be confirmed by an adequately powered randomized trial.(Crit Care Med 2009; 37:1594–1603)**

KEY WORDS: steroids; acute respiratory distress syndrome; acute lung injury

***See also p. 1800.**

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Dr. Tang has full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Dr. Tang organized the study concept and design. Drs. Tang, Eslick, and Seppelt acquired the data. Drs. Tang and Craig analyzed and interpreted data. Drs. Tang, Eslick, Seppelt, Craig, and McLean drafted the manuscript. Statistical analysis was performed by Dr. Tang.

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Acute lung injury has a substantial impact on public health. It has a very high hospital mortality rate of 38% to 50% and substantial associated morbidity (1, 2). In the United States alone, acute lung injury (ALI) causes 74,500 deaths each year (1), far exceeding that of breast cancer or human immunodeficiency virus (3, 4). Among those who survived, only 34% were well enough to be discharged home directly (1). It is estimated that the annual incidence of ALI will double in the next 25 years, as the population ages (1). The development of an effective therapy, therefore, has important implication for the planning of critical care services, rehabilitation, and resource provision.

ALI is characterized by an intense host inflammatory reaction against the pulmonary parenchyma, triggered by insults, such as pneumonia, sepsis, and trauma. Corticosteroids have been investigated as a potential treatment for ALI because of their anti-inflammatory properties. Early trials using time-limited high-dose corticosteroids failed to demonstrate a survival benefit (5–8). More recently, trials that used prolonged low-to-moderate dose corticosteroid regimens showed promise in reducing morbidity and mortality (9, 10). However, controversy remains because earlier mortality benefit in unresolving ARDS (9) has not been confirmed in a more recent multicenter trial (11). In addition, several recent meta-analyses add further uncertainties because they produced conflicting findings (12–14).

So far, several important issues remain unresolved. First, it is unclear whether low-to-moderate dose corticosteroids improve both mortality and morbidity outcomes. The recent meta-analyses were limited because they included studies of high-dose corticosteroids (12, 14) and they did not assess all the relevant outcomes (12–14). Second, clinicians have raised significant concern over the side effect profile of corticosteroids, particularly, the increase in infectious and neuromyopathic complications. Again, existing meta-analyses did not fully address these concerns. Third, there is considerable un-

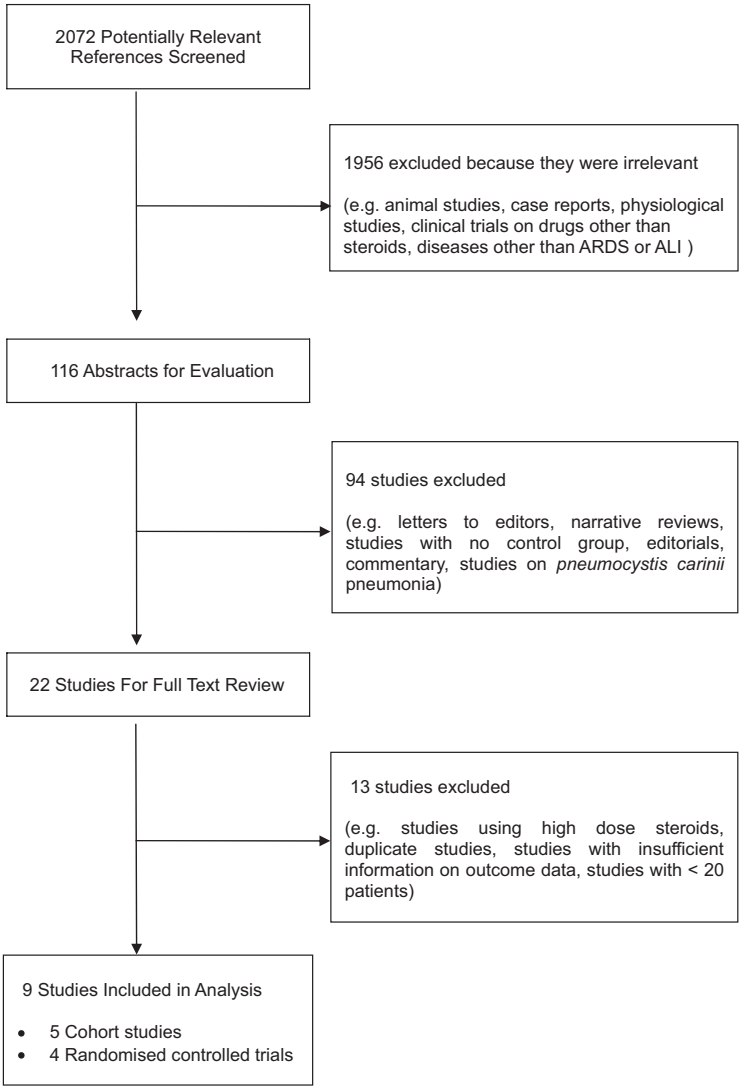

Figure 1. Study identification, inclusion, and exclusion. *ARDS*, acute respiratory distress syndrome; *ALI*, acute lung injury.

Table 1. Study and subject summary characteristics

	Keel et al (31)	Varpula et al (32)	Huh et al (33)	Lee et al (34)	Annane et al (35)	Meduri et al (9)	Confalonieri et al (20)	ARDSNet (11)	Meduri et al (10)
Study design	Cohort	Cohort	Cohort	Cohort	Cohort	RCT (crossover design)	RCT	RCT	RCT (crossover design)
Year of study	1995	1998	1998	2003	1999	1996	2003	2003	2002
Country	Switzerland	Finland	South Korea	South Korea	France	USA	Italy	USA	USA
Total (n)	31	31	48	20	177	24	46	180	91
Mean age (yrs)	50	43	61	67	60	48	63	49	51
Subjects	Nontrauma patients with ARDS	Patients with primary ALI	Patients with ARDS	Post-thoracic surgery patients	Septic shock patients with ARDS	Patients with severe ARDS	Patients with severe pneumonia with Pa_{O_2}/Fi_{O_2} <250	Patients with persistent ARDS	Patients with severe early ARDS
Dose equivalent (methylprednisolone)	100–250 mg/d	120 mg/d	140 mg/d	140 mg/d	40 mg/d	140 mg/d	48 mg/d	140 mg/d	70 mg/d
Days of ALI/ARDS (d)[a]	15.0	9.7	8.0	4.4	0.0	9.2	0.0	11.3	3.0
Length of treatment (d)	8.0	27.0	7.0	9.5	7.0	32.0	7.0	25	28
Tapering of therapy	Yes	Yes	Yes	Yes	No	Yes	No	Yes	Yes
Mortality of treatment vs. control groups[b]	38% vs. 67%	19% vs. 20% (30 d)	43% vs. 74%	8% vs. 88%	53% vs. 75% (28 d)	12% vs. 62%	0.0% vs. 30%	29% vs. 29% (60 d)	24% vs. 43%

RCT, randomized controlled trial; ALI, acute lung injury; ARDS, acute respiratory distress syndrome.
[a]Number of days of established ALI/ARDS before steroid treatment; [b]hospital mortality is given unless otherwise specified in parentheses.

Table 2. Adverse events

	Keel et al (31)	Varpula et al (32)	Huh et al (33)	Lee et al (34)	Annane et al (35)	Meduri et al (9)	Confalonieri et al (20)	ARDSNet (11)	Meduri et al (10)
Number of patient (treatment:control)	13:18	16:15	14:34	12:8	85:92	16:8	23:23	89:91	63:28
Infection		9:5		4:0	12:12	12:6	0:4	20:30	27:17
Neuromyopathic complications							0:3	26:21	4:1
Gastrointestinal bleeding					5:2		1:1		1:0
Hyperglycemia							5 (31%):4 (50%)		45 (71.4%):18 (64.3%)
Other adverse events (n)[a]				Arrhythmia (12), psychosis (4), and pneumothorax (2)	Psychiatric disorder (1)		Acute renal failure (3), arrhythmia (4), liver failure (1), heart failure (2), and hepatitis (1)		Pneumothorax (11), pancreatitis (2)

[a]Number in parentheses indicate total events of treatment and control groups.

Table 3. Subgroup analysis on mortality

	Subtotal (n)	Risk Ratio (95% Confidence Interval)	p^a
Early vs. late ARDS			
Early (less than 7 d)	334	0.48 (0.22–1.03)	0.64
Late (7 d or more)	314	0.67 (0.44–1.04)	
Tapering of steroid			
Yes	425	0.59 (0.39–0.89)	0.15
No	223	0.36 (0.03–3.94)	
Formulation			
Hydrocortisone	223	0.36 (0.03–3.94)	0.15
Methylprednisolone	425	0.59 (0.39–0.89)	
Year of study[b]			
Pre-2000	311	0.68 (0.47–0.99)	0.65
Post-2000	337	0.46 (0.19–1.10)	
Crossover RCT design			
Yes	115	0.41 (0.16–1.02)	0.06
No	226	0.37 (0.03–4.71)	

ARDS, acute respiratory distress syndrome; RCT, randomized controlled trial.

[a]*p* Values of test of interaction between subgroups; [b]year 2000 was chosen as a cutoff point when the ARDS network low tidal volume trial was published (21).

certainty over how the therapy should be administrated. The impact of important clinical variables, such as dose or treatment duration, on the effectiveness of the corticosteroids is unclear.

We performed a systematic review and quantitative synthesis to address all the above issues. In particular, we included studies missed by previous meta-analyses and assessed all relevant mortality and morbidity outcomes. Furthermore, we comprehensively evaluate the side effect profile of low-to-moderate dose corticosteroids. Finally, we undertook subgroup and meta-regression analyses to determine the association between the effects of corticosteroids and important clinical variables, such as dose, treatment duration, and timing of the therapy. Our study, therefore, represents the most comprehensive review to date on the therapeutic effect of prolonged corticosteroids therapy in ALI.

METHODS

Search Strategy and Selection Criteria. We prespecified our search strategy, selection criteria, and subgroup analysis before undertaking our study. We report our study's findings in accordance with the Quality of Reporting of Meta-analyses conference statement (15).

We searched, without language restriction, for all publications on ALI and ARDS between January 1967 and September 2007 using electronic databases, including MEDLINE, EMBASE, Current Content, Database of Abstracts of Reviews of Effects, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. Because the number of randomized trials is few and often underpowered, we included both randomized and nonrandomized studies. Additionally, we included studies that enrolled patients with only acute respiratory distress syndrome (ARDS), a more severe form of ALI (16).

The search strategy used medical subject heading terms and text words: 1) ALI; 2) ARDS; and 3) acute respiratory failure. We hand searched the reference lists of each primary study for additional publications.

We included all cohort studies and randomized trials that 1) used low-dose corticosteroid (e.g., 0.5–2.5 $mg \cdot kg^{-1} \cdot d^{-1}$ of methylprednisolone or equivalent); 2) enrolled patients with ALI or ARDS; and 3) included subjects aged 18 years or older. Our primary outcome was hospital mortality. Secondary outcomes were length of mechanical ventilation, length of intensive care unit stay, Multiple Organ Dysfunction Syndrome Score, Lung Injury Score, and Pao_2/Fio_2 ratios. Outcome data on adverse events included infection, neuromyopathic complications, gastrointestinal bleeding, and hyperglycemia. Data on other complications (e.g., arrhythmia, psychiatric disorders, and organ failure), where available, were also collected.

Studies were excluded if they were duplicated studies, did not use a control group, used high-dose corticosteroid therapy (e.g., 30 $mg \cdot kg^{-1} \cdot d^{-1}$ of methylprednisolone or equivalent), or enrolled subjects with other systemic inflammatory diseases, such as *Pneumocystis carinii* or idiopathic pulmonary fibrosis.

Data Extraction. Data were extracted independently by two reviewers and disagreements were resolved by consensus. Information extracted included year of publication, country of origin, clinical settings, trial duration, participant demographics, sample size, proportion of patients with sepsis, drug dosage and formulation, duration of established ALI before corticosteroid treatment, phase of ARDS (early vs. late), whether there was tapering of the corticosteroids when treatment ended, disease severity indices, such as Pao_2/Fio_2 ratios and Acute Physiology and Chronic Health

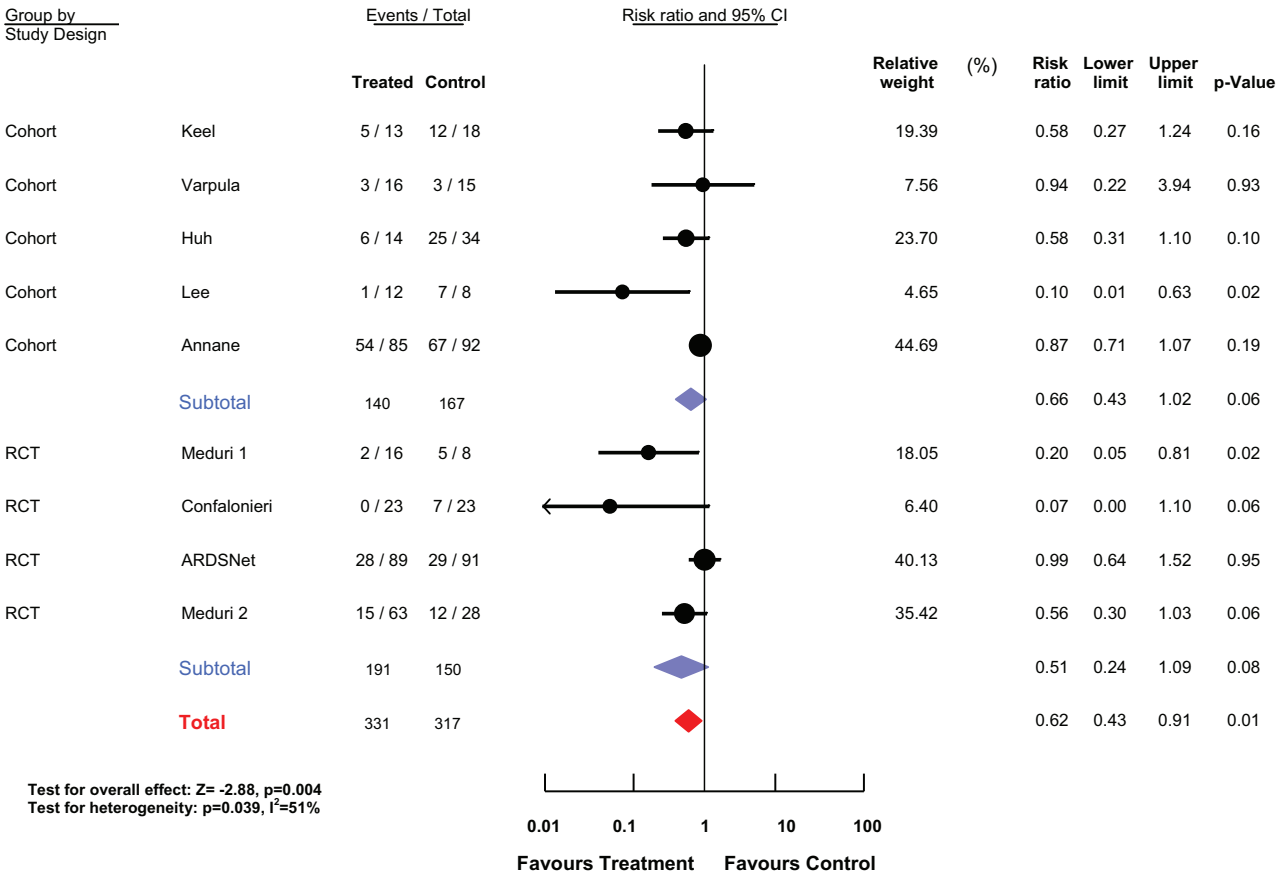

Figure 2. Effect of steroid on mortality. Size of data markers is proportional to the weight of each study in the forest plot. *RCT*, randomized controlled trial; *CI*, confidence interval.

Evaluation Scores. We contacted authors if further study details were needed.

Quality Assessment. The methodologic quality of each study was assessed by a four-item checklist. Randomized trials were assessed using criteria based on the Cochrane Collaboration guidelines, namely, reporting of randomization method, allocation concealment, blinding of outcome assessment, and completeness of follow-up (17). Cohort studies were assessed using criteria based on the Health Technology Assessment Program guidelines, which provided evidence-based recommendations on the assessment of nonrandomized trials (18). The criteria included baseline comparability of the treatment against control groups, adjustment for confounders, blind outcome assessment, and completeness of follow-up.

Statistical Analysis. For all studies, we calculated the risk ratio (relative risk) for all the dichotomous outcomes, such as death, infection, or neuropathy/myopathy. We calculated weighted difference in means between treatment and control groups for continuous outcomes, including length of mechanical ventilation, length of intensive care unit stay, Multiple Organ Dysfunction Syndrome Scores, and Lung Injury Scores. For Pao_2/Fio_2 ratios, we calculated the standardized weighted difference in means between groups to account for the variation in ventilator setting practices between studies (i.e., all ratios were normalized by their own SD to make them comparable with each other). The number to treat was calculated as the inverse of the absolute risk reduction, based on the pooled risk ratio and the baseline risk (19). Heterogeneity was assessed using Cochran's Q statistic and quantified using the I^2 statistic, which indicated the proportion of variability across studies that was due to heterogeneity rather than sampling error.

The outcome measures were pooled using a random effects model because we anticipated the presence of significant heterogeneity, caused by differences in treatment regimens and variations in local critical care practices. We explored sources of heterogeneity by using subgroup and meta-regression analyses. Variables for such analyses were planned before the study was undertaken. They included, for meta-regression, treatment duration, percentage of patients with sepsis, age, dose, sex, baseline Pao_2/Fio_2 ratios, and Acute Physiology and Chronic Health Evaluation Scores; for subgroup analysis, early/late ARDS, tapering of corticosteroids, formulation, year of study, and study design. A test of interaction was done on all subgroups to establish if the difference in effect size between subgroups was statistically significant. Results were considered as statistically significant for p values <0.05.

RESULTS

Of the 2072 references screened, nine studies were included in the final analysis (Fig. 1). Four studies were randomized controlled trials (RCTs) and five studies were cohort studies (Table 1). In total, 648 subjects were analyzed, with 307 subjects in cohort studies and 341 in randomized trials. The study population was relatively young (mean age 51 years), with a mean Acute Physiology and Chronic Health Evaluation II Score of 18 and mean baseline Pao_2/Fio_2 ratio of 126 mm Hg. Most studies (n = 8) included

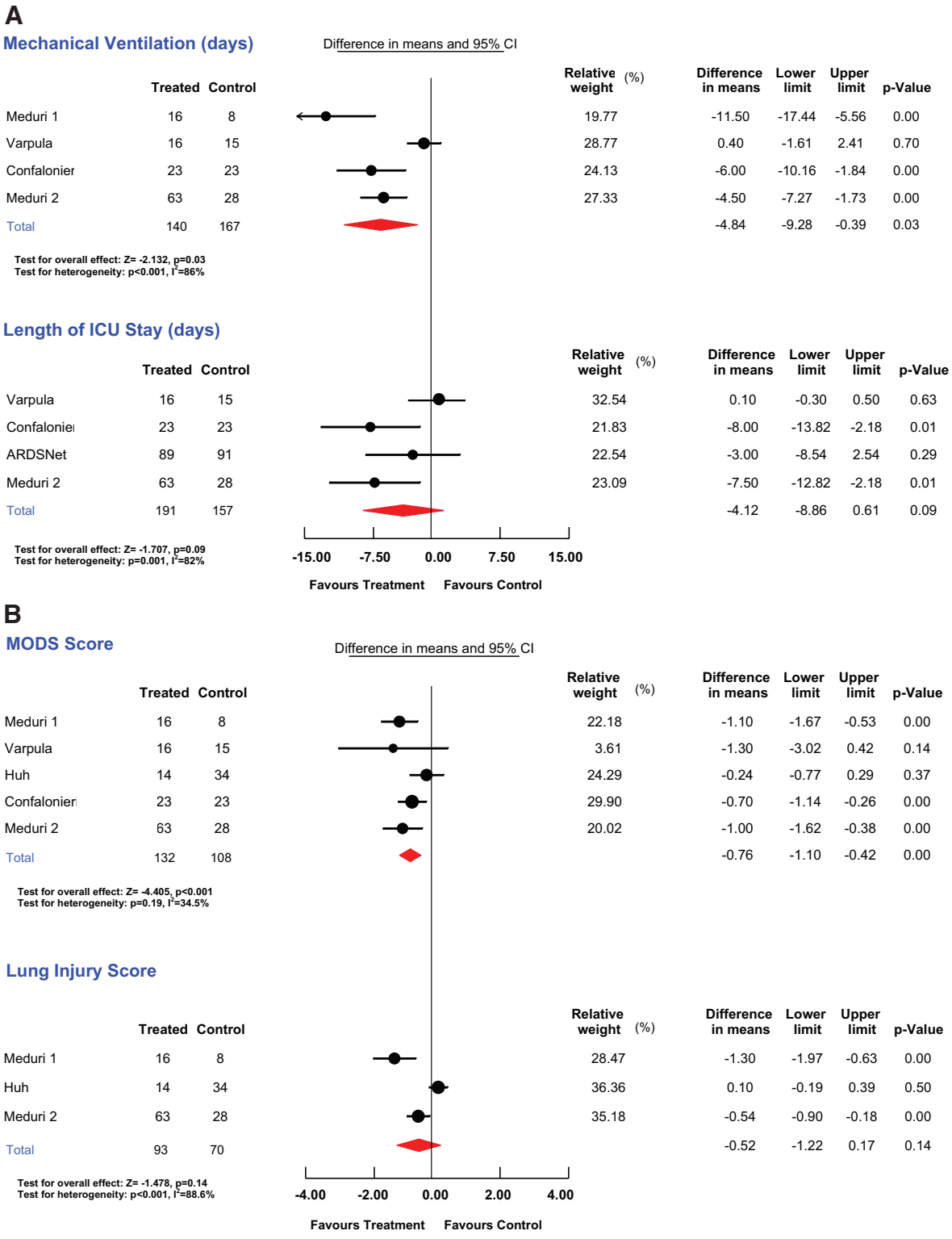

Figure 3. *A*, Effect of steroid on duration of mechanical ventilation and length of intensive care unit (*ICU*) stay (days). Size of data markers is proportional to the weight of each study in the forest plot. Horizontal bars = 95% confidence interval (*CI*). *B*, Effect of steroid on multiple organ dysfunction syndrome (*MODS*) and lung injury scores. Size of data markers is proportional to the weight of each study in the forest plot. Horizontal bars = 95% CI. *C*, Effect of steroid on the Pao_2/Fio_2 ratios. Size of data markers is proportional to the weight of each study in the forest plot. Horizontal bars = 95% CI. *MV*, mechanical ventilation; *ARDS*, acute respiratory distress syndrome; *LIS*, lung injury score.

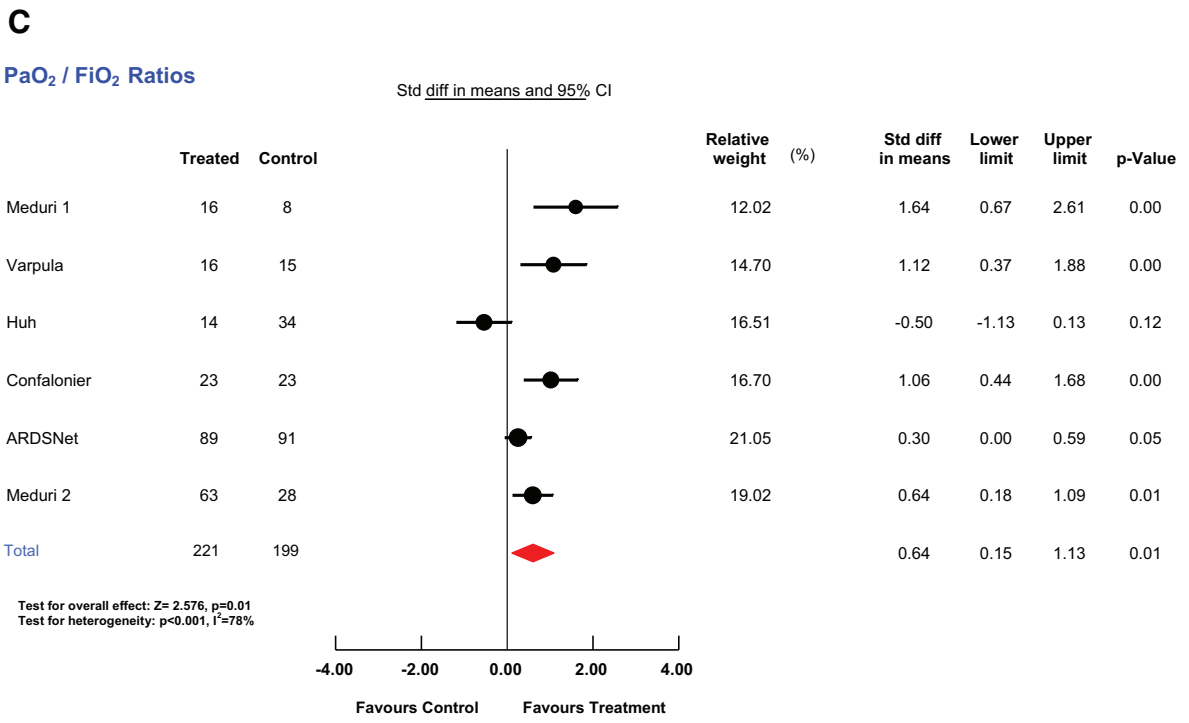

Figure 3. (Continued).

patients with sepsis, varying from 22% to 100%. There were significantly more male than female subjects, with a median male/female ratio of 2.3.

Treatment regimens varied considerably between studies (Table 1). Corticosteroid dose ranged from 40 to 250 mg/d of methylprednisolone or equivalent (mean 140 mg/d). Duration of treatment was also different among studies, ranging from 7 to 32 days (mean 8 days). Corticosteroid doses were tapered in most studies (n = 7) when treatment ended. However, one trial rapidly removed treatment 48 hours after extubation (11). Four studies used corticosteroids in the early phase of the disease (within 1 week of diagnosis) and five studies in the later phase of the disease. A reduction in mortality was reported in most studies (Table 1).

Incidence of adverse reactions was reported in most studies (Table 2). The most common complications reported were infection, followed by neuropathy/myopathy and gastrointestinal bleeding. Hyperglycemia was mentioned in only two studies (10, 20). Other less frequently reported complications included arrhythmia, pneumothorax, renal failure, liver failure, heart failure, or psychiatric disorder (Table 2).

Methodologic quality was fair in most studies. Randomized trials provided data on 75% of the quality assessment items and cohort studies provided data on 82% of such items.

Mortality Outcomes. Both cohort studies and RCTs showed a trend toward mortality reduction (Fig. 2). RCTs had a relative risk of 0.51 (95% CI 0.24–1.09) and cohort studies had a relative risk of 0.66 (95% CI 0.43–1.02). The direction of effect was consistent in all studies, with all favoring corticosteroids compared with controls. Mortality reduction did not reach statistical significance in either randomized trials ($p = 0.08$) or cohort studies ($p = 0.06$) because of small sample size. When both groups of studies were combined, the mortality reduction reached statistical significance ($p = 0.01$; Fig. 2) with an overall relative risk of 0.62 (95% CI 0.43–0.91).

Morbidity Outcomes. Corticosteroid treatment improved all morbidity outcomes (Fig. 3). It reduced the duration on mechanical ventilation and length of stay in intensive care units by more than 4 days. When ventilator-free days were used instead of duration of mechanical ventilation, the results were very similar (4.8 vs. 4.4 days). The corticosteroid treatment reduced disease severity scores, namely, the Multiple Organ Dysfunction Syndrome Score by 32% and Lung Injury Score by 18%. It also improved oxygenation (Pao_2/Fio_2 ratios) by over half of an SD. Again, the direction of effect was consistently in favor of corticosteroids in all summary estimates, with over half reaching statistical significance (Fig. 3).

Adverse Effects. The corticosteroid treatment had a favorable side effect profile (Fig. 4). There was no difference in the incidence of infection or neuromyopathic complications between the treatment and control groups. We also examined other major adverse events, including gastrointestinal bleedings and life-threatening complications, such as major organ failure (heart, kidney, and liver). When all major adverse events were combined (including infection and neuromyopathic complications), again we found no difference between treatment and control groups (Fig. 4).

Examination of Heterogeneity. There was moderate-to-large heterogeneity, as indicated by Cochran's Q and I^2 statistics, in mortality and morbidity outcomes (Figs. 2 and 3). For mortality outcome, the degree of heterogeneity was moderate ($I^2 = 51\%$) and for morbidity outcomes, the degree of heterogeneity was large ($I^2 > 75\%$ in all but one outcome). We, therefore, examined the impact of heterogeneity on overall treatment effect by performing subgroup and meta-regression analyses. Subgroup analysis indicated that the treatment effect was con-

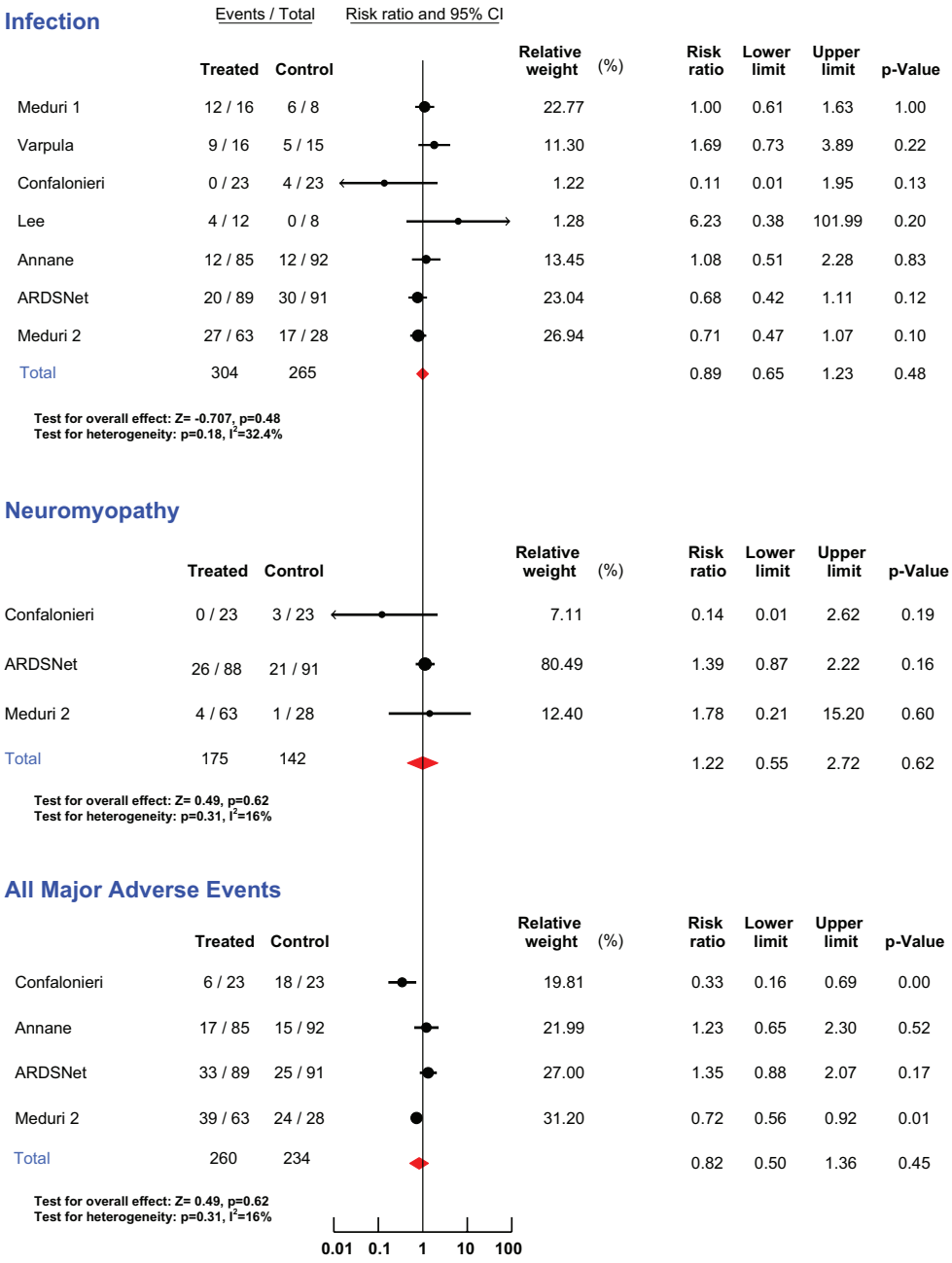

Figure 4. Complications. Size of data markers is proportional to the weight of each study in the forest plot. Horizontal bars = 95% confidence interval (*CI*).

sistent, despite variations in treatment regimens between studies (Table 3). It showed that the difference in relative risk between subgroups was not statistically significant with regard to time (early vs. late ARDS), formulation (hydrocortisone vs. methylprednisolone), or whether tapering was used. The treatment effect was also similar between studies performed before and after the publication of the National Institute of Health ARDS network low tidal volume ventilation study (21). For randomized trials, the use (or not) of a crossover design did not affect the treatment effect significantly. Meta-regression analysis showed that an increase in disease severity (reflected by an increase in Acute Physiology and Chronic Health Evaluation Scores) was associated with a lesser treatment effect (Table 4). None of the other variables affected treatment effect, including age, sex, dose, time and duration of treatment, percentage of patients with sepsis, and baseline Pao_2/Fio_2.

DISCUSSION

Use of corticosteroid in ALI is associated with a reduced mortality risk and an improvement in all morbidity outcomes. The effect on mortality was consistent in both randomized and nonrandomized studies. Importantly, the treatment was not accompanied by an increase in adverse events, such as infection, neuromyopathy, or other major complications.

Acute respiratory failure is the most common form of organ failure in critically ill patients (22) and ALI accounts for one quarter of such cases (1). Despite the anticipated worldwide increase in the prevalence of ALI, there is currently no proven pharmacologic therapy for this highly lethal disease

Table 4. Univariate meta-regression analysis

	Slope	95% Confidence Intrerval	p
Treatment duration (d)	−0.006	−0.03 to 0.02	0.57
Sepsis patients (%)	0.002	−0.003 to 0.008	0.40
Age (yrs)	0.001	−0.03 to 0.03	0.96
Dose (mg/methylprednisolone)	−0.002	−0.005 to 0.001	0.29
Gender (male/female)	−0.03	−0.1 to 0.05	0.46
Baseline Pa_{O_2}/F_{IO_2}	−0.01	−0.02 to 0.001	0.07
Duration of ARDS before treatment began (d)	−0.012	−0.04 to 0.02	0.48
APACHE III[a]	0.01	0.002–0.02	0.015

ARDS, acute respiratory distress syndrome; APACHE, Acute Physiology and Chronic Health Evaluation.
[a]Results are similar for APACHE II scores.

Table 5. Comparing outcomes between cohort studies and RCTs

	Cohorts Point Estimates (95% CI)	RCTs Point Estimates (95% CI)	p[a]
Mortality	0.66 (0.43–1.02)	0.51 (0.24–1.09)	0.60
Mechanical Ventilation (d)	0.40 (−1.61 to 2.41)	−6.56 (−10.08 to −3.04)	<0.0001
Length of ICU stay (d)	0.10 (−0.30 to 0.50)	−6.15 (−9.35 to −2.94)	<0.0001
MODS scores	−0.44 (−1.25 to 0.37)	−0.88 (−1.19 to −0.58)	0.07
Lung Injury Score	0.10 (−0.19 to 0.39)	−0.86 (−1.6 to −0.13)	<0.0001
Pa_{O_2}/F_{IO_2}	0.30 (−1.29 to 1.89)	0.78 (0.29–1.27)	0.16
Infection	1.40 (0.81–2.41)	0.76 (0.57–1.01)	0.05
Neuromyopathy	NA	1.22 (0.55–2.72)	NA
All major adverse events	1.23 (0.65–2.30)	0.73 (0.40–1.35)	0.18

CI, confidence interval; MODS, multiple organ dysfunction syndrome; RCT, randomized controlled trials; ICU, intensive care units; NA, not available.
[a]*p* Values of test of interaction between cohort studies and RCTs.

(23). Corticosteroids have been the most studied drugs for ALI and are the only agents that have shown promise as a potential treatment. However, current evidence to support their use is sparse because of the small number of randomized trials available. We, therefore, combined data from both randomized and nonrandomized studies. The increase in sample size has allowed us to detect a significant treatment effect in terms of mortality reduction. The in-hospital number needed to treat was 4 (95% CI 2.4–10), making low-dose corticosteroid therapy a highly effective treatment for ALI.

Combining RCTs and cohort studies together in a meta-analysis has both advantages and disadvantages. The advantage is that, by including a greater number of studies, the increase in sample size helped minimize type II error. This was especially the case on the primary outcome (i.e., mortality). The disadvantage is that cohort studies do not control for unknown variables and, hence, can potentially confound the findings. In fact, estimates from cohort studies on secondary outcome data are significantly different from those of RCTs (Table 5). However, it is important to note that RCTs contributed more weight in the secondary outcomes (RCTs weighting in random effect model; mechanical ventilation 71.2%, length of intensive care unit stay 67.5%, Multiple Organ Dysfunction Syndrome Score 72.1%, Lung Injury Score 63.6%, and Pa_{O_2}/F_{IO_2} ratios 68.8%). As a result, the summary estimates on morbidity outcome were dominated by RCTs.

There is significant heterogeneity in the included studies. The heterogeneity comes mostly from differences in the magnitude, and in some cases, the direction of the treatment effect. We anticipated the presence of significant heterogeneity *a priori* and, therefore, used a random effect model in all our analyses. Random effect model assumes that individual treatment effect varies from one study to another because of patient-level and study-level characteristics. Mathematically, it captures the within-studies and the between-studies differences. As a result, the pooled estimates provided by the random effect model take into account the heterogeneity among the studies.

Several patient-level variables previously thought to influence treatment effect did not play a significant role in our findings. For example, low-dose corticosteroids have been shown to reduce mortality in patients with sepsis in two meta-analyses (24, 25). It was possible, therefore, that some of the therapeutic effect of corticosteroid therapy in ALI might have been contributed by its effect on sepsis. However, we found that the proportion of septic patients did not have an impact on the treatment effect. This suggests that the effect of corticosteroids on patients with ALI was independent of its effect on sepsis. In fact, the recently completed Corticosteroid Therapy of Septic Shock study showed that corticosteroid did not reduce mortality in a largely surgical population with septic shock (26). Previously, it has also been unclear as to when corticosteroids should be given for ALI. There is concern that the efficacy of the corticosteroid therapy may be lost once the end-stage fibrosis has been established (27). In addition, there is a suggestion that commencing corticosteroids very late (beyond 2 weeks) might even increase the risk of death (11), although mortality difference lost significance when adjusted for baseline imbalances (28). Our findings, however, suggested that the reduction in mortality risk is not significantly affected by the timing of the treatment. Finally, there is also concern that abrupt cessation of the corticosteroid therapy could cause rebound inflammation, hence, reducing treatment effect. Although our findings suggested that the treatment effect was consistent whether corticosteroids were tapered at the end of the treatment, ample experimental and clinical data provide evidence for rebound inflammation and physiologic deterioration with rapid removal of corticosteroids (13).

Evaluation of study-level variables also revealed interesting findings. In randomized trials, the use of a crossover design has been thought to bias results in favor of the corticosteroid treatment (29). However, we found that the risk reduction was similar between trials that used crossover design and those that did not use such a design. The year of study was also thought to be important because of the publication of the National Institute of Health ARDS network low tidal volume ventilation study in 2000 (21). This study demonstrated the benefit of a more conservative ventilation strategy, which protected lungs from the trauma of excessive tidal volume ventilation. It is, therefore, possible that after 2000, the popular adoption of low tidal volume ventilation

strategy might have contributed to a reduced incidence of pulmonary inflammation in patients with ALI, hence, diluting the effect of any anti-inflammatory therapy, such as corticosteroids. However, our findings suggested that the treatment effect of post-2000 studies did not differ significantly from pre-2000 studies.

The above findings on patient-level and study-level variables need to be interpreted with caution. Although subgroup and meta-regression analyses were useful in demonstrating that the impact of these variables on the overall treatment effect was minimal, they can be underpowered to detect such effects because of the small number of studies available for analysis. It is still possible, for example, that tapering of corticosteroids is needed to prevent rebound inflammation. This caveat needs to be borne in mind when investigators design future RCT.

Potential limitations of our systematic review include the need to combine results from nonrandomized and randomized studies. In particular, on mortality outcome, cohort studies carried more weight than the RCTs in the random effect model (59.5% vs. 40.5%). The pooled estimate was, therefore, biased slightly more toward the cohort studies. However, on morbidity outcomes, cohort studies provided more conservative estimates (Table 5). Therefore, the overall effect of corticosteroids on morbidity was, if anything, underestimated. Another limitation of our study was that not all studies monitored closely all the potential adverse events. It was, therefore, possible that some events might be underreported. A further limitation was that we were unable to assess the effect of corticosteroids on nonresponders vs. responders to corticotrophin stimulation, a test used to predict the presence of adrenal insufficiency and identify those patients who are most likely to respond to corticosteroid therapy, because most studies did not provide such information. Corticosteroids also have a wide range of systemic effects, such as those on plasma interleukin-6 levels, neutrophil counts, C-reactive protein levels, and shock reversal. Again, we could not calculate summary estimates on these outcomes because they were not reported in most studies. There are other important outcomes of ALI, such as residual pulmonary dysfunction and sequelaes related to neuromuscular, cognitive, and psychological dysfunction (30). We could not assess them because the duration of follow-up was too short in most studies to include such long-term outcomes. Finally, other variables (e.g., ventilation mode, weaning protocol, or critical care resources) may also affect the mortality/morbidity outcomes and steroids alone may not help if these other variables are not controlled. However, we did not have enough data to assess the impact of these variables.

This study has implications for the design of future clinical trials. Given the wide variations in treatment regimens, future RCTs should focus on establishing a standardized treatment regimen. Aspects of the regimen that need to be standardized included (1) timing; (2) dosage and formulation; (3) duration; and (4) length of tapering. Additionally, trial enrolment should include stratified subgroups to determine the effect of corticosteroids on nonresponders vs. responders to corticotrophin stimulation.

CONCLUSIONS

The use of low-dose corticosteroids was associated with improved mortality and morbidity outcomes and a favorable side effect profile. The consistency of results in both study designs and all outcomes suggests that they are an effective treatment for ALI or ARDS. However, to confirm our findings, an adequately powered randomized trial is needed in the future.

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Revisión

Principales características de la pandemia por el nuevo virus influenza A (H1N1)

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RESUMEN

A finales de marzo de 2009 fue aislado un nuevo virus influenza A (H1N1) de origen porcino en 2 niños de California con síntomas de gripe. Dicho virus se diseminó inicialmente por México y EE.UU., y después internacionalmente. A primeros de junio la infección había alcanzado 74 países, producido cerca de 30.000 casos y 145 muertes y poseía una propagación comunitaria sostenida en 6 países. El 11 de junio la Organización Mundial de la Salud (OMS) declaró establecida la situación de pandemia.

La combinación de segmentos genéticos del nuevo virus nunca había sido vista antes. Contiene 5 segmentos de origen porcino, 2 aviares y 1 humano, y posee una hemaglutinina HA adaptada a la transmisión humana, que genética y antigénicamente diverge respecto a la del virus H1N1 hasta ahora circulante. Su transmisibilidad es ligeramente superior a la de la gripe estacional, y equivalente a la de las anteriores pandemias. Su patogenicidad y virulencia son bajas.

El cuadro clínico es similar al típico de la gripe estacional, con curación espontánea, si bien el espectro clínico es extenso, pues va desde casos asintomáticos hasta neumonía grave o mortal. La población afectada ha sido predominantemente joven, de menos de 30 años. Menos de la mitad de los pacientes hospitalizados en EE.UU. y de los casos mortales en México presentaban enfermedades crónicas o procesos de base concomitantes. Para la prevención y control de la infección, a través de la reducción de susceptibles, se ha dispuesto el uso de una vacuna monovalente específica contra el virus.

Main features of the new influenza virus a pandemic (H1N1)

Keywords:
Pandemic influenza
Influenza-like illness
Influenza virus A (H1N1)
Swine influenza virus
Sustained community transmission
Flu vaccination

ABSTRACT

At the end of March 2009, a new influenza virus A (H1N1) of porcine origin was isolated in two children from California presenting flu-like clinical syndrome. This virus was initially disseminated in Mexico and US and then worldwide. Eight weeks later, it had reached 74 countries with almost 30,000 cases and had caused 145 deaths. The virus had also sustained community transmission in 6 countries. On June 11th, WHO stated the onset of a pandemic.

The genetic combination of this virus is completely new, containing five segments of porcine origin, two avian, one human and a HA hemaglutinin adapted for human transmission, which is genetically and antigenically different compared with the H1N1 seasonal virus. Its transmissibility is slightly higher than the one observed in seasonal influenza and similar to previous pandemics. Its pathogenicity and virulence are low.

Clinical manifestations are similar to seasonal influenza, with spontaneous resolution. Nevertheless, the variety of symptoms is large and range from asymptomatic to severe fatal pneumonia. The affected population is mainly young, aged under 30 years. Less than a half of the hospitalized patients in US and of the fatal cases in Mexico had concomitant chronic diseases or other baseline conditions. A specific monovalent vaccine against the virus is currently being produced in order to prevent and control the infection through the reduction of susceptible population.

Introducción

Si en el año 2006 escribíamos en estas páginas que existía una notable preocupación mundial por el posible advenimiento de una pandemia de gripe de origen aviar[1], ahora, desde finales de abril, la preocupación se ha girado hacia la súbita eclosión y rápida diseminación de una epidemia de enfermedad respiratoria, producida por un nuevo subtipo de virus influenza de origen porcino, que en fecha 11 de junio ha sido declarada pandemia por la Organización Mundial de la Salud (OMS)[2].

Las pandemias gripales ocurren cuando se concatenan 3 requisitos: la emergencia y diseminación de un virus influenza

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que posee una hemaglutinina (HA) o una combinación de hemaglutinina y neuraminidasa (HA/NA), al que la mayor parte de la población humana no ha sido expuesta, es decir, no posee resistencia inmunitaria, la capacidad de replicarse en humanos y una transmisión eficiente de persona a persona.

En el pasado siglo ocurrieron 3 pandemias: la de 1918 o ''gripe española'', producida por el subtipo A (H1N1), la de 1957 o ''gripe asiática'', por el virus A (H2N2), y la de 1968 o ''gripe de Hong Kong'', por el subtipo A (H3N2). La primera fue debida a la transmisión completa de un virus aviar H1N1 al ser humano; los ocho segmentos de ARN del virus procedían de un virus aviar. En la segunda se produjo una reordenación entre el virus circulante H1N1 y un virus aviar H2N2; así el nuevo virus humano H2N2 incorporó 3 segmentos genéticos del virus aviar: HA, NA y PB1, y mantuvo 5 segmentos del virus H1N1 de 1918. En la tercera, tuvo lugar una reordenación entre el virus circulante H2N2 y un virus aviar H3; el nuevo virus humano H3N2 incorporó 2 segmentos del virus aviar: HA y PB1, y mantuvo 5 del virus H1N1 de 1918[3,4]. Debe destacarse que, en cada ocasión, la elevada circulación del virus pandémico anuló la del virus que hasta aquel momento circulaba.

En la gripe estacional o interepidémica la tasa de ataque clínica puede alcanzar el 10–20% en la población general[5]. En esta gripe, la mortalidad se concentra de forma especial en las personas de más de 65 años. En cambio, en las pandemias la mayor parte de la mortalidad se produce en la población de menos de 65 años de edad, aunque en los años posteriores dicha mortalidad aumenta de forma progresiva en las personas mayores y disminuye en los jóvenes y adultos[6]. Tanto en las pandemias como en la gripe estacional, los escolares y los adolescentes son los principales diseminadores de la infección en la comunidad[7].

Los virus que producen la gripe estacional son los 2 subtipos actualmente circulantes: el H3N2, establecido en 1968, y el H1N1, reintroducido en 1977. El virus H1N1 de 1918 dejó de circular en 1957 al emerger el H2N2, y reapareció en 1977 tras escaparse accidentalmente de un laboratorio[3]. Durante el período de circulación entre 1918 y 1957 este virus experimentó una considerable deriva genética *(antigenic drift)* debida a la presión selectiva inducida por la inmunidad humana, que entre 1977 y 2009 ha proseguido con intensidad, pues en este intervalo el componente H1 de la vacuna anual ha requerido hasta 8 actualizaciones[8].

El cerdo está considerado el principal huésped intermediario para la deseminación interespecies de los virus influenza, por ello, ha sido denominado el buque de mezcla de los virus *(mixing vessel)*[7]. Posee receptores tanto para los virus aviares como para los de mamíferos, por lo puede coinfectarse con virus influenza aviares y humanos, además de los porcinos; esta característica puede facilitar la aparición de nuevos subtipos. Hasta la aparición de la presente epidemia de gripe, no ha sido probada la implicación directa del cerdo en la aparición de una pandemia gripal[9].

En el presente artículo se revisa la diseminación de la infección hasta mediados de julio de 2009, el origen y composición del nuevo virus influenza A (H1N1), así como las principales características epidemiológicas y clínicas de la presente fase inicial de la pandemia.

Diseminación de la infección

El día 17 de abril de 2009, el gobierno de EE.UU. notificó a la Organización Mundial de la Salud (OMS), a través del punto de contacto para el Reglamento Sanitario Internacional, la detección de un nuevo virus influenza A (H1N1) de origen porcino en un niño de 10 años y una niña de 9, con un síndrome gripal leve. Las manifestaciones clínicas se habían iniciado en los días 28 y 30 de marzo. Los niños no tenían antecedente de contacto con cerdos, y residían en condados cercanos del sur de California. Las investigaciones epidemiológicas iniciales no hallaron ningún nexo epidemiológico entre ambos. Acudieron a centros ambulatorios, donde se les tomó un frotis nasofaríngeo, dado que un centro participaba en un estudio clínico y el otro en un proyecto de vigilancia de la gripe. Algunos familiares de los niños también presentaron fiebre y síntomas respiratorios, pero no se les tomaron muestras para estudio[10,11].

Se determinó que el virus influenza aislado en cada niño, además de ser similar, presentaba una composición genética que no había sido identificada antes, ni en aislados porcinos ni en humanos, tanto en EE.UU. como en otros países, según los análisis de secuencias genómicas disponibles en el GenBank[10]. La ausencia de exposición conocida a cerdos aumentaba la posibilidad de que hubiese ocurrido una transmisión de persona a persona.

En fecha de 24 de abril de 2009 en EE.UU. se habían notificado 4 casos adicionales en California y 2 en Texas, en los que fue confirmado el aislamiento del nuevo virus; asimismo, los Centers for Disease Control (CDC) informó que la misma cepa viral se había aislado en muestras de pacientes provenientes de México[12].

Por su parte, el gobierno de México había notificado a la OMS en marzo y a inicios de abril un aumento de los casos de enfermedad respiratoria en diversas áreas del país[13]. También había notificado un brote de enfermedad tipo influenza en La Gloria, localidad de 2.155 habitantes del estado de Veracruz; el 28,5% de la población había sido afectada, no existiendo casos graves ni muertes[14,15]. El 17 de abril, ante notificaciones de brotes de neumonía rápidamente progresiva, el Ministerio de Salud intensificó en todo el país la vigilancia epidemiológica de la enfermedad respiratoria aguda y la neumonía[16–18]. Debido a que México no disponía de ningún laboratorio especializado para identificar nuevos subtipos de virus influenza, solicitó asistencia técnica a la Agencia de Salud Pública de Canadá y a la División de Influenza del CDC. El 24 de abril, la OMS informó que 18 de los casos de México habían sido confirmados en Canadá como gripe A (H1N1), de los que 12 eran genéticamente idénticos a los virus aislados en California[13].

El 27 de abril la OMS elevó el nivel de alerta pandémica de fase 3 a 4, después de verificar la existencia de transmisión interhumana capaz de causar brotes a nivel de la comunidad[19]. El día 28 del mismo mes Canadá notificó 6 casos confirmados y España 2, entre otros países, y ya eran 64 los casos confirmados en EE.UU.: 10 en California, 45 en Nueva York, 6 en Texas, 2 en Kansas y 1 en Ohio; todo lo cual significaba que la infección se diseminaba rápidamente[20]. El día 29, al verificar la transmisión comunitaria sostenida en al menos 2 países de la Región de las Américas, la OMS elevó la alerta de pandemia a fase 5[21].

Además de su continuada expansión en México, EE.UU. y Canadá, el nuevo virus alcanzó enseguida una amplia diseminación internacional, pues el 6 de mayo había 23 países afectados, con 1.893 casos declarados. En esta fecha México había notificado 942 casos, con 29 muertes en pacientes confirmados, y EE.UU. 642 casos, con 2 muertes; en estos países la infección se hallaba territorialmente muy extendida, pues se detectaron casos en más del 84% de sus estados. Por su lado, Canadá había notificado 165 casos[22,23]. El virus se diseminó muy rápidamente por Europa, pues en el citado 6 de mayo España había notificado un total de 73 casos, el Reino Unido 28, Alemania 9, Italia y Francia 5, entre otros países[23]. Estos casos se hallaban, fundamentalmente, en relación con viajeros llegados de México.

La propagación nacional e internacional prosiguió con fuerza durante los meses de mayo y junio, pues en fecha 1 de junio 62 países habían notificado a la OMS 17.410 casos con 115 muertes, y a 1 de julio eran 104 los países, con 77.201 casos y 332 muertes[24,25]. Los modernos medios de transporte y la elevada

frecuencia actual de los viajes han contribuido a la extensa diseminación alrededor del globo, posiblemente asociada a los flujos de transporte mundiales. Hasta mediados de junio la infección predominó en el hemisferio norte, pero posteriormente se ha extendido con intensidad por América del Sur, Australia y Nueva Zelanda. En el continente asiático el país más afectado ha sido Japón. En África se han registrado casos en muchos países, aunque las cifras son reducidas. Debe tenerse en cuenta que los países han notificado a la OMS solamente los casos de gripe H1N1 2009 confirmados por el laboratorio, que han sido los más graves y hospitalizados, dejando de lado los moderados y leves de difícil captación y registro; por este motivo la casuística real debe considerarse mucho más elevada.

El 11 de junio, la OMS elevó la fase de alerta de pandemia, de la 5 a la 6, o de pandemia establecida, al verificarse la existencia de transmisión comunitaria mantenida en al menos un país de una región de la OMS distinta. La transmisión comunitaria mantenida era patente en México, EE.UU., Canadá y Chile, en la Región de Las Américas; en Australia, en la del Pacífico Occidental; y en el Reino Unido, en la de Europa. En todos estos países, la imposibilidad existente de trazar o definir las cadenas de propagación interhumana indicaba una diseminación activa en la población[2].

La curva epidémica de la enfermedad en México (fig. 1) muestra una abrupta subida unos días después de la intensificación de la vigilancia epidemiológica de enfermedad respiratoria aguda y neumonía, con una cifra máxima de más de 400 casos; la intensificación de la vigilancia motivó, además, el diagnóstico retrospectivo de casos. Durante el mes de mayo, debido seguramente al cierre de escuelas y a otras medidas de distanciamiento social, se registró un notable declive. Después la epidemia ha proseguido, pues en junio aumentaron sensiblemente los casos, declarando en este mes 3.651 nuevos casos[15,25,26].

En España, hasta el día 6 de julio de 2009 se han declarado un total de 737 casos. En la figura 2 se presenta la curva epidémica del 19 de abril al 6 de julio de 2009; en ella puede observarse que del 19 al 27 de abril se registró un incremento rápido de los casos diarios; el día 27 se alcanzó la cifra máxima, a la que siguió un declive que concluyó el 8 de mayo. Después de 4 días sin casos, se detectaron 2 en la tercera semana de mayo, para aparecer luego un brote en la academia militar de Hoyo de Manzanares (Madrid), con inicio de síntomas entre el 16 y el 31 de mayo, y 62 casos confirmados. Posteriormente, apareció un brote en un colegio de Leganés (Madrid), con 126 casos, originado a partir de un caso importado de EE.UU., y otros brotes en 21 colegios de municipios de Madrid. A partir del 21 de junio se notificaron agrupaciones de casos en colectivos diferentes: en un campamento escolar, en un grupo de estudiantes norteamericanos de intercambio, en una fiesta de trabajadores sanitarios y en viajeros a República Dominicana y Mallorca[27].

Según la información disponible en fecha 6 de julio, en España ha habido 137 casos importados. El país de procedencia de los casos con antecedentes de viaje fue México en 84 casos, EE.UU. en 38 casos, República Dominicana en 8, y otros países en 7 casos. Sin contar los casos de la academia militar y los colegios, se han notificado 35 casos confirmados secundarios sin antecedentes de viaje a áreas con transmisión comunitaria, y 9 casos terciarios. El tipo de contacto entre casos primarios, secundarios y terciarios en su mayoría fue entre familiares y amigos. Se han notificado 8 casos con diagnóstico de neumonía, y el 30 de junio falleció el primer caso por la infección en España, una mujer de 20 años, embarazada de 29 semanas y con antecedentes de asma[27]. En España, la epidemia ha mostrado 2 fases diferenciadas, según muestran las 2 curvas de la figura 2: primero hubo una fuerte entrada inicial de infectados en marzo y abril que no dio lugar a brotes ni a propagación comunitaria, debido al aislamiento de los

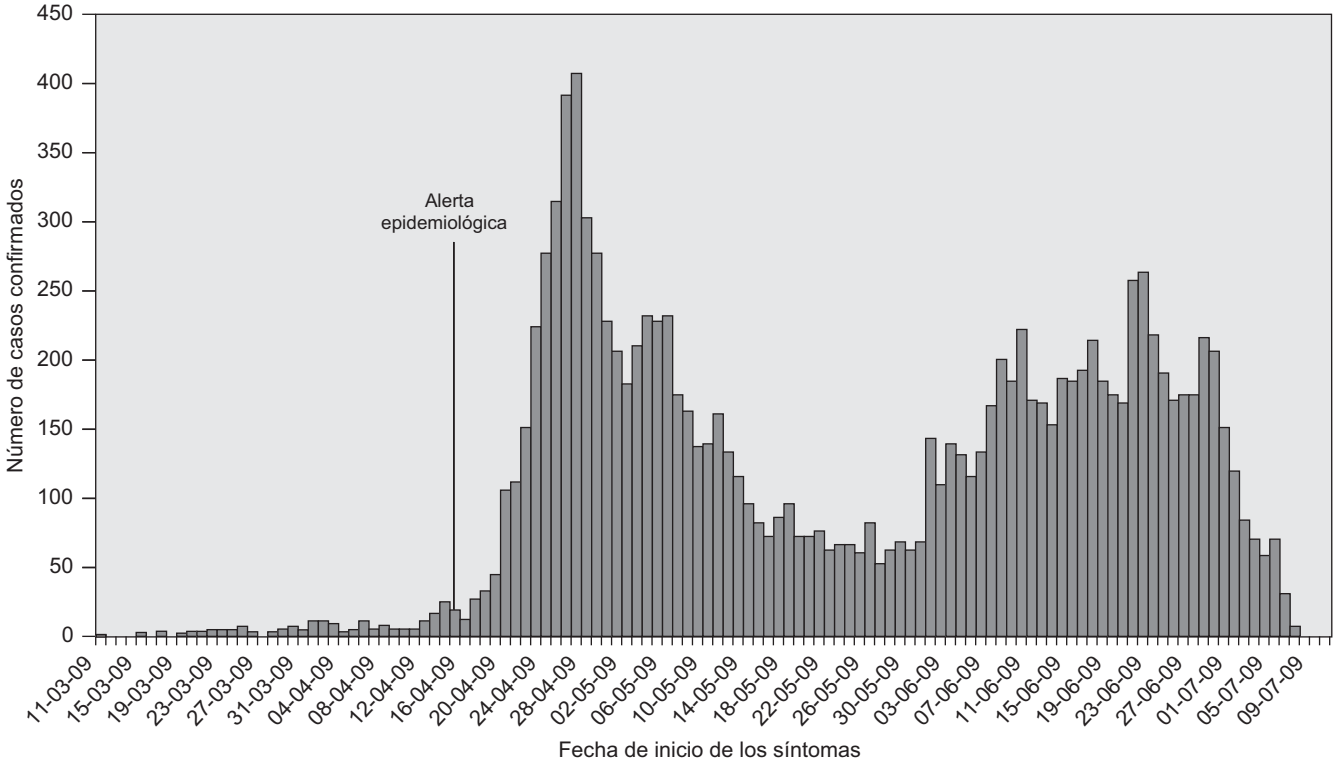

Figura 1. Curva epidémica de los casos confirmados por el laboratorio de infecciones por el nuevo virus influenza A (H1N1), según la fecha del inicio de los síntomas. Total: 12.645 casos. México, 11 de marzo-9 julio de 2009. Fuente: Ministerio de Salud, México[26].

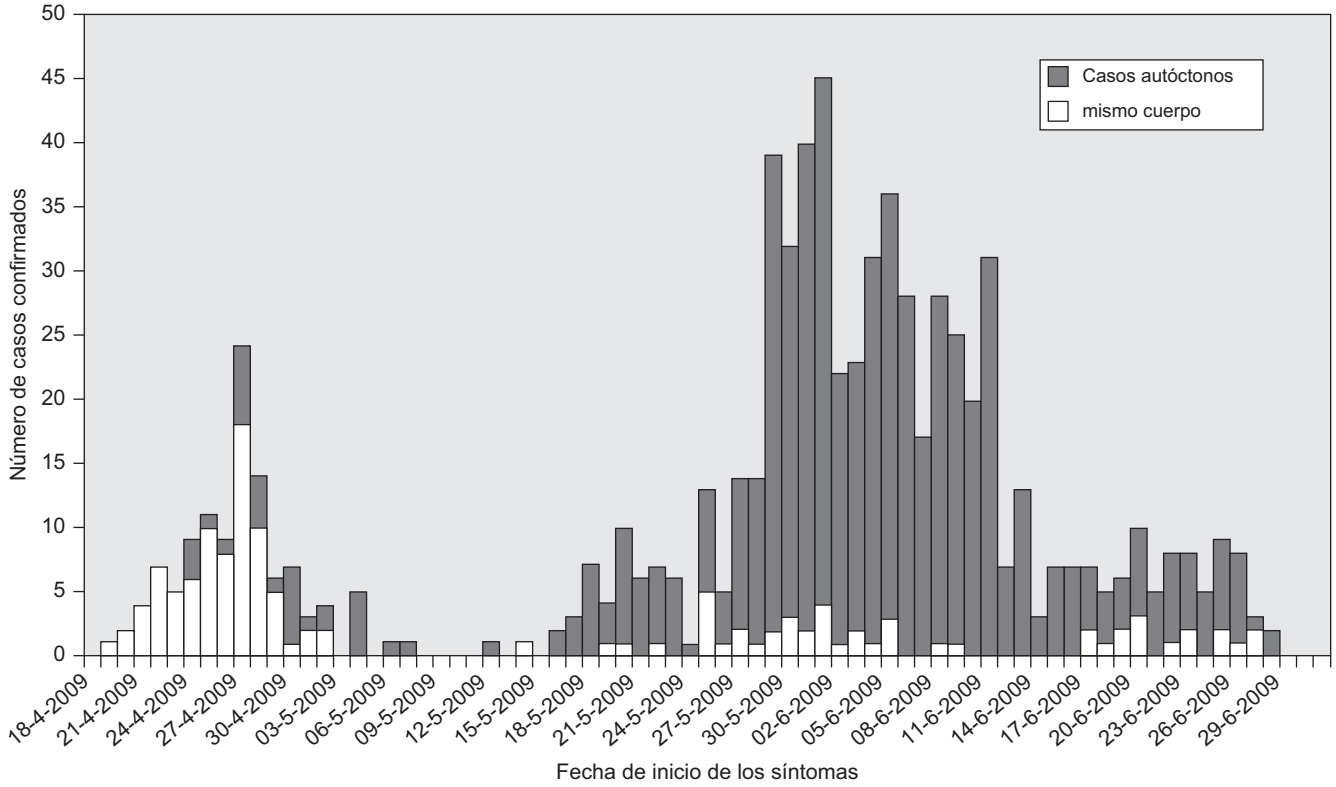

Figura 2. Curva epidémica de los casos confirmados por el laboratorio de infecciones por el nuevo virus influenza A (H1N1), según la fecha de inicio de los síntomas y origen: 737 casos. España, 19 de abril-6 de julio de 2009. Fuente: Ministerio de Sanidad y Política Social[27].

casos y al escaso número de contactos que eventualmente éstos mantuvieron, y, después, a partir de mediados de mayo, se han desarrollado brotes en colectivos compuestos por muchos integrantes y una mayor tasa de contactos.

Antecedentes de la gripe humana de origen porcino

En ocasiones los virus influenza porcinos pueden transmitirse al ser humano y producir enfermedad. El mecanismo de propagación suele ser gotitas respiratorias y aerosoles de los cerdos, que por contacto o proximidad física pasan a la boca, mucosas y vías aéreas del hombre. El principal factor de riesgo es la exposición laboral a cerdos[28].

En 1974 se produjo el primer aislamiento de virus influenza de origen porcino en humanos[29]. Durante 1974 y 1975 existe constancia en EE.UU. de 5 casos esporádicos de gripe humana de origen porcino, 4 de ellos con exposición conocida a cerdos y sin evidencia de transmisión interhumana más allá del núcleo familiar[30]. Una revisión publicada en 2007 identificó 37 casos en todo el mundo. En general, el cuadro clínico es más leve o similar al de la gripe estacional, aunque a veces ha habido complicaciones y muerte, incluso en sujetos sin enfermedades de base. La propagación descrita de estos virus de persona a persona ha sido escasa, produciendo una sola generación de casos y sin cadenas de propagación[31]. Los subtipos víricos transmitidos al hombre son los que hospeda el cerdo: H1N1, H1N2 y H3N2, además de virus con reordenaciones triples, con segmentos genómicos porcinos, aviares y humanos, detectados en EE.UU. y Tailandia[32,33].

Solamente se ha descrito una epidemia humana por virus influenza porcino: el brote ocurrido en el campamento militar de Fort Dix, en el estado de New Jersey, EE.UU., en enero y febrero de 1976. Tuvo notable importancia tanto por su magnitud como por su repercusión en la salud pública del país. El 5 de enero de 1976, tras finalizar el permiso de Navidad, se identificó un brote de enfermedad febril respiratoria en reclutas. En total hubo 230 enfermos, con 12 hospitalizaciones y una muerte. El laboratorio identificó en la mayor parte de las muestras el subtipo A (H3N3), la cepa humana circulante aquella temporada, pero en 5 se aisló el virus porcino Hsw1N1. Durante el mes de febrero los estudios serológicos pudieron identificar 8 nuevos casos de soldados con Hsw1N1. De los 13 casos positivos uno murió, siendo los estudios post mórtem compatibles con neumonía vírica. Investigaciones posteriores no hallaron ningún antecedente de exposición a cerdos. Por otra parte, el virus porcino no tuvo diseminación fuera del campamento[34].

Poco después, la autoridad sanitaria tomó la decisión de proceder a la vacunación masiva de la población estadounidense, y rápidamente se vacunó a 40 millones de personas. La aparición en personas vacunadas de un excesivo número de casos de síndrome de Guillain-Barré, probablemente asociados a la vacunación, además de la falta de circulación del virus porcino durante la estación gripal, supusieron la suspensión de la campaña[35,36].

En España, en noviembre del 2008, un médico que formaba parte del sistema de vigilancia centinela de la gripe, identificó a una paciente con un cuadro gripal, en una población de 200 habitantes de Teruel. Dicha paciente trabajaba en una granja de cerdos familiar; no se encontró ningún caso más en la familia. En las muestras tomadas, el laboratorio del Centro Nacional de Gripe, del Instituto de Salud Carlos III, identificó un virus A subtipo H1 filogenéticamente cercano al A/Switzerland/8808/2002 aislado en humanos, de origen porcino[37].

El nuevo virus A (H1N1) 2009

Tras su detección, se observó que el nuevo virus A (H1N1) 2009 presentaba una composición muy diferente de sus segmentos

genéticos en relación con la de los virus circulantes, y que dichos segmentos procedían de linajes porcinos conocidos[8,11,38,39].

En EE.UU. el virus porcino H1N1 derivado de la pandemia de 1918 o virus de la "gripe porcina clásica", circuló de forma antigénicamente estable entre los años 1930 y 1990 del siglo pasado. En 1997–1998 se reordenó con un virus humano H3N2 contemporáneo y con un virus influenza aviar de subtipo desconocido, de lo que resultó un virus con una reordenación triple: porcina, humana y aviar, que desde entonces circula en los cerdos de Norteamérica junto a la cepa clásica o endémica; fue aislado por primera vez en 1998[40]. Posteriormente, el virus reordenado se recombinó de nuevo con el virus clásico, dando lugar a nuevas cepas con reordenaciones triples[8].

El virus porcino clásico ha permanecido estable durante decenios, mientras que el virus H1N1 estacional humano ha experimentado una sustancial deriva antigénica. En razón a la divergencia entre ambos se considera que el cerdo se ha convertido en un reservorio de virus H1, que podría causar brotes e incluso pandemias. La eclosión de la presente pandemia podría deberse a esta situación[8].

En Europa, el virus porcino H1N1 de 1918 se detectó esporádicamente en los años 1950, y desde 1976 circuló de forma extensa seguramente tras ser introducido a partir de cerdos importados de EE.UU. Aproximadamente en 1979 fue desplazado por un linaje aviar-like, que desde entonces circula enzoóticamente en Europa y Asia, junto a los subtipos H3N2 y H1N2. Los segmentos genéticos de este virus de origen aviar son filogénica y antigénicamente distintos del linaje clásico americano; además, su evolución molecular ha sido divergente[41]. Este virus no ha sido detectado fuera de Euroasia.

El nuevo virus, causante de la pandemia, es el resultado de una reordenación entre el virus porcino americano reordenado de 1997-1998 y el de Euroasia de 1976 (fig. 3)[8,11,38,39]. La combinación de segmentos genéticos del nuevo virus no había sido vista antes. Los segmentos NA y M proceden del linaje porcino euroasiático; los segmentos HA, NP y NS del porcino americano; los segmentos PB1, PB2 y PA, o complejo polimerasa, del virus porcino con reordenación triple, si bien el primero procede del componente humano que tuvo su origen en el virus humano H3N2 emergido en 1968, y los otros dos del componente aviar. Por lo tanto, el nuevo virus contiene 5 segmentos de origen porcino, 2 aviares y 1 humano (fig. 3).

El lugar donde ocurrió la reordenación del virus actual se desconoce. Para Smith et al[38] la transmisión o salto de especie a humanos ocurrió pocos meses antes de la detección de los primeros casos, si bien la reordenación de los linajes porcinos se produjo años antes. En todo caso, parece que el paso al hombre ocurrió en un solo evento o mediante eventos múltiples desde un *pool* genético homogéneo, pues la identidad de los aislados víricos es muy elevada (99,9%). En EE.UU. se han detectado 5 variantes menores del genoma, que se atribuyen a diferentes introducciones del virus desde México[8].

Un aspecto relevante del nuevo virus es que no presenta ninguna de las características moleculares conocidas que le podrían conferir un incremento de la transmisibilidad o de la patogenicidad. Por lo tanto, de momento se desconocen los elementos moleculares responsables de la elevada transmisibilidad del nuevo virus, así como los que han propiciado el salto de especie.

Garten et al[8] han observado que en el hurón, animal utilizado como modelo para el estudio de la gripe humana, el suero antiinfeccioso contra el virus H1N1 estacional humano, no reacciona contra el nuevo virus porcino H1N1. Los autores comentan que esta ausencia de reacción podría ser diferente en el hombre, pues en los humanos el tipo de respuesta es más compleja que en el hurón. En este ámbito, el CDC ha señalado que la vacunación contra la gripe estacional H1N1 de los años 2005 a 2009 no protege contra el nuevo virus. Es un resultado concordante con la gran divergencia genética que existe entre ambos virus, pues mientras entre los estacionales la secuencia de aminoácidos de la porción HA1 de la hemaglutinina tiene una identidad del 97–98%, entre el nuevo virus y los estacionales es sólo del 72–73%[42].

En resumen, el nuevo virus H1N1 posee una hemaglutinina HA adaptada a la transmisión humana, que genética y antigénicamente

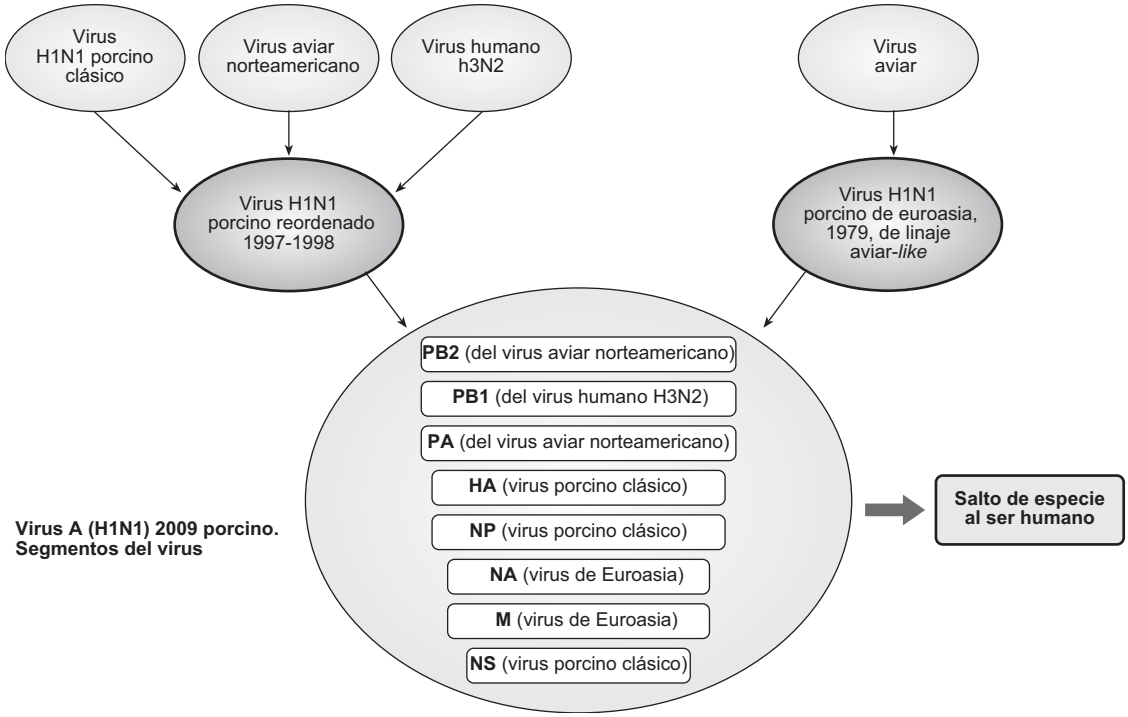

Figura 3. Génesis del virus influenza porcino A (H1N1) 2009 a partir del virus reordenado de 1997–1998 y del porcino de Euroasia, e indicación del origen de sus segmentos genéticos.

diverge respecto a la del virus H1N1 estacional; además, la composición general del virus es única, al combinar linajes porcinos americanos con el linaje euroasiático.

Aspectos epidemiológicos

- *Edad de los casos confirmados.* En México, el 78,7% de los casos acumulados hasta el 9 de julio tenía menos de 30 años; los de 30 a 59 años eran el 19,1%, y los de más de 60 años el 2,2%; la mayor frecuencia ha correspondido a la década de 10-19 años, con el 33,9% de los casos; la primera década ha representado el 27,9%[26]. En EE.UU. las dos franjas de edad más afectadas han sido la de 10 a 18 años, con el 39,8%, y la de 19 a 50 años, con el 35,2%; en este país los casos de 18 años o menos han representado el 53,7% y los de 50 y más años el 5%[11]. Es decir, la población afectada ha sido predominantemente joven, de edad inferior o igual a 30 años. En este sentido, Nishiura et al[43] han expuesto que en Japón la transmisión se sostiene a través de los escolares y jóvenes, debido a que actúan como reservorio de las cadenas de transmisión, circunstancia que concuerda con estudios previos[7].
- *Razón hombre/mujer.* La afectación ha sido similar para ambos sexos[11,18].
- *Tasas de ataque.* Según el CDC, en el brote de La Gloria la tasa de ataque clínica fue del 28,5%[15], aunque Fraser et al[44] apreciaron una tasa más elevada y una marcada variación según la edad; así, para estos autores fue del 61% en los menores de 15 años y del 29% en los de 15 y más años. Por otro lado, en una escuela de Nueva York un brote por el H1N1 de 2009 ocasionó síntomas en el 33% de los alumnos y en el 11% de los profesores[45]. Es decir, en los 2 brotes las tasas de ataque en los jóvenes han sido más del doble de las de los adultos. No se han dado a conocer valoraciones de la tasa de ataque serológica por el nuevo virus, que irá variando en función de los niveles de infección producidos en cada país. La tasa de ataque secundaria, que permite medir la infectividad en una familia o comunidad a partir de un caso o casos índice, ha sido estimada por la OMS entre el 22 y el 33%; como la de la gripe estacional se sitúa entre el 5 y el 15%, es muy posible que el nuevo virus posea una mayor capacidad infectiva[46].
- *Período de incubación.* La OMS ha estimado una mediana de 3–4 días, y se han observado los siguientes recorridos: 1–5 días en España; 4–6 días en el Reino Unido, y 2–7 días en EE.UU.[18]. El período de incubación de la gripe estacional es de 2 días, con un recorrido de 1–4[5], por lo que el del virus de la presente pandemia es ligeramente más largo.
- *Período de transmisibilidad.* No se dispone de datos, aunque se ha indicado que debe ser similar al de la gripe estacional, en el que la transmisión se inicia un día antes del inicio de los síntomas, y finaliza 5–7 días después o al resolverse las sintomatología[11]. Los niños y las personas inmunodeprimidas podrían ser contagiosas durante más tiempo[5].
- *Curva epidémica.* En la curva epidémica de México, tras unas semanas con casos esporádicos, se produjo un ascenso exponencial que alcanzó un pico máximo, al que siguió un marcado declive[15,26] (fig. 2). Para la primera fase de la curva, entre el 9 y el 24 de abril, Boë]lle et al[47] han comprobado la bondad de un ajuste exponencial. Es decir, en México se produjo una típica eclosión exponencial de la gripe.
- *Número básico de transmisión, Ro.* En el brote de La Gloria, Fraser et al[44] han estimado un valor puntual de 1,58, con un intervalo de confianza del 95% de 1,34–2,04; estos mismos autores, en otro análisis a partir de los datos generales de México, han estimado un intervalo de 1,4–1,6. En las simulaciones matemáticas desarrolladas por Boë]lle et al[47] con los datos de la epidemia en México han obtenido valores de: 2,2–3,1. En Japón se ha estimado un valor de 2,3[43]. En función de estos datos puede decirse que la actual pandemia presenta una transmisibilidad moderadamente superior a la de la gripe estacional y equivalente a la de las anteriores pandemias[48].
- *Tiempo de generación.* Fraser et al[44] han estimado un valor de 1,91 días en el brote de La Gloria, con un intervalo de confianza del 95% de 1,30–2,70. Es un valor corto, inferior al período de incubación medio, e indica una rápida propagación de la infección.
- *Patogenicidad.* Según un informe de la OMS, han requerido ingreso hospitalario el 2–5% de los afectados en EE.UU. y el 6% en México[49]. En una evaluación posterior, Garske et al[50] han estimado una tasa bruta de hospitalización del 8,9% en EE.UU., el 9,2% en Canadá y el 3,4% en el Reino Unido. Los autores consideran la tasa de este último país como la más ajustada a la situación epidemiológica poblacional, pues la consideran menos afectada por la falta de declaración y detección de los casos moderados y leves, circunstancia que puede producir su sobredimensionamiento al ser inadecuado el denominador. Estos porcentajes pueden considerarse altos en relación con la cifra esperable en una gripe estacional, que suele ser inferior al 1%.
- *Letalidad.* En fecha 1 de julio, el país con más muertes declaradas ha sido EE.UU. con 195, seguido de México con 116, Argentina con 26 y Canadá con 25[25]. Fraser et al[44] han estimado para México una tasa bruta aproximada del 0,40%. A partir de los casos y defunciones notificadas a la OMS, Garske et al[50] han calculado una letalidad, ajustada por retraso diagnóstico, del 0,68% en EE.UU., 1,23% en México, 0,43% en Canadá, 0,24% en el Reino Unido y 0,20% en la Unión Europea; los autores informan que estas tasas seguramente son superiores a las reales, pues en general el denominador corresponde sólo a los casos graves u hospitalizados confirmados por el laboratorio, ya que los países no captan ni confirman los casos moderados y leves. Como la letalidad de las pandemias de 1957 y 1968 se estima en un 0,20%, puede inferirse que la actual letalidad en EE.UU., México y Canadá es más elevada. El retraso en la administración de antivíricos y en el ingreso hospitalario puede haber contribuido a la elevada letalidad registrada en México[51]. De todas maneras, para conocer el impacto efectivo en cuanto a letalidad, deberá esperarse a que la pandemia alcance una fase más madura.
  En un informe sobre 2.155 casos de neumonía grave asistidos en México, en los meses de marzo y abril de 2009, atribuidos al nuevo virus, aunque sin confirmación diagnóstica, con 821 hospitalizaciones y 100 muertes, el 71% de los casos de neumonía grave y el 87% de las muertes ocurrieron en personas entre 5 y 59 años; los respectivos porcentajes correspondientes a la gripe estacional de los años 2006–2008 fueron 32% y 17%. La categoría de edad de 25 a 44 años mostró el porcentaje más elevado de neumonías, mientras que las muertes se concentraron en las categorías de 20 a 49 años[52]. Estos datos podrían indicar que la presente gripe, de forma similar a la pandemia de 1918 y a diferencia de la estacional, ocasiona una más elevada patogenicidad y letalidad en los jóvenes y adultos que en los ancianos y los menores de 5 años, aunque en estos últimos no deja de ser elevada.
- *Circulación viral.* En algunos países se ha detectado una circulación predominante del nuevo virus; por ejemplo, ya en la última semana de mayo constituía el 89% de los virus influenza circulantes en EE.UU. y el 90% en Chile[53,54].

Características clínicas

Los síntomas más frecuentes suelen ser fiebre, tos, malestar general, rinorrea, cefalea, dolor de garganta, mialgias, dolor articular y, en ocasiones, diarrea y náuseas. En general es un

cuadro muy similar al de la gripe estacional, con curación espontánea, si bien se ha observado un espectro clínico extenso, pues va desde casos asintomáticos hasta neumonía grave o mortal. Algunos pacientes, tanto atendidos ambulatoriamente como hospitalizados, no han presentado fiebre[11,18,22,26,55–57].

En el brote de La Gloria el síntoma más frecuente fue la tos, seguido de fiebre, rinorrea y malestar general a cierta distancia[44] (tabla 1). En la serie de los EE.UU. han destacado por igual la tos y la fiebre, y un porcentaje no desdeñable presentó síntomas digestivos[11]. En la serie europea los síntomas más frecuentes han sido la fiebre (74%), seguido de la tos (71%) y a cierta distancia la cefalea, dolor de garganta y mialgias[56]. En los casos españoles la sintomatología ha sido muy variada, con tos, fiebre y malestar general como manifestaciones más frecuentes; también cabe destacar la presencia de síntomas digestivos, y la existencia de dificultad respiratoria en un 13,4% de los pacientes[27]. En el brote publicado de una escuela de Nueva York destaca la elevada frecuencia de los síntomas respiratorios, generales y digestivos[45]. La síntomatología no ha sido diferente en países como Brasil, que han sido afectados más tarde por la pandemia[58].

En la mayor parte de los casos mortales se ha producido una afectación respiratoria grave, con neumonía de rápida evolución. En México la duración mediana de la hospitalización desde el inicio de la enfermedad ha sido de 6 días y en EE.UU. de 4[57]. En México los principales síntomas en las 108 primeras defunciones fueron disnea, empeoramiento general, expectoración, mialgias, cianosis, rinorrea y hemoptisis. Además, ha sido especialmente notable la evolución clínica de las neumonías graves, con infiltrados multifocales y opacidades radiográficas bilaterales nodulares y alveolares, y un rápido desarrollo de distrés respiratorio, acompañado de insuficiencia renal y fallo multiorgánico en el 24% de los casos. Los pacientes cursan sin leucocitosis, con aumento de la lactatodeshidrogenasa, linfopenia y un frecuente aumento de la creatincinasa. Las lesiones tisulares han consistido en necrosis de las paredes alveolares y daño alveolar difuso. En EE.UU. la mitad de los casos ingresados presentaron neumonía confirmada radiológicamente, incluidos pacientes con neumomediastino, neumonía necrotizante y empiema; el 36% requirió ingreso en la UCI, de los cuales el 18% tuvo fallo respiratorio que exigió ventilación mecánica; el 82% de los pacientes se recuperó del episodio agudo, aunque un niño de 22 meses de edad con miastenia *gravis* neonatal y una mujer embarazada de 33 años fallecieron[11,18,51,55,57].

El 41% de los pacientes hospitalizados en los EE.UU. y un 46% de los casos mortales en México presentaban situaciones concomitantes de fragilidad: embarazo, asma, enfermedades respiratorias crónicas, diabetes, obesidad mórbida, enfermedades autoinmunes y tratamientos inmunodepresores asociados, trastornos cardiovasculares y enfermedades neurológicas[57]. Los anteriores porcentajes indican que más de la mitad de los pacientes no tenían ningún factor de riesgo. Así, en un estudio sobre 18 casos confirmados de neumonía hospitalizados en México, que tenían una edad media de 38 años y de los que 7 murieron, se destaca que 10 no tenían ningún factor de riesgo o enfermedad de base conocida, hallándose en un buen estado de salud antes de la infección; los autores manifiestan desconocer los factores de riesgo de la infección y del agravamiento de los pacientes[51].

La obesidad y el embarazo parecen constituir claros factores de riesgo de complicaciones. La primera fue observada en series generales de la infección[57], y recientemente ha sido claramente identificada en un estudio sobre 10 pacientes ingresados por la gripe H1N1 en una UCI de EE.UU., de los que murieron 3, 9 eran obesos y de éstos 7 eran extremadamente obesos. Para los autores, la obesidad constituye un claro factor de riesgo de complicación que hasta ahora no había sido identificado[59]. La vulnerabilidad de la embarazada se observó también tempranamente en la presente infección, pues en abril y mayo en EE.UU., de una serie de 20 mujeres embarazadas con síntomas gripales, 3 requirieron ser hospitalizadas y 1 murió a los 13 días del inicio, habiendo recibido tratamiento antiviral[60]. También debe señalarse que el primer caso fallecido por la nueva gripe en España corresponde a una embarazada[27]. La experiencia de las anteriores pandemias señala que la mujer embarazada, especialmente en el tercer trimestre, puede ser afectada de forma desproporcionada en relación con la no embarazada[61]. Otro grupo a tener en cuenta son los niños de corta edad, pues en las anteriores pandemias gripales en ellos se ha descrito un consistente exceso de mortalidad[62].

Prevención y control

Las principales medidas para la prevención y control de las epidemias y pandemias de gripe son el uso de fármacos antivíricos y la vacunación, aparte de las clásicas de la salud pública, que no comentaremos.

Tabla 1
Características clínicas de los casos confirmados de infecciones por el nuevo virus influenza A (H1N1)[11,27,44,45,55,56,58]

País/síntoma	México, brote de La Gloria, de 15 de febrero a 13 de abril: 616 casos (44)	México, a 9 de junio: 108 casos mortales (55)*	EE.UU., a 5 de mayo: 642 casos (11)	Europa, 22 países, a 17 de junio: 879 casos (56)	España, a 6 de julio: 737 casos (27)	EE.UU., brote en una escuela de Nueva York, 20-24 de abril: 44 casos (45)	Brasil, a 15 de julio: 1.175 casos (58)
Tos (%)	82	84,3	92	71	91,4	98	89,6
Fiebre (%)	68	84,3	94,2	74	80,8	96	92,5
Malestar general (%)	47,8	56,5	–	–	73,9	89	–
Cefalea (%)	33,8	20,4	–	41	64,4	82	27,3
Rinorrea (%)	61,2	25,9	–	34	60,7	82	50
Dolor de garganta (%)	50,2	17,6	65,9	40	57,3	82	41
Mialgias (%)	–	30,6	–	38	54,9	80	50,6
Estornudos (%)	–	–	–	19	30,9	–	–
Dolor articular (%)	21,9	–	–	22	26,5	46	17,4
Conjuntivitis (%)	9	–	–	5	14,1	–	4,9
Diarrea (%)	–	2,8	25,3	11	16,7	48	5,3
Dificultad respiratoria (disnea) (%)	–	74,1	–	12	13,4	–	11,1
Náuseas (%)	–	–	–	13	8,4	24	–
Vómitos (%)	–	8,3	25,1	10	10	–	–
Sangrado nasal (%)		–	–	3	2	–	–

* Otros síntomas: expectoración, 50,9%; cianosis, 25,9%; dolor torácico, 16,7%.

Fármacos antivíricos

Disponen de autorización para su uso contra los virus influenza A, 2 tipos de fármacos: los adamantanos, que inhiben los canales de calcio, y los inhibidores de la neuraminidasa, oseltamivir y zanamivir. Su uso terapéutico permite reducir la intensidad de los síntomas, la duración de la enfermedad y la infecciosidad del paciente, y su uso profiláctico disminuye la probabilidad de que el sujeto adquiera la infección.

La mayor parte de los virus humanos H1N1 y H3N2, algunos virus aviares H5N1, y la mayor parte de los virus porcinos europeos H1N1, H1N2 y H3N2 son resistentes a los adamantanos. El virus H1N1 de 2009 también es resistente[8,11,18]. Según ensayos in vitro e in vivo, el nuevo virus es sensible a los inhibidores de la neuraminidasa[8,11,63]. En los ensayos clínicos ha sido muy rara la aparición de resistencia a estos inhibidores; sin embargo, en los últimos años ha aumentado de forma muy notable la tasa de virus H1N1 resistentes en EE.UU. y otros países[64]. Esta resistencia puede haber emergido en pacientes inmunodeprimidos en los que la prolongada replicación vírica ha originado una selección de mutaciones que han incrementado la capacidad de resistencia del virus[65]. En la presente fase de pandemia y a efectos de tratamiento se recomienda la administración de inhibidores de la neuraminidasa a los pacientes con una presentación clínica grave o con factores de riesgo manifiestos.

Vacunas

Las vacunas estacionales contra la gripe incluyen virus influenza humanos A de los subtipos H1N1 y H3N2 y un virus influenza B. Deben ser revisadas anualmente para incorporar las principales mutaciones en las proteínas HA y NA de los virus circulantes *(antigen drift).* El objetivo de la vacunación es reducir la tasa de susceptibles en la población; induce una respuesta inmunitaria específica de cepa.

En este momento se ha iniciado la producción de una vacuna monovalente frente al nuevo virus H1N1, que debe estar disponible en unos meses. El 5 de junio la OMS facilitó a los laboratorios productores la secuencia genética de la cepa seleccionada[66]. Un aspecto relevante a precisar son los grupos a los que de forma prioritaria se recomendará la vacunación, que con probabilidad serán, las embarazadas, los niños y adultos con enfermedades crónicas y el personal sanitario y de emergencias.

Conclusiones y perspectivas

En pocas semanas el nuevo virus H1N1 se ha extendido por muchos países y es previsible que en los próximos meses prosiga con intensidad su diseminación. La nueva gripe tiene una transmisibilidad más elevada que la estacional, pero su patogenicidad y virulencia son bajas, aunque en este momento no es posible saber qué ocurrirá en cuanto a su impacto sobre la salud si el virus se disemina por zonas con escasa infraestructura sanitaria, elevada incidencia de la infección por el virus de la inmunodeficiencia humana (VIH), extensa malnutrición o en poblaciones aborígenes.

Existe preocupación por los posibles cambios que pueda presentar el virus en función de la presión selectiva inducida por la inmunidad que progresivamente vaya adquiriendo la población, y también por la eventual reordenación con algún virus humano circulante, dando lugar a subtipos más transmisibles o patogénicos. Estos interrogantes son aspectos importantes a seguir de cerca en la evolución de la pandemia durante los próximos meses.

El nuevo virus no ha sido aislado en cerdos, pero conserva el potencial de diseminarse en ellos, en los que podría reordenarse de nuevo produciendo virus más transmisibles o patogénicos. El paso al ser humano de un virus porcino con una reordenación triple ha puesto en evidencia la ausencia de un sistema global de vigilancia de la gripe en animales. Es de esperar que tras la alarma y gran riesgo que ha evidenciado la pandemia se organice un eficaz sistema eficaz.

En la actualidad la vacunación se configura como la principal medida para reducir el riesgo de adquirir la infección.

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JAMA | Special Communication

Medical Care of Adults With Down Syndrome
A Clinical Guideline

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IMPORTANCE Down syndrome is the most common chromosomal condition, and average life expectancy has increased substantially, from 25 years in 1983 to 60 years in 2020. Despite the unique clinical comorbidities among adults with Down syndrome, there are no clinical guidelines for the care of these patients.

OBJECTIVE To develop an evidence-based clinical practice guideline for adults with Down syndrome.

EVIDENCE REVIEW The Global Down Syndrome Foundation Medical Care Guidelines for Adults with Down Syndrome Workgroup (n = 13) developed 10 Population/Intervention/Comparison/Outcome (PICO) questions for adults with Down syndrome addressing multiple clinical areas including mental health (2 questions), dementia, screening or treatment of diabetes, cardiovascular disease, obesity, osteoporosis, atlantoaxial instability, thyroid disease, and celiac disease. These questions guided the literature search in MEDLINE, EMBASE, PubMed, PsychINFO, Cochrane Library, and the TRIP Database, searched from January 1, 2000, to February 26, 2018, with an updated search through August 6, 2020. Using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology and the Evidence-to-Decision framework, in January 2019, the 13-member Workgroup and 16 additional clinical and scientific experts, nurses, patient representatives, and a methodologist developed clinical recommendations. A statement of good practice was made when there was a high level of certainty that the recommendation would do more good than harm, but there was little direct evidence.

FINDINGS From 11 295 literature citations associated with 10 PICO questions, 20 relevant studies were identified. An updated search identified 2 additional studies, for a total of 22 included studies (3 systematic reviews, 19 primary studies), which were reviewed and synthesized. Based on this analysis, 14 recommendations and 4 statements of good practice were developed. Overall, the evidence base was limited. Only 1 strong recommendation was formulated: screening for Alzheimer-type dementia starting at age 40 years. Four recommendations (managing risk factors for cardiovascular disease and stroke prevention, screening for obesity, and evaluation for secondary causes of osteoporosis) agreed with existing guidance for individuals without Down syndrome. Two recommendations for diabetes screening recommend earlier initiation of screening and at shorter intervals given the high prevalence and earlier onset in adults with Down syndrome.

CONCLUSIONS AND RELEVANCE These evidence-based clinical guidelines provide recommendations to support primary care of adults with Down syndrome. The lack of high-quality evidence limits the strength of the recommendations and highlights the need for additional research.

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Supplemental content

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Down syndrome is the most common chromosomal condition[1] and in 2010-2014 occurred in 1 of every 700 live births in the US.[1] Individuals with Down syndrome have a significantly lower risk for some conditions, including solid malignancies, but a higher risk for other conditions, including congenital cardiac conditions, autoimmune diseases, and Alzheimer disease. Average life expectancy for people with Down syndrome has substantially increased, from 25 years in 1983[2] to 60 years in 2020.[3] According to one estimate, the number of people with Down syndrome living in the US was approximately 206 000 in 2010,[4] although exact and current prevalence is unknown because of lack of data, changing survival rates across decades, and trends in live births vs termination rates.

Because individuals with Down syndrome are living longer, guidance is needed to support high-quality care. Although guidelines based on expert opinion exist,[5,6] evidence-based clinical practice guidelines (CPGs) for adults with Down syndrome have not been developed. This Special Communication presents a clinical guideline with recommendations to support high-quality primary care for adults with Down syndrome.

Methods

The Global Down Syndrome Foundation (GLOBAL), a nonprofit in the US dedicated to improving the lives of people with Down syndrome through research, medical care, education and advocacy, recruited expert Down syndrome clinicians, many of whom are members of the Down Syndrome Medical Interest Group–USA, and the ECRI (originally the Emergency Care Research Institute) Evidence-based Practice Center to form the Global Medical Care Guidelines for Adults with Down Syndrome Workgroup (Workgroup) and create an evidence-based CPG for clinicians, adults with Down syndrome, and families/caregivers.

In 2017, the 13-member Workgroup (11 Down syndrome experts, 1 ECRI guideline methodologist, and 1 parent representative/advocacy leader and expert from GLOBAL) convened a 29-member committee, including all 13 members of the Workgroup plus 16 volunteers (listed at the end of this article). There was consensus among Workgroup members that these guidelines should provide guidance to support primary care clinicians in caring for adults with Down syndrome. The 29 experts were assigned to 9 committees representing the 9 topic areas prioritized for inclusion in these guidelines: behavior, dementia, diabetes, cardiac disease, obesity, atlantoaxial instability, osteoporosis, thyroid disease, and celiac disease. Workgroup members prioritized clinical topics for consideration and developed 10 questions using the standardized Population/Intervention/Comparator/Outcome (PICO) format (summaries of the full-length PICO questions are reported in **Box 1**).

Clinicians caring for adults with Down syndrome must often decide in what situations "standard" guidelines for adults without Down syndrome (such as US Preventive Services Task Force [USPSTF]recommendations) should be followed. For most of the key questions, the Workgroup anticipated that limited published research would include adults with Down syndrome. Thus, several PICO questions sought to identify differences in disease prevalence between adults with Down syndrome and the

Box 1. Population/Intervention/Comparator/Outcome (PICO) Questions[a]

Behavioral Health (PICO 1 and PICO 2)

PICO 1: In adults with Down syndrome, do clinical symptoms of depression, OCD, mood disorder, catatonia, GAD, and regression/disintegrative disorder differ from the general population?

PICO 2: In adults with Down syndrome, does performing a psychosocial assessment (by clinical assessment or by caregiver or patient questionnaire) to screen for mental health disorders (such as depression, anxiety, OCD, psychosis/regression/disintegrative disorder) improve recognition and diagnosis of medical conditions or health outcomes?

Dementia (PICO 3)

What is the prevalence of dementia in adults with Down syndrome by decade?

Diabetes (PICO 4)

A. What is the prevalence of diabetes (type 1 or 2) in adults with Down syndrome compared with the general population (by decade)?
B. Does screening asymptomatic adults with Down syndrome for diabetes improve cardiovascular outcomes, diabetic comorbidities, and functional outcomes?
C. Does screening adults with Down syndrome and obesity (BMI ≥30) more often improve outcomes (cardiovascular, diabetic comorbidities, and functional outcomes?

Cardiovascular Disease (PICO 5)

A. What is the prevalence of coronary artery disease and stroke secondary to atherosclerosis in adults with Down syndrome (compared with the general population)?
B. In adults with Down syndrome and hyperlipidemia, does treatment of total cholesterol, LDL-C, or triglycerides improve clinical outcomes?

Obesity (PICO 6)

A. Are treatments for obesity safe and effective for reducing complications of obesity (obstructive sleep apnea, joint pain, heart disease, diabetes, mental health problems) or improving quality of life in adults with Down syndrome?
B. What target BMI is optimal for reducing comorbidities of obesity in adults with Down syndrome?

Atlantoaxial Instability (PICO 7)

A. What is the prevalence of atlantoaxial instability in asymptomatic adults with Down syndrome (compared with the general population)?
B. Does screening with imaging (radiography, CT, MRI) asymptomatic (ie, no symptoms or examination findings) adults with Down syndrome for atlantoaxial instability improve outcomes?

Osteoporosis (PICO 8)

A. What is the prevalence of osteopenia, osteoporosis, spinal compression, hip or femur fractures in Down syndrome (by decade of life) compared to general population?
B. What is the clinical utility of screening asymptomatic adult patients with Down syndrome with DEXA (to detect osteopenia or osteoporosis)?
C. In adults with Down syndrome and no known history of low bone density, do lifestyle factors or serum markers (vitamin D, calcium, PTH, or thyrotropin) predict diagnosis of osteopenia, osteoporosis or fracture?
D. What pharmacological treatments are effective for prevention of osteoporotic fractures in adults with Down syndrome?

(continued)

Box 1. (continued)

Thyroid (PICO 9)

A. What is the prevalence of hypothyroidism in adults with Down syndrome by decade?
B. What is the diagnostic accuracy of thyrotropin, free thyroxine, and antithyroid antibodies for hypothyroidism in asymptomatic adults with Down syndrome?
C. Does treating elevated thyrotropin levels in asymptomatic adults with Down syndrome improve clinical or functional outcomes?
D. What is the clinical utility of using antithyroid antibodies to screen for thyroid disease in adults with Down syndrome and autoimmune disease (celiac disease, rheumatoid arthritis, lupus, alopecia areata)?

Celiac Disease (PICO 10)

A. What is the accuracy of tTG-IgA or total IgA (compared with duodenal biopsy) for diagnosing celiac disease in adults with Down syndrome?
B. What is the clinical utility of screening asymptomatic adults with Down syndrome for celiac disease using tTG-IgA or total IgA?
C. Does HLA antigen haplotype DQ2 or DQ8 predict risk of developing celiac disease in adults with Down syndrome?
D. Does a gluten-free diet improve symptoms in adults with Down syndrome and celiac disease?

Abbreviations: BMI, body mass index; CT, computerized tomography; DEXA, dual-energy x-ray absorptiometry; GAD, generalized anxiety disorder; HLA, human leukocyte antigen; IgA, immunoglobulin A; LDL-C, low-density lipoprotein cholesterol; MRI, magnetic resonance imaging; OCD, obsessive-compulsive disorder; PTH, parathyroid hormone; tTG-IgA, tissue transglutaminase IgA.

[a] Questions presented here are an abbreviated summary of full-length PICO questions developed for the systematic review.

general population to inform where existing clinical recommendations might warrant modification. The PICO format was used for all questions; however, for questions focused on prevalence, the PICO category of "intervention" was not applicable. Questions targeting prevalence did include population and outcome, along with a comparator if the comparative prevalence was addressed.

Using these PICO questions, ECRI performed a systematic review. A medical librarian performed a comprehensive literature search in MEDLINE, EMBASE, PubMed, PsycINFO, the Cochrane Library, and the TRIP database from January 1, 2000, to February 26, 2018. Titles and abstracts were screened, followed by a full-text assessment based on predefined inclusion/exclusion criteria. Detailed PICO questions, search strategies, and selection criteria are reported in eMethods 1 and eMethods 2 in Supplement 1. An updated literature search was performed on August 6, 2020; 2 additional articles were identified and included.

To conduct the literature review, a "best evidence" approach was used, which has previously been used for systematic reviews underpinning CPGs.[7,8] For each PICO question, we identified any relevant previously published English-language systematic reviews rated as good quality as per USPSTF criteria.[9] If multiple relevant systematic reviews were identified, the most recent, relevant, and comprehensive (eg, the review with the most high-quality studies) was selected for inclusion to avoid multiple ratings of a similar evidence base. If no relevant systematic reviews met those criteria, relevant studies were identified with the highest-quality study designs (eg, randomized clinical trials for intervention PICOs). If no studies were identified that focused on a specific question, lower-quality studies (eg, observational studies) were considered for inclusion. For example, for PICOs that addressed prevalence (prevalence addressed varies by PICO question), observational studies with 300 or more adults with Down syndrome were sought. However, if no studies met these criteria, studies with fewer patients (eg, $n \geq 100$) were included.

Data regarding study design, population characteristics, intervention(s), prevalence estimates, and outcome measures were extracted from all included studies, and a narrative synthesis (qualitative synthesis of evidence) was performed. Study quality for individual studies was assessed using USPSTF methods except for prevalence studies, which were assessed using prespecified items (see eMethods 2 in Supplement 1). Overall quality of evidence for each outcome was assessed using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology.[10]

The 13-member Workgroup participated in a 3-day in-person meeting from January 23 to 25, 2019. A patient advocate and families (n = 3) were also present for selected sessions. Workgroup members reviewed evidence from the systematic review and used the GRADE Evidence-to-Decision framework to formulate recommendations.[11,12] This framework uses 4 domains to determine a recommendation's strength (strong or weak): (1) balance of desirable and undesirable outcomes, (2) confidence in evidence quality, (3) patient values and preferences, and (4) other implications (including equity, feasibility, and subgroup considerations).[10] A strong recommendation indicates a high or moderate confidence in the quality of the available evidence, a clear difference in magnitude between the benefits and harms of an intervention, and similar values and preferences, along with consideration of other implications.

If the Workgroup had less confidence after assessment across these domains and determined that additional evidence could change the recommendation, it generally assigned a weak recommendation. A statement of good practice (SOGP) was made when there was a high level of certainty, based on clinical assessment of anticipated benefits and harms, that the recommendation would do more good than harm but there was little direct evidence.[13] The Workgroup's consideration of each domain for every recommendation included in this guideline is reported in eTable 1 in Supplement 1.

After recommendations were drafted, Workgroup members voted with verbal assent (or dissent) to adopt (or reject) the recommendation. If unanimous consent was not present, objections and suggested modifications to the recommendation were discussed and another vote was taken. In the event unanimous consent could not be reached, a two-thirds majority of Workgroup members was required for the recommendation to be adopted. Disclosures and potential conflicts of interest for all Workgroup members were obtained and updated throughout the process.

For key questions for which no direct evidence was identified in the patient population (ie, adults with Down syndrome),

Workgroup members considered additional indirect evidence from other patient populations (eg, children with Down syndrome, people with intellectual disability) and arrived at consensus regarding whether evidence was "direct enough" to inform care for adults with Down syndrome. This approach has been used to develop evidence-based CPGs in contexts with limited direct evidence.[14]

To obtain input from patients and caregivers, a 7-day online focus group was conducted in October 2019 and included 7 adults with Down syndrome and 27 caregivers (including parents and siblings), to solicit feedback on draft recommendations, usability, importance, and areas requiring clarification. In addition, the draft guidelines were reviewed by 7 members of the American Academy of Developmental Medicine and Dentistry. All feedback was reviewed, and updates were incorporated by the Workgroup. The full guidelines, complete methods, systematic review, and implementation tools are available in eAppendix 1 in Supplement 2 or at https://www.globaldownsyndrome.org/global-adult-guidelines/.

Since creation of these guidelines did not involve human participants in research, this project was determined to be exempt from institutional review board (IRB) approval as confirmed by the Colorado Multiple IRB.

Results

Searches identified 11 295 citations, of which the systematic review included 20 studies (3 systematic reviews[15-17] and 17 primary studies, including 1 randomized clinical trial,[18] 4 cohort studies,[19-22] 11 cross-sectional studies,[23-33] and 1 case series).[34] An updated literature search on August 6, 2020, identified 2 additional cross-sectional studies[35,36] relevant to recommendations (eFigure 1 and eTable 2 in Supplement 1). No studies addressing PICO 2 (efficacy of psychosocial assessment for recognition of mental or health conditions) were identified. Fourteen recommendations and 4 SOGPs were formulated (**Table 1**). A 1-page checklist tool summarizing all recommendations and SOGPs for families/caregivers to easily track care and support adherence with the guideline recommendations was also created (eFigure 2 in Supplement 1).

Diagnosis and Treatment of Behavioral Health Conditions

Recommendation 1

When concern for a mental health disorder in adults with Down syndrome is present, medical professionals should refer the patient to a clinician knowledgeable about the medical, mental health disorders, and common behavioral characteristics of adults with Down syndrome.

Recommendation 2

When concern for a mental health disorder in adults with Down syndrome is present, medical professionals should follow guidelines for diagnosis in the *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition) (*DSM-5*).[37] The *Diagnostic Manual–Intellectual Disability 2: A Textbook of Diagnosis of Mental Disorders in Persons with Intellectual Disability* (*DM-ID-2*)[38] also may be used to adapt diagnostic criteria from the *DSM-5*.

Evidence Summary

No studies directly compared symptoms in adults with Down syndrome with the general population. However, 1 systematic review[15] included 3 cross-sectional studies that described symptoms of unipolar depression. Individuals with Down syndrome who met criteria for major depressive episodes had common symptoms (anhedonia, depressed mood, and disturbed sleep) but also hallucinations, and a subset presented with a "deficit" syndrome (apathy, abulia, anhedonia, and mutism) without obvious mood changes or psychosis. A case series (n = 30) reported that symptoms of patients with Down syndrome with regression included changes in mood, behavior, and psychotic symptoms.[34] Confidence in the quality of evidence was very low.

Rationale for Recommendation 1

Behavioral and mental health conditions are common in Down syndrome and many clinicians are not familiar with distinctive behaviors in this population, which differ from those in the general population. Thus, despite very low confidence in quality of evidence, the potential benefits, including identifying salient psychosocial issues requiring attention, avoiding misdiagnosis of adaptive behavior as a disorder, and limiting unnecessary use of psychotropic medications, warranted a weak recommendation for referral to medical professionals familiar with the common behaviors and presentation of medical and mental health conditions in adults with Down syndrome.

Rationale for the Recommendation 2

In the absence of tools validated specifically for Down syndrome, given distinctive challenges of diagnosing mental health disorders, clinicians should use the *DSM-5* complemented by the *DM-ID-2*, an expert consensus tool helpful in recognizing mental health disorders in people with intellectual and developmental disabilities.

Statements of Good Practice 1 and 2 and Rationale

A review of behavioral, functional, adaptive, and psychosocial factors should be performed as part of an annual history that clinicians obtain from all adults with Down syndrome, their families, and caregivers (SOGP 1).

When concern for a mental health disorder in adults with Down syndrome is present, medical professionals should evaluate patients for medical conditions that may present with psychiatric and behavioral symptoms (SOGP 2).

Diagnosis of Dementia

Recommendation 3

Caution is needed when diagnosing age-related, Alzheimer-type dementia in adults with Down syndrome younger than 40 years because of its low prevalence before this age.

Recommendation 4

Medical professionals should assess adults with Down syndrome and interview primary caregivers about changes from baseline function annually, beginning at age 40 years. Decline in 6 domains specified by the National Task Group–Early Detection Screen for Dementia (NTG-EDSD)[39] should be used to identify early-stage age-related Alzheimer-type dementia, a potentially reversible medical condition, or both.

Table 1. Recommendations and Statements of Good Practice

Recommendation/statement of good practice	Strength of recommendation	Confidence in quality of evidence
Recommendations		
Behavior		
Recommendation 1. When concern for a mental health disorder in adults with Down syndrome is present, medical professionals should refer to a clinician knowledgeable about the medical, mental health disorders, and common behavioral characteristics of adults with Down syndrome	Weak	Very low
Recommendation 2. When concern for a mental health disorder in adults with Down syndrome is present, medical professionals should follow guidelines for diagnosis in the *DSM-5*[37]; the *DM-ID-2*[38] also may be used to adapt diagnostic criteria from the *DSM-5*	Weak	Very low
Dementia		
Recommendation 3. Caution is needed when diagnosing age-related, Alzheimer-type dementia in adults with Down syndrome younger than 40 y because of its low prevalence before this age	Weak	Low
Recommendation 4. Medical professionals should assess adults with Down syndrome and interview their primary caregivers about changes from baseline function annually beginning at age 40 y; decline in the following 6 domains as per the NTG-EDSD[39] should be used to identify early-stage age-related Alzheimer-type dementia and/or a potentially reversible medical condition: • Cognition, memory, and executive function • Behavior and personality • Communication • Adaptive functioning • Ambulation and motor skills • General decline in established skills	Strong	Moderate
Diabetes		
Recommendation 5. For asymptomatic adults with Down syndrome, screening for type 2 diabetes using HbA1c or fasting plasma glucose should be performed every 3 y beginning at age 30 y	Weak	Moderate
Recommendation 6. For any adult with Down syndrome and comorbid obesity, screening for type 2 diabetes using HbA1c or fasting plasma glucose should be performed every 2-3 y beginning at age 21 y	Weak	Moderate
Cardiovascular disease		
Atherosclerotic cardiovascular disease		
Recommendation 7. For adults with Down syndrome without a history of ASCVD, the appropriateness of statin therapy should be assessed every 5 y starting at age 40 y and using a 10-y risk calculator as recommended for adults without Down syndrome by the USPSTF[40]	Weak	Low
Stroke		
Recommendation 8. For adults with Down syndrome, risk factors for stroke should be managed as specified by the American Heart Association/American Stroke Association guidelines for the primary prevention of stroke[41]	Weak	Very low
Recommendation 9. In adults with Down syndrome with a history of congenital heart disease, given the elevated risk of cardioembolic stroke, a periodic cardiac evaluation and a corresponding monitoring plan should be reviewed by a cardiologist	Weak	Very low
Obesity		
Recommendation 10. Monitoring for weight change and obesity should be performed annually by calculating BMI in adults with Down syndrome; the USPSTF behavioral weight loss interventions to prevent obesity-related morbidity and mortality in adults should be followed[42]	Weak	Very low
Atlantoaxial instability		
Recommendation 11. In adults with Down syndrome, routine cervical spine radiographs should not be used to screen for risk of spinal cord injury in asymptomatic individuals; instead, annual screening of adults with Down syndrome should include signs and symptoms of cervical myelopathy using targeted history and physical examination	Weak (against)	Very low
Osteoporosis		
Recommendation 12. For primary prevention of osteoporotic fractures in adults with Down syndrome, there is insufficient evidence to recommend for or against applying established osteoporosis screening guidelines, including fracture risk estimation; thus, good clinical practice would support a shared decision-making approach to this issue	Neither for nor against	NA
Recommendation 13. All adults with Down syndrome who sustain a fragility fracture should be evaluated for secondary causes of osteoporosis, including screening for hyperthyroidism, celiac disease, vitamin D deficiency, hyperparathyroidism, and medications associated with adverse effects on bone health	Weak	Very low
Thyroid		
Recommendation 14. Screening adults with Down syndrome for hypothyroidism should be performed every 1-2 y using a serum thyrotropin test beginning at age 21 y	Weak	Moderate

(continued)

Table 1. Recommendations and Statements of Good Practice (continued)

Recommendation/statement of good practice	Strength of recommendation	Confidence in quality of evidence
Statements of good practice[a]		
Behavior		
Statement 1. A review of behavioral, functional, adaptive, and psychosocial factors should be performed as part of an annual history that clinicians obtain from all adults with Down syndrome, their families, and caregivers		
Statement 2. When concern for a mental health disorder in adults with Down syndrome is present, medical professionals should evaluate for medical conditions that may present with psychiatric and behavioral symptoms		
Obesity		
Statement 3. Healthy diet, regular exercise, and calorie management should be followed by all adults with Down syndrome as part of a comprehensive approach to weight management, appetite control, and enhancement of quality of life		
Celiac disease		
Statement 4. Adults with Down syndrome should receive an annual assessment for gastrointestinal and nongastrointestinal signs and symptoms of celiac disease using targeted history, physical examination, and clinical judgment of good practice		

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; *DM-ID-2*, *Diagnostic Manual-Intellectual Disability 2: A Textbook of Diagnosis of Mental Disorders in Persons with Intellectual Disability*; *DSM-5*, *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition); HbA_{1c}, glycated hemoglobin; NTG-EDSD, National Task Group—Early Detection Screen for Dementia; USPSTF, US Preventive Services Task Force.

[a] Statements of Good Practice are made when there is a high level of certainty a recommendation will do more good than harm but there is little supporting direct evidence. As per GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodology, statements of good practice are not assigned a formal strength rating.

Evidence Summary

One moderate-quality Dutch study[23] (n = 506 adults with Down syndrome) found dementia prevalence of 8.9% (95% CI, 5%-12%) in 45- to 49-year-olds; prevalence increased every 5 years to 32.1% (95% CI, 22%-42%) in 55- to 59-year-olds and decreased to 25.5% (95% CI, 12%-40%) in patients 60 years or older. An additional study (n = 878 adults with Down syndrome)[35] reported increasing prevalence of dementia in adults with Down syndrome older than 45 years and 40% prevalence after age 45, but dementia diagnosis was based on administrative data. One low-quality study from Spain and the UK[36] (n = 388) also reported increasing prevalence rates for dementia in adults with Down syndrome after age 40 years, with rates rising from approximately 10% (for 40- to 45-year-olds) up to 90% to 100% (for 65- to 70-year-olds).

Three studies assessed prevalence in patients younger than 40 years.[19,24,36] However, only 1 study[36] (n = 388) used a validated measure for diagnosis and reported 0% prevalence in adults with Down syndrome aged 30 to 39 years. Two additional large studies (n > 5000 adults with Down syndrome)[19,24] did not confirm diagnosis based on validated tests but found similar low prevalence in younger adults (18-39 years). Confidence in the quality of evidence was low for prevalence in patients younger than 40 years but moderate for those older than 45 years.

Rationale for Recommendation 3

Because clinicians may attribute symptoms of Down syndrome to Alzheimer-type dementia without adequately considering alternative causes, a weak recommendation suggests that clinicians should exercise caution when attributing symptoms to Alzheimer-type dementia in adults with Down syndrome younger than 40 years. Benefits of considering other causes, including treatable conditions (eg, hypothyroidism, sleep apnea), significantly outweighed potential harms (underdiagnosis of true Alzheimer-type dementia).

Rationale for Recommendation 4

Because dementia prevalence increases after age 40 years, adults with Down syndrome and primary caregivers should be interviewed annually beginning at age 40 to establish a baseline and identify changes in baseline function in the adult with Down syndrome, which could suggest potential Alzheimer-type dementia. The justification was based on the benefits of early identification of dementia, treatment of potentially reversible causes of cognitive decline, or both, which outweigh potential harms associated with more testing.

Despite absence of disease-modifying dementia treatments, most adults with Down syndrome and their families/caregivers place high value on early diagnosis, accurate diagnosis, or both to modify existing supports and allow for additional resource planning. Individuals with mild to moderate dementia will typically have changes across multiple domains (memory and executive function, behavior and personality, language and communication, gait and motor skills, activities of daily living, continence, and sleep patterns) as described in the NTG-EDSD,[39] which was developed for dementia diagnosis in individuals with intellectual disability.

Diabetes

Recommendation 5

For asymptomatic adults with Down syndrome, screening for type 2 diabetes using glycated hemoglobin or fasting plasma glucose levels should be performed every 3 years beginning at age 30 years.

Recommendation 6

For any adult with Down syndrome and comorbid obesity, screening for type 2 diabetes using glycated hemoglobin or fasting plasma

glucose level should be performed every 2 to 3 years beginning at age 21 years.

Evidence Summary

One population-based study in the UK[19] (n = 3808) found that diabetes prevalence was higher in adults with Down syndrome compared with general population–matched controls (3.5% vs 0.7%, respectively, for ages 16 to 30 years and 5.5% vs 2.7%, respectively, for 30 years or older). Confidence in the quality of evidence was rated moderate.

Rationale for Recommendations 5 and 6

The American Diabetes Association (ADA) recommends screening for abnormal blood glucose level and type 2 diabetes in all adults beginning at age 45 years.[43] Given risks associated with premature aging in adults with Down syndrome (with increased risk for cataracts and kidney and peripheral nervous system damage),[44-46] screening should be initiated earlier, beginning at age 30 years and to be repeated every 3 years if results of blood glucose screening are normal (weak recommendation).

The ADA recommends that individuals who are overweight or obese (body mass index [BMI] ≥25, calculated as weight in kilograms divided by height in meters squared) and with 1 additional risk factor begin screening for abnormal blood glucose levels every 3 years and for type 2 diabetes after puberty.[43] Because obesity is common in Down syndrome and associated with increased risk for diabetes, for adults with Down syndrome and obesity, screening should be initiated at age 21 years and repeated every 2 to 3 years with or without the presence of an additional risk factor outlined by the ADA (weak recommendation). Benefits of earlier identification and management of diabetes were judged to outweigh potential harms of obtaining laboratory testing and potential for overtreatment (eg, hypoglycemia).

Cardiovascular Disease Prevention

Recommendation 7

For adults with Down syndrome without a history of atherosclerotic cardiovascular disease (ASCVD), the appropriateness of statin therapy should be assessed every 5 years starting at age 40 years and using a 10-year risk calculator as recommended by the USPSTF for adults without Down syndrome.[40]

Evidence Summary

No studies assessed whether treatment to reduce levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), or triglycerides improve clinical outcomes. However, an Australian study[20] that compared hospitalized patients with Down syndrome (n = 1706) with age-matched controls (n = 6828) found that in patients 50 years or younger myocardial infarction events were similar, but in patients 51 years or older (n = 1845) events were reduced in adults with Down syndrome (8.1% for those with Down syndrome vs 13.3% for controls). A second UK study[19] (n = 3808) also reported a mildly lower incidence of ischemic heart disease in adults with Down syndrome compared with controls (absolute annual incidence per 100 person-years for Down syndrome of all ages was 0.19 [95% CI, 0.15-0.25] with an incidence rate ratio of 0.9 compared with matched controls). For those older than 30 years (50.5% of the study population) the absolute rate was 0.28 (95% CI, 0.21-0.38), with an incidence rate ratio of 0.8 and an overall prevalence of 1.5% for adults with Down syndrome 30 years or older.[19] True incidence of ASCVD may be even lower because the study did not distinguish between atherosclerotic ischemia vs nonatherosclerotic ischemia due to conditions such as sleep apnea, congenital heart disease, and pulmonary hypertension, all of which the study found were more common in Down syndrome. Confidence in the quality of the evidence was low.

Rationale for Recommendation 7

No studies evaluated if elevated lipid levels are predictive of ASCVD for adults with Down syndrome. While limited available evidence suggests a reduced risk of ASCVD, given very low certainty in effect size estimates, there was insufficient justification to recommend adults with Down syndrome be treated differently. Altogether, benefits of treating potential atherosclerotic events slightly outweighed potential harms including adverse events associated with statin therapy and polypharmacy. Thus, USPSTF guidance (using a 10-year risk calculator and personalizing lipid goals) should be followed (weak recommendation).

The American Board of Internal Medicine Choosing Wisely campaign, in cooperation with the AMDA—The Society for Post-Acute and Long-Term Care Medicine (2017), recommends against routinely prescribing lipid-lowering medications in individuals with limited life expectancy.[47] Weighing the ideal time to discontinue screening and treatment for individuals with Down syndrome may also involve consideration of shorter average life expectancy (60 years) for adults with Down syndrome.[48]

Stroke Prevention

Recommendation 8

For adults with Down syndrome, risk factors for stroke should be managed as specified by the American Heart Association/American Stroke Association's (AHA/ASA) Guidelines for the Primary Prevention of Stroke.[41]

Recommendation 9

In adults with Down syndrome with a history of congenital heart disease, given the elevated risk of cardioembolic stroke, a periodic cardiac evaluation and a corresponding monitoring plan should be reviewed by a cardiologist.

Evidence Summary

One Australian study[20] compared strokes in hospitalized adults with Down syndrome (n = 1706) with those in matched controls (n = 6828). Adults with Down syndrome had more strokes across both age groups: 1.8% vs 0.5% (ages 19-50 years) and 9.8% vs 4.9% (age ≥51 years) ($P < .05$ for both comparisons). On average, strokes occurred at a younger age in adults with Down syndrome compared with controls (mean age, 41.8 vs 57.1 years), with cardioembolic strokes being most common. Confidence in the quality of the evidence was very low.

Rationale for Recommendations 8 and 9

Given increased risk of cardioembolic stroke in adults with Down syndrome, the established guidelines for risk factor management for stroke prevention should be followed as specified in the AHA/ASA guidelines (weak recommendation). Typical risk factors such as hypertension are uncommon in Down syndrome,[19] while moyamoya

disease,[49] obstructive sleep apnea,[50,51] and congenital heart disease are more common. As many as 50% of children with Down syndrome are born with congenital heart disease, which increases the risk of cardioembolic stroke.[52,53] Thus, all patients with a history of congenital heart disease should receive a cardiac evaluation and monitoring plan reviewed by a cardiologist (weak recommendation).

Obesity Screening and Management

Recommendation 10

Monitoring for weight change and obesity should be performed annually by calculating BMI in adults with Down syndrome. The USPSTF recommendation for behavioral weight loss interventions to prevent obesity-related morbidity and mortality in adults should be followed.[42]

Evidence Summary

Three randomized clinical trials (RCTs) from 2 systematic reviews[16,17] assessed exercise interventions in obese adults with Down syndrome (n = 84). Mentored physical activity had no effect on weight or waist circumference at 9 weeks,[16] and aerobic exercise and progressive resistance exercise had no effect on weight at 9 to 12 weeks (Cohen d, 0.09; $P = .37$).[17] Quality of evidence was rated very low. Studies excluded patients with orthopedic conditions, cardiac disease, or metabolic disease, further limiting applicability. These studies reported no adverse effects from physical activity[16] and no abnormal electrocardiogram findings (aerobic exercise or progressive resistance exercise). Quality of evidence for safety outcomes was rated moderate.

No studies assessed other interventions for obesity or the effect of various BMI targets for reducing comorbidities of obesity.

Rationale for Recommendation 10

USPSTF guidelines recommend referring obese adults to intensive, multicomponent behavioral interventions.[42] These trials in people with Down syndrome[16,17] did not provide sufficient justification to warrant differing from USPSTF guidance. First, trials did not assess multicomponent interventions but only exercise alone (potentially limiting efficacy). Second, many factors may contribute to obesity in Down syndrome, including medication adverse effects, conditions (hypothyroidism, obstructive sleep apnea), poor appetite-satiety control, and lack of physical activity. Because obesity is common, clinicians may not consider obesity a modifiable condition. However, weight loss or stabilization is possible through activity interventions such as swimming, dancing, or working with a personal trainer and through diet management, portion control, and consistency of mealtimes. Although trials failed to demonstrate benefit, they reported no adverse effects. Thus, given long-term harms of obesity, the benefits of monitoring for obesity with annual BMI and adhering to USPSTF guidance for adults outweighed potential harms.

Statement of Good Practice 3 and Rationale

Healthy diet, regular exercise, and calorie management should be followed by all adults with Down syndrome as part of a comprehensive approach to weight management, appetite control, and enhancement of quality of life (SOGP 3).

Although no interventions reviewed demonstrated effects on weight, obesity is a common concern in adults with Down syndrome. Adults with Down syndrome, families, and clinicians should support generally accepted practices for overall wellness.

Screening for Atlantoaxial Instability

Recommendation 11

In adults with Down syndrome, routine cervical spine radiographs should not be used to screen for risk of spinal cord injury (SCI) in asymptomatic individuals. Instead, annual screening of adults with Down syndrome should include a review of signs and symptoms of cervical myelopathy, such as altered gait, new incontinence, brisk reflexes, or clonus, using targeted history and physical examination.

Evidence Summary

No studies assessed utility of screening for atlantoaxial instability (AAI) with cervical spine radiographs. However, 2 cross-sectional studies reported prevalence of AAI. An Australian registry-based survey (n = 197) found that 8.1% (95% CI, 4.35%-11.9%) of adults with Down syndrome younger than 30 years had AAI.[25] A similar prevalence (11% [95% CI, 2.7%-19.5%]) was reported by a Spanish chart review (n = 144).[27] Neither study provided criteria used to establish AAI or presence of signs or symptoms of myelopathy. Confidence in the quality of evidence was very low.

Rationale for Recommendation 11

Cervical spine radiographs have been used to identify individuals with Down syndrome at risk for SCI with physical activity. Although AAI prevalence is approximately 10% in adults younger than 30 years,[25,27] no studies have assessed if radiographs are effective for identifying at-risk individuals or preventing SCI. While avoiding potential SCI is important, restricting asymptomatic individuals with AAI from participating in physical activities is also undesirable for reasons related to physical and psychological health. Additional indirect evidence has suggested that SCI from AAI is uncommon. A 1995 review from the American Academy of Pediatrics Committee on Sports Medicine noted only 41 well-documented, published cases of symptomatic AAI in adults with Down syndrome.[54] In addition, Special Olympics organizers report no spinal cord injuries from more than 50 000 individuals with Down syndrome who participated in Special Olympics activities over 20 years.[55]

Because the true risks of SCI are unknown, the benefits of allowing physical activity slightly outweighed the potential harms of SCI. Cervical radiographs should not be used to screen for AAI in asymptomatic individuals; instead, targeted history and physical examination should be used for evaluation of signs or symptoms of myelopathy (weak recommendation).

Adults with Down syndrome, and their families/caregivers, may differ in preferences to avoid risk of SCI; thus, a shared decision-making approach is endorsed that considers potential benefits and harms of restricting participation in high-risk activities, including but not limited to gymnastics, diving, skiing, and horseback riding.

Screening for Osteoporosis

Recommendation 12

For primary prevention of osteoporotic fractures in adults with Down syndrome, there is insufficient evidence to recommend for

or against applying established osteoporosis screening guidelines, including fracture risk estimation; thus, good clinical practice would support a shared decision-making approach.

Recommendation 13

All adults with Down syndrome who sustain a fragility fracture should be evaluated for secondary causes of osteoporosis, including screening for hyperthyroidism, celiac disease, vitamin D deficiency, hyperparathyroidism, and medications associated with adverse effects on bone health.

Evidence Summary

Only 6 small, poor-quality studies (total n = 796) reported prevalence for osteopenia, osteoporosis, or osteoporotic fracture in adults with Down syndrome, with wide-ranging prevalence estimates for osteoporosis (1.4% to 45.1%).[28-33]

No studies assessed utility of dual-energy x-ray absorptiometry (DEXA) screening or efficacy of pharmacological treatments for osteoporotic fracture prevention.

Rationale for Recommendations 12 and 13

Although the Fracture Risk Assessment Tool (FRAX) is typically used to assess fracture risk,[56] this model may not be applicable to adults with Down syndrome because it was derived from epidemiologic data from the general population. Populations with small body size or constitutionally short stature may require volumetric bone mineral density measurement or other adjustments for bone characteristics relevant to fracture risk.[57] Based on the available evidence, standard DEXA is not helpful for assessing risk of osteoporotic fracture in Down syndrome. Furthermore, reduced bone formation, rather than excessive bone resorption, may drive skeletal dynamics in adults with Down syndrome,[58] although this has not been consistently observed.[59] If true, bisphosphonates, which reduce bone resorption, may not be effective for individuals with Down syndrome. Given the absence of studies demonstrating benefit of DEXA screening and concerns regarding applicability of DEXA, to acknowledge the uncertainty, the recommendation is neither for nor against osteoporosis screening, noting that a shared decision-making approach should be used to incorporate patient and family preferences.

The 2016 American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guideline[60] for postmenopausal women with osteoporosis recommended evaluation for secondary causes of osteoporosis, some of which are common in Down syndrome. Given the low harms associated with testing, potential benefits of avoiding fragility fractures, and additional health benefits of treating relevant diseases, adults with Down syndrome who sustain a fragility fracture should receive an evaluation for secondary causes of osteoporosis such as hyperthyroidism, celiac disease, vitamin D deficiency, hyperparathyroidism, and medications with adverse effects on bone health (weak recommendation).

Screening for Thyroid Disease

Recommendation 14

Screening adults with Down syndrome for hypothyroidism should be performed every 1 to 2 years using a serum thyrotropin test beginning at age 21 years.

Evidence Summary

Three studies reported a similar high prevalence of hypothyroidism in adults with Down syndrome. A study from the UK[19] (n = 3808) found a prevalence of 39% (95% CI, 36%-42%) in adults with Down syndrome aged 18 to 29 years and 51% (95% CI, 49%-53%) in those 30 years or older. Two additional clinic-based studies performed in Spain[27] (n = 144) and the US[31] (n = 141) reported similar rates: 43% (ages 18-29 years) and 57% to 61% (age ≥30 years)[27]; 39% (ages 18-49 years) and 42% (age ≥50 years).[31] Confidence in the quality of evidence was moderate.

No studies assessed treating elevated thyrotropin levels in asymptomatic patients, the diagnostic accuracy of thyrotropin, free thyroxine or antithyroid antibodies, or the clinical utility of antithyroid antibodies to screen for thyroid disease in adults with Down syndrome and autoimmune disease.

Rationale for Recommendation 14

Symptoms of hypothyroidism are challenging to distinguish because weight gain and constipation are common in Down syndrome. Furthermore, adults with Down syndrome may have difficulty communicating fatigue or cold intolerance.

Prevalence of hypothyroidism in adults with Down syndrome is substantially higher (approximately 50% in adults older than 30 years[19]) compared with prevalence in US adults without Down syndrome,[61] and treatment may improve cognitive function and weight management. Thus, adults with Down syndrome should be screened for hypothyroidism every 1 to 2 years (weak recommendation).

Screening for Celiac Disease

Statement of Good Practice 4

Adults with Down syndrome should receive an annual assessment for gastrointestinal and nongastrointestinal signs and symptoms of celiac disease using targeted history, physical examination, and clinical judgment of good practice (SOGP 4).

Rationale for Statement of Good Practice 4

Celiac disease is more common in individuals with Down syndrome, with an estimated prevalence of 11% among people with Down syndrome.[27] However, diagnosis presents unique challenges because gastrointestinal and nongastrointestinal symptoms can be difficult to recognize. In addition, some gastrointestinal problems (eg, constipation, loose stools, and cramping) are common in Down syndrome. These may also be more challenging to identify, depending on communication skills. No studies assessed utility of screening asymptomatic adults with Down syndrome or efficacy of a gluten-free diet, and studies assessing diagnostic accuracy of tissue transglutaminase IgA and biopsy had significant flaws.[21,22]

Discussion

Providing care for the increasing number of adults with Down syndrome can be challenging, given their broad phenotypic variation in health and function. As the first, to our knowledge, evidence-based guideline for adults with Down syndrome, these recommendations provide guidance across a wide range of clinical conditions and support clinicians in providing high-quality medical care for adults with Down syndrome.

Table 2. Recommendations Compared With Existing Guidance

Recommendation	Existing guideline
Recommendations in Down syndrome guidelines concur with existing guidance for the general population	
Recommendation 7. Statin therapy for lowering cardiovascular risk for adults with Down syndrome	Agrees with USPSTF guidance for the general population, statin use for the primary prevention of cardiovascular disease in adults: preventive medication[40]
Recommendation 8. Managing risk factors for stroke prevention for adults with Down syndrome	Agrees with AHA/ASA guidelines for primary prevention of stroke[41] for the general population
Recommendation 10. Obesity screening for adults with Down syndrome	Agrees with USPSTF guidance for the general population, Behavioral Weight Loss Interventions to Prevent Obesity-Related Morbidity and Mortality in Adults[42]
Recommendation 13. Evaluating secondary causes of osteoporosis for adults with Down syndrome	Agrees with American Association of Clinical Endocrinologists/ American College of Endocrinology (2016) guideline,[60] Diagnosis and Treatment of Postmenopausal Osteoporosis for the General Population
Recommendations in Down syndrome guidelines differ from existing guidance for the general population	
Recommendation 5. Diabetes screening in asymptomatic individuals with Down syndrome	Recommendation (screen starting at age 30 y [instead of 45] every 3 y[43]) differs from ADA guidance for the general population
Recommendation 6. Diabetes screening in adults with Down syndrome and obesity	Recommendation (screen starting at age 21 y and every 2-3 y [instead of every 3 y] without requiring any additional risk factors[43]) differs from ADA guidance for the general population
Recommendation in Down syndrome guidelines neither for or against existing guidance for the general population	
Recommendation 12. Screening for primary prevention of osteoporosis for adults with Down syndrome	Neither for or against osteoporosis risk prediction tools (FRAX) for the general population
New recommendations in Down syndrome guidelines	
Recommendations 1 and 2. Diagnosis of behavioral health conditions for adults with Down syndrome	
Recommendations 3 and 4. Diagnosis and screening for Alzheimer-type dementia for adults with Down syndrome	
Recommendation 9. Refer adults with Down syndrome and history of congenital heart disease for cardiac evaluation and monitoring plan for adults with Down syndrome	
Recommendation 11. Screening for atlantoaxial instability for adults with Down syndrome	
Recommendation 14. Screening for hypothyroidism for adults with Down syndrome	

Abbreviations: ADA, American Diabetes Association; AHA/ASA, American Heart Association/American Stroke Association; FRAX, Fracture Risk Assessment Tool; USPSTF, US Preventive Services Task Force.

The process for developing these guidelines adhered to standards for trustworthy guidelines established by the Institute of Medicine[62] and used the Evidence-to-Decision framework[12] (eTable 1 in Supplement 1) to formulate 14 clinical recommendations along with 4 SOGPs. As anticipated, evidence was limited for many PICO questions. To address this challenge, a pragmatic approach was utilized, using evidence of differences in prevalence and age of onset in adults with Down syndrome to consider if changes to existing guidance for the general population were justified.

Half of the recommendations (n = 7) pertained to guidance for the general population from existing CPGs (**Table 2**). Four recommendations (managing cardiovascular risk [recommendation 7], stroke prevention [recommendation 8], screening for obesity [recommendation 10], and evaluation for secondary causes of osteoporosis [recommendation 13]) agreed with existing guidance. Conversely, for diabetes screening (recommendations 5 and 6), earlier and more frequent screening was recommended based on studies demonstrating high prevalence and earlier onset in adults with Down syndrome.

Regarding optimal screening for osteoporosis, based on clinical experience, the existing tools (FRAX) for predicting fracture risk are likely poor predictors in adults with Down syndrome. There is concern that patients estimated to be at increased risk for fracture based on FRAX, perceived to have osteoporosis on the basis of DEXA measurement, or both, often receive bisphosphonates, which have potential adverse effects. If causes of osteoporosis in Down syndrome differ from those in the general population, it is possible bisphosphonates may not be effective. Thus, these concerns were highlighted by making a recommendation neither for nor against current osteoporosis risk prediction tools.

Remaining recommendations addressed evaluation for mental health disorders (recommendations 1 and 2), screening and diagnosis of Alzheimer-type dementia (recommendations 3 and 4), cardiology referrals for adults with history of congenital heart disease (recommendation 9), screening for AAI (recommendation 11), and screening for hypothyroidism (recommendation 14). Because rates of dementia increase after age 40 years from approximately 10% to 20% (ages 45-50 years)[23,36] to as high as 50% (ages 55-59 years),[36] a strong recommendation to initiate screening for behavioral changes at age 40 years was made (recommendation 4). In these guidelines, age 40 years was chosen because dementia prevalence is low (<1%) in patients younger than 40 years,[19,24,36] and initiating screening at this age allows a baseline to be established. Since dementia is rare in patients younger than 40 years, caution is required in making a dementia diagnosis in this age group, a recommendation intended to prevent inaccurate attribution of cognitive symptoms to dementia. The high prevalence of hypothyroidism in adults with Down syndrome (50% in adults aged ≥30 years)[19] was also the basis for recommending screening for hypothyroidism every 1 to 2 years.

Adults with Down syndrome benefit from receiving care from clinicians familiar with common behaviors, which might otherwise

Box 2. Future Research Priorities (Abbreviated)[a]

Behavior

Create a standardized assessment tool specific to people with Down syndrome to help further evaluate co-occurring medical conditions associated with psychiatric and behavioral issues

Review if existing tools validated in and treatments effective for people with IDD are useful in people with Down syndrome

Identify potential mental health risk factors, protective factors, or both in adults with Down syndrome

Dementia

Research prevalence and clinical emergence of age-related dementia symptoms in adults with Down syndrome

Expand and validate the use of available biomarkers into clinical practice to help inform diagnosis and decision-making

Further validate and refine existing dementia screening tools for adults with IDD, including expanding their repertoire of application and usefulness in different settings

Diabetes

Research whether early treatment of type 2 diabetes reduces the extent of tissue and end-organ damage to reduce or prevent long-term complications in Down syndrome

Determine the prevalence of type 1 and type 2 diabetes in adults with Down syndrome

Identify genetic and/or immunological risk factors for diabetes in Down syndrome

Cardiovascular Disease

Evaluate modifiable risk factors for atherosclerotic disease in adults with Down syndrome and better understand which risk factors identified are relevant for this population regarding disease prevention

Identify strategies to prevent stroke in adults with congenital heart disease and the potential impact of lowering lipid levels for stroke prevention

Determine the prevalence of atherosclerotic cardiovascular disease and myocardial infarctions in people with Down syndrome

Obesity

Study impact of leptin and ghrelin hormonal circuitries, whose dysregulation could affect appetite control in Down syndrome

Determine what weight loss strategies (including medications) are effective in people with Down syndrome, including what modifications or adaptations to existing fitness strategies better manage weight and appetite regulation

Identify the effects of obesity in people with Down syndrome and the potential health benefits of weight

Atlantoaxial Instability

Research the symptomatic true incidence of AAI in adults with Down syndrome, what factors are predictive of the future development of symptoms, and what interventions are best at preventing spinal cord injury

Determine the comparative impact on morbidity and mortality of conservative (watchful waiting) vs surgical intervention of AAI

Study compliance of medical professionals to universal precaution of proper neck positioning for people with Down syndrome during medical procedure, treatment, or recovery

(continued)

Box 2. (continued)

Osteoporosis

Describe the unique epidemiology of skeletal fracture in people with Down syndrome and determine optimal prevention, screening, and treatment strategies

Review the comparative effectiveness of medications and other interventions for prevention and treatment of osteoporotic fracture in adults with Down syndrome

Create a screening tool or test for assessing risk for skeletal fracture in people with Down syndrome

Thyroid Disease

Determine the precise thyrotropin level at which problems manifest and over what time frame these can be corrected with treatment

Research the clinical application of predictive biologic markers (antithyroid antibodies) and the discovery of new markers (proteomic and molecular DNA) that predate disease in people with Down syndrome

Explore the role of autoimmune thyroid disease and the clustering effect of autoimmune conditions seen in people without Down syndrome to determine if hypothyroidism in Down syndrome could potentially indicate a higher risk of other autoimmune conditions more common in this population

Celiac Disease

Describe specific HLA antigen types and risks for developing autoimmune disorders in adults with Down syndrome

Correlate HLA antigen type with tTG-IgA levels and small-bowel biopsy results in adults with Down syndrome

Compare magnitudes of tTG-IgA values to help define cutoffs more appropriate for adults with Down syndrome. Formalize a diagnostic protocol for celiac disease in Down syndrome

Abbreviations: AAI, atlantoaxial instability; HLA, human leukocyte antigen; IDD, intellectual and developmental disability; tTG-IgA, tissue transglutaminase IgA.

[a] For a complete list of all future research priorities, see eTable 3 in Supplement 1.

be mistaken as indicative of pathology. Recommendations 1 and 2 highlight the importance of referral to an experienced clinician and use of tools designed for individuals with intellectual and developmental disabilities if concerns for mental health disorders such as depression, anxiety, or regression arise.

Although prevalence of AAI was found to be approximately 10%, no studies assessed whether screening using cervical radiographs allows identification of otherwise asymptomatic individuals at risk for SCI. Participation in physical activities offers highly desirable, potential physical and psychological benefits. In the absence of other evidence, reports from Special Olympics organizers of no SCI over the past 20 years was considered. After considering the potential benefits and harms (including SCI), a weak recommendation was made against cervical spine radiography for screening asymptomatic individuals, reasoning that no evidence suggests that cervical spine radiographs are helpful, whereas restricting patients from physical activity has known harms.

In some cases for which no evidence was identified, aspects of care many would consider standard were highlighted. To accomplish this, 4 SOGPs were formulated pertaining to mental health

disorders (SOGP 1 and SOGP 2), healthy practices for obesity (SOGP 3), and assessment for signs/symptoms of celiac disease at annual examinations (SOGP 4) (Table 1). Based on identified evidence gaps, key priorities for future research across each clinical domain were identified (**Box 2**; eTable 3 in Supplement 1).

Limitations

The guideline development process had several limitations. First, limited evidence meant recommendations were often based on little, indirect, or low-quality evidence. However, it is important to provide guidance where possible, despite very low-quality evidence, as others have affirmed.[63] Second, recommendations for screening interventions would ideally be based on clinical trials that demonstrated that screening resulted in better clinical outcomes. However, because it was anticipated that the evidence would be limited, PICO questions were formulated to identify whether sufficient evidence justified alterations to existing guidance for the general population (eg, initiating screening earlier based on higher prevalence at earlier age). Although the Evidence-to-Decision framework is typically used for interventions, using this framework provided a transparent, systematic process for considering benefits, harms, and other important factors in drafting clinical guidance.

Conclusions

These evidence-based practice guidelines provide recommendations to support primary care of adults with Down syndrome. The lack of high-quality evidence limits the strength of the recommendations and highlights the need for additional research.

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RESEARCH REVIEW

Pneumonia and respiratory infections in Down syndrome: A scoping review of the literature

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Abstract

Pneumonia and respiratory infections impact infants and children with Down syndrome; pneumonia is a leading cause of mortality in adults with Down syndrome. We aimed to review the literature to evaluate gaps and address key questions. A series of key questions were formulated a priori to inform the search strategy and review process; addressed prevalence, severity, etiology, risk factors, preventive methods, screening, and financial costs, potential benefits or harms of screening. Using the National Library of Medicine database, PubMed, detailed literature searches on pneumonia and respiratory infections in Down syndrome were performed. Previously identified review articles were also assessed. The quality of available evidence was then evaluated and knowledge gaps were identified. Forty-two relevant original articles were identified which addressed at least one key question. Study details including research design, internal validity, external validity, and relevant results are presented. Pneumonia and respiratory infections are more prevalent and more severe in individuals with Down syndrome compared to healthy controls through literature review, yet there are gaps in the literature regarding the etiology of pneumonia, the infectious organism, risk factors for infection, and to guide options for prevention and screening. There is urgent need for additional research studies in Down syndrome, especially in the time of the current COVID-19 pandemic.

KEYWORDS

Down syndrome, pneumonia, respiratory, trisomy 21

1 | INTRODUCTION

Pneumonia and respiratory infections are an important consideration in individuals with Down syndrome (DS) at the beginning and the end of life. Early in life, infants with DS are at an increased risk for dysphagia and silent aspiration, both of which are risk factors for and can present as pneumonia (Stanley et al., 2019). In the first year of age, pneumonia is associated with dysphagia in children with DS (Jackson, Maybee, Wolter-Warmerdam, DeBoer, & Hickey, 2019). Then, in childhood, pneumonia is the #1 cause of hospital admissions, and lower respiratory tract infections accounted for 40% of admissions (Hilton, Fitzgerald, & Cooper, 1999). Of ICU admissions for DS, 10 of 23 (43%) were due to pneumonia and five of 23 (22%) which required use of a ventilator were due to pneumonia (Hilton et al., 1999). In children with neurologic disorders, including DS, respiratory syncytial virus (RSV) was a common cause of community-acquired pneumonia (Millman et al., 2016). And children with DS and concurrent RSV infection are at increased risk for hospitalization, mortality, and need for mechanical ventilator support compared to controls (Beckhaus & Castro-Rodriguez, 2018). Children with DS can have pulmonary complications, such as pulmonary hypertension, sleep-disordered breathing and airway anomalies, as well as respiratory infections (McDowell & Craven, 2011).

Then, later in life, pneumonia is seen as a cause of death in DS. In 151 deceased adults with Down syndrome (DS), the largest contributors to in-hospital mortality were: respiratory failure, dementia, and pneumonia (Uppal, Chandran, & Potluri, 2015). In adults with DS, there was an increased incidence of pneumonia and respiratory failure in comparison to controls (Uppal et al., 2015). Pneumonia has been known to be a leading cause of death in DS for decades (Weiner & Stimson, 1948).

Taken together, we know that pneumonia is an important cause of morbidity in childhood, and later is a relevant cause of mortality in adulthood. It is unclear if these two findings are related to a common etiology. Further, it is also unclear how pneumonia might impact those with DS from adolescence to early adulthood. We began this review to understand what is known about pneumonia in individuals with DS across the lifespan. We wanted to know if pneumonia is an ongoing concern throughout the lifespan as supported by the published literature. We also wanted to evaluate the literature for related questions, such as, the infectious organism causing pneumonia and respiratory infections or risk factors for developing pneumonia in DS. We wanted to evaluate gaps in the published literature to guide future research. Given that pneumonia and respiratory infections are of clinical importance in childhood, and then an important cause of mortality in adults with DS, we sought to increase awareness of this risk among geneticists providing care for patients with DS and highlight the need for additional research on this issue.

The overarching goal of this review was to use our literature review process which previously focused on health conditions in adults with DS (Capone et al., 2018) to focus on pneumonia and respiratory infections and expand to include the lifespan from birth to death. Specifically, we outlined these five goals:

Goal 1: Use PubMed to identify original research articles that address the prevalence, severity, etiology, risk factors, and methods of prevention, screening or evaluation of individuals with DS with pneumonia or respiratory infections.

Goal 2: Guided by key questions formulated a priori determine the quality of the available evidence (see Section 2 for the seven Key Questions).

Goal 3: Using the review articles on adults with DS in National Library of Medicine (NLM) database PubMed (MEDLINE) previously identified (Capone et al., 2018), review discussion of pneumonia and respiratory infections.

Goal 4: Identify critical areas of deficit in our clinical knowledge.

Goal 5: Discuss the implication of these findings for the development of practice guidelines and the direction of future clinical research.

2 | METHODS

The Down Syndrome Medical Interest Group DSMIG-USA Adult Health Care Workgroup consists of physicians and medical professionals providing care to individuals with DS, who are members of the Down Syndrome Medical Interest Group. Previous review focused on prevalence, public health importance, and impact on clinical practice (Capone et al., 2018; Capone et al., 2020). Using the literature review framework in those previous reviews, in this literature review we focused on pneumonia and respiratory illness due to its high impact on morbidity and mortality. Literature review was conducted using the NLM PubMed database (NCBI 1943–2020).

2.1 | Key questions

In accordance with USPSTF practice we formulated a series of key questions as outlined in our initial review (Capone et al., 2018). By consensus the following seven key questions were formulated by the Workgroup:

1. What is the prevalence of pneumonia (and respiratory infections) in DS across the lifespan?
2. What is the clinical severity of pneumonia (and respiratory infections) in DS across the lifespan?
3. What are common etiologies of pneumonia (and respiratory infections) in DS across the lifespan?
4. In addition to DS, what other risk factors pose an increased risk for pneumonia (and respiratory infections)?
5. What has been studied for prevention of pneumonia (and respiratory infections) for individuals with DS?
6. Does screening for pneumonia (and respiratory infections) lead to reduced morbidity or mortality?
7. What are the financial costs, potential benefits or harms of screening for pneumonia (and respiratory infections)?

2.2 | PubMed literature search

Literature searches were conducted in 2020 using the NLM biomedical literature database PubMed (MEDLINE) (NCBI 1946–2020) to identify original research manuscripts addressing our prioritized topics. We used the Medical Subject Headings (MeSH) (the NLM controlled vocabulary thesaurus for indexing) to capture related entry terminology in our searches. For example, the MeSH term “Down syndrome” included the search entry terms: Downs syndrome, Down's syndrome, Mongolism, Trisomy 21, Partial Trisomy 21. The MeSH term “Down syndrome” was combined with other MeSH main heading terms related to pneumonia and respiratory illness (Table 1) to capture literature (unfiltered). Then, the limiters “Human”, “English” were applied to narrow the scope of the search (filtered). We did not use subject age as a limiter. Abstracts from Medline were reviewed and excluded according to their relevance in pertaining to key questions. Whenever an abstract made mention of any key question (or there was doubt) the full article was procured. Sections 2 and 3 were then reviewed to determine which articles met inclusion or exclusion criteria. A single reviewer from our group was chosen to conduct the literature searches, reviewed articles for inclusion, and extracted data. See Table 1 for results of PubMed searches, and Table S1 for details of extracted data.

TABLE 1 PubMed search terms, excluded and included articles by condition

Condition	MeSH search term(s) Down syndrome: ((“down syndrome”[mesh] OR “down syndrome”[tiab] OR “Down's syndrome”[tiab] OR “downs syndrome”[tiab] OR “trisomy 21”[tiab])) AND	Unfiltered search hits	Filtered search hits	Excluded from review	Included in review
Pneumonia	*Pneumonia*: *pneumonia* [MeSH major topic] *OR aspiration pneumonias* [MeSH terms] *OR atypical pneumonia, primary* [MeSH terms] *OR atypical pneumonia, primary* [MeSH terms] *OR bacterial pneumonia* [MeSH terms] *OR chlamydial pneumonia* [MeSH terms] *OR bronchial pneumonia* [MeSH terms]	185	137	103 Not key question (35) No original data (10) Case series <5 (54) No DS-specific data (4) Filter = not English (1)	33
Respiratory infection (virus or other)	Virus: Viruses [MeSH major topic] OR Respiratory syncytial virus [MeSH terms]	144	122	113 Not key question (38) Virus, not respiratory (43) No original data (4) Case series <5 (8) Filter = not human (20)	9

Article inclusion criteria were: data addresses at minimum one key question, supporting data is original (not previously published), case series includes >5 participants, or uses a cohort, case-series or case–control research design or randomized clinical trial. Exclusion criteria were: data does not address at least one key question, study uses an uninterpretable methodology, data has been previously published or does not provide supporting data. Using only the PubMed articles meeting inclusion, data pertaining to key questions was extracted from the abstract, Section 2, and 3 and entered into a preformatted Excel data template for analysis. See Table 2 for a summary of the articles used for the data extraction.

2.3 | Evidence ratings by condition

Included articles were critically appraised by reviewers to determine each study's research design, subject ascertainment, total number of subjects, source of control subjects, and the extent of internal validity and external validity. The evaluation of *internal validity* considers study design factors such as ascertainment and selection bias, test procedures and consideration of confounding variables. For example, the internal validity of a cohort study is rated as good if it “Meets all criteria: comparable groups are assembled initially and maintained throughout the study (follow-up ≥80%); reliable and valid measurement instruments are used and applied equally to all groups; interventions are spelled out clearly; all important outcomes are considered; and appropriate attention to confounders in analysis. In addition, intention-to-treat analysis is used for RCTs.” *External validity* considers the generalizability of findings to a broader (more representative) population (United States Preventative Services Task Force, 2015). See appendix VII in the USPSTF report for criteria on research design hierarchy and the rating system used for scoring internal and external validity. See Table 2 for summary of evidence rating, and the Table S1 for rating of each article.

2.4 | Other sources

Additional records identified through other sources of reference not indexed in PubMed included: books and book chapters (Chicoine & McGuire, 2010; Pueschel, 2006; Pueschel & Pueschel, 1992; Rubin & Crocker, 1989), guidance documents prepared for health providers (Sullivan et al., 2006; van Cleve, Cannon, & Cohen, 2006; Van Cleve & Cohen, 2006), and journal articles (Henderson, Lynch, Wilkinson, & Hunter, 2007; K. M. Jensen, Taylor, & Davis, 2013; Määttä et al., 2011; Real de Asua, Quero, Moldenhauer, & Suarez, 2015; van Allen, Fung, & Jurenka, 1999; van Buggenhout et al., 1999; Prasher, 1994; Kerins, Petrovic, Bruder, & Gruman, 2008). These sources were identified through previous Workgroup review (Capone et al., 2018; Capone et al., 2020). Review of these additional records is presented separately in the Section 2.

3 | RESULTS

3.1 | Original literature review

Through review of the literature, we identified 42 total articles which fit our criteria of having original data, answering a key question, in

TABLE 2 Characteristics of the articles used for data extraction by condition

	Publications (N) dates	Subjects (N)	Age range	Source of subjects	Methods	Study designs	Research design hierarchy	Internal validity category	External validity category
Pneumonia	(20) 1982–2018	DS = 13,765	Newborn–74 years	Hospitals, parent conference, inpatient database, outpatient clinics, survey, death records and mortality database	Prospective survey, retrospective review,	Cohort (14), case–control (6), Matched case–control (1)	II-2 (10), III (10)	Good (14), Fair (6)	Fair (16), Good (3)
Viral respiratory infection	(9) 2007–2017	DS = 3,441	Newborn–2 years	National registers, databases, hospitals	Retrospective review, prospective observation	Case–control (5), Matched case–control (2), Cohort (2)	II-2 (7), III (2)	Good (7), Fair (2)	Fair (7), Good (2)
Pneumonia or respiratory infection: In subset of DS with specific comorbidity	(13) 1986–2018	DS = 1,876	Newborn–21 years	Medical centers, hospitals, outpatient clinics, databases	Retrospective review, prospective observation	Cohort (11), case–control (2)	III (12), II-2 (1)	Fair (7), Good (6)	Fair (12), Good (1)

humans, and reported on more than five cases (Figure 1). These articles were published from 1982 to 2018 and included patients from newborn to age 74 years. Among those with age listed, most were focused on pediatric patients or mortality data (Figure 2). Various study designs were used and included retrospective review of databases, registries, clinical visits in the electronic medical record, and survey. Through use of databases and registries, some articles had large sample size and in total, these 42 articles summarize data from 17,817 individuals with DS. Of these 42 articles, 13 used a case–control design, 27 reported on cohorts, and three were matched case–control studies. From the case–control studies, studies used inpatient admission data of patients without DS (Cairo et al., 2019; Jensen et al., 2015; Kristensen, Hjuler, Ravn, Simões, & Stensballe, 2012; Pérez-Padilla et al., 2010; Ramphul, Mejias, & Joynauth, 2019; Sánchez-Luna et al., 2017; Zachariah, Ruttenber, & Simões, 2012; Zhang, Guo, Langley, & Bai, 2013) healthy controls (Boylan et al., 2016; Megged & Schlesinger, 2010; Uppal et al., 2015), and sibling controls (Bloemers et al., 2007; Nisihara, Utiyama, Oliveira, & Messias-Reason, 2010). Of the 42 articles, 29 provide data which is most relevant to individuals with DS in general, while 13 articles focused on a subset within DS with a specific comorbidity (Table 3).

Data extracted from original literature review which addressed one of our seven key questions is presented here:

1. What is the prevalence of pneumonia (and respiratory infections) in DS across the lifespan? Nine articles provided data on prevalence with 20% of 105 and 36% of 70 outpatients with DS reporting having pneumonia (Kapoor, Bhayana, Singh, & Kishore, 2014; Skotko, Davidson, & Weintraub, 2013), recurrent pneumonia in 16% of 70 and 21% of 150 outpatients with DS (Kapoor et al., 2014; Nisihara et al., 2010), and frequent or major respiratory tract infections in 34% of 237 patients with DS (Hou & Wang, 1989). Pneumonia was the cause for admission in 1,757 admissions (26%) of patients with DS (Jensen et al., 2015). The ages of patients in eight of these prevalence articles ranged from birth to 21 years; one article studied prevalence of pneumonia in adults and found that pneumonia was the highest reason for hospital admission in 30% of adults over 21 (Hayes, Kutty, Thomas, Johnson, & Yetman, 2017). One article studying 558 individuals with DS found that pneumonia was increased in prevalence compared to controls (RR: 6.598, 95% CI: 4.444–9.795) ((Uppal et al., 2015). Three articles reported on the prevalence of RSV: with 10% of 814 and 13% of 630 patients with DS hospitalized for RSV (Grut, Söderström, & Naumburg, 2017; Zachariah et al., 2012) and 18% of 222 hospitalizations in DS due to RSV (Megged & Schlesinger, 2010); these three articles focused on age birth to 2 years.

2. What is the clinical severity of pneumonia (and respiratory infections) in DS across the lifespan? Thirteen articles provided data indicating increased severity of illness as a result of respiratory infection among individuals with DS. The studies showed increased rate of hospitalizations for pneumonia in DS (25.6% of 6,869) compared to controls (6.4% of 99,305, $p < .01$) (Jensen et al., 2015), greater likelihood to require admission for respiratory infections (OR: 2.1, 95%

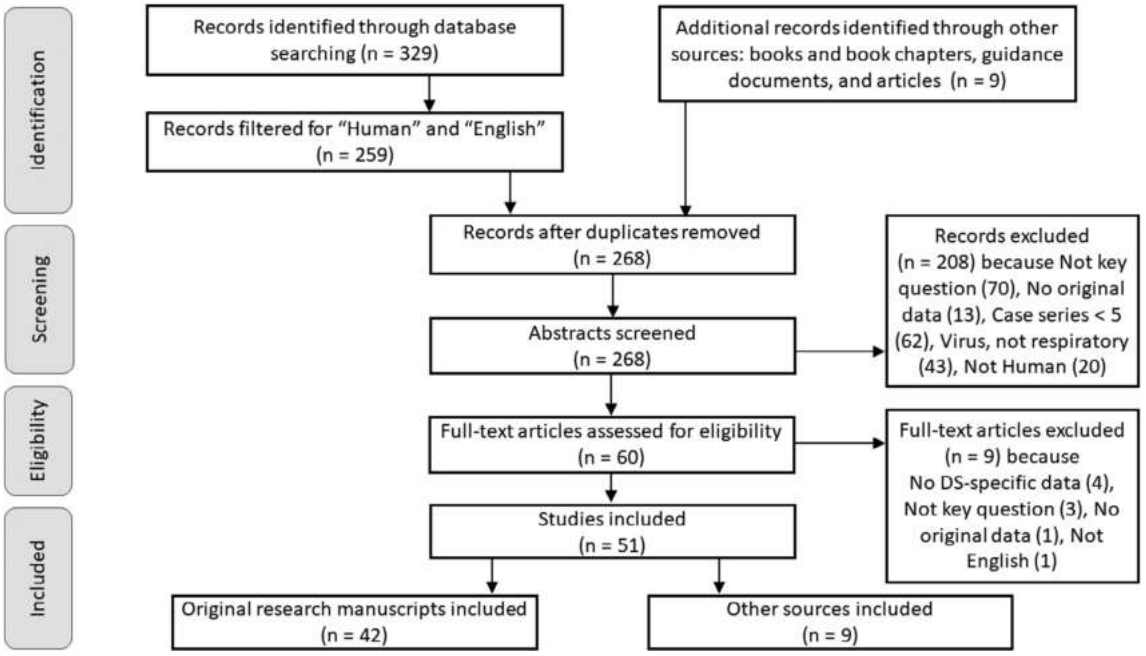

FIGURE 1 PRISMA diagram of articles identified, screened, eligible, and included in review of pneumonia and respiratory illnesses in Down syndrome

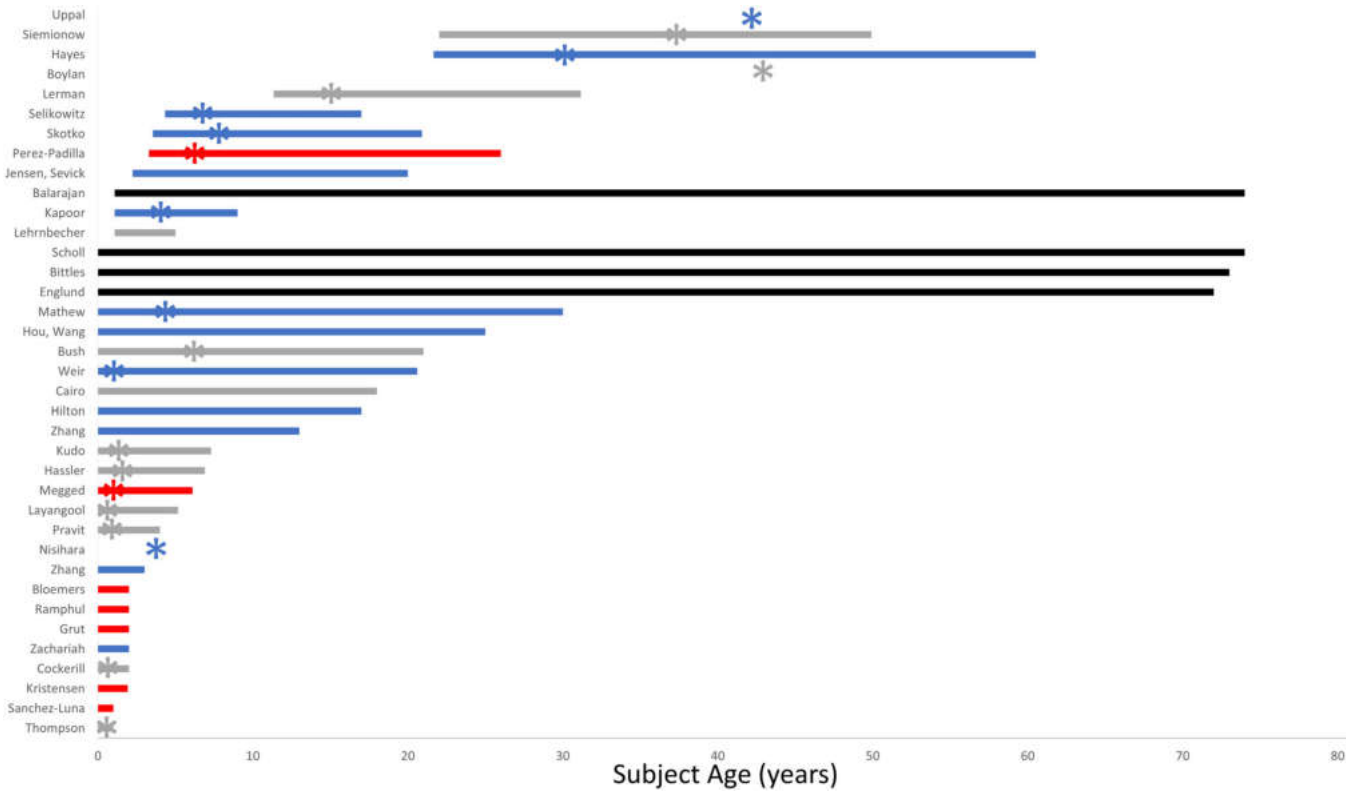

FIGURE 2 Subject ages in 37 articles identified through literature review on pneumonia and respiratory infections in Down syndrome. Bars show the age range of subjects included in the study by the first author on the y-axis, asterisks show mean or median. Articles are color-coded by topic: pneumonia, blue; virus, red; comorbidity, gray; death record data, black [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Twenty-nine articles answering key questions—pneumonia (PNA) and respiratory infections in Down syndrome (DS)

First author	Year	N w/ DS	What is the prevalence across the lifespan?	What is the clinical severity across the lifespan?	O key questions:	USPTF rating research design/ internal validity/external validity
Jensen	2015	6,869 hosp with DS	Of 6,869 hospitalizations with DS, 1,757 were admissions due to PNA (25.6%)	Increased admissions in comparison to non-DS (6.4% of 99,305, $p < .01$)	Risk factor for PNA: Higher elevations (>1,500 m)	II-2/good/good
Kapoor	2014	70	Symptoms (tachypnea or PNA) in 36%, recurrent PNA in 16%, admissions due to PNA or LRI in 13%, in genetics clinic cohort			III/fair/fair
Selikowitz	1992	204	Parents report 8 with bronchitis and 2 with PNA			III/fair/fair
Nisihara	2010	150	Of 150 with DS in clinic, 32 patients with RECURRENT PNA (21%)			III/fair/fair
Hilton	1999	86	86 patients had 232 admissions; of those with respiratory cause (54%), 18% were due to PNA, 7% bronchiolitis, and 6.5% croup.	Of the 232 admissions of patients with DS, 23 to ICU (equal to 14 pts); 24 newborns to PICU (of which 3 needed mechanical ventilation). Median length of stay for: T21 with pneumonia = 8 days, T21 + CHD with pneumonia = 10.9 days, comp. To controls = 4.5 days.	Risk factor: Respiratory infection is risk for 20 PNA Costs: Total cost for PNA admission 2–3-fold increased for T21 ($3904, $5319) comp. To non-T21 ($2180).	II-2/good/fair
Skotko	2013	105	Of 105 in DS clinic, PNA in 21 (20%) and RSV hosp. In 14 (13.3%).			II-2/good/fair
Zhang	2013	35	Of 10,836 hospital admissions for CAP, 810 needed ICU. Among these, 35 with DS, of which 10 had DS + CHD.	On regression analysis, among those with PNA admitted to PICU, T21 risk factor for fatality (OR: 6.823, 95% CI: 2.446–19.032).	Etiology: Infectious organism id'd in 21—RSV(9), Influenza (3), S. pneumo (3), Hib (2), M. pneum (2), Other (2)	III/good/fair
Hayes	2017	193	Of 193 adults at tertiary care center, highest reason for admission was pneumonia— in 37 (30%).	23 deaths due to: CHF (57%), and pneumonia (17%), among others.		III/good/fair
Zhang	2013	9	Of 295 admit to ICU for PNA, 9 with DS	In multivariate analysis, T21 associated with risk for death in RSV.		III/fair/fair
Medrano	2007	760 with CHD	Of 79 hospitalizations, 17.7% for T21.	Among those with CHD, T21 is risk factor for admission for respiratory infections (OR: 2.1, 95% CI: 1.1–4.2).		II-2/good/good
Weir	2007	150 who had VFSS			Risk factor: Among those with VFSS, DS is a risk factor to develop PNA (OR: 22.10); abnormal VFSS increases risk for PNA.	III/fair/poor

TABLE 3 (Continued)

First author	Year	N w/ DS	What is the prevalence across the lifespan?	What is the clinical severity across the lifespan?	O key questions:	USPTF rating research design/ internal validity/external validity
Hou	1989	237	81 (34%) with frequent or major respiratory tract infections.	14 of 28 deaths due to PNA; 1 isolated, 13 with CHF/CHD		III/good/fair
Balarajan	1982	37 deaths		10 died of bronchopneumonia		III/fair/fair
Mathew	1990	284		PNA was COD in 5 of 20 who died during time of study		II-2/good/fair
Scholl	1982	793		Resp. tract infections were leading COD for all ages; PNA was COD in 127. Influenza deaths increased for age 20–34+ yrs.		II-2/good/fair
Oppewal	2018	45 deaths		Resp. disease is the largest 1^{O} COD; resp failure COD in 33.		II-2/good/fair
Uppal	2015	558; 151 deaths	Increased prevalence of PNA in DS comp to controls (RR: 6.598, 95% CI: 4.444–9.795).	PNA is a RF for in-hospital mortality (RR:11.946, 95% CI: 7.292–19.569); PNA is one of the most sig factors related to mortality. Respiratory failure predicts mortality in DS comp to controls.		II-2/good/good
Bittles	2006	1,332; 298 deaths		PNA and resp. infections are COD through the lifespan: 33.1% in childhood (0–18 yrs), 23.1% in adulthood (19–40 yrs), 39.6% over 40 yrs.		II-2/good/fair
Englund	2013	1,930 deaths		PNA is leading COD from 1969 to 2003; 40.9% of total deaths. PNA as COD is more frequent than in the general population (SMOR: 5.580)		II-2/good/fair
Zachariah	2012	630	Of 630 with DS, 85 admitted for RSV (13%)	Increased risk of hospitalization vs. control: OR: 5.99, 95% CI: 6.68–5.38.	Risk factor: Co-infection with RSV and bacterial PNA	III/good/fair
Grut	2017	814	Of 814 with DS, 82 hospitalized with RSV; rate of hospitalization = 10%. Hazard ratio for DS 0–1 year of 4.00 (95% CI: 1.58–10.13), hazard ratio for DS 0–2 years of 6.60 (95% CI: 2.83–15.38)	Hospitalizations cont into the second year of life for DS only.		II-2/good/fair
Manzoni	2017	459		DS predicts RSV hospitalizations (OR: 2.25, 95% CI:1.31–3.89)		II-2/good/fair
Ramphul	2016	806	Of 72,151 RSV cases, 806 had DS (1%).Of 14,029 DS adm (6%) for RSV.	DS longer LOS (10.7 days) than controls and higher $ of stay ($p < .01$)		II-2/good/good

(Continues)

TABLE 3 (Continued)

First author	Year	N w/ DS	What is the prevalence across the lifespan?	What is the clinical severity across the lifespan?	O key questions:	USPTF rating research design/ internal validity/external validity
Kristensen	2012	399	Of 399 with DS, 78 hospitalized with RSV	DS is a RF for hospitalization (IRR: 3.43, 95% CI: 2.66–4.42) and for duration of hospitalization.		II-2/good/fair
Paes	2012	193	Of 193 with DS, 13 hospitalized with resp infection (7%); 3 were + RSV.			III/fair/fair
Perez-Padilla	2010	60		In H1N1 pandemic, greater likelihood of hospitalization (crude OR: 15.9), intubation (crude OR: 8.2), and death (crude OR: 335) in DS.		III/fair/fair
Megged	2010	222	Of 222 with DS hospitalized at medical center, 41 hospitalizations of 39 children with RSV; rate of hospitalization for RSV = 18%.	In RSV infection, patients with DS were older than and needed longer hospitalization; mean duration of hospitalization in DS = 10.9 days		II-2/good/fair
Bloemers	2007	395	Of 395 with DS, 9.9% hospitalized for RSV.	DS is a risk factor for severe RSV (OR: 12.6, 95% CI: 2.9–54.5)		II-2/good/fair
Sanchez-Luna	2016	93	Of 93 infants with DS, 44.1% were hospitalized for RSV.	Higher hospitalization rate for RSV in DS vs. controls (7.7%). More frequent RSV hospitalizations.	Prevention: 33 of 93 with DS received RSV prophylaxis; of those, only one was admitted for RSV (vs. 8 of 60 who did not).	II-2/good/good

Note: US Preventative Task Force Ratings: I, II-1, II-2, II-3, III—for Research design; Good, Fair, Poor—for Internal validity; Good, Fair, Poor—for External validity (generalizable).
Abbreviations: CHD, congenital heart disease; CHF, congestive heart failure; CI, confidence interval; COD, cause of death; ICU, intensive care unit; IRR, incidence rate ratio; LOS, length of stay; LRI, lower respiratory infection; OR, odds ratio; resp., respiratory; RF, risk factor; RR, relative risk; RSV, respiratory syncytial virus; T21, trisomy 21.

CI: 1.1–4.2) (Medrano et al., 2007), and increased likelihood of admission to intensive care unit or need for mechanical ventilation (Hilton et al., 1999). Among those with community-acquired pneumonia requiring admission to the pediatric ICU, DS was associated with greater chance of fatality compared to those without DS (Zhang, Guo, Bai, & MacDonald, 2013). Similarly, in those with RSV infection, DS was associated with increased risk of death compared to those without DS (Zhang, Guo, Langley, & Bai, 2013). Eight of the articles addressing viral respiratory infection included data indicating severity of infection. DS was an identified risk factor for severe RSV (Bloemers et al., 2007), for hospitalization with RSV (Manzoni et al., 2017; Sánchez-Luna et al., 2017), for longer duration of hospitalization (Kristensen et al., 2012), and increased cost of hospitalization (Ramphul et al., 2019). Hospitalizations for RSV can continue into the second year of age for children with DS, but did not occur in controls (Grut et al., 2017). One pediatric cohort impacted by 2009 H1N1 influenza infections showed increased risk of hospitalization (16-fold), intubation (eightfold), and death (335-fold) in those with DS compared to controls (Pérez-Padilla et al., 2010). Eight articles with subjects of varying ages found that pneumonia or respiratory tract infections were the cause of death in DS; three cohort studies found pneumonia as the cause of death in 25–50% of adults with DS (Balarajan, Donnan, & Adelstein, 1982; Hou & Wang, 1989; Mathew et al., 1990), one found respiratory disease to be the largest primary cause of death in hospital records (Oppewal et al., 2018), while four identified pneumonia and respiratory tract infections as the leading cause of death from national death records (Bittles, Bower, Hussain, & Glasson, 2007; Englund, Jonsson, Zander, Gustafsson, & Annerén, 2013; Scholl, Stein, & Hansen, 1982; Uppal et al., 2015). Uppal et al. compared mortality data in 558 with DS to 5,580 gender-matched controls, showing that respiratory failure was a predictor of mortality in DS only (RR: 9.791, 95% CI:1.600–59.928), while pneumonia was a risk factor for mortality in DS (RR: 4.475, 95% CI: 1.531–13.077) and controls (RR: 6.643, 95% CI: 3.362–13.129)(Uppal et al., 2015) One study of mortality in DS through the lifespan found pneumonia as the cause of 33.1% of 148 deaths in childhood, 23.1% of 39 in adulthood, and 39.6% of 111 deaths in those over age 40 (Bittles et al., 2007).

3. What are common etiologies of pneumonia (and respiratory infections) in DS across the lifespan? One article included details regarding the specific infective organisms underlying pneumonia in the sample of individuals with DS (Zhang, Guo, Bai, & MacDonald, 2013). This study showed 21 individuals with DS and congenital heart disease had had six different identified infective organisms; 14 patients had a viral cause and seven were bacterial (Zhang, Guo, Bai, & MacDonald, 2013). Among the articles focused on specific comorbidities in DS, specific pathogens for infection were reported in two articles focused on specific protocols for patients with DS and leukemia (Hassler et al., 2016; Lehrnbecher et al., 2004).

4. In addition to DS, what other risk factors pose an increased risk for pneumonia (and respiratory infections)? Four articles identified general risk factors for patients with DS to develop pneumonia, including: co-infection with RSV (Zachariah et al., 2012) or other respiratory infection (N = 3 of 86) (Hilton et al., 1999), higher geographic elevation (35.5% of 429 at >1,500 m elevation compared to 24.9% of 6,440, 95% CI, −1.9% to 23.1%) (Jensen et al., 2015), and an abnormal videofluoroscopic swallow study (N = 6 with DS) (Weir et al., 2007) though it is unclear if these factors differ from controls. A protective factor reported in one study with a small sample (N = 33 with DS who received RSV prophylaxis vaccination), was use of RSV prophylaxis vaccination prior to hospitalization for acute respiratory tract infections; of the nine patients admitted for RSV, one had received RSV prophylaxis vaccination and eight had not (Sánchez-Luna et al., 2017). Eleven articles describe specific cohorts with DS and an additional diagnosis which may give insight into risk factors. Specifically, pneumonia and respiratory infections were described in those: undergoing treatment for DS-AML (Hassler et al., 2016; Kudo et al., 2007; Lehrnbecher et al., 2004), with congenital heart disease (Bush et al., 2018; Layangool et al., 2014; Thompson, McElhinney, Jue, & Hodge, 1999), and those who had undergone orthopedic procedures (Boylan et al., 2016; Lerman, Emans, Hall, & Karlin, 2003; Siemionow, Hansdorfer, Janusz, & Mardjetko, 2017), intestinal surgeries (Buchin, Levy, & Schullinger, 1986; Cairo et al., 2019), or airway procedures (Cockerill, Frisch, Rein, & Orvidas, 2016; Pravit, 2014). Airway anomalies, GERD, and pulmonary hypertension were associated with recurrent pneumonia (Bush et al., 2018; Pravit, 2014; Thompson et al., 1999).

5. What has been studied for prevention of pneumonia (and respiratory infections) for individuals with DS? No articles addressed this question through original data presented.

6. Does screening for pneumonia (and respiratory infections) lead to reduced morbidity or mortality? Although articles showed that pneumonia is a risk factor for mortality (Uppal et al., 2015), no articles addressed the impact of screening for pneumonia on morbidity or mortality through original data presented.

7. What are the financial costs, potential benefits or harms of screening for pneumonia (and respiratory infections)? Although articles showed the increased cost of hospitalization for pneumonia and RSV infections in those with DS (Hilton et al., 1999; Ramphul et al., 2019), no articles addressed the cost, benefits or harms of screening for pneumonia through original data presented.

The authors drafted recommendations for prospective research studies to address the gaps identified in our review, and summarized in Table 4.

The data that support the findings of this study were derived from the following resources available in the public domain: PubMED at https://www.ncbi.nlm.nih.gov/pubmed/ and the full data from our review is listed in the Table S1.

3.2 | Other sources

Nine additional records identified through previous review, including key review articles were evaluated for specific information related to pneumonia and respiratory infections which addressed one of the

TABLE 4 Recommended study to fill gaps in Key Questions (prevalence, severity, etiology, risk factors, preventive methods, screening, and financial costs, potential benefits or harms of screening) in Down syndrome

Recommendation for prospective study to fill identified gaps	Key question to be addressed
Collection of samples to identify the specific pathogen(s) which cause pneumonia and respiratory infections for individuals with DS	Etiology
Evaluate the cause of pneumonia in adults with DS to understand why it is the leading cause of death in DS, and learn ways to prevent it	Etiology/potential screening
Study within DS cohorts to evaluate multiple etiologies such as, hypotonia, GERD, relative immunodeficiency (Ram & Chinen, 2011), or risk of leukopenia (Akin, 1988) in relation to risk for pneumonia and respiratory infection	Risk factors
In patients with DS, evaluate if trouble swallowing and PNA could be a heralding sign of mortality in those with AD as in the non-DS population	Risk factors
Future study could evaluate if clinical history from patient and caregiver regarding associated symptoms such as, coughing, gagging, choking can predict which patients will develop pneumonia	Risk factors/ potential screening
Evaluate the effectiveness of vaccination and vaccine strategies to prevent pneumococcal pneumonia in children and adults with DS	Preventive methods
Evaluate potential harms and costs of vaccination in children and adults with DS; include if vaccination decreases costs related to hospitalizations or decreased intensive care unit admissions	Preventive methods
Evaluate the effectiveness of other vaccines (influenza, respiratory syncytial virus, and eventually COVID-19) in children and adults with DS as well as harms and costs	Preventive methods
Lack of data on prevention and screening: Studies on immune response to standard childhood and adult vaccinations in DS population to evaluate if the immune response is complete or blunted	Preventive methods
Prospective evaluation of the benefit of RSV prophylaxis could be useful to guide universal administration to all patients with DS	Preventive methods

seven key questions of: prevalence, severity, etiology, risk factors, preventive methods, screening, and financial costs, potential benefits or harms of screening through the lifespan (Capone et al., 2018; Capone et al., 2020).

In one study, the prevalence of pneumonia in DS differed by age with 40% age 0–29 years, and 31% age 30 years and older impacted (Määttä et al., 2011). Among participants of all ages, 47 (34%) had pneumonia at least once in the lifetime and 25 (18%) had repeated pneumonias, some because of aspiration (Määttä et al., 2011). In van Allen et al., (van Allen et al., 1999), in a cohort in a residential facility, up to 55.2% of adults with DS had documented pneumonia some time during their residence. Recurrent pneumonia with incomplete recovery occured more often as mobility declined with prevalence of 50% in 18 patients age 30–43 years, and 60% in 20 patients age 47–68 years; and some (30% of 20 patients age 47–68 years) had chronic interstitial changes of the lungs of insidious onset, attributable to chronic, recurrent aspiration (van Allen et al., 1999). Lower esophageal sphincter incompetence and gastroesophageal reflux disease, obesity, and a sedentary lifestyle were risk factors for aspiration (van Allen et al., 1999). One review article noted pneumonia as a cause of death; two specific cases of a patient with DS who died of pneumonia in 30s and a second with DS who died of pneumonia in 50s were provided (van Allen et al., 1999) In that study, five of nine elderly adults with DS were deceased with AD and pneumonia (van Allen et al., 1999). One article described the immunization status among 89 adults with DS and found that while all individuals followed "standard immunizations", only 28 (44%) had been immunized against influenza, 24 (38%) against pneumococcus, and none were immunized against hepatitis B (Henderson et al., 2007). Pneumonia or respiratory infections were not noted in three review articles (Henderson et al., 2007; Jensen et al., 2013; Real de Asua et al., 2015).

4 | DISCUSSION

Pneumonia disproportionately impacts individuals with DS through the lifespan: beginning in infancy, and then as an important cause of mortality (Uppal et al., 2015; Weiner & Stimson, 1948). This is an important, timely topic given the current COVID-19 pandemic and evidence that COVID-19 may present a greater risk for people with IDD (Turk, Landes, Formica, & Goss, 2020). We began this literature review of pneumonia and respiratory infections in DS throughout the lifespan, to answer key questions and to identify gaps in the literature. Given that many geneticists provide care for patients with DS, this literature review raises awareness of pneumonia and respiratory infections for clinical care and to guide future research. We know that individuals with DS have:

1. An increased prevalence of pneumonia and risk of hospitalization.
2. An increased severity of illness, including risk of mechanical ventilation.
3. Specific increased individual periods of heightened risk including treatment for leukemia and postoperatively.

Through literature review and analysis of review articles, we identified 42 articles which addressed at least one of our key questions about prevalence, severity, risk factors and the link of pneumonia to mortality. The prevalence of pneumonia was found to be increased sevenfold in DS compared to controls (Uppal et al., 2015); with

increased number of admissions for pneumonia relative to controls (Jensen et al., 2015). The severity of illness was increased in individuals with DS and respiratory infection compared to controls as reflected in an increased risk of hospitalization for pneumonia and for RSV, a greater likelihood to require admission for respiratory infections, and an increased likelihood of admission to intensive care unit or need for mechanical ventilation. The articles reviewed did not give data to explain why the prevalence and severity of pneumonia and respiratory infections are increased in DS; in our opinion, multiple etiologies such as, hypotonia, GERD, relative immunodeficiency (Ram & Chinen, 2011), or risk of leukopenia (Akin, 1988) could be considerations. We suggest that the etiology may be multifactorial, and we feel this is an important area for future research.

In order to improve the outcomes and change the trajectory for individuals with DS, it is necessary to focus on these critical areas which were identified in this literature review:

1. The knowledge gaps in infectious organism identification.
2. The lack of data on prevention and screening of risk factors for pneumonia.
3. An estimate of the financial costs and potential benefits of preventing pneumonia.

Given the increase in prevalence and severity compared to controls, it is important to remain vigilant to diagnose, treat, and prevent pneumonia and respiratory infections in individuals with DS. The specific infectious etiology of pneumonia was only given in one article, and did not show a consistent pathogen but rather a variety of causes. Identifying the specific infectious etiology could have important implications on prevention (e.g., through the use of pneumococcal vaccination to prevent *S. pneumoniae*), on antibiotic choice, and on identification of the underlying risk factor (e.g., a broad range of infectious organisms could point to aspiration pneumonia[Mier et al., 1993], or if acquired during a hospital admission could suggest hospital-acquired pneumonia). Specific subgroups of patients with DS provide insight into potential risk factors, such as patients with leukemia or who are postoperative for procedures. Thus, for patients with DS undergoing procedures or with specific comorbidities, it is important to consider pneumonia in the appropriate clinical setting and to have a low threshold for considering further evaluation or treatment. No articles were identified that addressed the key questions of methods of prevention, screening, and financial costs of prevention or screening, potential benefits or harms of prevention or screening of individuals with DS with pneumonia or respiratory infections.

The quality of the available evidence was fair to good, with many studies consisting of single-site cohorts or case–controls, a few multisite clinical cohorts, and some use of national birth and death record data. Most studies involved retrospective review, limiting the ability to collect specific variables or conduct research laboratory evaluation. In the future, a prospective study could allow for collection of samples to identify the specific pathogen(s) which cause pneumonia and respiratory infections for individuals with DS. Many studies focused on either pediatric populations, or death records, with limited studies reporting on pneumonia and respiratory infections in living adults with DS in either an outpatient or inpatient setting.

Critical areas of deficit in our clinical knowledge were identified. These include studies addressing three of our key clinical questions: methods of prevention, screening, and financial costs, potential benefits or harms of screening or preventing pneumonia or respiratory infections in individuals with DS. The case–control studies to date have compared individuals with DS to controls; comparison between subsets of individuals with DS could provide insight risk factors to develop pneumonia. In addition, additional information regarding the etiology for pneumonia and respiratory infections in DS; including the specific pathogen(s), and the pathophysiology could be very useful to guide studies of prevention and screening. Studies of RSV infection in individuals with DS showed increased prevalence and severity, shown through need for hospitalization and length of hospitalization, compared to non-DS controls. Prospective evaluation of the benefit of RSV prophylaxis could be useful to guide universal administration to all patients with DS. Similarly, given the burden of disease associated with pneumonia in patients with DS and deficits in knowledge about causal agents, further study is needed to evaluate the effectiveness of vaccination and vaccine strategies to prevent pneumococcal pneumonia in children and adults with DS as well as harms and costs (Kusters et al., 2013; Nurmi, Leinonen, Häivä, Tiilikainen, & Kouvalainen, 1982).

Limitations of this literature review include reliance on data presented in the published literature; this could exclude data which is unpublished, or variables which were not reported in an original publication. In addition, our review relies on the use of PubMED to identify articles of interest. Although we use a broad search with various MeSH terms and MeSH headings, it is possible that a relevant article may not have been identified through our searches. Summarizing articles which use distinct methods (for example, how authors defined pneumonia differed using hospital ICD-9 codes, death record data, or clinical symptoms, or varying degrees of generalizability of the data) may be a source of bias. We present original numeric results, but this has the potential for vote-counting based on significance of the individual studies. To address this, we have provided detailed information, original data and statistics to the extent possible in the Table S1. Future study could include additional statistical analysis for effect sizes, or metanalysis. A single reviewer from our group was chosen to conduct the literature searches, reviewed articles for inclusion, and extracted data which may be a potential source for bias/error. To address this, other Working group members reviewed the extracted data and accessed original articles. No discrepancies were identified.

Study across the lifespan with greater detail, such as radiographic findings, clinical symptoms, lung involvement, site of acquisition, and infectious organism, could be useful in comparing and contrasting pneumonia and respiratory infections seen at different ages. For example, is the cause of pneumonia in infants different from the cause of pneumonia in adults; or is there a unifying underlying cause? Swallowing difficulty in infants with DS is linked to risk for pneumonia. Although swallowing abnormalities are frequent in adults with DS, aspiration has not been directly linked to risk for pneumonia in adults with DS (Jasien, 2016). Should swallowing dysfunction and aspiration

be found to cause for pneumonia in adults with DS, it would be important to identify the age when this becomes a concern. Future study could evaluate if clinical history of symptoms such as, coughing, gagging, choking can predict which patients will develop pneumonia. In the general population, swallowing trouble is one of the first symptoms of dementia or Alzheimer's Disease (AD) (Naruishi, Nishikawa, Kido, Fukunaga, & Nagata, 2018). If this is also true for adults with DS, then trouble swallowing and PNA could be a heralding sign of AD in DS. As we learn more about the cause of pneumonia in adults with DS, this information could help us understand why pneumonia is the leading cause of death in DS, and ideally, identify ways to prevent it.

Given that pneumonia is a frequent cause of mortality in DS, it could be clinically useful to identify what the symptoms of pneumonia are in DS, what the clinical signs of pneumonia are in DS, and what the risk factors for pneumonia are in DS. In clinic, a physician would then be aware to screen for and educate families on these topics. Unfortunately, there is not yet sufficient data to specify how geneticists should screen for pneumonia in DS, but it is clear that this is more prevalent, more severe, and more likely to be associated with mortality.

5 | CONCLUSION

Pneumonia and respiratory infections are more prevalent and more severe in individuals with DS. Pneumonia is the leading cause of death in DS. There is urgent need for additional research studies in DS to guide options for prevention and study of the etiology of pneumonia and respiratory infections throughout the lifespan.

CONFLICT OF INTEREST

Dr. Stephanie L. Santoro receives research funding from the National Institutes of Health. Dr. Stephanie L. Santoro receives research funding from the LuMind IDSC Down Syndrome Foundation to conduct clinical trials for people with DS and serves on the Professional Advisory Board for the Massachusetts Down Syndrome Congress. The other authors have no conflicts of interest relevant to this article to disclose.

AUTHOR CONTRIBUTIONS

All authors confirm that this manuscript has not been published previously and is not under consideration elsewhere, that all authors are responsible for reported research, and that all authors have participated in the concept and design, analysis and interpretation of data, drafting or revising of the manuscript, and have read and approved the submission to the journal. We look forward to your feedback and review of this manuscript.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study were derived from the following resources available in the public domain: PubMED at https://www.ncbi.nlm.nih.gov/pubmed/ and the full data from our review is listed in the Supplemental Table.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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REPÚBLICA DE COLOMBIA
RAMA JUDICIAL DEL PODER PÚBLICO

JUZGADO CUARENTA Y CINCO CIVIL DEL CIRCUITO
DE BOGOTÁ D.C.
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Bogotá D.C., 17 de marzo de 2021

Ordinario No. 2012 – 00256

1. De los informes periciales allegado por el INMLCF y CAJA DE COMPENSACIÓN FAMILIAR COMPENSAR que anteceden, se **CORRE** traslado a los extremos procesales de litis por el término de tres (3) días, con fundamento en el numeral 1 del artículo 238 del C de P.C.

NOTIFÍQUESE,

GLORIA CECILIA RAMOS MURCIA
Jueza

NOTIFICACIÓN POR ESTADO:

La providencia anterior es notificada por anotación en estado No. 027, del 18 de marzo de 2021.

MÓNICA TATIANA FONSECA ARDILA
Secretaria