Universitat Autònoma de Barcelona

Facultat de Medicina

Departament de medicina

Implicación de la introducción de la vacuna neumocócica conjugada heptavalente en niños en la enfermedad neumocócica invasiva en adultos.

Memoria presentada por

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Para optar al grado de Doctor en Medicina.

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Julio 2013

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Certifican que la tesis titulada

"Implicación de la introducción de la vacuna neumocócica conjugada heptavalente en niños en la enfermedad neumocócica invasiva en adultos"

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Dr. Vicenç Falcó Ferrer **Dr. Albert Pahissa Berga**

En Barcelona, 26 de Julio de 2013

A Àngela y Martí

A mis padres

Producción científica

Los resultados obtenidos durante el proceso de investigación que ha llevado a la elaboración de esta tesis doctoral han sido publicados previamente en revistas científicas indexadas:

Articulos originals

Burgos J, Lujan M, Falcó V, Sánchez A, Puig M, Borrego A, Fontanals D, Planes AM, Pahissa A, Rello J. *"The spectrum of pneumococcal empyema in adults in the early 21st century".* Clinical Infectious Diseases. 2011;53:254-61. (Impact factor 2011: 9.154)

Burgos J, Falcó V, Borrego A, Sordé R, Larrosa MN, Martinez X, Planes AM, Sánchez A, Palomar M, Rello J, Pahissa A. *"Impact of the emergence of non-vaccine pneumococcal serotypes on the clinical presentation and outcome of adults with invasive pneumococcal pneumonia".* Clinical Microbiology and Infection. 2012;19:385-91. (Impact factor 2011: 4.54)

Burgos J, Peñaranda M, Payeras A, Villoslada A, Curran A, Garau M, Riera M, Crespo M, Navarro J, Van den Eynde E, Planes AM, Ribera E, Pahissa A, Falcó V. "*Invasive Pneumococcal Disease in HIV-Infected Adults: Clinical Changes After the Introduction of the Pneumococcal Conjugate Vaccine in Children"*. Journal of Acquired Immune Deficiency Syndrome. 2012;59:31-8. (Impact factor 2012: 4.425)

Artículos de revisión (Anexo)

Burgos J, Falcó V, Pahissa A. "*The increasing incidence of empyema*". Current Opinion of Pulmonary Medicine 2013, 19: 350-6. (Impact factor 2012: 3.08)

Falcó V, Burgos J, Pahissa A. *"The Spectrum of Invasive Pneumococcal Disease in adults in the XXI Century"* . Clinical Pulmonary Medicine 2013. [Epub ahead of print].

Editoriales (Anexo)

Falcó V, Burgos J. "*Pneumococcal pneumonia: epidemiological, diagnostic and therapeutic changes".* Enfermedades Infecciosas y Microbiología Clínica. 2011;29:247-9. (Impact factor 2011: 1.941)

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ABREVIATURAS

CI: Intervalo de confianza.

ENI: Enfermedad neumocócica invasiva.

OR: Razón de probabilidades.

UCI: Unidad de cuidados intensivos.

VCP7: Vacuna conjugada-polisacárida heptavalente.

VCP10: Vacuna conjugada-polisacárida decavalente.

VCP13: Vacuna conjugada-polisácarida trecevalente.

VIH: Virus de la inmunodeficiencia humana.

VP23: Vacuna polisacárida veintitresvalente

I. INTRODUCCIÓN

INTRODUCCIÓN

Epidemiología y factores de riesgo de la enfermedad neumocócica

A pesar de los importantes avances que se han producido en los cuidados de los pacientes críticos, la aparición de nuevos antimicrobianos y el desarrollo de las vacunas antineumocócicas, las infecciones por neumococo siguen siendo causa de una gran morbi-mortalidad en todo el mundo. Se estima que cada año mueren por enfermedades neumocócicas 1.6 millones de personas, de las cuales entre 0.7 y un millón son niños menores de 5 años (1). La mayoría de estas muertes se producen en países en vías de desarrollo, donde las infecciones respiratorias siguen siendo la principal causa de muerte en los niños. En los países desarrollados la mortalidad es menor, aunque *Streptococcus pneumoniae* sigue siendo el agente causal más frecuente de neumonía adquirida en la comunidad y de meningitis bacteriana en el adulto (2). Un reciente estudio epidemiológico indica que cada año se producen en Estados Unidos 40.000 casos de enfermedad neumocócica invasiva produciendo 4000 muertes, la mayoría de ellas en ancianos (3). Además, el impacto económico que tiene dichas infecciones es altísimo. El coste de la neumonía adquirida en la comunidad en adultos se ha estimado en más de 20 billones de euros anuales en Estados Unidos y de 10 billones de euros anuales en Europa, ocupando el segundo puesto en la lista de enfermedades con mayor impacto económico (4,5). Teniendo en cuenta que el neumococo es responsable de más de la mitad de todos los casos de neumonía en todo el mundo, se puede valorar la importancia que tiene este microorganismo en el coste sanitario en los diferentes países.

El riesgo de padecer una enfermedad neumocócica depende, entre múltiples factores, de la edad. La incidencia de enfermedad neumocócica invasiva (ENI), definida por el aislamiento del *Streptococcus pneumoniae* en un liquido orgánico estéril (sangre, liquido cefalorraquídeo, liquido pleural, etc...) varía de forma importante en función de la edad. En los niños menores de 2 años, debido a la inmadurez de su sistema inmune la incidencia de ENI es muy alta, con tasas de hasta 35 casos por 100.000 personas-año. En la población adulta la incidencia oscila entre 4 casos por 100.000 habitantes años en los jóvenes de 18 a 34 años, a tasas de más de 35 casos por 100.000 habitantes-año en adultos de más de 65 años (1-3).

Las enfermedades de base son otro de los factores que condiciona un mayor riesgo de sufrir una infección neumocócica. En un amplio estudio publicado en 2005 se observó que la incidencia de ENI en población adulta sana era de 8.8 casos por 100.000 personas-año, mientras que esta aumentaba hasta 51.4 casos por 100.000 personas-año en adultos afectos de diabetes mellitus, 62.9 casos en adultos con enfermedad pulmonar crónica y 93.7 casos con cardiopatía crónica. Los grupos de mayor riesgo fueron los pacientes inmunodeprimidos, como

aquellos que padecen neoplasias sólidas (incidencia de 300.4 casos por 100.000 personas-año), infección por el virus de la inmunodeficiencia humana (VIH) (422.9 casos/100.000 personas-año) o neoplasias hematológicas (503.1 casos/100.000 personas-año) (6).

Un caso especial es el de los pacientes con infección por VIH. En este grupo debido a la aparición y generalización del tratamiento antirretroviral de alta eficacia y la consecuente mejora inmunológico de los pacientes, se ha producido una importante reducción de la incidencia de enfermedad neumocócica de hasta el 50% (7,8). Sin embargo, y pese a estos avances, las tasas actuales siguen siendo inaceptablemente elevadas, estimándose que aún presentan un riesgo de presentar una infección neumocócica 50 veces superiores al de personas de igual edad sin infección por VIH (7,9).

Los pacientes con patologías autoinmunes como son la artritis reumatoide, las espondiloartropatías, psoriasis o la enfermedad inflamatoria intestinal tienen también un mayor riesgo de padecer enfermedad neumocócica, en parte debido a la propia enfermedad pero principalmente en relación a los tratamientos inmunomoduladores (10,11). De hecho, la neumonía bacteriana es una de las infecciones más comunes observadas en pacientes que reciben tratamiento con fármacos anti α-TNF.

Por último, un grupo de riesgo que está aumentando en los últimos años son los receptores de trasplante, tanto de órgano solido como de médula ósea (12,13). Todos estos pacientes han de ser considerados como de alto riesgo para enfermedad neumocócica invasiva.

Con el progresivo envejecimiento de la población y el consecuente aumento de comorbilidades por un lado, y el avance de la medicina con la generalización del uso de fármacos inmunosupresores e inmunomoduladores para diferentes enfermedades, es esperable que en los próximos años se produzca un aumento considerable del número de pacientes en riesgo de padecer una infección neumocócica.

Factores de virulencia: la cápsula de polisacárido y los serotipos

Streptococcus pneumoniae es un microorganismo capsulado cuyo principal reservorio es la nasofaringe del ser humano. La colonización de la nasofaringe varía con la edad, encontrándose en un 30-40% de los niños menores de 5 años, pero disminuyendo progresivamente hasta aislarse de forma transitoria, en menos de un 10% de los adultos (2,14). Este es, además, un proceso dinámico en el que el *Streptococcus pneumoniae* compite por ocupar el mismo nicho ecológico con otros microorganismos como son *Haemophilus*

influenzae o *Staphilococcus aureus*. Esta competición también se produce entre los diferentes serotipos de neumococo (15,16).

Una vez la colonización nasofaríngea ha tenido lugar, la infección puede producirse si el microorganismo llega a zonas donde, por diferentes motivos, no puede eliminarse rápidamente, como puede ser la trompa de Eustaquio, los senos nasales o los bronquios. En algunas circunstancias, el neumococo actúa como un organismo invasivo, penetrando a través de las barreras mucosas y llegando desde allí al torrente circulatorio (2,17). Neumococo causa enfermedad principalmente debido a que es capaz de resistir su eliminación por parte de las células fagocíticas del huésped. Esta capacidad antifagocítica se debe principalmente a la cápsula de polisacáridos, considerado su principal factor de virulencia (2,17,18). En función de los polisacáridos que conforman la cápsula y de la respuesta antigénica que originan, se han descrito más de 90 serotipos diferentes de neumococo.

Estudios experimentales en modelos animales han mostrado que la cápsula de los distintos serotipos difiere en la capacidad de resistir a la fagocitosis, en la habilidad de adherirse y penetrar en los tejidos o en la activación de la respuesta inflamatoria (19-21). Estas diferentes propiedades hacen que los distintos serotipos originen enfermedades con importantes variaciones tanto en la presentación clínica como en el pronóstico. De esta forma la propensión a originar enfermedad varía de forma importante entre los diferentes serotipos. Varios estudios han observado que los serotipos que más frecuentemente se aíslan en la nasofaringe originan de forma poco habitual enfermedad invasiva, mientras que los que raramente se encuentran como colonizadores tiene una mayor tendencia a invadir y originar enfermedad. Posiblemente los primeros realizan una colonización prolongada de la nasofaringe mientras que los segundos la deben realizar transitoriamente y como paso previo al desarrollo de la enfermedad. Según esta capacidad los serotipos se han clasificado en tres grupos: altamente invasivos (serotipos 1, 5 y 7F), de invasibilidad intermedia (serotipos 4, 14, 18 y 19) y baja invasibilidad (serotipos 3, 6, 8, 15, 19, 23 y 33). (22,23). Esta clasificación también se ha correlacionado con los pacientes a los que afectan. Los serotipos más invasivos predominan en adultos jóvenes sin patologías de base, mientras que los serotipos con menor potencial invasivo se comportan como gérmenes oportunistas, afectando a pacientes de mayor edad y con comorbilidades (24-26). La mortalidad de la enfermedad también se ha relacionado de forma independiente con el serotipo causante de la misma (27,28). Recientemente se ha publicado un meta-análisis que muestra que los serotipos 1, 5 y 7F se asocian a una enfermedad con menor mortalidad, de entorno al 7-14% (Razón de probabilidades (OR) en comparación con el serotipo 4 de 0.5-0.6), mientras que la mortalidad

es superior al 30% en las infecciones causada por el serotipo 3 (OR 1.9) y el serotipo 19F (OR 2.2) (29). La relación entre la cápsula de polisacárido y la enfermedad neumocócica es tan estrecha que incluso la presentación en forma de diferentes síndromes clínicos parece depender del serotipo causante de la infección (30,31). En la Tabla 1 se observa alguna de estas relaciones descritas en diferentes estudios.

Los mecanismos patogénicos por los que se producen estos fenómenos no son del todo conocidos. Se ha sugerido que la tendencia a la colonización o la invasión del neumococo puede estar en relación al grosor de la capsula de polisacáridos (32) y a la actividad metabólica del microorganismo (33). Los serotipos que más frecuentemente se encuentran como colonizadores parecen tener una mejor eficiencia metabólica, lo que les permitiría sobrevivir durante más tiempo en medios con poco nutrientes como es la nasofaringe. Además, esta ventaja metabólica les permite sintetizar cápsulas de polisacárido más gruesa lo que ayudaría a defenderse de la fagocitosis prolongando la colonización. Por el contrario los serotipos mas invasivos requieren mas nutrientes para sintetizar su cápsula por lo que serían incapaces de sobrevivir de forma prolongada en medios nutricionalmente deficientes, a la vez que desarrollan capsulas menos gruesas haciéndoles más vulnerables a la fagocitosis (32-34). Sin embargo, la cápsula dificulta la penetración del microorganismo en el interior de los tejidos y vasos sanguíneos al inhibir la adhesión e interacción del neumococo con las células epiteliales, paso necesario para el proceso de invasión (35,36). Esto ha sido corroborado por estudios de microscopia electrónica que muestran como el neumococo adelgaza su cápsula en el momento de penetrar a través de las superficies epiteliales (37). Podemos hipotetizar que los serotipos menos invasivos solo podrían originar esta invasión en casos en los que las barreras mucosas estén alteradas, como son estados pro-inflamatorios en los que se ha visto que se expresan nuevas proteínas de superficie epitelial que facilitan la adhesión, situaciones de inmunosupresión o edades avanzadas. Aun así no hay que olvidar que este fenómeno es altamente complejo y en él deben participan muchos otros factores no del todo explicados.

Una vez se ha producido la invasión, la cápsula vuelve a suponer una importante ventaja para el microorganismo. Se ha descrito, de acuerdo a estudios murinos y observaciones clínicas, que los serotipos que presentan un mayor contenido de polisacáridos con cápsulas de mayor grosor originan una enfermedad más grave, posiblemente debido a una mayor capacidad de resistencia ante las defensas del huésped e inducir una mayor respuesta inflamatoria (29,38). Esto, junto al hecho que afectan a pacientes mas debilitados, explicaría la mayor gravedad de las infecciones causadas por los serotipos menos invasivos.

Estas importantes discrepancias clínicas entre los distintos serotipos son las razones por los que algunos autores defienden que sería más correcto considerar las infecciones por diferentes serotipos como diferentes enfermedades, más que considerarlas como una única enfermedad neumocócica. Este hecho es extremadamente importante en vista de que las fluctuaciones en las frecuencias de los serotipos causantes de enfermedad pueden condicionar importantes cambios en las manifestaciones clínicas y el pronóstico de la enfermedad neumocócica.

Tabla 1: Asociación de diferentes serotipos con la edad y comorbilidad, presentación clínica y mortalidad de la enfermedad

Estudio	***Numero pacientes***	***Asociación de diferentes serotipos***			
		Edad	***Comorbilidad***	***Presentación clínica***	***Mortalidad***
Sjostrom et al.	494	Serotipos 1 y 7F en jóvenes. Serotipo 23F en acianos.		Serotipos 1,3,7F y 14 con neumonía	Serotipos 1, 4 y 7F menor mortalidad. Serotipo 3 mayor mortalidad.
Martens et al	410				Serotipo 1 menor mortalidad. Serotipo 3 mayor mortalidad
Jansen et al.	1142	Serotipo 1,5 y 7F en jóvenes Serotipos 3,6,8,15,23 y 33 en ancianos	Serotipo 1,5 y 7F con adultos sanos. Serotipos 3,6,8,15,23 y 33 adultos con comorbilidad	Serotipos 3,6,8,15,23 y 33 con meningitis y bacteriemia 1ª	Serotipo 1 y 7 menor mortalidad. Serotipo 3, 6B, 9F mayor mortalidad.
Colman et al.	5348			Serotipo 1,3 y 14 con peritonitis. Serotipo 10, 18 y 15 con meningitis. Serotipo 6, 14, y 23 con endocarditis. Serotipo 3, 6, 9, 14y 19 con bacteriemia 1ª	
Garcia-Vidal et al.	597			Serotipo 3 con séptico	
Lexeu et al.	9934				Serotipo 11A, 19F y 23F con mayor mortalidad

Vacunas antineumocócicas: polisacáridas simples y conjugadas

Paradójicamente, la infección neumocócica continúa siendo la primera causa de muerte prevenible con la vacunación en los diferentes grupos de edad. Actualmente existen disponibles dos tipos de vacunas contra el neumococo: las vacunas polisacáridas y las vacunas conjugadas.

Las vacunas polisacáridas utilizan elementos purificados de la cápsula del neumococo, el polisacárido capsular, que permiten originar una respuesta antigénica con producción de anticuerpos protectores. El primer gran ensayo clínico con estas vacunas se remonta a hace mas de 65 años y fue realizado en militares durante la segunda guerra mundial por Colin MacLeod y Michael Heidelberger (39). En este estudio, se observaron 5 casos de neumonía neumocócica en 8586 pacientes vacunados con extractos de polisacáridos, en comparación con los 26 casos que padecieron los 8449 pacientes en que se administró placebo. Estudios posteriores condujeron a la comercialización de la primera vacuna polisacárida en Estados Unidos en el año 1977, que incluía a catorce polisacáridos de 14 serotipos diferentes (40-43). En el año 1983, se aprobó la segunda generación de vacunas polisacáridas (VP23; Pneumovax 23®, Merck & Co) con cobertura para 23 serotipos diferentes que representaban el 87% de los serotipos causantes de neumonía bacteriémicas en aquel momento en Estados Unidos (44).

Estas vacuna polisacáridas mostraron tener una aceptable inmunogenicidad en personas sanas, estimulando la producción de anticuerpos contra los serotipos incluidos en la vacuna (45,46). Sin embargo y debido a su escasa antigenicidad, actúan únicamente sobre el sistema inmune no dependiente de las células T lo que origina una pobre respuesta en aquellas personas con cierto grado de inmunosupresión, además de no generar respuesta a nivel de mucosas ni tampoco una respuesta que perdurase en el tiempo. En consecuencia, la vacuna no era tan inmunogénica en las personas de mayor riesgo. De este modo no es útil en los niños menores de 2 años, al no tener estos aun desarrollada la respuesta inmune T independiente. Por otra parte, en los ancianos (47,48), y especialmente en pacientes con enfermedades pulmonares o cardiacas crónicas (49), así como en los pacientes con trastornos onco-hematológicos o infección por el VIH, la producción de anticuerpos ante estos antígenos vacunales es también escasa (50,51).

Desde un punto de vista clínico, y a pesar de los años transcurridos y los múltiples estudios realizados en las últimas décadas, su eficacia no está claramente establecida (52,53). Prueba de ello es que hay autores que defienden su eficacia basándose en un análisis de la Cochrane publicado en 2008 mientras que otros argumentan su falta de eficacia citando otro meta-análisis publicado en 2009 (54,55). Como resumen, los resultados de los ensayos clínicos y los

meta-análisis realizados son consistentes en que la vacuna polisacárida protege frente a la enfermedad invasora y a la neumonía neumocócica en adultos sanos, con una efectividad que oscila en función del estudio entre el 60-80% (52-55). Sin embargo, en los pacientes con comorbilidades, en estados de inmunosupresión así como en las edades extremas de la vida esta protección no ha podido demostrarse (52-55). Pese a todas estas dudas, la vacuna 23 valente polisacárida antineumocócica está ampliamente extendida y sigue recomendándose en todo persona adulta con riesgo de padecer una infección neumocócica (56).

Siendo evidente la necesidad de disponer de vacunas más inmunógenas para la prevención de infecciones neumocócicas en niños y en pacientes de alto riesgo, aparecieron en el años 2000 las vacunas conjugadas (57). Éstas se diferenciaban de las convencionales en que asociaban al polisacárido capsular una proteína transportadora que permitía aumentar de forma muy importante su antigenicidad. Esto posibilita que actúen estimulando una respuesta celular y humoral mediada por el sistema inmune T dependiente, lo que permite a su vez inducir una respuesta a nivel de mucosas y memoria inmunológica. Estas particularidades de las vacunas conjugadas hacen que puedan ser eficaces en los grupos de mayor riesgo para la infección neumocócica en los que las vacunas polisacáridas no habían mostrado ser eficaces, como son los niños, ancianos o personas inmunodeprimidas. La primera en autorizarse en el año 2000 para niños menores de 2 años fue la vacuna conjugada heptavalente (VCP7; Prevenar®, Pfizer) que incluía el polisacárido capsular de siete serotipos (4, 6B, 9V, 14, 18C, 19F y 23F) conjugado con la toxina diftérica atóxica CRM197 como transportador proteico (58). Su autorización se basó en la existencia de estudios inmunogénicos que mostraban un alta eficacia en la generación de anticuerpos contra los serotipos vacunales en niños pequeños, tanto sanos como afectos de alguna condición de inmunosupresión (59,60). Esta eficacia inmunogénica se correlacionó con una eficacia clínica en un amplio estudio realizado en California en más de 37.800 niños en el que la vacuna, mostró una eficacia del 97.4% (95% intervalo de confianza (CI); 82.7% a 99.9%) respecto a placebo en la prevención de enfermedad neumocócica invasiva causada por serotipos incluidos en la vacuna (61). En este ensayo no hubo evidencias de ningún incremento de enfermedad causada por los serotipos no incluidos en la vacuna. La vacuna también mostró ser eficaz en la prevención de neumonía y de otitis media de cualquier causa, con reducciones del 33% y del 6% respectivamente (61,62). Actualmente ya existen comercializadas vacunas conjugadas que incluyen a un mayor número de serotipos, como son la vacuna conjugada decavalente (VCP10; Synflorix®, GSK) y especialmente la trecevalente (VCP13; Prevenar 13®, Pfizer) (63). La eficacia protectora de estas vacunas no ha sido estudiada clínicamente, si no que sus autorización se ha basado en estudios de

inmunogenicidad que permiten extrapolar su eficacia protectora, de acuerdo a las recomendaciones de la la Organización Mundial de la Salud (64,65). La Prevenar 13® ha demostrado una respuesta inmune equivalente frente a los siete serotipos comunes compartidos con la Prevenar®, además de originar una producción de anticuerpos considerada protectora para los seis serotipos adicionales (66-68). La Prevenar 13® ha sido además la primera vacuna conjugada aprobada para su uso en adultos mayores de 18 años. Esta nueva indicación se basa en los datos clínicos de inmunogenicidad y seguridad obtenidos en más de 6.000 adultos de entre 50 y 95 años (69-71). Estos estudios pivotales han demostrado que VCP13 induce una respuesta de anticuerpos funcionales superior para ocho de los serotipos comunes en comparación de la vacuna polisacarida 23 valente (69-71). Existe además en marcha un ensayo clínico que evaluará la eficacia clínica frente a neumonía neumocócica causada por los serotipos vacunales en más de 85.000 adultos (ensayo CAPiTA) que se espera esté disponible en 2014 (72). La Tabla 2 muestra los serotipos incluidos por las diferentes vacunas asi como el porcentaje que representan respecto a los serotipos circulantes.

Tabla 2: Serotipos de neumococo contenido en las diferentes vacunas antineumocócicas.

Vacunas antineumocócicas	*Cobertura vacunal en adultos**	*Serotipos*
Vacuna conjugada 7 valente *(Prevenar®, VCP7)*	40-50%	4, 6B, 9V, 14, 18C, 19F y 23F
Vacuna conjugada 10 valente *(*Synflorix *®, VCP10)*	55-65%	1, 4, 5, 6B, 7F, 9V, 14, 18C,19F, 23F
Vacuna conjugada 13 valente *(Prevenar 13®, VCP13)*	60-75%	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19F, 19A, y 23F
Vacuna polisacárida 23 valente *(Pneumovax®, VP23)*	75-89%	1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, y 33F

* Porcentaje respecto a los serotipos circulantes entre los años 2005-2010 (Adaptado de Grabenstein J [73])

Cambios en la incidencia de de la enfermedad neumocócica tras la introducción de la vacuna conjugada heptavalente en niños

El primer país donde se introdujo la VCP7 a principios del año 2000 fue Estados Unidos. Su uso se extendió rápidamente, de tal forma que la cobertura vacunal en niños menores de 2 años pasó de ser del 9% en el año 1999 a superior al 93% en el año 2006 (74). La vacuna ofrecía

cobertura frente a las infecciones causadas por 7 serotipos que en el momento de su introducción, representaban a más del 80% de serotipos causantes de enfermedad en la población infantil (74). Los efectos protectores de la vacuna se observaron rápidamente con una drástica disminución de la incidencia de la enfermedad neumocócica producida por los serotipos vacunales a los pocos años de su introducción. En un amplio estudio epidemiológico nacional se observó un descenso del 69% de la incidencia de ENI en niños menores de 2 años, pasando de unas tasas de 188 episodios por 100.000 personas-años en 1999 a 59 episodios por 100.000 personas-año en el año 2001. Esta reducción fue debida principalmente a un descenso del 78% en las ENI causadas por los serotipos vacunales (75). Otro aspecto menos esperable que también se detectó rápidamente fue que la vacuna no tan solo protegía a las personas vacunadas sinó que ejercía un efecto sobre la población no vacunada tanto de niños mayores como de adultos. En estos grupos de edad se detectó un descenso de entre el 25% al 30% de incidencia de ENI (75). Este efecto a nivel poblacional conocido como "inmunidad de grupo", se debía a un descenso en la colonización nasofaríngea de los niños por los serotipos vacunales, consecuencia de la respuesta inmune a nivel de mucosas inducida por la vacuna. Al ser los niños el principal reservorio y fuente de transmisión del neumococo, la disminución de la colonización producía un descenso de la transmisión a niños mayores y adultos, y secundariamente una reducción de la incidencia de la enfermedad producida por estos serotipos en dichas poblaciones (76,77).

Sin embargo, otros efectos no tan beneficiosos y que no fueron pronosticados, también empezaron a observarse. A nivel de la nasofaringe de los niños, se produjo un fenómeno por el que el espacio que dejaban los serotipos vacunales fue ocupado por otros serotipos no incluidos en la vacuna y que tradicionalmente no actuaban como colonizadores (76,77). Este proceso de reemplazo se acompañó a su vez de un aumento en la incidencia de infecciones producidas por estos nuevos serotipos no vacunales, tanto en niños con incrementos del 27%, como en adultos (75). Este fenómeno fue especialmente llamativo en el caso del serotipo 19A. La incidencia de ENI causada por el serotipo 19A en Estados Unidos aumentó globalmente un 330% entre los años 2000 y 2005, y supuso el 36% de todos los aislamientos en niños menores de 2 años en 2005 frente al 2.5% del año 2000 (78). Otros de los serotipos cuya incidencia aumentó de forma importante fueron la de los serotipos 1, 3, 7F, 15B y 33F (79). Pese a ello, en Estados Unidos el aumento observado de estos serotipos no vacunales no fue tan importante como el descenso de los serotipos vacunales, con lo que globalmente la vacuna seguía siendo beneficiosa en la prevención de la enfermedad neumocócica para todos los

grupos de edad. Este efecto beneficioso era además perdurable en el tiempo, como demuestran varios estudios publicados años más tarde (79-81).

El efecto protector de la vacuna que se observó en Estados Unidos, sin embargo, no fue tan evidente en otras áreas geográficas. En Canadá, siete años tras la introducción de la vacuna, se detectó un descenso del 78% en la incidencia de ENI en niños menores de 5 años. En adultos, por el contrario, el descenso en los serotipos vacunales fue compensado por el incremento de los serotipos no incluidos en la vacuna sin producirse cambios significativos en la incidencia global de ENI (82). En Reino Unido y a pesar de que la cobertura de la VP23 aumentó del 49% al 70% en el periodo de entre 2002 al 2009 y que la de la VPC7 llegaba hasta el 98% en el 2009, la incidencia global de ENI aumento de 11.8 a 16.4 episodios por 100.000 personas-año (83). En Francia la vacuna conjugada se introdujo en 2003 y en el año 2006 la incidencia de ENI no solo no había disminuido, sinó que había aumentado en todos los grupos de edad de adultos (84). Similares resultados se han observado también en Holanda (85).

En Cataluña la vacuna conjugada heptavalente se introdujo en el año 2001 únicamente para los niños con un riesgo elevado de tener una infección neumocócica invasiva. Sin embargo, y a pesar de no estar financiada por el sistema público de salud, la administración de la vacuna en el ámbito privado se generalizó de tal forma que en el año 2006 alrededor del 50% de los niños habían sido vacunados (86). En el momento de su introducción, los 7 serotipos de la vacuna representaban al 68,2% de los serotipos causantes de enfermedad en niños de 0 a 4 años (87). Pese a estos datos, diferentes estudios hospitalarios han mostrado un aumento de la incidencia global de ENI en niños desde la introducción de la vacuna (88,89). De igual forma, aumentos de la incidencia de ENI en adultos han sido descritas (90). Recientemente se han presentado los datos de un estudio epidemiológico que engloba a más de 5.000 episodios de ENI entre los años 2001 y 2008 en Cataluña. Globalmente, la incidencia de ENI aumentó de 8.7 episodios por 100.000 pacientes-años en 2001 a 13.9 episodios en 2008. Por grupos de edad, el cambio más importante se observó en los niños de entre 2-4 años (pasa de 19.6 a 40.5) y en adultos de más de 65 años (de 18.8 a 29.8) (91). Este fenómeno se debe a la emergencia de nuevos serotipos no vacunales, como son el serotipo 1, 3, 6A, 7F, 14 y 19A causantes actualmente del 50.9% de las infecciones nemocócicas, a pesar del descenso de los serotipos vacunales, que pasaron de causar el 42.2% de las infecciones en 2001 al 19.1% en 2008 (91).

Implicación clínica de la introducción de la vacuna conjugada heptavalente en la enfermedad neumocócica en niños

Más allá de las variaciones en la incidencia de la enfermedad neumocócica observadas tras la introducción de la vacuna, es también preocupante la implicación clínica que pueden tener los cambios en la distribución de serotipos causantes de enfermedad. Como ya se ha comentado, los diferentes serotipos difieren de forma importante en la presentación clínica así como en el pronóstico de la enfermedad neumocócica que originan. En consecuencia, cambios en la distribución de los serotipos pueden implicar a su vez variaciones en la manifestación de la enfermedad.

Los primeros trabajos que alarmaban sobre este posible fenómeno se publicaron en los años 2005-2006 en Estados Unidos. En estos estudios hospitalarios se observó un importante aumento de la complicación en forma de empiema en niños con neumonía neumocócica, pasando del 17.5% en el periodo previo a la introducción de la VCP7 al 32% en periodo postvacunal. Los serotipos vacunales disminuyeron de un 37% a un 14% pero por el contrario los serotipos no vacunales aumentaron del 63% al 86%, siendo los serotipos 1 y 3 los responsables de la mayor parte de empiemas (92,93). Bender et al observó también un aumento del porcentaje de complicaciones en forma de neumonías necrotizante, incrementándose del 13% al 49% y asociándose otra vez al serotipo 3 (94). Datos epidemiológicos más recientes se obtienen del trabajo de Grijalva et al, estudio que utiliza una amplia base de datos nacional que incluye a 1.000 hospitales de Estados Unidos desde 1996 al 2007.

En este estudio se observó que en niños menores a 2 años, mientras que se producía un descenso en las hospitalizaciones por neumonía neumocócica del 61% (95% CI; 55% a 67%), el número de hospitalizaciones por empiema neumocócico aumentaba un 17% (95% CI; -32% a 88%). Mientras que en los niños de 2 a 4 años la neumonía neumocócica disminuía un 26% (95% CI; 16% a 34%) los casos complicados con empiema aumentaban más del doble, con un incremento del 117% (95% CI; 55% a 203%), pasando de 1.1 a 2.5 episodios por 100.000 niños-año (95). En este estudio no existe información sobre los serotipos causantes de la infección.

La edad media de los niños que sufren estas complicaciones supuradas es actualmente mayor, pasando de menos de 2 años a entre 2 y 4 años (93,95). Además, aunque la mortalidad causada por los empiemas parece ser similar, éstos presentan un mayor número de complicaciones con mas tasas de fístulas broncopulmonares, más necesidad de intervención quirúrgica y mayor estancia hospitalaria (93,96,97). Estas complicaciones se han asociado a la emergencia de los serotipos no vacunales 1, 3 y 19A, principalmente.

En España este cambio en la presentación clínica hacia neumonías con más complicaciones supuradas también ha sido observado en niños. Diferentes estudios han constatado un aumento de la tasa e incidencia de empiemas, con incrementos de hasta 8 veces respecto al periodo prevacunal (88,89,98). A modo de ejemplo, un estudio realizado en Barcelona estimó un incremento de empiemas en los niños menores de dos años de 2.2 a 9.2 casos por 100.000 personas-años (p=.055) y en niños de entre 2 y 4 años, de 1.5 a 9.2 casos (p=.006) (89). Parece así, que el reemplazo de serotipos observado en los niños se asocia a un aumento del número de complicaciones supuradas de la enfermedad neumocócica.

La repercusión clínica que han tenido estos cambios de serotipos en los adultos sin embargo está menos estudiada. A la vista de los datos expuestos, es necesario plantearse una serie de preguntas que aún quedan por contestar. ¿Existe, al igual que en los niños, un aumento de las complicaciones supuradas de la enfermedad neumocócica en la población adulta? ¿Se ha producido otros cambios en la presentación clínica mas allá de las complicaciones supuradas? En el caso que exista estos cambios ¿Son debidos a la emergencia de los mismos serotipos que en la población infantil? Estas cuestiones representan el punto de partida de la presente tesis doctoral.

II. JUSTIFICACIÓN DEL ESTUDIO E HIPÓTESIS DE TRABAJO

JUSTIFICACIÓN DEL ESTUDIO E HIPÓTESIS DE TRABAJO

Justificación del estudio

En el momento en que se inició este estudio, a principios del año 2008, existía una creciente evidencia del fenómeno de reemplazo de serotipos causantes de infección que estaba ocurriendo como consecuencia de la introducción de la VCP7 en niños. También se empezaban a conocer las implicaciones clínicas que tenía este cambio en los niños, con un incremento de las complicaciones supuradas. En nuestro hospital, existía por pate de los clínicos la sensación de que la enfermedad neumocócica en los adultos también estaba cambiando hacia una presentación de mayor gravedad. Sin embargo, a pesar de que había estudios publicados que describían un reemplazo en los serotipos causantes de infección en los adultos, no existan datos ni publicaciones respecto a los posibles cambios en la presentación clínica de la enfermedad como consecuencia de las variaciones de los serotipos predominantes.

El conocimiento de las repercusiones clínicas que podía tener la emergencia de nuevos serotipos en adultos es importante para entender el efecto global de la introducción de la vacuna a nivel poblacional así como para establecer nuevas estrategias de prevención, en especial con la llegada de las nuevas vacunas conjugadas con cobertura para un mayor número se serotipos.

La falta de estudios en este campo justifica el interés de desarrollar el presente estudio.

Hipótesis de trabajo

La introducción en España de la vacuna neumocócica conjugada heptavalente en el año 2001 ha provocado un cambio en los serotipos causantes de infección neumocócica lo cual ha condicionado cambios significativos en la presentación clínica de la enfermedad neumocócica invasiva en la población adulta.

III. OBJETIVOS

OBJETIVOS

El objetivo general del estudio es determinar si se han producido cambios en la presentación clínica de la enfermedad neumocócica invasiva en la población adulta entre el período previo a la introducción de la VCP7 (periodo prevacunal) y el periodo tras su implantación (periodo postvacunal). Este objetivo genérico se ha dividido en tres objetivos más específicos:

Objetivo primero

Estudiar si existen cambios en el porcentaje de complicaciones en forma de empiema de la neumonía neumocócica, así como variaciones en la incidencia global de empiema neumocócico en la población adulta entre el periodo prevacunal y postvacunal.

Objetivo segundo

Estudiar si existen cambios en la gravedad de la presentación clínica y el pronóstico de la neumonía neumocócica en la población adulta entre el periodo prevacunal y postvacunal.

Objetivo tercero

Estudiar si existen cambios en la incidencia, en la presentación clínica y su pronóstico, y en las características microbiológicas de la enfermedad neumocócica en una subpoblación de alto riesgo para ella como son los pacientes adultos con infección por VIH, entre el periodo prevacunal y postvacunal.

IV. MÉTODOS

MÉTODOS

Población a estudio

Se estudiaron todos los pacientes adultos diagnosticados de enfermedad neumocócica invasiva que ingresaron en el Hospital Vall d'Hebrón, hospital universitario terciario de Barcelona con una área de referencia de 411.227 personas.

Para la elaboración del estudio se realizaron colaboraciones con otros hospitales que estaban realizando estudios de seguimiento epidemiológicos similares. En concreto, se colaboró con el Hospital Parc Tauli (Sabadell, Barcelona), Hospital Son Dureta (Palma de Mallorca) y Hospital Son Llàtzer (Palma de Mallorca).

Diseño del estudio

Estudio de tipo observacional, multicéntrico. La recogida de datos se realizó de forma prospectiva desde el año 2008 y retrospectivamente en los años anteriores.

Periodo de estudio

El estudio se realizó incluyendo los casos diagnosticados entre los años 1996-2001 (periodo prevacunal) y 2005-2012 (periodo postvacunal). En el caso concreto de los pacientes con infección por VIH, se incluyeron todos los casos diagnosticados entre los años 1996 y 2012.

Criterios de inclusión

Se estudiaron todos los pacientes diagnosticados de infección neumocócica invasiva, que cumplían los siguientes criterios:

- Pacientes mayores de 18 años.
- Diagnóstico de enfermedad neumocócica invasiva. El diagnostico se estableció en todos los casos en que se aisló *Streptococcus pneumoniae* en un líquido estéril (sangre, líquido cefalorraquídeo, líquido pleural, líquido ascítico y líquido articular).

Recogida de información

La recogida de información de los pacientes se llevó a cabo a través de las historias clínicas hospitalarias, a través de un protocolo de recogida de datos previamente definido. De forma esquemática las variables que se incluyeron son:

- Datos demográficos: Datos de filiación, hábitos tóxicos y administración previa de vacuna polisacárida 23 valente.

- Antecedentes patológicos: Historia de enfermedades concomitantes y tratamientos que condicionen mayor susceptibilidad a tener una infección neumocócica e índice de Charlson.
- Adquisición de la infección: Comunitaria, nosohusial o hospitalaria.
- Datos de presentación clínica de la enfermedad:
    - Síndromes clínicos (Neumonía, Meningitis, Empiema, Bacteriemia sin foco, Artritis, Peritonitis, etc…).
    - Complicaciones clínicas (Insuficiencia respiratoria, shock séptico y complicaciones supuradas).
    - Patrón radiológico en caso de neumonía.
    - Escalas de valoración pronostica: Escala de FINE y CURB-65.
    - Datos evolutivos de la enfermedad: Necesidad de ingreso en Unidad de Cuidados Intesivos (UCI), necesidad de ventilación mecánica, mortalidad, estancia hospitalaria, secuelas.
- Datos respecto a tratamientos: Antibioterapia empírica, cambio de antibiótico, duración del tratamiento, uso de tratamientos coadyuvantes (corticoides, estatinas, etc…), colocación de drenaje torácico, uso de fibrinolíticos o necesidad de intervención quirúrgica.
- Datos microbiológicos de la enfermedad: Muestra en que se produce el aislamiento, sensibilidad antibiótica y serotipo de *Streptococcus pneumoniae.*

Definiciones

Las definiciones se establecieron siguiendo los criterios establecidos en la literatura:

La neumonía neumocócica invasiva se diagnosticó cuando un paciente tenía una clínica compatible, junto con un nuevo infiltrado pulmonar en la radiografía de tórax y aislamiento de *S. pneumoniae* en sangre y/o líquido pleural (99).

El diagnóstico de empiema se realizó siguiendo los criterios de Light (100,101). Estos criterios incluyen derrame pleural loculado, resultado positivo en la tinción de Gram o en el cultivo del liquido pleural y liquido purulento con pH < 7.2 o un nivel de glucosa < 40mg/dl. El empiema neumocócico se diagnosticó en todo paciente con derrame pleural paraneumónico complicado en que *Streptococcus pneumoniae* se aislara en sangre y/o liquido pleural.

La insuficiencia respiratoria se definió como una saturación de oxigeno < 90% a aire ambiente o una presión de oxigeno en sangre arterial en relación a la fracción inspirada de oxigeno (Pa02/FiO2) < 250 (102).

El shock séptico se consideró cuando fue necesaria la administración de drogas vasoactivas para conseguir una presión arterial adecuada pese a la resucitación previa con fluidoterapia (103).

Procedimientos de Laboratorio de Microbiología

En nuestro hospital todos los aislamientos microbiológicos en líquido estéril son recogidos de forma sistemática. La identificación del *Streptococcus pneumoniae* se realizó basándose en la tinción de Gram, susceptibilidad a optoquina, solubilidad a la bilis y técnicas de aglutinación en látex. La sensibilidad antibiótica se determinó utilizando técnicas de microdilución de acuerdo con los procedimiento del Clinical and Laboratory Standards Institute (104). El serotipado se realizó mediante la reacción de Quellung usando un antisuero específico al serotipo/serogrupo comercial en el Laboratorio Español de Referencia de Neumococo (Instituto de Salud Carlos III, Majadahonda, Madrid, España).

Los serotipos se clasificaron en dos grupos: Serotipos vacunales (serotipos incluidos en la VCP7; serotipos 4, 6B, 9V, 14, 18C, 19F, and 23F) y serotipos no vacunales (todos los otros).

Estimación de incidencias

La incidencia de empiema y de neumonía neumocócica invasiva, definida como el número de episodios por 100.000 personas-año, se calcularon para el global de la población y para los diferentes grupos de edad utilizando como numerador el número de adultos que viven en el área de referencia de los hospitales que participaron, obtenida del Departamento de Estadística de Cataluña (105). Para asegurar la fiabilidad de este método, se calculo también la incidencia de empiemas por 1.000 admisiones hospitalarias-año. Durante el periodo de estudio el número de ingresos hospitalarios por 100.000 personas del área de referencia se mantuvo contante.

En el caso de la incidencia de enfermedad neumocócica invasiva en pacientes con infección por VIH, la incidencia se calculó usando en el denominador el número de pacientes con infección por VIH controlados en cada hospital, de acuerdo con la base de datos de cada centro, y se expresó en casos por 1.000 pacientes-año. Los centros participantes tienen un programa activo (de internamiento y ambulatorios) para pacientes con infección VIH que da cuidado a la mayoría de los pacientes con esta infección del área de referencia. Todos los pacientes VIH se incluyen en una base de datos computerizada. Al final del estudio 4.692 pacientes con infección por VIH estaban incluidos en la base de datos.

Estudio caso-control

Para evaluar diferencias entre la población con infección por VIH y no VIH, se realizó un estudio caso-control. Los casos se definieron como pacientes con infección por VIH con episodio de ENI en el periodo de estudio, y los controles como pacientes sin infección por VIH con episodio de ENI. Por cada caso se selecciono un control apareado por hospital, edad (+/- 3 años) y periodo vacunal, con el fin de evitar posibles sesgos debido a las diferencias de edades entre ambas poblaciones. Los controles se seleccionaron en orden alfabético del registro microbiológico de pacientes ingresados en los hospitales con episodio de ENI, escogiendo el primer paciente al azar. Las mismas variables clínicas y microbiológicas se recogieron en los casos y controles.

Análisis estadístico

Para el análisis estadístico se utilizó el programa estadístico SSPS para Windows (versión 15.0; SPSS, Chicago, IL).

Las variables categóricas se definieron como número de casos y proporción, y se compararon mediante la prueba de Chi-cuadrado o, en los casos que lo requerían, el Test Exacto de Fisher. Las variables cuantitativas se definieron como media y desviación estándar, y se compararon con la prueba T de Student o, en los casos necesarios con la prueba no paramétrica de U de Mann-Whitney.

Las diferencias de medias de incidencia entre los periodos prevacunal y postvacunal se evaluaron utilizando el test de Mantel-Haenszel. El porcentaje de cambio (razón de odds) en la incidencia se presentó asociado a su intervalo de confianza del 95%.

Para identificar variables asociadas de forma independiente a empiema, shock séptico y mortalidad se realizó un análisis multivariado mediante un modelo de regresión logística. Las variables que mostraron diferencias significativas o próximas a la significación estadística ($p<0.1$) en el análisis univariante se incluyeron en el modelo multivariante.

Todos los análisis estadísticos se llevaron a cabo considerando un nivel de significación o valor de P menor de 0.05.

Confidencialidad de los datos y consentimiento informado

La recogida de datos se hizo con unos protocolos previamente establecidos y los datos se introdujeron en una base de datos con un sistema de codificación con el fin de proteger la información personal de cada paciente. En la hoja de recogida de datos el código se relacionó con el número de historia clínica. Estas hojas son custodiadas por el investigador responsable. El estudio fue aprobado por el Comité Ético del hospital coordinador (Hospital Vall d'Hebron;

PR(AG)15/2009). El consentimiento informado no fue necesario dado el carácter observacional del estudio.

V. RESULTADOS

RESULTADOS

Partiendo de la hipótesis de trabajo, el estudio se llevó a cabo mediante la elaboración de tres trabajos diferentes, que tratan de dar respuesta a cada uno de los objetivos planteados. La exposición de los resultados se estructurará en tres partes, correspondientes a cada uno de los trabajos.

A continuación, y como parte final de la memoria, se añade en forma de apartado Anexo varias publicaciones relacionadas que se llevaron a cabo durante la elaboración del presente trabajo, consistentes en dos artículos de revisión y dos editoriales. En la primera revisión, titulada "The increasing incidence of empyema", se realizó un repaso a los estudios publicados que evalúan cambios en la incidencia de empiema de cualquier etiología tanto en niños como en adultos. Además, discute los posibles motivos que han podido conducir a los cambios observados. En la segunda publicación, titulada "The Spectrum of Invasive Pneumococcal Disease in adults in the XXI Century", revisa las novedades y cambios más importantes que se han producido en la enfermedad neumocócica invasiva en adultos en la última década. En este trabajo se repasa desde la aparición de nuevos grupos de pacientes en riesgo de presentar infecciones por neumococo, hasta las nuevas técnicas diagnosticas y estrategias terapéutica, pasando por la dinámica de los serotipos de neumococo causantes de enfermedad y sus implicaciones clínicas. Por último se añade dos editoriales que tratan del empiema neumocócico y la enfermedad neumocócica.

Trabajo 1:

Estudio que evalúa cambios en el porcentaje de complicaciones en forma de empiema de la neumonía neumocócica así como variaciones en la incidencia de empiema neumocócico en la población adulta entre el periodo prevacunal y postvacunal.

Artículo

Burgos J, Lujan M, Falcó V, Sánchez A, Puig M, Borrego A, Fontanals D, Planes AM, Pahissa A, Rello J. *"The spectrum of pneumococcal empyema in adults in the early 21st century"*. Clin Infect Dis. 2011;53:254-61

Trabajo 2:

Estudio que evalúa cambios en la presentación clínica y el pronóstico de la neumonía neumocócica en la población adulta entre el periodo prevacunal y postvaunal.

Artículo

Burgos J, Falcó V, Borrego A, Sordé R, Larrosa MN, Martinez X, Planes AM, Sánchez A, Palomar M, Rello J, Pahissa A. *"Impact of the emergence of non-vaccine pneumococcal serotypes on the clinical presentation and outcome of adults with invasive pneumococcal pneumonia".* Clin Microbiol Infect. 2012;19:385-91

Trabajo 3:

Estudio que evalúa cambios de incidencia, de la presentación clínica y su pronostico, y en las características microbiológicas de la enfermedad neumocócica en una subpoblación de alto riesgo para ella como son los pacientes adultos con infección por VIH entre el periodo prevacunal y postvacunal.

Artículo

Burgos J, Peñaranda M, Payeras A, Villoslada A, Curran A, Garau M, Riera M, Crespo M, Navarro J, Van den Eynde E, Planes AM, Ribera E, Pahissa A, Falcó V. *"Invasive Pneumococcal Disease in HIV-Infected Adults: Clinical Changes After the Introduction of the Pneumococcal Conjugate Vaccine in Children"*. J Acquir Immune Defic Syndr. 2012;59:31-8.

Revisión 1:

Revisión de los estudios publicados que evalúan cambios en la incidencia de empiema de cualquier etiología tanto en niños como en adultos. Discusión de los posibles motivos que han podido conducir a los cambios observados.

Artículo

Burgos J, Falcó V, Pahissa A. The increasing incidence of empiema. Current Opinion of Pulmonary Medicine 2013, 19: 350-6.

Revisión 2:

Revisión de las novedades y cambios más importantes que se han producido en la enfermedad neumocócica invasiva en adultos en la última década. En este trabajo se repasa desde la aparición de nuevos grupos de pacientes en riesgo de presentar infecciones por neumococo, hasta las nuevas técnicas diagnosticas y estrategias terapéutica, pasando por la dinámica de los serotipos de neumococo causantes de enfermedad y sus implicaciones clínicas.

Artículo:

Falcó V, Burgos J, Pahissa A. *"The Spectrum of Invasive Pneumococcal Disease in adults in the XXI Century"* . Clinical Pulmonary Medicine 2013. [Epub ahead of print] .

Editorial 1:

Falcó V, Burgos J. Pneumococcal pneumonia: epidemiological, diagnostic and therapeutic changes. Enfer, Infecc Microbiol Clin 2011;29:247-9.

Editorial 2:

Burgos J. Pneumococcal empyema. International Pleural Newsletter 2011; 9:16-7.

MAJOR ARTICLE

The Spectrum of Pneumococcal Empyema in Adults in the Early 21st Century

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Background. Increased rates of empyema have been reported in children after the introduction of the pneumococcal conjugate vaccine (PCV7). Our objective was to describe the risk factors for pneumococcal empyema in adults and to analyze the differences in the incidence, disease characteristics, and serotype distribution between the pre- and post-PCV7 eras.

Methods. An observational study of all adults hospitalized with invasive pneumococcal disease (IPD) who presented with empyema in 2 Spanish hospitals was conducted during the periods 1996–2001 (prevaccine period) and 2005–2009 (postvaccine period). Incidences of empyema were calculated. A multivariate analysis was performed to identify variables associated with pneumococcal empyema.

Results. Empyema was diagnosed in 128 of 1080 patients with invasive pneumococcal disease. Among patients aged 18-50 years, the rates of pneumococcal pneumonia with empyema increased from 7.6% to 14.9% ($P = .04$) and the incidence of pneumococcal empyema increased from 0.5 to 1.6 cases per 100,000 person-years (198% [95% confidence interval {CI}, 49%–494%]). The incidence of empyema due to serotype 1 increased significantly from 0.2 to 0.8 cases per 100,000 person-years (253% [95% CI, 67%–646%]). Serotype 1 caused 43.3% of cases of empyema during the postvaccine period. Serotypes 1 (odds ratio [OR], 5.88; [95% CI, 2.66-13]) and 3 (OR, 5.49 [95% CI, 1.93-15.62]) were independently associated with development of empyema.

Conclusions. The incidence of pneumococcal empyema in young adults has increased during the postvaccine period, mainly as a result of the emergence of serotype 1. Serotypes 1 and 3 are the main determinants of development of this suppurative complication.

Significant declines in the incidence of invasive pneumococcal disease (IPD) due to vaccine serotypes were reported after the implementation of the 7-valent pneumococcal conjugated vaccine (PCV7), not only in children but also in adults [1–4]. Nevertheless, because of a replacement phenomenon, nasopharyngeal colonization of children by non-PCV7 serotypes was soon reported [5, 6]. As a consequence, the incidence of IPD caused by non-PCV7 serotypes increased in both children and adults [7–10].

This different pattern in serotype distribution of IPD has been accompanied by changes in disease characteristics, and increases in the incidence of empyema were soon reported in children after the introduction of the PCV7 [11–13]. Different studies have shown that capsular pneumococcal polysaccharides are associated with specific manifestations of pneumococcal disease and mortality [14–16]. Thus, pneumococcal serotypes 1 and 3 have been associated with the development of suppurative complications and necrotizing pneumonia in children [17, 18]. To date, it is unknown whether the same phenomenon is also occurring in adults.

In Spain, the PCV7 was introduced in June 2001, and it was estimated in 2006 that about 50% of children have been vaccinated and, as in other geographic areas,

Received 20 January 2011; accepted 25 April 2011.

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Clinical Infectious Diseases 2011;53(3):254–261

1058-4838/2011/533-0006$14.00
DOI: 10.1093/cid/cir954

the emergence of IPD caused by non-PCV7 serotypes after PCV7 introduction has also been reported [7, 19].

To our knowledge, there few published data about the actual incidence of pneumococcal empyema in adults, its clinical course, and the causal serotypes. The aim of our study was (1) to describe the clinical characteristics and risk factors for pneumococcal empyema and (2) to analyze the differences in the incidence of empyema, disease characteristics, and serotype distribution in adults with complicated parapneumonic pleural effusion caused by *Streptococcus pneumoniae* between the pre- and post-PCV7 eras.

METHODS

Study Population and Setting

Patients were enrolled as part of an ongoing observational study initiated in 1996 of all adults hospitalized with IPD in 2 teaching hospitals in Barcelona, Spain; in Hospital Universitari Vall d'Hebron and Hospital Parc Tauli, all adults with IPD who presented with an empyema were included. We included patients from 2 periods: the prevaccine period (from 1996 to 2001) and the postvaccine period (from 2005 to 2009). The study was approved by the Ethics Board of the coordinating hospital (Hospital Vall d'Hebron [PR(AG)15/2009]). Informed consent was waived because of the observational nature of the study.

Study Variables and Data Collection

We recorded the following variables: (1) sociodemographic data (age, sex, tobacco and alcohol abuse, and vaccination status with the 23-valent polysaccharide [PPV-23] vaccine), (2) underlying diseases and Charlson comorbidity index, (3) immunosuppressive conditions, (4) severity of the illness at presentation (respiratory failure, septic shock, and pneumonia severity index), (5) pleural fluid parameters, (6) microbiological data (serotype and antibiotic resistance pattern of the *S. pneumoniae* causal strain), (7) therapeutic measures (antimicrobial therapy, chest tube drainage placement, administration of fibrinolytic agents, and need for surgical intervention), and (8) variables related to clinical outcome (mortality, intensive care unit [ICU] admission, orotracheal intubation requirement, and length of hospital stay for survivors).

Definitions

Diagnosis of empyema was made on the basis of the criteria established by Light [20, 21]. These criteria included a loculated pleural effusion, positive results of Gram staining or culture of the pleural fluid, and a purulent pleural fluid with pH <7.2 or a glucose level <40 mg/dL. Pneumococcal empyema was considered in all patients with complicated parapneumonic pleural effusion in whom *S. pneumoniae* was isolated in blood and/or in pleural fluid culture. Invasive pneumococcal pneumonia was diagnosed when a patient had consistent clinical findings plus a new pulmonary infiltrate on chest radiography and isolation of *S. pneumoniae* in blood and/or pleural fluid cultures. Charlson comorbidity index and pneumonia severity index score were calculated as reported elsewhere [22, 23].

Microbiological Procedures

S. pneumoniae strains were identified by Gram staining, optochin susceptibility, bile solubility, and latex agglutination testing. Antimicrobial susceptibility was tested using the microdilution method, in accordance with Clinical and Laboratory Standards Institute (CLSI) procedures. Serotyping was performed by capsular swelling reaction, using commercial serogroup and serotype-specific antisera, with the quellung reaction at the Spanish Reference Laboratory (Instituto Carlos III, Madrid, Spain). Serotypes were classified in 2 groups: PCV7 serotypes were those that matched serotypes included in the vaccine (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F), and all other serotypes were designated as non-PCV7 serotypes.

To evaluate the evolution of antibiotic resistance, we used the breakpoints for penicillin prior to the revision by the CLSI in 2008, because with these new breakpoints nearly all strains were penicillin susceptible (96.7% and 98.3% of pneumococcal strains had minimum inhibitory concentration [MIC] ≤ 2 μg/mL during the pre- and postvaccine periods, respectively) [24]. So for the purpose of this study, isolates were classified as penicillin-susceptible (MIC, ≤ 0.06 μg/mL), penicillin-intermediate (MIC, 0.12–1 μg/mL), or penicillin-resistant (MIC, ≥ 2 μg/mL). Intermediate or resistant isolates were considered to be nonsusceptible.

Estimation of Incidence of Pneumococcal Empyema

Rates of pneumococcal empyema and incidence, defined as the number of episodes per 100,000 population per year, were calculated for the whole population and for different age groups using as the denominator the number of adults living in the referral areas of the 2 hospitals obtained from the Department of Statistics in Catalunya [25]. To ensure the reliability of this method to estimate the incidence, we have also calculated the incidence of empyema per 1000 adult patients admitted to our hospitals per year. To compare the incidence between the pre- and postvaccine periods, we used the mean of the yearly incidence during the period. To estimate the incidence of empyema due to vaccine or nonvaccine serotypes, we assumed that the distribution of serotypes for cases missing serotype information (4% of cases) was the same as the distribution for those cases with serotype information.

Statistical Analysis

Differences in means of the incidence between prevaccine and postvaccine periods were tested using the Mantel-Haenszel test. The percent reduction in incidence was reported with associated 95% confidence interval (CI). The χ^2 test or Fisher exact test,

when appropriate, was used to compare the distribution of categorical variables, and the Student *t* test or the Mann-Whitney *U* test for continuous variables. Results were considered statistically significant if the 2-tailed *P* value was <.05.

To assess the risk factors for pneumococcal empyema, we compared the 128 patients with empyema with 576 patients who had bacteremic pneumococcal pneumonia without empyema collected during the same study period. We performed univariate and multivariate logistic regression analysis to identify variables independently associated with pneumococcal empyema. Significant and nearly significant ($P < .10$) variables from the univariate analysis were included in the multivariate analysis.

To asses the association of the different serotypes with the risk of empyema, we have grouped serotypes in 3 different categories, as follows: (0) non-1, non-3 serotypes, which acted as a reference category; (1) serotype 1; and (2) serotype 3. The same model has been used for the combined variable serotype 4 and 14. All statistical analyses were performed using the statistical software package SPSS for Windows, version 15.0.

RESULTS

During the study period, 1080 episodes of invasive pneumococcal pneumonia were diagnosed in adults, 508 of them during the prevaccine period and 572 during the postvaccine period. Empyema was diagnosed in 128 (11.9%) of the 1080 patients with invasive pneumococcal pneumonia.

Clinical Characteristics of Patients With Pneumococcal Empyema

The mean age of patients with pneumococcal empyema was 59.1 ± 18.1 years, and 65.6% of the episodes occurred in men (Table 1). Seventy-four (57.8%) of the 128 patients had

Table 1. Basal Characteristics, Clinical Presentation, and Outcomes by Time Period Among Patients With Pneumococcal Empyema

Characteristic	All patients (*n* = 128)	Prevaccine period (*n* = 62)	Postvaccine period (*n* = 66)	*P*[a]
Sociodemographic variables				
Age, mean years ± SD	59.1 ± 18.1	63.2 ± 16.7	55.2 ± 18.7	.01
Male sex	65.6	69.4	62.1	.46
Smoking	22.2	27.9	16.9	.20
Alcohol consumption	59.5	65.6	53.8	.21
Underlying diseases				
Immunosuppressive condition[b]	28.3	37.1	20	.048
HIV infection	10.2	14.5	6.2	.15
Hematological cancer	4.7	9.7	0	.01
Solid cancer	12.6	12.6	16	.22
Chronic medical illness[c]	56.3	67.2	46.2	.002
Chronic lung disease	34.1	49.2	20	.001
Charlson comorbidity index, mean ± SD	2.19 ± 2.5	2.8 ± 2.6	1.63 ± 2.2	.08
Clinical presentation				
Respiratory failure	55.9	66.4	52.3	.47
Septic shock	20.5	14.5	26.2	.34
PSI, IV–V	72.8	77	68.7	.32
Outcome variables				
ICU admission	25.2	25.8	24.6	>.99
Length of ICU stay, mean days ± SD	16.6 ± 16.5	12.3 ± 13.5	21.7 ± 18.5	.14
Orotracheal intubation	14.2	11.3	16.9	.45
Length of hospital stay, mean days ± SD	23.5 ± 15.7	23.3 ± 15.4	23.8 ± 16.2	.87
Use of fibrinolytic agents	43	24.5	58.6	.03
Need of surgical intervention	12.4	5.3	18.8	<.001
Hospital mortality	11.8	11.3	12.3	>.99

NOTE. Data are percent of patients unless otherwise indicated. HIV, human immunodeficiency virus; ICU, intensive care unit; PSI, pneumonia severity index; SD, standard deviation.

[a] Comparison between pre- and postvaccine periods.

[b] Includes any of the following: HIV infection, hematologic cancer, solid cancer, solid-organ or bone marrow transplant, immunoglobulin deficiency, splenectomy or current immunosuppressive therapy (including systemic steroids).

[c] Includes any of the following: chronic heart disease, chronic lung disease, cerebrovascular disease, cirrhosis or chronic liver disease, diabetes or chronic renal insufficiency.

Table 2. Risk Factors for Pneumococcal Empyema in Unvaried and Multivariate Analysis

Variable	Empyema (n = 128)	Bacteremic pneumonia (n = 576)	Univariate analysis		Multivariate analysis	
			OR (95% CI)	P	OR (95% CI)	P
Previous receipt of PPV-23 *	12.3	20.4	0.43 (0.19–0.95)	.03	0.46 (0.17–1.25)	.13
Diabetes mellitus	12	25.7	0.49 (0.27–0.9)	.02	0.67 (0.27–1.67)	.39
Hematological cancer	4.8	10.3	0.44 (0.18–1.04)	.06	0.62 (0.15–2.53)	.51
Immunosuppressive condition	28.3	36.7	0.68 (0.45–1.04)	.08	1.58 (0.75–3.3)	.23
Serotype 1	28.9	8.7	4.12 (2.48–6.82)	<.001	5.88 (2.66–13)	<.001
Serotype 3	19	8.9	2.41 (1.39–4.18)	.003	5.49 (1.93–15.62)	.001
Serotype 4	2.5	6.9	0.34 (0.1–1.14)	.09	0.75 (0.15–3.78)	.72
Serotype 14	5.8	11.1	0.49 (0.28–1.11)	.09	1.07 (0.27–4.21)	.92
Penicillin susceptibility	82.5	74.5	1.61 (0.96–2.7)	.07	1.69 (0.62–4.64)	.31
ICU admission	25.2	17.4	1.61 (1.02–2.55)	.04	1.36 (0.68–2.75)	.38

NOTE. Data are percent of patients unless otherwise indicated. CI, confidence interval; ICU, intensive care unit; OR, odds ratio; PPV-23: 23-valent polysaccharide vaccine.

associated bacteremia. Globally, 56.3% of the patients had an underlying chronic medical illness. Chronic pulmonary disease (34.1% of the patients) and various immunosuppressive conditions (28.3% of patients) were the most common comorbidities. At presentation, 55.9% of patients had respiratory failure, 20.5% required vasoactive drugs, and 25.2% of them required ICU admission. Surgery, other than thoracic drainage with a chest tube, was performed for 12.4% of patients. The overall rate of hospital mortality was 11.8%.

Comparing the 2 periods, the mean age of the patients decreased from 63.2 to 55.2 years (P = .01). Patients with pneumococcal empyema during the postvaccine period were less likely to have chronic medical illness (67.2% vs 46.2%; P = .002), chronic lung disease (49.3% vs 20%; P = .001), or immunosuppressive conditions (37.1% vs 20%; P = .048).

We did not observe significant differences in the clinical presentation and outcome between the pre- and postvaccine periods. The proportion of patients with pneumococcal empyema who presented with respiratory failure and septic shock was similar during the 2 periods. The length of hospital stay for survivors and the overall case-fatality rate (11.3% vs 12.3%) remained unchanged in both periods.

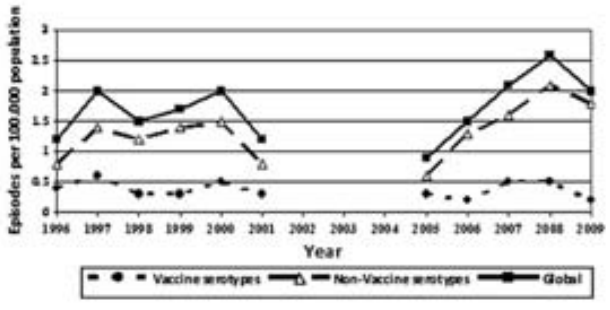

Figure 1. Incidence of pneumococcal empyema by year and serotype group.

Risk Factors for Pneumococcal Empyema

In the unadjusted univariate analysis, patients with empyema were less likely to have diabetes mellitus or immunosuppressive conditions and they had a greater need for ICU admission (Table 2). However, in the multivariate analysis, the only independent variables associated with an increased risk of pneumococcal empyema were infection caused by serotype 1 (adjusted odds ratio [OR], 5.88 [95% CI, 2.66–13]) and serotype 3 (adjusted OR, 5.49 [95% CI, 1.93–15.62]).

Changes in Disease Burden After PPV7 Implementation

The overall incidence of empyema did not change significantly between the pre- and postvaccine periods (1.6 and 1.8 cases per 100,000 population-years, respectively) (Figure 1). Significant changes were observed in patients aged 18–50 years (Table 3 and Figure 2). In this population, the rates of patients with pneumococcal pneumonia who had empyema increased from 7.6% to 14.9% (P = .04) and the incidence of pneumococcal empyema increased from 0.5 to 1.6 cases per 100,000 person-

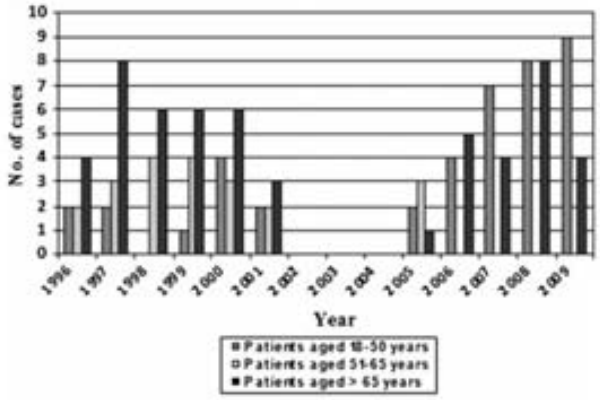

Figure 2. Cases of empyema by year.

Table 3. Mean Incidence of Empyema by Age Group, Serotypes, and Time Period Among Adult Patients

Empyema	Prevaccine period			Postvaccine period			Pre- vs postvaccine period				
							100 000 population-years		1000 admission-years		
	Proportion of patients with PE, %	Cases/100 000 population per year	Cases/1000 admissions per year	Proportion of patients with PE, %	Cases/1000 admissions per year	Cases/1000 admissions per year	Change, % (95% CI)	*P* [a]	Change, % (95% CI)	*P* [a]
Age group										
All adults	12.2	1.6	0.18	11.5	1.8	0.22	17 (−15 to 65)	.38	24% (−13 to 75)	.22
18–50 years	7.6	0.5	0.08	14.9	1.6	0.27	198 (49–494)	.001	224 (62–646)	<.001
50–65 years	17.3	1.4	0.25	11.5	1.2	0.25	−15 (−57 to 72)	.65	−2 (−51 to 97)	.96
>65 years	12.7	4.8	0.23	8.8	3.5	0.17	−27 (−57 to 25)	.25	−26 (57–26)	.26
Serotype 1										
All adults	14.8	0.2	0.026	43.3	0.8	0.087	253 (67–646)	<.001	237 (68–618)	.001
18–50 years		0.1	0.015		0.8	0.12	664 (73–3262)	.001	731 (89–3558)	.001
50–65 years		0.5	0.084		0.5	0.106	−0.1 (−65 to 240)	.87	26 (−69 to 291)	.686
>65 years		0.1	0.007		1.4	0.069	883 (24–676)	.008	893 (26–7839)	.007
Serotype 3										
All adults	24.6	0.4	0.043	13.3	0.2	0.027	−34 (−71 to 50)	.32	−38 (−74 to 47)	.273

Note. CI, confidence interval; PE, pneumococcal empyema.

[a] *P* value: differences in means of the incidence between prevaccine and postvaccine periods were tested using the Mantel-Haenszel test.

years (198% [95% CI, 49%–494%]). If we calculate the incidence by admissions, we obtain similar results, with increases in the incidence of empyema from 0.08 to 0.27 cases per 1000 admission-years (224% [95% CI, 62%–546%]) in young adults (Table 3).

Serotype Distribution and Antibiotic Susceptibility

A total of 26 different pneumococcal serotypes were isolated from patients with pneumococcal empyema, most of which (80.2%) were non-PCV7 vaccine serotypes (Figure 1 and Table 4). Although there were some changes in the incidence of empyema caused by PCV7 serotypes (−27% [95% CI, −67% to 62%]) and non-PCV7 serotypes (31% [95% CI, −11% to 93%]) when both periods were compared, they were not significant. Nevertheless, individual pneumococcal serotypes differed significantly between the 2 periods. Serotype 1, which caused 14.8% of pneumococcal empyemas during the prevaccine period, increased to 43.3% during the postvaccine period ($P < .001$). In terms of incidence, the incidence of empyema due to serotype 1 increased significantly from 0.2 to 0.8 cases per 100,000 person-years (253% [95% CI, 67%–646%]), especially among patients aged 18–50 years and patients aged >65 years. In contrast, we did not observe significant changes in the incidence or in the rates of empyema caused by serotype 3 (Table 3).

The proportion of pneumococcal empyema caused by penicillin-nonsusceptible strains decreased between the pre- and postvaccine periods from 28% to 9.4% ($P = .01$). Resistance to other antibiotics, such as cephalosporins and macrolides, also tended to decrease (Table 5).

Therapeutic Measures: Pleural Fluid Drainage and Thoracic Surgery

A chest tube for drainage of pleural fluid was inserted in 88.4% of patients. Surgical intervention, either thoracotomy with decortication or video-assisted thoracic surgery, was required in only 12.3% of cases. The number of patients undergoing surgical intervention increased from 3 (5.3%) of 57 cases during the prevaccine period to 12 (18.8%) of 64 cases during the postvaccine period ($P = .02$). Administration of fibrinolytic agents also increased, from 24.5% during the prevaccine period to 58.6% during the postvaccine period ($P < .001$). In 7 (53.8%) of the 13 adults with known serotype who required surgical intervention, the causal pneumococcal strain was serotype 1. When analyzed individually, serotypes 1, 3, and 7F had the highest rates of surgical intervention, with 21.9%, 9.5%, and 33%, respectively.

DISCUSSION

We observed a marked increase in the incidence of pneumococcal empyema in young adults after the implementation of the

Table 4. Serotypes More Often Isolated From Adults With Pneumococcal Empyema

Serotypes	No. (%) of isolates recovered			
	Total (n = 121)	Prevaccine period (n = 61)	Postvaccine period (n = 60)	P
Conjugate vaccine serotypes	24 (19.8)	15 (24.6)	9 (15)	.26
Serotype 4	3 (2.5)	1 (1.6)	2 (3.3)	.49
Serotype 9V	5 (4.1)	4 (6.6)	1 (1.7)	.36
Serotype 14	7 (5.8)	4 (6.6)	3 (5)	.51
Serotype 19F	3 (2.5)	1 (1.6)	2 (3.3)	.62
Non–conjugate vaccine serotypes	97 (80.2)	46 (75.4)	51 (85)	.26
Serotype 1	35 (28.9)	9 (14.8)	26 (43.3)	<.001
Serotype 3	23 (19)	15 (24.6)	8 (13.3)	.16
Serotype 5	4 (3.3)	2 (3.3)	2 (3.3)	.68
Serotype 6A	8 (6.6)	5 (8.2)	3 (5)	.72
Serotype 7F	6 (5)	2 (9.8)	4 (6.7)	.33
Serotype 8	5 (4.1)	4 (6.6)	1 (1.7)	.19
Serotype 19A	3 (2.5)	2 (3.3)	1 (1.7)	.65

pneumococcal conjugate vaccine in children. This change seems to be associated with the emergence of nonvaccine serotype 1.

The introduction of the PCV7 in children has been accompanied by substantial reductions in the incidence of IPD caused by serotypes of pneumococci that are included in the vaccine [1–4]. However, a dynamic process of replacement in the types of serotypes seems to have occurred and, as a consequence, the incidence of pneumococcal infections caused by nonvaccine serotypes has increased [5–9]. The clinical characteristics of pneumococcal infections caused by nonvaccine serotypes are somehow different, and, in children, increased rates of necrotizing pneumonia and empyema have been observed [11–13, 17, 18]. These suppurative complications of pneumonia have been associated with the emergence of the non-PCV7 serotypes 1 and 3 [11, 17, 18, 26].

Table 5. Antibiotic Susceptibility of Pneumococcal Strains Isolated From Patients With Pneumococcal Empyema

Antibiotic (MIC, μg/mL)	Susceptibility, %		
	Prevaccine period (n = 62)	Postvaccine period (n = 66)	P
Penicillin			
Susceptible (≤0.06)	72	90.6	.01
Intermediate (0.12–1)	12	3.1	
Resistant (≥2)	16	6.3	
Cephalosporins[a]			
Susceptible (≤0.5)	88.7	92.2	.56
Intermediate (1)	6.5	4.7	
Resistant (≥2)	4.8	3.1	
Macrolides[b]			
Susceptible (≤0.5)	76	84.4	.34
Intermediate (1)	2	0	
Resistant (≥2)	22	15.6	
Quinolones[c]			
Susceptible (≤2)	100	97.7	>.99
Intermediate (4)	0	0	
Resistant (≥8)	0	2.3	

NOTE. MIC, minimum inhibitory concentration.

[a] Cephalosporins: ceftriaxone or cefotaxime.

[b] Macrolides: erithromycin (susceptible ≤ 0.25, intermediate 0.5, resistant ≥1) or azithromycin (susceptible ≤ 0.5, intermediate 1, resistant ≥2).

[c] Quinolones: ofloxacin or levofloxacin.

We observed a significant change in the epidemiological characteristics of pneumococci causing empyema also in adults. Young adults aged between 18 and 50 years are the population most affected by this increase in the incidence of pneumococcal empyema. More than 40% of episodes of pneumococcal empyema in adults are now caused by serotype 1. The reasons for the high tendency of pneumococcal serotype 1 to cause empyema are not well understood. Some studies have shown its predisposition to affect young adults without previous comorbid conditions, causing pneumonia and empyema [16, 27]. In our study, 67.5% of patients aged between 18 and 50 years had no chronic underlying disease.

The explanation for why the epidemiology of pneumococcal disease has changed so significantly is most likely multifactorial [28]. Definitely, the effect of the implementation of the PCV7 in children plays an important role in explaining the emergence of new serotypes. Nevertheless, the increase in the incidence of pneumococcal empyema in children cannot easily be explained only by a vaccine effect. Temporal trends in pneumococcal serotype distribution have been described worldwide, with epidemic increases in the frequency of serotype 1 in the last years of the 20th century before the implementation of the PCV7 [29–31]. These fluctuations in the epidemiological characteristics of pneumococcal serotypes could be the reason why

increases in the incidence of pneumococcal empyema in children had already been reported before the introduction of the PCV7 in the United States and the United Kingdom [32, 33].

In the postvaccine era, we have observed an increased requirement for surgical management of pneumococcal empyema. These findings are quite different from the results reported by Byington et al, who found a decrease in surgical treatment of children during the postvaccine period [34]. Although these changes could be greatly influenced by different attitudes toward surgical intervention over time, both studies found similar and high rates of surgical management in pneumococcal empyema caused by serotype 1 (22% in our study and 28.7% in the Byington et al study).

Our study has several potential limitations. First, because it is not a population-based study, the incidence estimates may not be the most realistic. Second, it presents data from only 2 centers of the same area of Spain, so it might not be representative of other geographical areas where the specific serotype distribution could differ from that in other regions [35, 36]. Finally, other factors that might also modulate the epidemiology of pneumococcal empyema (eg, genetic properties of *S. pneumoniae* strains or viral coinfections) were not evaluated in our study.

Despite these limitations, we believe that our study reveals important and novel changes in the epidemiological characteristics of pneumococcal empyema in adults, with an increase in the incidence of empyema in younger adults without comorbidities. We have also identified pneumococcal serotypes 1 and 3 as the main determinants of development of this suppurative complication. In the near future, the introduction of the 13-valent pneumococcal conjugated vaccine, which contains serotypes 1 and 3, will provide information about the exact role that the PCV7 has had in the increased rates of episodes of pneumococcal empyema both in children and in adults, so continued surveillance on the epidemiology of pneumococcal infections is needed.

Acknowledgments

Role of authors: J. B. and V. F. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Author contributions were as follows:

Study concept and design: J. B., M. L., V. F., J. R.

Acquisition of data: J. B., M. L., V. F., A. S., M. P., A. B.

Analysis and interpretation of data: J. B., M. L., V. F., J. R.

Drafting of the manuscript: J. B., M. L., V. F., J. R.

Critical revision of the manuscript for important intellectual content: J. B., M. L., V. F., J. R., A. M. P., D. F., A. P.

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All authors approved the final version of the manuscript.

Financial support. This work was institutionally supported by the Spanish Network for Research in Infectious Diseases (REIPI), RD06/008 from the Ministry of Science and Innovation, "Instituto de Salud Carlos III" and Centro de Investigación Biomédica en Red (CIBER) de Enfermedades Respiratorias.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed in the Acknowledgments section.

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ORIGINAL ARTICLE 10.1111/j.1469-0691.2012.03895.x

Impact of the emergence of non-vaccine pneumococcal serotypes on the clinical presentation and outcome of adults with invasive pneumococcal pneumonia

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Abstract

The introduction of the 7-valent pneumococcal conjugate vaccine in children has led to a change in the pattern of pneumococcal serotypes causing pneumococcal disease. The aim of this study was to compare the clinical presentation and outcome of invasive pneumococcal pneumonia (IPP) in adults between the pre and post-vaccine era. We have conducted an observational study of all adults hospitalized with IPP, from 1996 to 2001 (pre-vaccine period), and from 2005 to 2009 (post-vaccine period). Incidence, serotype distribution and clinical data were compared between both periods. A total of 653 episodes of IPP were diagnosed. The overall incidence of IPP increased from 14.2 to 17.9 cases per 100 000 population-year (p 0.003). In the post-vaccine period IPP caused by vaccine serotypes decreased (−36%; 95% CI, −52 to −15) while IPP caused by non-vaccine serotypes increased (71%; 95% CI, 41–106). IPP in the post-vaccine period was associated with higher rates of septic shock (19.1% vs. 31.1%, p <0.001). Among patients aged 50–65 years there was a trend towards a greater proportion of case-fatalities (11.6–23.5%, p 0.087). Independent risk factors for septic shock were IPP caused by serotype 3 (OR 2.38; 95% CI, 1.16–4.87) and serotype 19A (OR 6.47, 95% CI, 1.55–27). Serotype 1 was associated with a lower risk of death (OR 0.1; 95% CI, 0.01–0.78). In conclusion, the incidence of IPP in the post-vaccine period has increased in our setting, it is caused mainly by non-vaccine serotypes and it is associated with higher rates of septic shock.

Keywords: invasive pneumococcal disease, pneumococcal conjugate vaccine, Pneumococcal pneumonia, pneumococcal serotypes, septic shock

Original Submission: 23 September 2011; **Revised Submission:** 27 March 2012; **Accepted:** 7 April 2012

Editor: J.-L. Mainardi

Clin Microbiol Infect

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Introduction

After the implementation of the 7-valent pneumococcal conjugate vaccine (PCV7) in the USA significant declines in invasive pneumococcal disease (IPD) due to vaccine serotypes were reported in children and adults [1–4]. However, due to a replacement phenomenon, increases of nasopharyngeal colonization of children by non-PCV7 serotypes was soon reported [5,6]. Simultaneously, increases in the incidence of IPD caused by non-PCV7 serotypes both in children and adults, were also observed [7,8]. These changes were due mainly to variations in the incidence of pneumonia, the most common clinical presentation of IPD, which represents nearly 80% of cases [1,4,6]. In Spain, PCV7 was introduced in June 2001, and in 2006 it was estimated that about 50% of children had been vaccinated [9]. The emergence of IPD caused by non-PCV7 serotypes after PCV7 introduction has also been described in our country [8,10,11].

Different studies have shown that capsular pneumococcal polysaccharide, which is the determinant of the different serotypes, is associated with specific manifestations of pneumococcal disease [4,12]. In this way, variations in serotype distributions of IPD may be accompanied by changes in

clinical presentation. In fact, high rates of empyema associated with the non-PCV7 serotypes 1 and 3 have been reported in the last years [13–15].

To our knowledge there are scarce data about the clinical impact of the emergence of invasive pneumococcal pneumonia (IPP) caused by non-PCV7 serotypes in adults after the introduction of the PCV7. The aim of our study was to analyse the differences in the incidence, disease characteristics and clinical outcome of IPP in adults before and after the introduction of the PCV7, in an area of Barcelona, Spain.

Patients and Methods

Study population and setting

We performed an observational study of all adults (aged ≥18 years) hospitalized with IPP from January 1996 to December 2001, and from January 2005 to December 2009, in the University Hospital Vall d'Hebron, a tertiary teaching hospital in Barcelona that serves a population of 411 227 people [16]. In our hospital, all microbiological strains isolated in sterile samples are collected systematically. Patients were classified into two groups according to the introduction of PCV7 in our area: pre-vaccine period (1996–2001) and post-vaccine period (2005–2009). We excluded the interim period (2002–2004) because of the low initial coverage of the vaccine. In Barcelona, the estimated vaccine uptake increased from 27% in 2004 [14] to 36% in 2005 and 47% in 2007 [10]. The study was approved by the Commission of Medical Ethics of our institution.

Study variables and data collection

The following variables were recorded: (i) sociodemographic data; (ii) underlying diseases; (iii) immunosuppressive conditions; (iv) severity of the illness at admission (respiratory failure, septic shock, Pneumonia Severity Index); (v) microbiological pneumococcal data (serotype and antibiotic resistance pattern); (vi) antimicrobial therapy and (vii) variables related to clinical outcome (hospital case-fatality, intensive care unit (ICU) admission, orotracheal intubation requirement, suppurative lung complications and length of hospital stay for survivors).

Definitions

Invasive pneumococcal pneumonia was diagnosed when a patient had signs and symptoms of an acute-onset lower respiratory tract infection plus a new pulmonary infiltrate on chest radiography and isolation of *S. pneumoniae* in blood and/or pleural fluid cultures [17]. Septic shock was considered when vasoactive drugs were necessary to obtain appropriate arterial pressure values after fluid replacement [18].

Microbiological procedures

Streptococcus pneumoniae isolates were identified by Gram staining, optoquin susceptibility, bile solubility testing and latex agglutination testing. Susceptibility of pneumococcal isolates was tested using the microdilution method, in accordance with the Clinical and Laboratory Standards Institute procedures. Serotyping was performed by capsular swelling (Quellung) reaction using commercial serogroup and serotype-specific antiserum at the Spanish Reference Laboratory (Instituto Carlos III, Madrid), where all isolates were routinely sent. Serotypes were classified into two groups: PCV7 serotypes (serotypes 4, 6B, 9V, 14, 18C, 19F and 23F) and non-PCV7 serotypes (all others). Information regarding serotype is lacking in 13.5% of the isolates, in most cases because samples were not sent to the reference centre. Only 1% of cases were non-typeable pneumococci.

Estimation of the incidence of invasive pneumococcal pneumonia

We calculated overall and group age incidence rates of IPP by 100 000 persons-year. In order to make these calculations we used as denominator the exact number of the population living in the reference area of the hospital per year according to the Department of Statistics in Catalunya [19]. Hospital Vall d'Hebron is the only tertiary hospital in the reference area and the contribution of other hospitals in the area is minimal and has not changed during the study period. In order to avoid some bias related to the reference population, we also calculated the incidence of IPP per 1000 adult admissions in our hospital per year. During the study period the overall number of admissions per 100 000 of the catchment population has been constant.

To estimate the incidence of IPP due to vaccine or non-vaccine serotypes, we assumed that the distribution of serotypes for cases missing serotype information was the same as the distribution for those cases with serotype information.

Statistical analysis

Statistical analyses were performed using the statistical software package SPSS for Windows, version 15.0. Differences in means of the incidence were tested using the Mantel–Haenszel test [20]. The absolute risk difference with corresponding 95% confidence intervals were reported. The chi-square test was used to compare the distribution of categorical variables and the Student's *t*-test for continuous variables. To asses differences in disease characteristics between the two periods we compared overall and age group patients. A univariable and multivariable logistic regression analysis was performed to identify variables independently associated with death and septic shock. Results were considered statistically significant if the two-tailed p value was <0.05.

when appropriate, was used to compare the distribution of categorical variables, and the Student *t* test or the Mann-Whitney *U* test for continuous variables. Results were considered statistically significant if the 2-tailed *P* value was <.05.

To assess the risk factors for pneumococcal empyema, we compared the 128 patients with empyema with 576 patients who had bacteremic pneumococcal pneumonia without empyema collected during the same study period. We performed univariate and multivariate logistic regression analysis to identify variables independently associated with pneumococcal empyema. Significant and nearly significant ($P < .10$) variables from the univariate analysis were included in the multivariate analysis.

To asses the association of the different serotypes with the risk of empyema, we have grouped serotypes in 3 different categories, as follows: (0) non-1, non-3 serotypes, which acted as a reference category; (1) serotype 1; and (2) serotype 3. The same model has been used for the combined variable serotype 4 and 14. All statistical analyses were performed using the statistical software package SPSS for Windows, version 15.0.

RESULTS

During the study period, 1080 episodes of invasive pneumococcal pneumonia were diagnosed in adults, 508 of them during the prevaccine period and 572 during the postvaccine period. Empyema was diagnosed in 128 (11.9%) of the 1080 patients with invasive pneumococcal pneumonia.

Clinical Characteristics of Patients With Pneumococcal Empyema

The mean age of patients with pneumococcal empyema was 59.1 ± 18.1 years, and 65.6% of the episodes occurred in men (Table 1). Seventy-four (57.8%) of the 128 patients had

Table 1. Basal Characteristics, Clinical Presentation, and Outcomes by Time Period Among Patients With Pneumococcal Empyema

Characteristic	All patients (*n* = 128)	Prevaccine period (*n* = 62)	Postvaccine period (*n* = 66)	*P*[a]
Sociodemographic variables				
Age, mean years ± SD	59.1 ± 18.1	63.2 ± 16.7	55.2 ± 18.7	.01
Male sex	65.6	69.4	62.1	.46
Smoking	22.2	27.9	16.9	.20
Alcohol consumption	59.5	65.6	53.8	.21
Underlying diseases				
Immunosuppressive condition[b]	28.3	37.1	20	.048
HIV infection	10.2	14.5	6.2	.15
Hematological cancer	4.7	9.7	0	.01
Solid cancer	12.6	12.6	16	.22
Chronic medical illness[c]	56.3	67.2	46.2	.002
Chronic lung disease	34.1	49.2	20	.001
Charlson comorbidity index, mean ± SD	2.19 ± 2.5	2.8 ± 2.6	1.63 ± 2.2	.08
Clinical presentation				
Respiratory failure	55.9	66.4	52.3	.47
Septic shock	20.5	14.5	26.2	.34
PSI, IV–V	72.8	77	68.7	.32
Outcome variables				
ICU admission	25.2	25.8	24.6	>.99
Length of ICU stay, mean days ± SD	16.6 ± 16.5	12.3 ± 13.5	21.7 ± 18.5	.14
Orotracheal intubation	14.2	11.3	16.9	.45
Length of hospital stay, mean days ± SD	23.5 ± 15.7	23.3 ± 15.4	23.8 ± 16.2	.87
Use of fibrinolytic agents	43	24.5	58.6	.03
Need of surgical intervention	12.4	5.3	18.8	<.001
Hospital mortality	11.8	11.3	12.3	>.99

NOTE. Data are percent of patients unless otherwise indicated. HIV, human immunodeficiency virus; ICU, intensive care unit; PSI, pneumonia severity index; SD, standard deviation.

[a] Comparison between pre- and postvaccine periods.

[b] Includes any of the following: HIV infection, hematologic cancer, solid cancer, solid-organ or bone marrow transplant, immunoglobulin deficiency, splenectomy or current immunosuppressive therapy (including systemic steroids).

[c] Includes any of the following: chronic heart disease, chronic lung disease, cerebrovascular disease, cirrhosis or chronic liver disease, diabetes or chronic renal insufficiency.

(from 0.9 to 0.1 episodes per 100 000 population-year; 95% CI, −99 to −56) and a 60% reduction of infections by serotype 9V (from 0.8 to 0.3 episodes per 100 000 population-year; 95% CI, −1 to −84). In non-PCV7 serotypes we found a 125% increase of IPP caused by serotype 1 (from 1.2 to 2.6 episodes per 100 000 population-year; 95% CI, 39–263), a 316% increase of infections by serotype 7F (from 0.5 to 1.9 episodes per 100 000 population-year; 95% CI, 107–736) and an 874% increase of infections by serotype 19A (from 0.1 to 1.3 episodes per 100 000 population-year; 95% CI, 195–3117).

In patients aged 18–50 years, the IPP incidence increased from 8 to 13.9 cases per 100 000 persons-year (74%; 95% CI, 32–129), mainly due to an increase of non-PCV7 serotypes (Table 1).

Sociodemographic variables and underlying diseases

Comparing the two periods, the mean age of the patients decreased from 62 to 58.5 years (p 0.023). The pattern of underlying diseases varied depending on the age. In younger patients (aged between 18 and 50 years) we found a significant reduction in the proportion of HIV infections (60.8% vs. 28.7%, p <0.001). On the other hand, patients aged 51–65 years had greater proportions of chronic medical illness (43.5% vs. 63.4%, p 0.021) in the post-vaccine period (Table 2).

Clinical presentation and outcome

The proportion of patients with IPP who presented with septic shock (19.1% vs. 31.1%, p <0.001) and required ICU admission (13.7% vs. 21.6%, p 0.011) was significantly higher in the post-vaccine era (Table 2). These specially affected patients aged 51–65 years, in whom the proportion with septic shock increased from 17.2% to 35.9% (p 0.015). They also had a higher PSI score (score ≥IV: 54.5% vs. 76.3%, p 0.008). The proportion of case-fatalities remained unchanged in both periods (15.2% vs. 17.1%). However, among patients aged 51–65 years we found an apparent trend towards an increase from 11.6% to 23.5% in the post-vaccine period (p 0.087). The proportion of case-fatalities showed a possible downward trend in younger patients (16.9% vs. 8.5%, p 0.111).

After adjustment, the independent risk factor for septic shock was pneumonia caused by serotype 3 and serotype 19A. Regarding death, high alcohol consumption and haematological cancer were found to be risk factors, and pneumonia caused by serotype 1 a protective factor (Table 3).

Pattern of serotypes

In young adults, the non-vaccine serotypes 1 and 7F were the most prevalent and caused 35.3% of cases of IPP in the

TABLE 2. Basal characteristics, clinical presentation and outcomes by age group and time period among adult patients

	All adults			Adults 18–50 years			Adults 51–65 years			Adults >65 years		
	Pre-vaccine period (n = 308)	Post-vaccine period (n = 345)	p value	Pre-vaccine period (n = 82)	Post-vaccine period (n = 127)	p value	Pre-vaccine period (n = 69)	Post-vaccine period (n = 83)	p value	Pre-vaccine period (n = 156)	Post-vaccine period (n = 135)	p value
Basal characteristics												
Age (years, mean)	62	58.5	0.023	36	36.2	0.886	59	59	1	76.9	79.1	0.024
Sex male	65.9%	61.7%	0.29	68.3%	63%	0.461	71%	77.1%	0.457	62.2%	51.1%	0.059
Chronic medical illness[a]	50%	52.7%	0.530	30%	27.4%	0.640	43.5%	63.4%	0.021	62.8%	69.7%	0.261
Immunosuppressive conditions[b]	36.4%	34.6%	0.681	62.2%	37.9%	0.001	30.4%	46.3%	0.065	25.2%	24.2%	0.891
Clinical presentation												
Respiratory failure	46%	55%	0.289	20.5%	35.5%	0.382	58.3%	68.8%	0.516	56.5%	64.2%	0.490
Septic shock	19.1%	31.1%	0.001	19.7%	29.3%	0.176	17.2%	35.9%	0.015	19.7%	29.8%	0.063
Pneumonia Severity Index[c]	64%	65.9%	0.666	32.9%	36%	0.756	54.5%	76.3%	0.008	85.1%	88.1%	0.585
Outcomes variables												
ICU admission	13.7%	21.6%	0.011	19.2%	25.9%	0.304	13%	33.1%	0.138	11%	16.5%	0.21
Length of ICU stay[d]	12.4	14.2	0.244	10	13.6	0.151	12.6	16.1	0.261	13.8	13.4	0.841
Orotracheal intubation	11%	13.1%	0.455	11.7%	18.3%	0.311	11.6%	12.8%	1	10.3%	8.3%	0.675
Length of hospital stay[d]	11.2	18.6	0.074	11.2	20.1	0.369	8.4	21	0.068	13	13	0.994
Empyema	13.1%	12.5%	0.903	10.5%	16.9%	0.295	19%	13.4%	0.37	11.9%	7.9%	0.314
Hospital case-fatality	15.2%	17.6%	0.455	8.5%	16.9%	0.111	11.6%	23.5%	0.087	16%	22.5%	0.208

[a]Includes any of the following: chronic heart disease, chronic lung disease, cerebrovascular disease, cirrhosis or chronic liver disease, diabetes or chronic renal insufficiency.
[b]Includes any of the following: HIV infection, haematological cancer, solid cancer, solid organ or bone marrow transplant, immunoglobulin deficiency, splenectomy or current immunosuppressive therapy (including systemic steroids).
[c]Pneumonia Severity Index: indicates a Pneumonia Severity Index ≥4 at the moment of admission to the Emergency Department.
[d]Expressed in days (mean).

TABLE 3. Variables associated with (a) septic shock and (b) death

	Univariate OR (95% CI)	p value	Multivariate OR (95% CI)	p value
(a) Septic shock				
Male sex	1.69 (0.13–2.53)	0.007	1.21 (0.72–2.03)	0.472
Age, 18–50 vs. >50 years	1 (0.68–1.49)	0.528		
Post-vaccine period	1.91 (1.3–2.79)	0.001	1.24 (0.74–2.1)	0.414
Smoking	1.08 (0.71–1.78)	0.394		
Heavy alcohol consumption	1.67 (0.98–2.82)	0.004	1.65 (0.9–3.32)	0.106
Chronic lung disease	1.13 (0.71–1.78)	0.347		
Chronic medical illness[a]	0.99 (0.69–1.44)	0.522		
Haematological cancer	0.95 (0.50–1.78)	0.504		
Solid cancer	1.7 (1.04–2.79)	0.026	1.67 (0.84–4.87)	0.140
Immunosuppressive condition[b]	1.1 (0.69–1.48)	0.518		
Serotype 1	0.78 (0.4–1.53)	0.294		
Serotype 3	2.08 (1.16–3.74)	0.012	2.38 (1.16–4.87)	0.018
Serotype 4	0.512 (0.19–1.13)	0.118		
Serotype 6B	1.42 (0.48–4.16)	0.351		
Serotype 7F	0.89 (0.37–2.12)	0.496		
Serotype 8	1.39 (0.66–2.91)	0.246		
Serotype 9V	0.37 (00.08–1.65)	0.141		
Serotype 14	0.95 (0.49–1.83)	0.511		
Serotype 19A	2.79 (0.99–7.87)	0.049	6.47 (1.55–27)	0.010
Serotype 19F	2.22 (0.92–5.32)	0.063	2.46 (0.97–6.21)	0.058
Serotype 23F	0.55 (0.12–2.53)	0.345		
Penicillin susceptibility[c]	1.08 (0.7–1.7)	0.402		
Cephalosporin susceptibility[d]	1.24 (0.63–2.41)	0.326		
(b) Death				
Male sex	1.36 (0.85–2.15)	0.119		
Age, 18–50 vs. >50 years	0.58 (3.52–9.58)	0.019	0.61 (0.29–1.31)	0.206
Post-vaccine period	1.22 (0.85–2.15)	0.212		
Smoking	0.77 (0.47–1.27)	0.190		
Heavy alcohol consumption	1.68 (0.92–3.06)	0.066	2.15 (0.05–4.39)	0.036
Chronic lung disease	0.89 (0.46–1.32)	0.446		
Chronic medical illness[a]	1.06 (0.69–1.63)	0.433		
Haematological cancer	1.89 (1.01–3.56)	0.039	3.77 (1.42–10)	0.008
Solid cancer	3.05 (1.82–5.11)	<0.001	1.63 (0.62–4.27)	0.317
Immunosuppressive condition[b]	1.96 (1.27–3.03)	0.02	1.08 (0.47–2.48)	0.85
Serotype 1	0.08 (0.01–0.57)	<0.001	0.1 (0.01–0.78)	0.028
Serotype 3	1.49 (0.75–2.95)	0.168		
Serotype 4	0.69 (0.24–1.99)	0.341		
Serotype 6B	1.47 (0.48–4.56)	0.339		
Serotype 7F	0.74 (9.25–2.16)	0.397		
Serotype 8	0.9 (0.34–2.39)	0.532		
Serotype 9V	0.35 (0.05–2.72)	0.260		
Serotype 14	1.53 (0.77–3.03)	0.153		
Serotype 19A	2.03 (0.63–6.53)	0.191		
Serotype 19F	0.77 (0.22–2.64)	0.473		
Serotype 23F	0.99 (0.21–4.54)	0.672		
Penicillin susceptibility[c]	0.69 (0.43–1.23)	0.092	0.83 (0.43–1.6)	0.58
Cephalosporin susceptibility[d]	0.77 (0.39–1.56)	0.243		

[a]Includes any of the following: chronic heart disease, chronic lung disease, cerebrovascular disease, cirrhosis or chronic liver disease, diabetes or chronic renal insufficiency.
[b]Includes any of the following: HIV infection, haematological cancer, solid cancer, solid organ or bone marrow transplant, immunoglobulin deficiency, splenectomy or current immunosuppressive therapy (including systemic steroids).
[c]Includes isolates with MIC ≤0.06 μg/ml.
[d]Includes isolates with MIC ≤0.5 μg/ml.

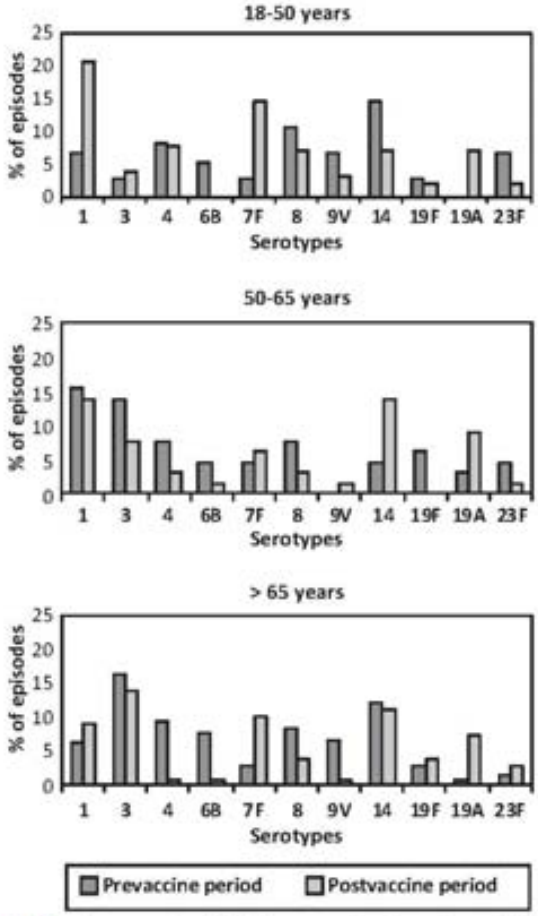

FIG. 2. Serotypes causing IPP in the pre and post-vaccine periods by age groups.

post-vaccine period. Otherwise, serotypes 3, 14 and 19A were identified in 31.9% of cases of IPP in patients aged >50 years, in the same period (Fig. 2). Regarding clinical presentation, pneumococcal serotypes most often isolated in cases of septic shock were 3, 19A and 19F (septic shock developed in 46.7% of infections by serotype 19F, in 40.9% by serotype 19A and in 38.2% by serotype 3). Interestingly, none of the patients with IPP caused by serotypes 1 and 5 died.

The proportion of IPP caused by penicillin non-susceptible strains decreased during the two periods, from 28.3% to 19.7% (p 0.012) (Table S1).

Discussion

In this study we have observed significant changes not only in the incidence but also in the clinical presentation and severity of IPP in adults after the implementation of the

PCV7 vaccine in children. These clinical changes coincide with a replacement of the pneumococcal serotypes.

In the United States, after the introduction of the PCV7, the overall incidence of IPD decreased significantly in children and adults [1–4]. However, in other geographical areas these changes have not been so evident. In France, Holland and Spain, as in our study, the incidence of IPD increased significantly in adults [8,14,21,22]. Interestingly, there seems to be some differences in the burden of IPD in adults in the United States and Europe. The different vaccine coverage between USA and Europe could explain in part this discrepancy [1,9,21]. Other factors such as fluctuations of serotypes or outbreaks of infections in a specific geographical area may play a role [8].

The question of why the disease is increasing in younger adults may be related to the emergence of specific serotypes. Non-vaccine serotypes 1, 5 and 7F have a high invasive potential [23,24], and have been associated with invasive disease in younger adults [12,25,26]. In our study the emergence of serotypes 1 and 7F could explain the increases in the incidence of IPP in this age group.

One of the most important findings of our study is that the severity of pneumococcal disease has changed in the post-vaccine period. We have found higher rates of septic shock and an apparent trend towards greater proportion of case-fatalities in patients aged 51–65 years, while in younger people this has tended to decrease. The explanation for these findings is probably multifactorial but the emergence of new serotypes could play a role. Lexau *et al.*[4] observed an increase in mortality rates in adults aged 50 years or older, from 15.7% in 1998 to 19.5% in 2003, and also found that the non-vaccine serotypes 3, 11A, 19A were independently associated with higher mortality. Although we have not been able to find a significant association between case-fatality and specific serotypes, we have observed important differences depending on the causal serotype. The proportion of case-fatalities for IPP caused by serotypes 3 and 19A, more prevalent in older adults, was 18%, compared with 4% for IPP caused by serotypes 1 and 7F. The possible downward trend in proportion of case-fatalities that we have observed in young adults might be related to the increased incidence of the serotypes 1 and 7F, which have been associated with lower mortality rates [12,26–28]. Moreover, in our study serotype 1 was a protective factor for death in the multivariable analysis.

Other factors such as underlying co-morbidity should also be taken into account. Some studies, as ours, have observed an increase of chronic medical illness in adults in the post-vaccine era [4,5]. It has been reported that co-morbidity could predispose to infections due to serotypes with low invasive disease potential, which may behave as opportunistic pathogens causing higher mortality rates [12,25–28]. In this way, the greater proportion of case-fatalities in patients aged 50–65 years may be also related to the higher rates of co-morbid conditions in adults in the post-vaccine era.

The increase in the number of patients with IPP who present with septic shock is another striking finding. Pneumonia caused by serotype 3 has been reported to be associated with septic shock [18]. We have also observed that serotypes 3 and specially 19A were associated with the development of septic shock. Although 19A is a PCV7-related serotype, there is evidence of lack of effectiveness of PCV7 against it [29]. In fact, different studies have shown an important increase of this serotype after the implementation of PCV7 [2,4,7]. This serotype has been particularly associated with severe illness and high mortality [25,27,30]. The important emergence of serotype 19A observed in our setting could explain the increase in the number of cases of IPP with septic shock.

Our study has some limitations. Because it is not a population-based study, the incidence estimates might not be the most realistic; nevertheless, the results are consistent with other studies in our area [8,14]. In addition, the hospital is the only major centre in the reference area, and also the number of hospital admissions per catchment population has been constant over the period of study. Secondly, the small number of episodes caused by some serotypes precluded analysing their potential correlation with clinical presentation. Finally, other factors that might also modulate the epidemiology and clinical presentation of IPP (e.g. genetic properties of *S. pneumoniae* strains, effect of polysaccharide vaccine, viral co-infections) have not been evaluated in our study.

In conclusion, our study shows an important replacement of serotypes with an increase in the overall incidence of IPP in adults since the introduction of the PCV7 vaccine. The emergence of these new serotypes seems to be associated with changes in clinical presentation and outcomes of IPP, especially with higher rates of septic shock. These last findings are novel and deserve additional investigation with studies focused on the clinical and outcomes of IPP in order to understand the real impact of pneumococcal vaccines, especially with the introduction of the 13-valent pneumococcal conjugate vaccine that includes the main new emerging serotypes.

Transparency Declarations

The authors have no conflicts of interest in this article. No financial support was required for this study.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Incidence of the invasive pneumococcal pneumonia by years, serotype groups and age.

Table S1. Antibiotic susceptibility of pneumococcal isolates obtained from hospitalized patients with invasive pneumococcal pneumonia (IPP) in the pre- and post-PCV7 periods.

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Invasive Pneumococcal Disease in HIV-Infected Adults: Clinical Changes After the Introduction of the Pneumococcal Conjugate Vaccine in Children

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Background: Few data exist on the implications of widespread use of 7-valent pneumococcal conjugate vaccine in children in the invasive pneumococcal disease (IPD) in HIV-infected adults. We conducted a multicenter study to analyze differences in clinical presentation of IPD between HIV-infected and non HIV-infected adults in the prevaccine and postvaccine era.

Methods: Study of all cases of IPD in HIV-infected adults diagnosed since 1996 to 2010. Episodes were classified into prevaccine (1996 2001), early postvaccine (2002 2004), and late postvaccine period (2005 2010). For each case, we identified an HIV-negative control patient with IPD matched by hospital, age, and vaccine period.

Results: Two hundred twenty-one episodes of IPD in HIV-infected patients were diagnosed. The incidence of IPD decreased from 7.81 to 3.69 episodes per 1000 patient-years (−53%; 95% confidence interval: −65% to −36%, $P < 0.001$) between prevaccine and late postvaccine period. There was an 81% (95% confidence interval: −88% to −69%, $P < 0.001$) decrease of IPD caused by vaccine serotypes. In late postvaccine period IPD in HIV-infected patients was associated to higher rates of respiratory failure (28.4% vs. 48.4%, $P = 0.011$), greater intensive care unit admission (8.2% vs. 21.7%, $P = 0.02$) and a higher need for mechanical ventilation (5.9% vs. 16.3%, $P = 0.033$). In the prevaccine period, non HIV-infected patients had a more severe illness than in those with HIV infection; however, these differences disappeared in the late postvaccine period.

Conclusions: In the late postvaccine era, the incidence of IPD in HIV-infected patients has decreased, however, clinical presentation seems to have changed to a more severe illness. The widespread use of highly active antiretroviral therapy, polyssacharide vaccine, and 7-valent pneumococcal conjugate vaccine has contributed to these changes.

Key Words: HIV-infected patients, invasive pneumococcal disease, pneumococcal conjugated vaccine, *Streptococcus pneumonia*

(*J Acquir Immune Defic Syndr* 2012;59:31 38)

Received for publication July 20, 2011; accepted October 13, 2011.

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Supported by Red Temática de Investigación en SIDA (RIS G03/173-RETIC RD06/0006/0039). The study was not supported by the Pharmaceutical Industry.

Preliminary results of this work were presented at the 18th Conference of Retroviruses and Opportunistic infections, February 27 to March 2, 2011, Boston, MA. Abstract 901.

The authors Drs J.B., and V.F. had full access to all the data in the study and took the responsibility for the integrity of the data and the accuracy of the data analysis.

The authors contributions were as follows: Study concept and design: J.B., V.F. Acquisition of data: J.B., M.P., A.P., A.V., M.G., A.M.P., V.F., Analysis and interpretation of data: J.B., V.F., Drafting of the article: J.B., V.F., Critical revision of the article for important intellectual content: J.B., M.P., A.P., A.C., M.R., M.C., J.N., E.V., M.R., A.P., V.F. Statistical expertise: J.B., V.F. Study supervision: M.R., V.F.

All authors approved the final version of the article.

The authors have no conflicts of interest to disclose.

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INTRODUCTION

The introduction of highly active antiretroviral therapy (HAART) in the mid-1990s led to dramatic improvements in the length and quality of life of HIV-infected patients, with an important declined incidence of common opportunistic illnesses and AIDS death. Indeed, different studies demonstrated a greater than 50% decrease in the incidence of invasive pneumococcal disease (IPD) in HIV-infected adults.[1 5] Nevertheless, despite the introduction of HAART, the incidence rates of IPD in HIV-infected patients remain significantly higher than in non–HIV-infected population.[2] Moreover, some studies suggest that mortality may have increased in the HAART period.[3,6]

The 7-valent pneumococcal conjugate vaccine (PCV7) was developed to prevent IPD in high-risk population such as children younger than 2 years. After the implementation of the PCV7 in children, significant declines in the incidence of IPD caused by vaccine serotypes were reported both in children and adults.[7 12] However, this change has been accompanied

to the emergence of serotypes not included in the PCV7, and increases in the incidence of IPD due by this serotypes were also observed in different populations. These changes in serotype distribution of IPD have been accompanied by changes in disease characteristics and complications, such as high rates of empyema in children and adults.[13 16] In Spain, PCV7 was introduced in June 2001 and has been extensively used in the private medicine, thus in 2006, it was estimated that about 50% of children had been vaccinated.[17]

To our knowledge, there are very few published data regarding the changes in the serotypes causing IPD and the potential clinical implications in HIV-infected adults after the widespread use of the PCV7 in children. The aim of our study was to evaluate possible changes in incidence, clinical presentation, and serotypes causing IPD in adults with HIV infection during the last decade. In addition, we have conducted a case–control study to analyze the differences in clinical presentation and outcome of IPD between HIV-infected and non–HIV-infected adults in the prevaccine and postvaccine era.

MATERIALS AND METHODS

Study Population and Setting

We performed a multicenter observational study of all HIV-infected adults hospitalized with IPD from January 1996 to December 2010 in 3 hospitals from Spain; the University Hospital Vall d'Hebron (a 1200-bed tertiary care teaching hospital in Barcelona, that serves an estimated population of 500,000 people), the Hospital Son Dureta (a 900-bed tertiary care teaching hospital in Palma de Mallorca, that serves an estimated population of 295,000 people), and Hospital Son Llâtzer (a 350-bed community hospital in Palma de Mallorca, that serves an estimated population of 225,000 people). Our institutions have an active program for HIV-infected patients (inpatients and outpatients care) that provide care to most of this population in our reference areas. All HIV-infected patients are included in a computerized database. At the end of the study, 4692 HIV-infected patients were included in this database.

The study was approved by the Commission of Medical Ethics of Hospital Vall d'Hebron.

Study Variables and Data Collection

From each patient, the following variables were recorded: (1) sociodemographic data (age, gender, current tobacco smoking, long-term alcohol abuse, and active prior injecting drug use); (2) prior vaccination with the 23-valent pneumococcal polysaccharide vaccine (PPV), (3) predisposing factors for pneumococcal infection other than HIV infection (chronic lung disease, chronic liver disease, solid neoplasm and hematological malignancy, and other underlying diseases); (4) HIV infection–related data (HIV infection risk factors, current or prior AIDS-defining illnesses, CD4 lymphocyte count, HIV-1 viral load, trimethoprim–sulfamethoxazole (TMT-SMZ) prophylaxis, and current use of HAART); (5) clinical syndrome (pneumonia, meningitis, peritonitis, arthritis, endocarditis and primary bacteraemia); (6) severity of the illness at presentation (respiratory failure, septic shock, Pneumonia Severity Index at the moment of admission to the Emergency Department and chest radiograph pattern); (7) microbiological data (serotype and antibiotic resistance pattern of the *Streptococcus pneumoniae* causal strain); (8) antimicrobial therapy; and (9) variables related to clinical outcomes [hospital mortality, intensive care unit (ICU) admission, orotracheal intubation requirement, suppurative lung complications, and length of hospital stay]. The measurement of CD4 lymphocyte count and HIV-1 viral load was performed during or a maximum of 2 months around the episode. Information was extracted from hospital medical records using a standard data collecting form.

Definitions

IPD was defined as isolation of *S. pneumoniae* from a normally sterile site (blood, cerebrospinal fluid, pleural fluid, peritoneal fluid). Invasive pneumococcal pneumonia was diagnosed when a patient had consistent clinical findings plus a new pulmonary infiltrate on chest radiography and isolation of *S. pneumoniae* in blood and/or pleural fluid culture. Other clinical syndromes (eg, empyema, meningitis, peritonitis. and bacteremia without focus) were defined according to current accepted criteria. AIDS was diagnosed on the basis of the 1993 Centers for Disease Control and Prevention AIDS case definition.[18] HAART was defined as the use of an antiretroviral agent combination based on current guidelines for HIV infection management.[19,20] Chronic liver disease was defined according to the presence of typical clinical, laboratory, ultrasonography signs, and/or the presence of histological findings in liver biopsy. Chronic lung disease was defined on the basis of clinical and/or functional tests and included chronic obstructive pulmonary disease, severe asthma, and interstitial lung disease.

Septic shock was considered when vasoactive drugs were necessary to obtain appropriate arterial pressure values after fluid replacement.

Vaccinated patients included all patients who had written record of receipt of 23-valent polysaccharide pneumococcal vaccine before the IPD episode.

Microbiological Procedures

S. pneumoniae strains were identified by gram staining, optoquin susceptibility, bile solubility testing, and latex agglutination testing. Antimicrobial susceptibility was tested using the microdilution method, in accordance with Clinical and Laboratory Standards Institute procedures.[21] For the purpose of this study, isolates were classified as penicillin susceptible (MIC $\leq$ 0.06 ug/mL), penicillin intermediate (MIC 0.12–1 ug/mL), or penicillin resistant (MIC $\geq$2 ug/mL). Intermediate or resistant isolates were considered to be nonsusceptible.

Serotypes were performed by capsular swelling reaction using commercial serogrup and serotype-specific antisera, using the quellung reaction at the Spanish Reference Laboratory (Instituto Carlos III, Madrid, Spain). Serotypes classified as PCV7 serotypes were those that matched serotypes

included in the vaccine (4, 6B, 9V, 14, 18C, 19F, and 23F); all other serotypes were designated as non-PCV7 serotypes. We have available information of serotypes in 46.7% of *S. pneumoniae* strains.

Clinical and Microbiological Changes After the Implementation of PCV7 in Children

To evaluate possible changes in clinical presentation and serotypes causing IPD in adults with HIV infection during the period of study, we classified the patients into 3 groups according to the introduction of PCV7 in our area: prevaccine period (1996–2001), early postvaccine period (2002–2004), and late postvaccine period (2005–2010). We subdivided the postvaccine era into 2 periods because in the years immediately after the introduction de PCV7 in Spain, the coverage was low, and so in consequence, the replacement of serotypes could have not occurred. This classification has been used in previous studies.[9] The comparison between periods was performed excluding the early postvaccine period because we consider it as a transition period.

Estimation of the Incidence of IPD

The annual incidence of IPD was calculated using as the denominator the number of HIV-infected persons alive each year registered in the database and is expressed as cases per 1000 HIV patients per year. We also estimated the incidence of IPD by group vaccine serotype and specific serotype.

Case–Control Study

To asses differences between HIV and non-HIV population, we conducted a case–control study.

A case was defined as the occurrence of IPD in HIV-infected patients in the period of study, and controls were non–HIV-infected patients with an IPD. One control was selected for each patient and matched by hospital, age (±3 years) and time period. We selected the matched control in alphabetical order from the microbiological register of all adults admitted to hospital with isolation of *S. pneumoniae* from a normally sterile site. The same clinical and microbiological variables (except those related to HIV infection) were collected for cases and controls. With this approach, we avoid the possible bias due to age differences between both populations.

Statistical Analysis

Statistical analyses were performed using the statistical software package SPSS for Windows, version 15.0. Differences in means of incidence between periods were tested using Mantel–Haenszel Chi test. The percent reduction in incidence was reported with their associated 95% confidence interval (CI). The χ^2 test or Fischer exact test, when appropriate, were used to compare the distribution of categorical variables and the Student T test for continuous variables. Results were considered statistically significant if the 2-tailed P value was <0.05.

RESULTS

Sociodemographic Variables and Underlying Diseases in HIV-Infected Patients

In the 15 years of the study, 221 episodes of IPD in HIV-infected patients were diagnosed. The mean age of the patients was 39.9 (±10.2) years, and 72.4% of the episodes occurred in men. A chronic medical illness, other than HIV infection, was present in 47.3% of the patients. One hundred thirteen (59%) patients had a previous diagnosis of AIDS, and 150 (68%) patients were injection drug users. To note, in 49% episodes, patients had a CD4 cell count >200 cells per microliter.

Table 1 shows a comparison of the basal characteristics of HIV-infected patients between the prevaccine and late postvaccine periods. The mean age of the patients increased from 37.7 to 42.5 years ($P = 0.002$). We did not observe significant differences in the comorbid conditions between prevaccine and postvaccine periods. In contrast, we found some changes in the characteristics of HIV infection. In the late postvaccine era, there was a greater number of patients on HAART (47.3% vs. 32.1%, $P = 0.043$), patients had a higher CD4 cell counts (289 cells/μL vs. 214 cells/μL, $P = 0.045$), and a higher proportion of them had a viral load <400 HIV-1 RNA copies per milliliter (37.6% vs. 13.6%, $P = 0.01$).

Polysaccharide vaccine had been previously administered to 6% of patients in the prevaccine period and 27.5% in the late postvaccine period ($P < 0.001$).

Incidence of IPD in HIV-Infected Patients

The overall incidence of IPD in HIV-infected patients decreased significantly from 7.81 episodes per 1000 patients-years in the prevaccine period to 3.78 and 3.69 episodes per 1000 patients-year in the early and late postvaccine periods, respectively (Fig. 1). Compared with the prevaccine period, there was a 53% decrease of the incidence (95% CI: −65% to −36%, $P < 0.001$) in the late postvaccine period.

Reductions in the incidence of the IPD in the late postvaccine era were due mostly to an 81% reduction of IPD caused by PCV7 serotypes (from 5.04 to 0.96 episodes per 1000 patients-year (95% CI: −88% to −69%, $P < 0.001$), although the incidence of IPD caused by nonvaccine serotypes remained unchanged (−2%, 95% CI: −36% to 53%, $P = 0.94$). Nonvaccine serotypes comprised 35.6% of the isolates in the prevaccine period, 53.3% in the early postvaccine period, and 73.9% in the late postvaccine period ($P <0.001$).

Reductions in PCV7 serotypes in the late postvaccine era were due mostly to a 95% reduction of IPD caused by serotype 6B (95% CI: −99% to −66%), a 75% reduction of infections by serotype 14 (95% CI: −90% to −49%), and a 92% reduction of infections due serotype 23F (95% CI: −98% to −61%). Although no significant changes in other specific serotypes were seen, we observed an important increase in the incidence of nonvaccine serotype 19A (311%; 95% CI: −47% to 3088%, $P = 0.141$) and serotype 8 (199%; 95% CI: −62 to 2293%, $P = 0.277$).

TABLE 1. Basal Characteristics, Clinical Presentation, and Outcome by Time Period Among HIV-Infected Patients

	Prevaccine Period, 1996–2001 (n = 86)	Early Postvaccine Period, 2002–2004 (n = 39)	Late Postvaccine Period, 2005–2010 (n = 96)	Prevaccine vs Late Postvaccine period, *P*
Sociodemographic variables				
Age (yrs)*	37.7 (±9.4)	38.6 (±7.9)	42.5 (±10.9)	0.002
Sex male	72.1%	74.4%	71.9%	1
Pneumococcal vaccination	6%	11.8%	27.5%	<0.001
Underlying diseases				
Chronic liver disease	31.1%	26.3%	38.9%	0.443
Chronic lung disease	8.4%	10.5%	16.8%	0.118
Any chronic medical illness†	44.2%	34.2%	55.2%	0.181
Hematological cancer	7%	0	6.3%	1
Solid cancer	1.2%	2.6%	3.1%	0.623
HIV infection–related data				
Intravenous drug use	72.3%	81.1%	59.1%	0.081
History of AIDS	55.4%	42.1%	54.8%	1
CD4 cell counts <200 cells/μL	55.6%	44.7%	48.4%	0.363
CD4 cell counts (cell/μL)*	213.8 (±200)	258.1 (±224)	289.3 (±286)	0.045
Viral load <400 copies/μL	13.6%	25.6%	37.6%	0.01
HAART therapy‡	32.1%	35.9%	47.3%	0.047
Cotrimoxazole prophylaxis	26.2%	12.8%	20.4%	0.379
Clinical presentation				
Pneumonia	84.9%	76.9%	91.5%	0.245
Meningitis	8.1%	2.3%	2.1%	0.089
Respiratory failure	28.4%	41.7%	48.4%	0.011
Septic shock	17.6%	21.1%	20.4%	0.705
Bilateral radiologic infiltrates	12.5%	30.8%	27.5%	0.170
PSI ≥4§	25.4%	37.9%	49.4%	0.003
Outcome				
Empyema	8.2%	0	5.8%	0.755
ICU admission	8.2%	23.1%	21.7%	0.02
Orotracheal intubation	5.9%	20.5%	16.3%	0.033
Length of hospital stay (days)‖	9.5	9.5	9	0.614
Hospital mortality	11.6%	25.6%	11.8%	1

*Mean and standard deviation.
†Includes any of the following: chronic heart disease, chronic lung disease, cerebrovascular disease, chronic liver disease, diabetes, or chronic renal insufficiency.
‡HAART therapy at the moment of presentation of IPD.
§PSI, Pneumonia Severity Index only in patients with pneumonia.
‖For survivors, expressed in median.

Clinical Presentation and Outcomes in HIV-Infected Patients

The most common clinical presentation of IPD was bacteremic pneumonia, which accounted for 86.3% of all 221 episodes, followed by peritonitis for 5.5% and meningitis for 4.6%. Overall, 5.8% of patients developed empyema (Table 1).

In the late postvaccine period, IPD in HIV-infected patients was associated with a more severe clinical presentation, with higher rates of respiratory failure (28.4% vs. 48.4%, $P = 0.011$), greater ICU admission (8.2% vs. 21.7%, $P = 0.02$), and a higher need for mechanical ventilation (5.9% vs. 16.3%, $P = 0.033$). When we analyzed only the group of patients with pneumonia, we found similar findings, with a higher Pneumonia Severity Index score (score IV or V: 25.4% vs. 49.4%, $P = 0.003$) and a trend to a higher proportion of patients with bilateral infiltrates in the chest radiograph (12.5% vs. 27.5%, $P = 0.170$) in the late postvaccine era. These changes were also observed when patients were stratified by CD4 count more or less than 200 cells/μl (data not shown). The case-fatality rate remained unchanged, with mortality of 11.6% in the prevaccine period and 11.8% in the late postvaccine period. Worth to note, in the postvaccine period, only 1 patient with previous PPV vaccination died, compared with 23 in the group without previous PPV vaccination (3.6% vs. 20.2%, $P = 0.042$).

Regarding antibiotic susceptibility, the proportion of IPD caused by penicillin nonsusceptible strains decreased along the 3 periods, from 53.5% in the prevaccine period to 26% in early postvaccine period and to 20.2% in the late postvaccine period ($P < 0.001$). Rates of resistance to cephalosporins also decreased, and resistance to macrolides also tended to decrease (Table 2).

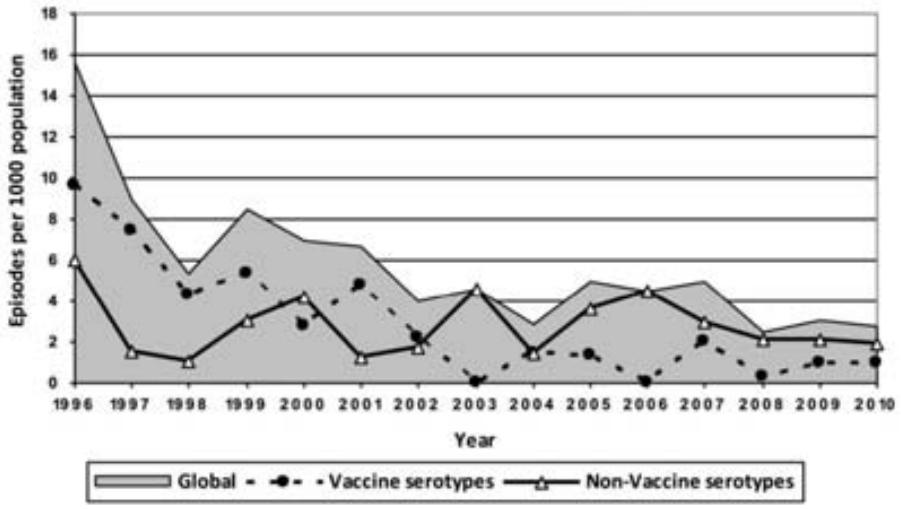

FIGURE 1. Incidence of IPD by year and serotype group.

Comparison Between HIV-Infected and Non–HIV-Infected Patients With IPD: Case–Control Study

We have compared the characteristics of the IPD between HIV-infected and non–HIV-infected patients (Table 3). In the prevaccine period, IPD was associated to a more severe illness in non–HIV-infected patients than in those with HIV infection with higher rates of septic shock (17.6% vs. 32.1%, $P = 0.034$) and ICU admission (8.2% vs. 38.8%, $P < 0.001$). In contrast, in the late postvaccine period, the severity of the disease in HIV-infected patients tend to be equal than in non–HIV-infected patients with similar rates of septic shock (20.4% vs. 25.3%, $P = 0.489$) and ICU admission (21.7% vs. 26.3%, $P = 0.497$). Interestingly, rates of empyema were higher in non–HIV-infected patients in the late postvaccine period (5.8% vs. 19.3%, $P = 0.01$)

The pattern of serotypes was somehow different in both populations (Fig. 2). In the prevaccine period, the percentage of infections caused by PCV7 serotypes were 64.4% and 41.7% in HIV-infected and non–HIV-infected patients, respectively ($P = 0.01$). This percentage decreased to 26.7% and 16.7% ($P = 0.157$) in the late postvaccine period. Regarding to specific serotypes, in the late postvaccine period, we observed a trend to increase in illness caused by serotype 19A (1.7% vs. 10.9%, $P = 0.084$) and serotype 8 (1.7% to 8.7%, $P = 0.166$) in HIV-infected patients, and significant increases in infections caused by serotypes 1 (8.3% to 29.2%, $P = 0.004$) and 7F (3.3% to 14.8%, $P = 0.043$) in non-HIV infected. Penicillin susceptibility of the pneumococcal isolates was also different; in the prevaccine period, the rates of penicillin susceptibility were significantly higher in non–HIV-infected patients

TABLE 2. Antibiotic Susceptibility of Pneumococcal Strains Isolated from HIV-Infected Patients

Antibiotic, (MIC*, ug/mL)	Prevaccine Period, 1996–2001 (n = 86)	Early Postvaccine Period, 2002–2004 (n = 39)	Late Postvaccine Period, 2005–2010 (n = 96)	Prevaccine Versus Late Postvaccine Period, P
Penicillin				
Susceptible (≤0.06)	46.5%	73.5%	79.8%	<0.001
Intermediate (0.12–1)	36.6%	20.6%	14.6%	
Resistant (≥2)	16.9%	5.4%	5.6%	
Cephalosporins†				
Susceptible (≤0.5)	77.6%	87.5%	89.8%	0.045
Intermediate (1)	22.4%	12.5%	9.1%	
Resistant (≥2)	0	0	1.1%	
Macrolides‡				
Susceptible	69.4%	87.5%	85.2%	0.076
Intermediate	0	0	0	
Resistant	30.6%	12.5%	14.8%	

*Clinical Laboratory Standard Institute meningeal break points for penicillin and cefotaxime.
†Cephalosporins: ceftriaxone, or cefotaxime.
‡Macrolides: erithromycin (susceptible ≤ 0.25, intermediate 0.5, resistant ≥1) or azithromycin (susceptible ≤0.5, intermediate 1, resistant ≥2).

TABLE 3. Underlying Diseases, Clinical Presentation and Outcomes by Time Period Among HIV-infected Patients and Non–HIV-Infected Patients with IPD

	All Periods			Prevaccine Period, 1996–2001			Early Postvaccine Period, 2002–2004			Late Postvaccine Period, 2005–2010		
	HIV (n = 221)	Non-HIV (n = 221)	*P*	HIV (n = 86)	Non-HIV (n = 86)	*P*	HIV (n = 39)	Non-HIV (n = 39)	*P*	HIV (n = 96)	Non-HIV (n = 96)	*P*
Underlying disease												
Chronic liver disease	34.3%	12.0%	<0.001	31%	16.3%	0.131	26.3%	7.9%	0.065	38.9%	13.5%	<0.001
Any chronic medical illness*	47.3%	29.1%	<0.001	44.2%	27.1%	0.025	34.2%	35.9%	1	55.2%	28.1%	<0.001
Clinical presentation												
Pneumonia	86.3%	78.7%	0.044	84.9%	68.6%	0.018	76.9%	82.1%	0.786	91.5%	86.5%	0.356
Meningitis	4.6%	11.4%	0.019	8.1%	18.8%	0.046	2.3%	6.7%	0.137	2.1%	5.2%	0.444
Respiratory failure	39.8%	41.1%	0.841	28.4%	38.3%	0.234	41.7%	51.4%	0.484	48.4%	39.6%	0.241
Septic shock	19.4%	30.1%	0.014	17.6%	32.1%	0.034	21.1%	40.5%	0.083	20.4%	25.3%	0.489
Bilateral radiologic infiltrates	22.9%	22.4%	1	12.5%	20%	0.695	30.8%	30.8%	1	27.5%	17.9%	0.325
PSI ≥4†	38.4%	45.2%	0.233	25.4%	47.4%	0.015	37.9%	55.2%	0.292	49.4%	40%	0.273
Outcome												
Empyema	5.8%	13.2%	0.019	8.2%	6.8%	1	0	9.4%	0.238	5.8%	19.3%	0.01
ICU admission	16.7%	34.1%	0.014	8.2%	38.8%	<0.001	23.1%	43.2%	0.087	21.7%	26.3%	0.497
Orotracheal intubation	13%	25.3%	<0.001	5.9%	28.2%	<0.001	20.5%	37.8%	0.130	16.3%	17.9%	0.847
Length of hospital stay‡	10	10	0.938	9.5	11	0.259	9.5	8.5	0.909	9	9	0.336
Hospital mortality	14.2%	14.4%	1	11.6%	16.7%	0.384	25.6%	27%	0.599	11.8%	8.5%	0.479
30-day mortality	13.3%	12.6%	0.886	11.6%	13.1%	0.819	23.1%	27%	0.477	10.8%	6.4%	0.309

*Includes any of the following: chronic heart disease, chronic lung disease, cerebrovascular disease, cirrhosis or chronic liver disease, and diabetes or chronic renal insufficiency.
†PSI, Pneumonia Severity Index only in patients with pneumonia.
‡For survivors, expressed in median of years.

(76.8% vs. 46.5%, $P = 0.001$), however, this difference disappeared in the late postvaccine period (93.5% vs. 89.8%, $P = 0.625$).

DISCUSSION

In this study, we have confirmed a marked reduction in the incidence of IPD in HIV-infected patients. Several factors may explain this phenomenon such as the widespread use of HAART,[1 3] the improvement in the immunological status of the patients, and probably the expanded use of the PPV.[4,22 24] Indeed, we believe that the implementation of PCV7 has also played a key role in this effect, which is reflected in the pattern of serotypes causing IPD. These data are consistent with those previously observed in other studies. A large population-based study in United States observed a significant 19% decrease in IPD among HIV-infected patients between 1998 and 2003.[25] Seven years after the implementation of the PCV7, overall reductions of 41% in IPD were noted in the same setting with a decrease of 91% in infections due to vaccine serotypes.[26] Other epidemiological studies in United States have noted similar results with overall reductions of 62.5% from 1998–1999 to 2004–2005.[27]

In our study, several factors may probably have influenced the trends on incidence observed during this period. Thus, in our centers, an informative campaign to encourage doctors to vaccinate their HIV-infected patients with the polysaccharide vaccine was performed in 2003, and in 2005, about 50% of them had been vaccinated.[4] In fact, in our setting, we have observed a beneficial effect on the incidence of IPD and bacterial pneumonia in HIV-infected patients after the implementation of this campaign.[4,21] Nevertheless, the change in the pattern of serotypes with an important reduction of vaccine serotypes and the timing of these changes suggest that the implementation of the conjugate vaccine should have played an important role.

Not only the pattern of serotypes has changed but we have also observed important changes in the clinical presentation of IPD with a higher proportion of patients with severe manifestations. Despite the clinical presentation of IPD seems to have worsened in the late postvaccine period, case-fatality rate has not changed significantly. Conflictive data on the evolution of mortality in patients with IPD have been reported. Although Grau et al[6] observed an increase in 30-day mortality in the postvaccine period (8% to 25%, $P = 0.017$), others not only have not found an increased mortality but also a slight but significant decrease (8.4% to 6.3%, $P < 0.0001$).[26]

Several factors might have contributed to explain these changes in the clinical pattern of the disease. It has been suggested that the impairment of immunity may decrease the inflammatory response in HIV-infected patients with IPD, so it would be expected that an improvement of immunity may enhance the inflammatory response against a bacterial infection

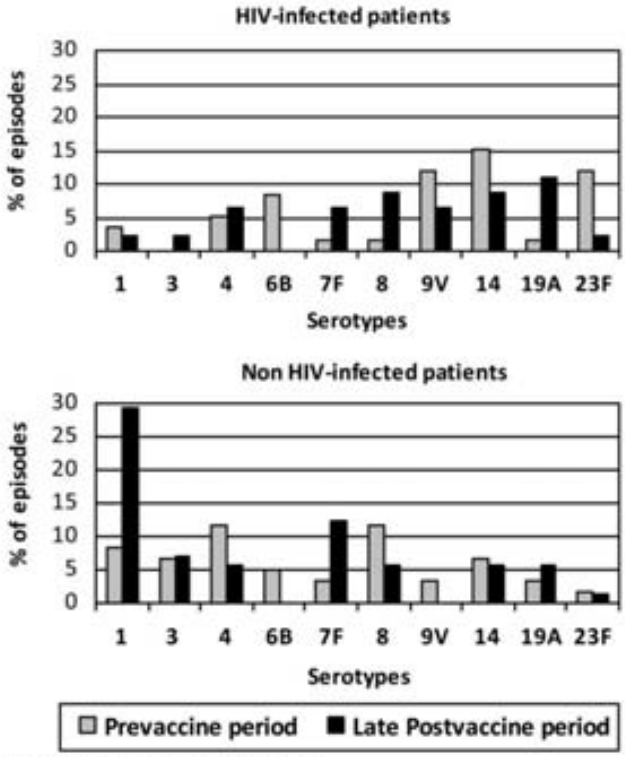

FIGURE 2. Serotype distribution.

and consequently, this would be associated with increased severity.[6,28] We have not evaluated the inflammatory response in our study, however, interestingly, we have observed that IPD in non–HIV-infected patients in the prevaccine period had a more severe illness than HIV-infected patients. In the postvaccine period, in which HIV-infected patients have a better immunological status, the severity of IPD tends to be equal to what occurs in non–HIV-infected patients. The increasing severity could also be related to the increased age and associated comorbidities in this population. This age distribution probably reflects the overall aging of HIV-infected population as a result of their prolonged survival.

In contrast, other factors may explain that, despite severity of the illness has increased, mortality remains stable. We can hypothesize that because the proportion of vaccinated patients with the PPV is high in the postvaccine period, in those in whom PPV fails to prevent the pneumococcal infection, it protects against mortality. In a previous study, we have observed that prior vaccination with PPV may provide some beneficial effects improving clinical outcomes in those who develop IPD.[29] Thus, in our study, in the postvaccine era, when a large number of patients had received PPV vaccine, only 1 (3.6%) patient with previous PPV vaccination died, compared with 23 (20.2%) in the group without previous administration of PPV. Finally, changes in the pattern of pneumococcal serotypes causing IPD might also play an important role in this increased severity of IPD. Studies in general population in adults have found that IPD caused by the nonvaccine serotypes 3, 11A and 19A, were independently associated to higher mortality in the postvaccine period.[30] In the same way, high rates of empyema associated to serotypes 1 and 3 have been reported in children and adults.[13,16,31] In our study, the limited number of isolates for each specific serotype has not led us to find significant associations.

In our setting, after the implementation of the PCV7 vaccine, the serotype distribution has been somehow different in HIV-infected population than in non-HIV. Thus, although in non-HIV population, we have observed an increase of nonvaccine serotypes with high invasive potential, such as 1 and 7F, in HIV-infected population, the number of infections caused by nonvaccine serotypes with low invasive disease potential such as serotypes 8 and 19A tend to increase. Other studies have also reported similar findings with an emergence of infections caused by serotypes 8 and 19A, both with low potential for invasiveness.[6,27,32] The reason of this different distribution of serotypes is not clearly established but, in our opinion, it is possible that the different PPV vaccine coverage between both populations have played a role in the causal serotypes. This difference in the pattern of serotypes could also contribute to the differences observed in the trends of severity of illness in both populations.

Some limitations of our study must be pointed out. First, because it is not a population-based study, our cohort could differ from other HIV-infected populations and the incidence estimates might not be extrapolated to other settings, however, the multicenter nature of the study could mitigate this limitation. Second, the number of episodes for some serotypes is too small to explore in more detail potential correlations with clinical presentation. Third, in the case–control study, the selection bias is possible because controls were chosen retrospectively and matched only by hospital, age, and time period. Finally, other factors that might also modulate the epidemiology and clinical presentation of IPD (eg, genetic properties of *S. pneumoniae* strains, viral coinfections, and inflammatory response) have not been evaluated in our study.

In conclusion, our study confirms the progressive decline of the incidence of IPD in HIV-infected patients. The cumulative effect of widespread use of HAART, use of polyssacharide vaccine, and also the introduction of the conjugate vaccine in children play a key role in this change. The disease seems to have changed to a more severe illness and tend now to be similar to what occurs in non–HIV-infected patients. Despite infections caused by vaccine serotypes have significantly decreased in both populations, the change in serotypes causing IPD is somehow different in HIV-infected and non–HIV-infected population. These findings require a continued surveillance and new strategies for prevention of IPD in HIV-infected patients.

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VI. DISCUSIÓN

DISCUSIÓN

Trabajo 1: Cambios en la el porcentaje de complicaciones en forma de empiema de la neumonía neumocócica y variaciones en la incidencia de empiema neumococico, en la población adulta entre el periodo prevacunal y postvacunal

En el primer estudio realizado en el Hospital Vall d'Hebrón de Barcelona en colaboración con el Hospital Parc Taulí de Sabadell, se recogieron 1.080 episodios de neumonías neumocócicas invasivas con 128 (11.9%) episodios complicados con empiema entre 1996-2001 (periodo prevacunal) y 2005-2009 (periodo postvacunal). Este estudio observó un aumento marcado de la incidencia de empiema neumocócico en el subgrupo de adultos jóvenes (entre 18 a 50 años), pasando de una tasa de 0.5 episodios /100.000 personas-año en la era prevacunal a 1.56 episodios/100.000 personas-año en la era postvacunal, lo que suponía un incremento del 198% (95% CI, 49 a 494%). El porcentaje de neumonías complicadas con empiema también se incrementó pasando del 7.6% al 14.9% (Tabla 3). Este incremento se asoció a un aumento de las infecciones producidas por el serotipo no vacunal 1, causante de más del 40% de los empiemas en la era postvacunal (Tabla 4). Al comparar los pacientes con empiema en los dos periodos, se observó que en el periodo postvacunal eran más jóvenes y con menos comorbilidades.

TABLA 3. Media de incidencia de empiema por grupo de edad, serotipo y periodo de tiempo.

EMPIEMA NEUMOCOCICO	*PERIODO PREVACUNAL*		*PERIODO POSTVACUNAL*		*PERIODO PREVACUNAL vs POSTVACUNAL*	
	% de pacientes con EP [a]	*Casos/100000 personas por año*	*% de pacientes con EP* [a]	*Casas/100000 personas por año*	*100000 personas-año Cambio, % (CI 95%)*	*valor de P* [b]
GRUPOS DE EDAD						
Todos los adultos	*12.2%*	*1.6*	*11.5%*	*1.8*	*17 (-15 to 65)*	*.38*
Adultos de 18-50 años	*7.6%*	*0.5*	*14.9%*	*1.6*	*198 (49 to 494)*	*.001*
Adultos de 50-65 años	*17.3%*	*1.4*	*11.5%*	*1.2*	*-15 (-57% to 72)*	*.65*
Adultos de > 65 años	*12.7%*	*4.8*	*8.8%*	*3.5*	*-27 (-57 to 25)*	*.25*
SEROTIPOS						
Serotipo 1						
Todos los adultos	*14.8%*	*0.2*	*43.3%*	*0.8*	*253 (67 to 646)*	*<.001*
Adultos de 18-50 años		*0.1*		*0.8*	*664 (73 to 3262)*	*.001*
Adultos de 50-65 años		*0.5*		*0.5*	*-0.1 (-65 to 240)*	*.87*
Adultos de > 65 años		*0.1*		*1.4*	*883 (24 to 676)*	*.008*
Serotype 3						
Todos los adultos	*24.6%*	*0.4*	*13.3%*	*0.2*	*-34 (-71 to 50)*	*.32*

[a] *EP: Empiema neumocócico*

[b] *Valor de P: Diferencias en medias de incidencia entre periodo prevacunal y postvacunal ustilizando el Test de Mantel-Haenszel.*

TABLA 4: Serotipos más frecuentes aislados en adultos con empiema neumocócico.

SEROTIPOS	NUMERO (%) DE AISLAMIENTOS			
	Total (n=121)	Periodo Prevacunal (n=61)	Periodo Postvacunal (n=60)	Valor de P
Serotipos incluidos en VCP7	24 (19.8%)	15 (24.6%)	9 (15%)	.255
Serotipo 4	3 (2.5%)	1 (1.6%)	2 (3.3%)	.494
Serotipo 9V	5 (4.1%)	4 (6.6%)	1 (1.7%)	.365
Serotipo 14	7 (5.8%)	4 (6.6%)	3 (5%)	.509
Serotipo 19F	3 (2.5%)	1 (1.6%)	2 (3.3%)	.619
Serotipos no incluidos en VCP7	97 (80.2%)	46 (75.4%)	51 (85%)	.255
Serotipo 1	35 (28.9%)	9 (14.8%)	26 (43.3%)	<.001
Serotipo 3	23 (19%)	15 (24.6%)	8 (13.3%)	.164
Serotipo 5	4 (3.3%)	2 (3.3%)	2 (3.3%)	.684
Serotipo 6A	8 (6.6%)	5 (8.2%)	3 (5%)	.717
Serotipo 7F	6 (5%)	2 (9.8%)	4 (6.7%)	.332
Serotipo 8	5 (4.1%)	4 (6.6%)	1 (1.7%)	.187
Serotipo 19A	3 (2.5%)	2 (3.3%)	1 (1.7%)	.652

Como se ha comentado previamente, en los niños ya se había observado un incremento de las complicaciones supuradas en forma de neumonía necrotizante y empiema tras la introducción de la vacuna conjugada (88,89,92-95,106-113). Estas complicaciones se han asociado a la emergencia de serotipos no incluidos en la VCP7, en concreto con los serotipo 1 y 3 (88,89,92-94,98,106,111). Sin embargo y hasta el momento de la presentación de este trabajo, este fenómeno no había sido descrito en los adultos.

Posteriormente se publicó un nuevo estudio que aporta más datos sobre la incidencia de empiema en adultos en Estados Unidos entre 1996 y 2007 (109). En este trabajo se observó un importante aumento de la incidencia de empiema en todos los grupos de edad, con especial relevancia en los adultos de 40-64 años donde pasó de 3.96 episodios en 1996 a 8.1 episodios /100.000 personas en 2008. Aún así hay que resaltar que este incremento ocurrió a expensas de un aumento de las infecciones producidos por *Stahphilococcus aureus* así como de otras especies de estreptococos diferentes al *Streptococcus pneumoniae*, manteniéndose la incidencia del empiema neumocócico estable. Esta discrepancia respecto a nuestros hallazgos puede ser debida a que en Estados Unidos la incidencia global de la enfermedad neumocócica en los adultos ha disminuido tras la introducción de la vacuna, algo que no ha ocurrido en nuestro medio en el que por el contrario se ha observado un incremento. Recientemente, varios estudios que utilizan nuevas técnicas moleculares para el diagnostico etiológico del empiema han descrito que una importante proporción de los empiemas con cultivos negativos son causados realmente por neumococos, especialmente por el serotipo 1 (98,117-117). Es

posible que en este estudio en el que el 62.4% de los empiemas son de etiología desconocida, se esté infra diagnosticando la etiología neumocócica. Diferencias regionales en la distribución de los serotipos también pueden explicar en parte estas discrepancias.

Los motivos por los que la epidemiologia de la enfermedad neumocócica está cambiando tanto en los últimos años es posiblemente multifactorial (118). Si bien parece claro que la introducción de la vacuna conjugada ha jugado un papel importante en el fenómeno de reemplazo con la emergencia de nuevos serotipos, el incremento de incidencia de empiema neumocócico no puede ser explicado solo por la vacuna. Variaciones temporales en la distribución de los serotipos han sido descritas en todo el mundo a lo largo de los años, observándose en la última década del siglo XX y previo a la introducción de la vacuna, un aumento de la frecuencia del serotipo 1 (119-121). Estas fluctuaciones en los serotipos puede ser una de las razones por las que el aumento de la incidencia de empiema neumocócico en niños se haya descrito antes de la introducción de la vacuna (122-132). Otros factores como son las coinfecciones por diferentes virus respiratorios, o bien el incremento de pacientes inmunodeprimidos en riesgo de padecer infecciones neumocócicas también pueden haber influido en los cambios observados.

Otro de los hallazgos de este estudio es que el empiema neumocócico en la época postvacunal se asoció a un mayor requerimiento de cirugía (diferente al del drenaje torácico), pasándose de unas tasas del 5.3% al 18.8% ($p<.001$). Aunque esto puede ser debido a un cambio en la actitud terapéutica de los clínicos con el paso del tiempo, estos datos coinciden con la mayor tasa de intervención quirúrgica y de estancia hospitalaria observado en niños (93,96,97). A modo de ejemplo, Mckee et al encontró un incremento en la tasas de empiemas complicados con fistula broncopulmonar, pasando del 1% en 2002-2007 al 33% in 2008-2009 (97), asociándose a un incremento de la tasa de intervención quirúrgica (2% vs. 14%). Esta complicación se relacionó con infecciones debidas a los setotipos 1 y 3. El motivo por el que estos serotipos tienen esta alta propensión a originar infecciones pleurales así como cuadros supurativos no es del todo conocido. Se ha hipotetizado que puede ser debido a una mayor habilidad para translocarse a través de las células mesoteliales permitiendo llegar al espacio pleural (133) y contener una importante cantidad de polisacárido capsular lo que induciría un mayor acumulo de células polimorfonucleares (134)

En resumen, este estudio muestra importantes y novedosos cambios en la epidemiologia del empiema neumocócico en los adultos observándose un incremento de incidencia en los adultos más jóvenes y sin comorbilidades. Los serotipos 1 y 3, al igual que ocurre con la población pediátrica, se identificaron como los principales determinantes de estas

complicaciones supuradas. En el futuro, la introducción de la vacuna conjugada trecevalente que contiene a los serotipos 1 y 3 puede proporcionar más información sobre el exacto papel que ha tenido la vacuna conjugada heptavalente en el aumento del empiema neumocócico tanto en niños como en adultos.

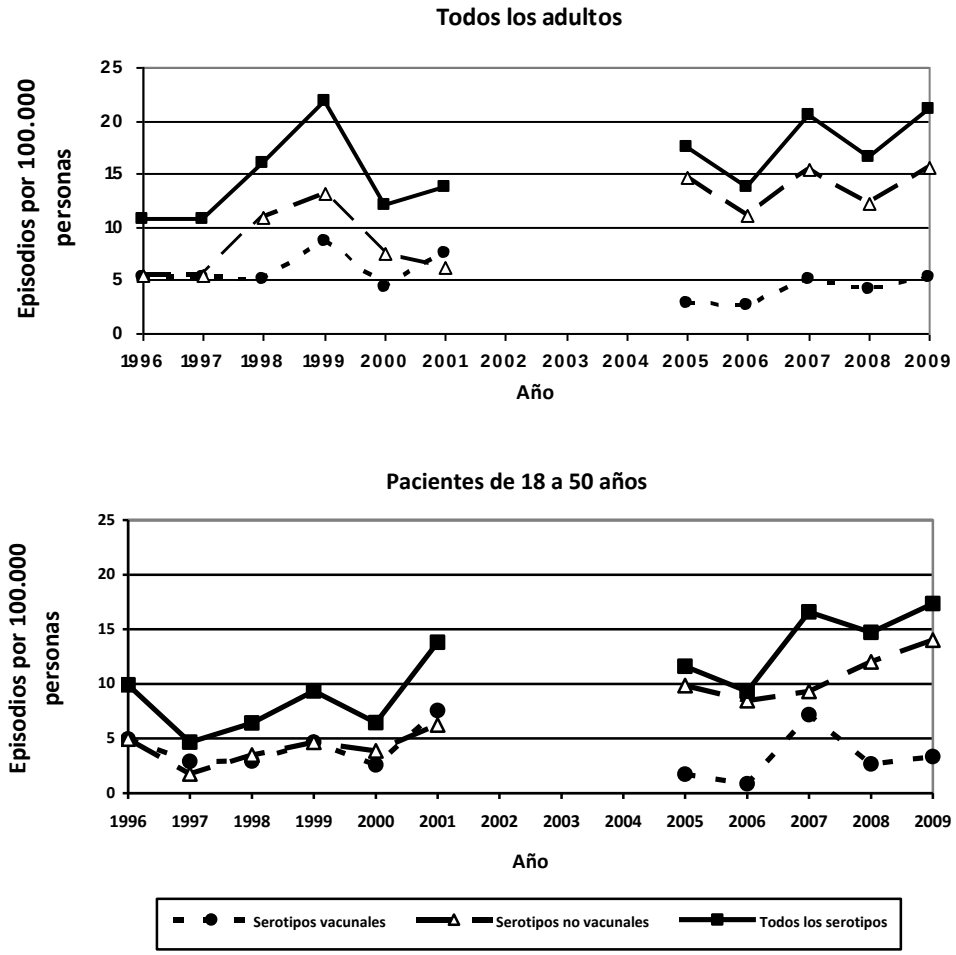
Trabajo 2: Cambios en la presentación clínica y el pronóstico de la neumonía neumocócica en la población adulta entre el periodo prevacunal y postvaunal

El segundo estudio realizado en el Hospital Vall d'Hebrón, se centró en la evaluación de cambios en la presentación clínica y gravedad de la neumonía neumococica. Se recogieron 653 episodios de neumonías neumocócicas invasivas entre 1996-2001 (periodo prevacunal) y 2005-2009 (periodo postvacunal). En este trabajo se observó un aumento global de la incidencia de neumonía invasiva, pero especialmente en los adultos jóvenes de entre 18 y 50 años, en los que se pasó de tasas de 8 episodios/100.000 personas-año en la era prevacunal a 13.9 episodios/100.000 personas-año en la era postvacunal, un incremento del 74% (95% CI, 32% a 130%) (Figura 1). Este cambio fue debido a que si bien se observó un descenso del 36% de las infecciones causadas por los serotipos incluidos en la vacuna, éste se acompañó de un incremento del 71% de los serotipos no vacunales. Estos resultados contrastaban con el descenso de incidencia de enfermedad neumocócica en adultos observado en Estados Unidos (75,79,80) pero coincidía con los estudios que habían sido publicados en Europa (83-85,135). Las discrepancias en la incidencia entre estas dos regiones pueden ser debidas en parte a diferencias en la cobertura vacunal, que se estimó en el 2006 superior al 90% en Estados Unidos, mientras que en España no llegaba al 60% (79,84,136). Además, los serotipos circulantes en estas dos áreas en el momento de la introducción de la vacuna eran ligeramente diferentes. En Estados Unidos los 7 serotipos incluidos en la VCP7 representaban a más del 80% de los serotipos causantes de infección mientras que en Cataluña suponían el 68% (74,91). Otros factores como son las fluctuaciones en la distribución de serotipos o epidemias de serotipos en particular pueden ayudar a explicar las diferencias observadas entre estas dos áreas geográficas (119-121).

La razón por la que la enfermedad neumocócica está aumentando en los adultos jóvenes parece estar relacionada con la emergencia de serotipos particulares. Los serotipos 1, 5 y 7F se caracterizan por tener una gran capacidad de invasión (22,23) y se han asociado a infecciones en adultos jóvenes sin comorbilidades (24-26). La emergencia de los serotipos 1 y 7F

observado en nuestro estudio, puede explicar el aumento de infecciones en este grupo de de edad.

Figura 1. Incidencia de la Neumonía neumocócica invasiva por grupos de serotipos y edad.



El hallazgo más interesante y novedoso de este trabajo es, sin embargo, que la severidad de la enfermedad neumocócica parece estar aumentando en la época postvacunal (Tabla 5). Tras la introducción de la vacuna se observó un aumento de la presentación en forma de shock séptico (19.1% vs .31.1%, p=.001) y del requerimiento de ingreso en UCI (13.7% vs. 21.6%, p=.011) de la neumonía neumocócica. La mortalidad en el subgrupo de pacientes de 51 a 65 años mostró una tendencia a incrementarse (11.6% vs. 23.6%, P=.087) mientras que en los adultos más jóvenes tendió a disminuir (16.9% vs 8.5%, p=.111).

TABLA 5: Características basales, presentación clínica y evolución por grupos de edad y periodo vacunal en adultos.

	TODOS LOS ADULTOS			ADULTOS DE 18 A 50 AÑOS		
	Periodo prevacunal (n=308)	Periodo postvacunal (n=345)	Valor de P	Periodo prevacunal (n=82)	Periodo postvacunal (n=127)	Valor de P
Características basales						
Edad (años, media)	62	58.5	.023	36	36.2	.886
Sexo masculino	65.9%	61.7%	.29	68.3%	63%	.461
Enfermedad medica crónica [a]	50%	52.7%	.530	30%	27.4%	.640
Inmunosupresión [b]	36.4%	34.6%	.681	62.2%	37.9%	.001
Presentación clínica						
Insuficiencia respiratoria	46%	55%	.289	20.5%	35.5%	.382
Shock séptico	19.1%	31.1%	.001	19.7%	29.3%	.176
FINE grave [c]	64%	65.9%	.666	32.9%	36%	.756
Ingreso en UCI	13.7%	21.6%	.011	19.2%	25.9%	.304
Estancia en UCI [d]	12.4	14.2	.244	10	13.6	.151
Intubación orotraqueal	11%	13.1%	.455	11.7%	18.3%	.311
Estancia hospitalaria [d]	11.2	18.6	.074	11.2	20.1	.369
Empiema	13.1%	12.5%	.903	10.5%	16.9%	.295
Mortalidad	15.2%	17.6%	.455	16.9%	8.5%	.111

[a] *Incluye alguna de las siguientes: enfermedad cardiaca crónica, enfermedad pulmonar crónica, enfermedad cerebrovascular, cirrosis o enfermedad hepática crónica, diabetes o insuficiencia renal crónica.*
[b] *Incluye alguna se las siguientes: Infección por VIH, neoplasia hematológica, neoplasia sólida, trasplante de organo solido o trasplante hematopoyético, déficit de inmunoglobulinas, esplenectomía o tratamiento inmunosupresión (incluyendo tratamiento corticoideo sistémico)*
[c] *Indica un valor de la escala FINE ≥ 4 en el momento de la admission en el departamento de urgencias.*
[d] *Expresado en dias (mediana).*

Estos cambios parecen estar otra vez estrechamente relacionados con la aparición de nuevos serotipos. El shock séptico en la neumonía neumocócica se ha asociado a infecciones causadas por el serotipo 3 (103). En nuestro estudio, el análisis multivariante mostró que el serotipo 3 (OR 2.38 (95% CI, 1.16 a 4.87)) y especialmente el serotipo 19A (OR 6.47 (95% CI, 1.55 a 27)) eran factores independientes para el desarrollo de esta complicación (Tabla 6). Aunque el 19A es un serotipo relacionado con el serotipo vacunal 19F, existe evidencia de la escasa eficacia de la vacuna en contra de él (137). De hecho, diferentes estudios han mostrado un importante incremento de las infecciones causadas por este serotipo tras la introducción de la vacuna. EL importante aumento del serotipo 19A observado en nuestra población puede explicar el incremento del número de casos de neumonía neumocócica que se presentan con shock séptico.

TABLA 6: Variables asociadas a shock séptico en adultos.

Shock séptico	*Univariante OR (95% CI)*	*Valor de P*	*Multivarinate OR (95% CI)*	*Valor de P*
Sexo masculino	*1.69 (0.13-2.53)*	*.007*	*1.21 (0.72-2.03)*	*.472*
Edad, 18-50 vs. > 50 años	*1 (0.68-1.49)*	*.528*		
Periodo postvacunal	*1.91 (1.3-2.79)*	*.001*	*1.24 (0.74-2.1)*	*.414*
Tabaquismo	*1.08 (0.71-1.78)*	*.394*		
Consumo importante de alcohol	*1.67 (0.98-2.82)*	*.004*	*1.65 (0.9-3.32)*	*.106*
Enfermedad pulmonar crónica [a]	*1.13 (0.71-1.78)*	*.347*		
Enfermedad medica crónica	*0.99 (0.69-1.44)*	*.522*		
Neoplasia hematológica	*0.95 (0.50-1.78)*	*.504*		
Neoplasia solida	*1.7 (1.04-2.79)*	*.026*	*1.67 (0.84-4.87)*	*.140*
Inmunosupresion [b]	*1.1 (0.69-1.48)*	*.518*		
Serotipo 1	*0.78 (0.4-1.53)*	*.294*		
Serotipo 3	*2.08 (1.16-3.74)*	*.012*	*2.38 (1.16-4.87)*	*.018*
Serotipo 4	*.512 (0.19-1.13)*	*.118*		
Serotipo 6B	*1.42 (0.48-4.16)*	*.351*		
Serotipo 7F	*0.89 (0.37-2.12)*	*.496*		
Serotipo 8	*1.39 (0.66-2.91)*	*.246*		
Serotipo 9V	*.37 (00.08-1.65)*	*.141*		
Serotipo 14	*.95 (0.49-1.83)*	*.511*		
Serotipo 19A	*2.79 (0.99-7.87)*	*.049*	*6.47 (1.55-27)*	*.010*
Serotipo 19F	*2.22 (0.92-5.32)*	*.063*	*2.46 (0.97-6.21)*	*.058*
Serotipo 23F	*.55 (0.12-2.53)*	*.345*		
Sensibilidad penicilina [c]	*1.08 (0.7-1.7)*	*.402*		
Sensibilidad cefalosporina [d]	*1.24 (0.63-2.41)*	*.326*		

[a] *Incluye alguna de las siguientes: enfermedad cardiaca crónica, enfermedad pulmonar crónica, enfermedad cerebrovascular, cirrosis o enfermedad hepática crónica, diabetes o insuficiencia renal crónica.*

[b] *Incluye alguna se las siguientes: Infección por VIH, neoplasia hematológica, neoplasia sólida, trasplante de organo solido o trasplante hematopoyético, déficit de inmunoglobulinas, esplenectomía o tratamiento inmunosupresión (incluyendo tratamiento corticoideo sistémico)*

[c] *Incluye aislamientos con una CMI ≤ 0.06 ug/ml.*

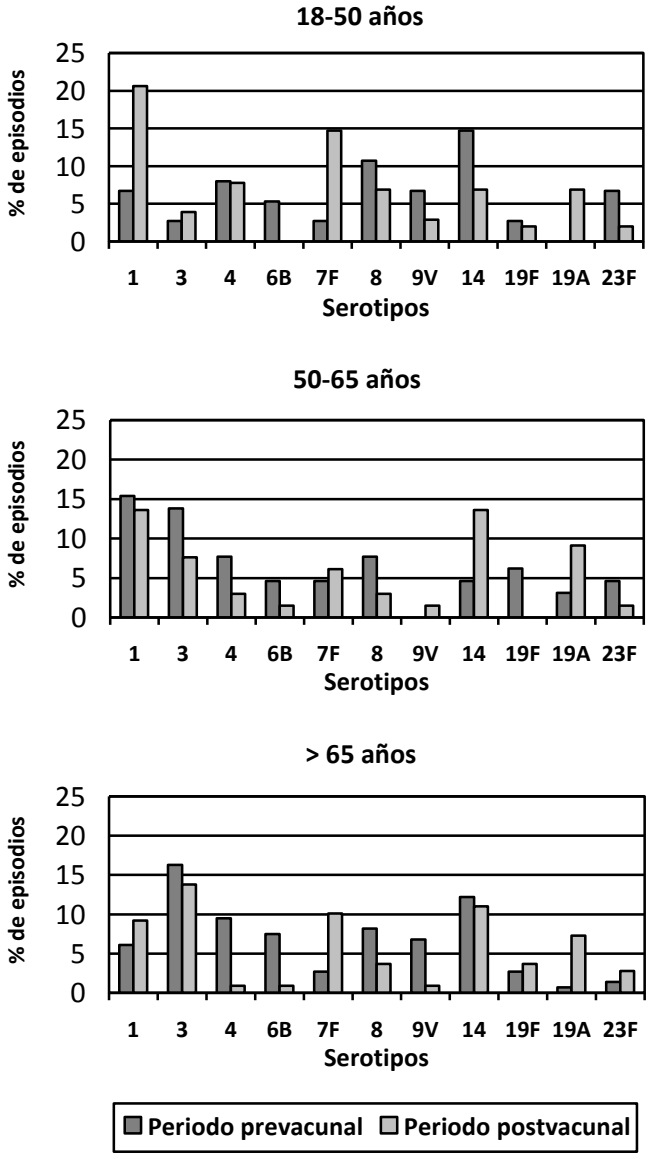
[d] *Incluye aislamientos con CMI ≤ 0.5 ug/ml.*

Las causas por las que puede haberse modificado la mortalidad son mas difíciles de explicar. Lexeu et al observó en un amplio estudio en pacientes mayores de 50 años un incremento de la mortalidad del 15.7% en 1998 al 19.5% en 2003, asociándolo al incremento de los serotipos no vacunales 3, 11A y 19A (135). En nuestro estudio, debido al limitado número de serotipos no se ha podido establecer una correlación significativa entre el incremento de mortalidad y determinados serotipos. Aun así hay datos bastante llamativos; mientras que la mortalidad de la neumonía neumocócica causada por los serotipos 3 y 19 A fue del 18%, la causada por los serotipos 1 y 7F no superó el 4%. Estos últimos serotipos, a pesar de tener una mayor capacidad invasiva se han asociado a una baja mortalidad (25,27-29), lo que puede explicar en parte el descenso observado en la mortalidad en los adultos más jóvenes (Figura 2). De hecho, en nuestro análisis de factores asociados a mortalidad, el serotipo 1 fue el único identificado

como protector (OR 0.1 (95% CI, 0.01-0.78)). La presencia de comorbilidades es otro de los factores que pueden influenciar el pronóstico de la enfermedad. Diferentes estudios, como el nuestro, han observado un incremento en la proporción de enfermedades de base en los adultos en la era postvacunal (135). Se ha descrito además que las enfermedades crónicas predisponen para infecciones por serotipos menos invasivos que se comportarían como patógenos oportunistas, asociándose a una mayor mortalidad (25,27-29,138). De esta forma, este incremento en la mortalidad observado en pacientes de 50 a 65 años puede estar en relación con el aumento de las comorbilidades observadas en este grupo de pacientes en la era postvacunal.

En conclusión, este estudio muestra un importante reemplazamiento de los serotipos causantes de neumonía neumocócica en adultos desde la introducción de la vacuna y especialmente un cambio en la presentación clínica de la enfermedad hacia formas de mayor gravedad. Estos cambios parecen asociarse a la emergencia de serotipos no incluidos en la vacuna heptavalente. Es de especial interés el incremento en las tasas de shock séptico, asociados al incremento del serotipo 19A. Es necesario continuar realizando estudios de vigilancia epidemiológica con el fin de predecir posibles cambios clínicos asociados a cambios en la distribución de serotipos, especialmente en la era de las vacunas conjugadas.

Figura 2. Serotipos causantes de neumonía neumocócica invasiva en periodo prevacunal y postvacunal por grupos de edad en adultos.



Serotipos incluidos en VCP7: 4, 6B, 9V, 14, 18C, 19F, 23F

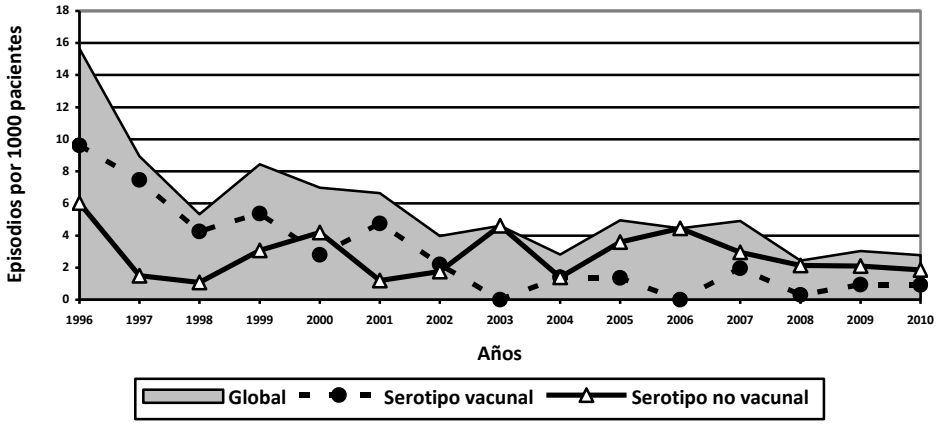
Trabajo 3:

Cambios de incidencia, de la presentación clínica y pronóstico, y en las características microbiológicas de la enfermedad neumocócica en una subpoblación de alto riesgo para ella como son los pacientes adultos con infección por VIH, entre el periodo prevacunal y postvacunal

El tercer estudio evalúa la implicación que ha tenido la introducción de la vacuna conjugada heptavalente en los niños, en la enfermedad neumocócica invasiva en pacientes con infección por VIH. Realizado en el Hospital Vall d'Hebrón de Barcelona en colaboración con los Hospital Son Dureta y Son Llàtzer, se recogieron 201 episodios de enfermedad neumocócica invasiva entre el periodo prevacunal (1996-2001), periodo postvacunal precoz (2002-2004) y postvacunal tardío (2005-2010). Además se realizó un estudio caso-control con pacientes sin infección por VIH, apareados por edad, hospital y periodo de estudio.

Al analizar la incidencia de ENI se observó un marcado descenso pasando de tasas de 7.81 episodios/1000 pacientes-año en periodo prevacunal a 3.69 episodios/1000 pacientes-año en periodo postvacunal tardío, lo que representa una disminución del 53% (95%CI, -65% a -36%, p<.001). En esta sub-población también se observó el fenómeno de reemplazo de serotipos observados en la población general. Los serotipos vacunales disminuyeron un 81% a lo largo del estudio, mientras que los serotipos no incluidos en la vacuna se mantuvieron de forma global. Aun así, se observó incrementos en algunos de los serotipos no vacunales, especialmente en el serotipo 19A (311%; 95% CI, -47% a 3088%, p=.141) y el serotipo 8 (199%; 95% CI, -62 a 2293%, p=.277) (Figura 3).

Figura 3: Incidencia de enfermedad neumocócica invasiva en adultos con infección por VIH por año y grupo de serotipos.



Estos resultados son consistentes con otros trabajos publicados previamente. Un amplio estudio epidemiológico realizado en Estados Unidos observó un descenso del 18% de la ENI en pacientes con infección por VIH desde 1998 al 2003 (139). Siete años más tarde de la introducción de la vacuna la reducción era del 41% en la misma población, con un descenso del 91% de las infecciones causadas por los serotipos vacunales (140). Otros estudios han descrito resultados similares (141). Son varios los factores que pueden explicar este descenso en la incidencia de la enfermedad neumocócica. La generalización del tratamiento antirretroviral de alta eficacia y la mejora inmunológica que ha supuesto en los pacientes con infección por VIH es sin duda uno de los factores principales (7,8,142). El uso de la vacuna polisacárida en esta población probablemente también ha tenido un papel importante (143-146). De hecho, en nuestra cohorte de pacientes con infección VIH se inició una campaña de vacunación en el año 2003 que ha favorecido una reducción de la incidencia de ENI, como se ha comunicado en varias publicaciones (143,144). Aún sin olvidar estos factores, nosotros consideramos que la introducción de la vacuna conjugada también ha jugado un papel importante en la disminución de la incidencia, como refleja el hecho de que se hayan producido cambios en la distribución de serotipos causantes de enfermedad en consonancia con lo observado en la población general.

Uno de los hallazgos más importantes de este estudio, más allá de las variaciones en la incidencia, es sin duda el cambio en la presentación clínica de la enfermedad hacia una mayor gravedad (Tabla 7). En el período postvacunal los pacientes tuvieron una mayor tasa de insuficiencia respiratorio (28.4% vs 48.4%, P=.011), mayor requerimiento de ingreso en UCI (8.2% vs 21.7%, p=.02) así como una mayor necesidad de ventilación mecánica (5% vs 16.3%, P=.033). No se encontraron diferencias, por el contrario, respecto a las tasas de empiema (8.2% vs 5.8%, p=.755) y mortalidad (11.6% vs. 11.8%, p=1). En el caso concreto de la mortalidad, existen importantes discrepancias entre los datos publicados en diferentes trabajos. Mientras que Frau et al observó un aumento de la mortalidad en el periodo postvacunal (8% vs. 25%, p=.017) (147), otros estudios han encontrado un descenso de la misma (8.4% vs. 6.3%, p<.0001) (140).

TABLA 7: Características basales, presentación clínica y evolución por grupos de edad y periodo de tiempo en pacientes adultos con infección por VIH.

	Periodo prevacunal 1996-2001 (n=86)	Periodo postvacunal precoz 2002-2004 (n=39)	Periodo postvacunal tardio 2005-2010 (n=96)	Periodo prevacunal vs. postvacunal tardio. Valor de P
Características basales				
Edad (años, media)	37.7 (+/-9.4)	38.6 (+/-7.9)	42.5 (+/.10.9)	.002
Sexo masculino	72.1%	74.4%	71.9%	1
Vacunación antineumócica	6%	11.8%	27.5%	<.001
Enfermedad hepática crónica	31.1%	26.3%	38.9%	.443
Enfermedad pulmonar crónica	8.4%	10.5%	16.8%	.118
Enfermedad medica crónica [a]	44.2%	34.2%	55.2%	.181
Neoplasia hematológica	7%	0	6.3%	1
Neoplasia sólida	1.2%	2.6%	3.1%	.623
Datos relacionados con la infección por VIH				
ADVP	72.3%	81.1%	59.1%	.081
Historia de SIDA	55.4%	42.1%	54.8%	1
Recuento de células CD4 < 200 cel/µl	55.6%	44.7%	48.4%	.363
Recuento de células CD4 (cel/µl) [a]	213.8 (+/-200)	258.1 (+/-224)	289.3 (+/-286)	.045
Carga viral de VIH < 400 copias/µl	13.6%	25.6%	37.6%	.01
Tratamiento antirretroviral [b]	32.1%	35.9%	47.3%	.047
Profilaxis con cotrimoxazol	26.2%	12.8%	20.4%	.379
Presentación clínica				
Neumonía	84.9%	76.9%	91.5%	.245
Meningitis	8.1%	2.3%	2.1%	.089
Insuficiencia respiratoria	28.4%	41.7%	48.4%	.011
Shock séptico	17.6%	21.1%	20.4%	.705
Infiltrados radiológicos bilaterales	12.5%	30.8%	27.5%	.170
FINE grave [c]	25.4%	37.9%	49.4%	.003
Evolución				
Empiema	8.2%	0	5.8%	.755
Ingreso en UCI	8.2%	23.1%	21.7%	.02
Intubación orotraqueal	5.9%	20.5%	16.3%	.033
Estancia hospitalaria [d]	9.5	9.5	9	.614
Mortalidad	11.6%	25.6%	11.8%	1

[a] *Incluye alguna de las siguientes: enfermedad cardiaca crónica, enfermedad pulmonar crónica, enfermedad cerebrovascular, cirrosis o enfermedad hepática crónica, diabetes o insuficiencia renal crónica.*

[b] *Tratamiento antirretroviral en el momento del episodio de ENI*

[c] *Indica un valor de la escala FINE ≥ 4 en el momento de la admission en el departamento de urgencias.*

[d] *Expresado en dias (mediana).*

Son diversos los factores que pueden ayudar a explicar los cambios observados en las manifestaciones clínicas de la enfermedad. Una de las razones que se argumenta es el de la "hipótesis inmunológica" por la que una situación inmune deteriorada puede disminuir la respuesta inflamatoria del paciente ante una infección, disminuyendo así la manifestación de ésta. Por el contrario, dada la mejora del estado inmunológico observado en los últimos años en esta población, sería esperable que se acompañase de una mayor respuesta inflamatoria y así un incremento en la severidad de la infección (140,147). En este estudio nosotros no

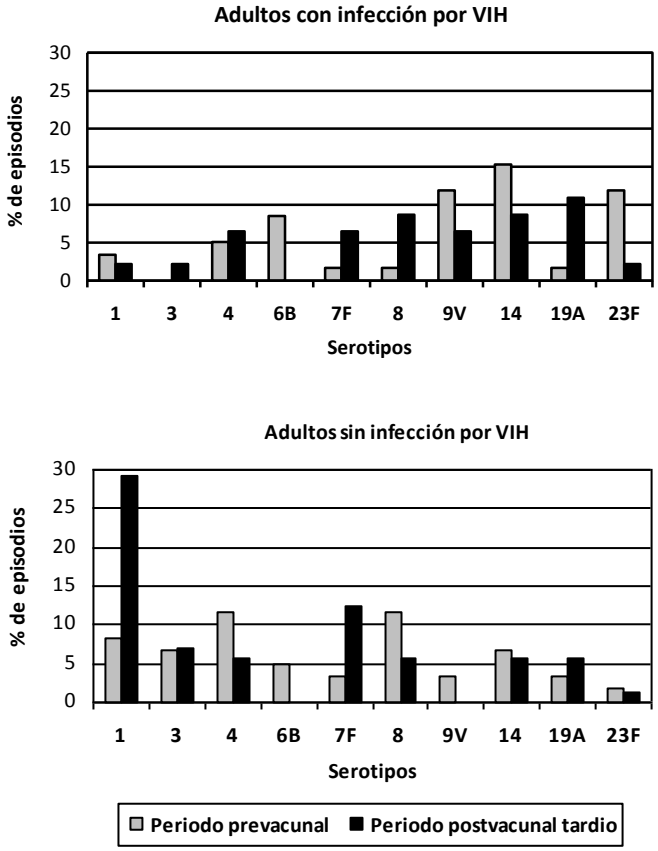
evaluamos la respuesta inflamatoria, pero sí observamos un aspecto interesante que parece corroborar esta hipótesis. En la época prevacunal, los pacientes sin infección por VIH y así con buen estado inmunológico tenían una enfermedad de mayor gravedad que los pacientes con infección por VIH. Por el contrario, en el periodo postvacunal, la severidad de la enfermedad se equiparó entre las dos poblaciones, debido fundamentalmente a un aumento de la gravedad de la enfermedad los pacientes con infección por VIH pese a la mejorar de su situación inmunológica. El incremento en la edad media de los pacientes y el consecuente aumento de comorbilidades observado como consecuencia del aumento de la supervivencia global, puede también tener un papel importante en el aumento de la severidad.

Otros factores pueden argumentarse para explicar por qué pese al aumento en la severidad de la enfermedad, la mortalidad se mantenga estable. Se ha planteado que la administración de la vacuna polisacárida puede tener unos efectos beneficiosos en aquellos pacientes en que falla y acaban presentando una neumonía en términos de disminución de la mortalidad de la enfermedad (149-151). De hecho, en un estudio previo realizado en nuestro hospital observamos este beneficio en pacientes con infección por VIH (152). Nosotros hipotetizamos que este factor, al ser la proporción de pacientes vacunados con la vacuna polisacárida en el periodo postvacunal mucho mayor, puede influenciar positivamente en el pronóstico de la enfermedad y compensar en parte el aumento de la severidad debido a la mejora inmunológica o al aumento de las comorbilidades. En nuestro estudio, en la era postvacunal sólo un paciente (3.6%) previamente vacunado murió, en comparación con los 23 (20.2%) que fallecieron del grupo sin previa vacunación.

Finalmente, y al igual que parece ocurrir en la población general, los cambios en la distribución de los serotipos causantes de enfermedad pueden estar influyendo en el aumento de la severidad observada en la época postvacunal. Desafortunadamente, debido al limitado número de aislamientos de cada uno de los serotipos específicos estas correlaciones no se han podidos establecer en nuestro estudio.

Hay que destacar, sin embargo, que en nuestra población tras la introducción de la vacuna conjugada se ha observado un cambio en la distribución de serotipos algo diferente al que ocurre en los pacientes sin infección por VIH. Así, mientras que en los pacientes no infectados por el VIH se ha observado un incremento en los serotipos no vacunales con alta capacidad invasiva, como son los serotipos 1 y 7F, en los pacientes con infección por VIH han aumentado los serotipos no incluidos en la vacuna pero con un bajo potencial invasivo, en concreto el serotipo 8 y 19ª (Figura 4). La emergencia de estos serotipos en la población VIH también ha sido observada en otros estudios (153).

Figura 4: Distribución de serotipos causantes de enfermedad neumocócica invasiva en adultos con y sin infección por VIH y por periodo.



En resumen, este trabajo confirma el progresivo descenso de la incidencia de ENI en los pacientes con infección por VIH, posiblemente debido al efecto conjunto de la generalización del tratamiento antirretroviral, del uso de vacuna polisacárida y también de la introducción de la vacuna conjugada en niños. La enfermedad parece haber cambiado hacia una forma más severa y ahora tiende a ser similar a la que ocurre en los pacientes no infectados por VIH. Si bien se ha producido un fenómeno de reemplazo con un descenso de los serotipos incluidos en la vacuna, el cambio de los serotipos que ahora causan enfermedad parece ser diferente entre los pacientes con o sin infección por el VIH.

Perspectivas de futuro

Los resultados presentados en esta tesis, así como los datos discutidos, siembran la duda del efecto positivo que ha tenido la introducción de la vacuna conjugada en estos últimos años. En el momento de la presentación de esta tesis se está produciendo además un nuevo acontecimiento como es la implantación de una nueva vacuna conjugada que se espera que tenga un efecto importante en la prevención de la enfermedad neumocócica. Sin embargo y a la luz de lo ocurrido en la última década, es imposible no plantearse una serie de interrogantes difíciles de responder en este momento y que quedaran pendientes para en los años venideros. En este último apartado de la discusión, he querido al menos deliberar sobre varios de estos interrogantes.

¿Cuál va a ser el papel de la nueva vacuna conjugada trecevalente?

Recientemente y como consecuencia de las limitaciones de la PCV7 en la prevención de la infección causada por los serotipos no incluidos en la vacuna, se ha comercializado una nueva vacuna conjugada trecevalente (Prevenar 13®, PCV13). Esta nueva vacuna incluye a seis nuevos serotipos (serotipos 1, 3, 5, 6A, 7F Y 19A) responsables de una gran carga de enfermedad invasora, además de los siete serotipos ya presentes en la PCV7. Estos trece serotipos representan cerca del 88% de los episodios de ENI en niños menores de 5 años (154), y entre el 58%-71% de episodios en adultos en Europa (73). Su implementación ha sido además muy extensa de tal forma que a final del 2011, estaba comercializada en 104 países y en 54 de ellos incluida en el calendario vacunal nacional. Es esperable que esta vacuna tenga un impacto inicial muy beneficioso en la reducción de las tasas de enfermedad, dada la seguridad e inmunogenicidad que ha demostrado en diferentes estudios (67,68), a que incluye los principales serotipos causantes de enfermedad, y su amplia distribución. De hecho, los primeros estudios tras su comercialización muestran una reducción significativa de la incidencia global de ENI en los niños, sin observarse emergencia de nuevos serotipos, algo que también ocurrió en los primeros estudios de la vacuna VCP7 (155,156). Además, podría tener un impacto beneficioso en la reducción de la incidencia de empiemas dado que incluye los serotipos más relacionados con estas complicaciones supuradas, como son el serotipo 1, 3 y 19A. Un estudio preliminar realizado en el norte de Inglaterra muestra un descenso del empiema pediátrico tras la introducción de VCP13 (157). Sin embargo, existen dudas sobre si con el paso del tiempo el mismo fenómeno de reemplazo que se observó tras la introducción de la VCP7 puede ocurrir con esta nueva vacuna conjugada. SI bien un estudio preliminar realizado en niños vacunados con VCP13 muestra un descenso en la colonización nasofaríngea por los serotipos 7F y 19A sin la emergencia de otros serotipos (158), otros estudios han

observado ya aumentos en la colonización por serotipos no incluidos en la VCP13, como es el serotipo 15A (159). Queda por ver en qué grado se produce este reemplazo de serotipos, y si es superior al descenso que se espera debido a la reducción de los serotipos incluidos en la VCP13.

¿Aumentarán las infecciones producidas por otros microorganismos a expensas de la reducción de la enfermedad neumocócica?

El fenómeno de reemplazo del que hemos ido hablando, es un suceso que se produce no tan solo entre los diferentes serotipos de neumococo sinó que puede ocurrir entre diferentes microorganismos. La nasofaringe humana es el reservorio de múltiples patógenos, entre los que existe una dinámica e importante interacción. Descensos en la tasas de portador de uno de estos microorganismos, puede favorecer que otros ocupen su lugar. Un reciente estudio muestra esta asociación competitiva entre *Haemophilus influenzae* y *Streptococcus pneumoniae* (160). De igual forma, varios estudios muestran como la reducción de la tasas de portador de neumococo observado en los pacientes vacunados se asocia a un aumento de la colonización por *Staphylococcus aureus.* (161-163). Este reemplazo entre microorganismos a nivel de la nasofaringe puede favorecer que, en un segundo paso, se produzca un aumento de las infecciones causadas por estas bacterias. De hecho, y como ya hemos mencionado previamente, se ha observado un aumento muy importante de la incidencia de empiemas por *Staphylococcus aureus* tanto en niños como adultos en EEUU (95,114). Por todo ello existe la duda acerca de si la introducción de esta nueva vacuna que incluye a siete serotipos de neumococo más, puede suponer un paso más en este fenómeno de reemplazo entre bacterias. Para responder a estas interrogantes es imprescindible continuar con estudios de vigilancia epidemiológica que permitan detectar precozmente cambios entre serotipos o microorganismos causantes de infecciones, así como sus correspondientes implicaciones clínicas.

¿Cuáles son las nuevas estrategias vacunales del futuro?

Respecto al futuro inmediato ya se está llevando a cabo investigaciones para el desarrollo de una nueva vacuna conjugada por parte de Merck que incluye a 15 serotipos (164). Esta vacuna incluye además de los trece serotipos de la VCP13, los serotipo 22F y 33F seleccionados por haberse identificado como serotipos emergentes tras la introducción de la VCP7 (79).

Posiblemente es más interesante el estudio de nuevas vacunas dirigidas no contra la cápsula del neumococo, sino contra otros factores de virulencia que este implicados en el proceso de invasión, por ejemplo, evitando la adherencia del neumococo en las células del epitelio

pulmonar. Estas vacunas podrían proteger de la infección sin alterar la colonización del nicho ecológico de la nasofaringe, lo que podría ser la solución para combatir el fenómeno de reemplazo. Vacunas antineumocócicas basadas en estas proteínas (como son la proteína A de superficie, la pneumolisina u otras proteínas de superficie) están siendo estudiadas en ratones (165-167). Es probable que estas nuevas vacunas proteicas puedan ayudar a reducir la incidencia de enfermedad neumocócica en un futuro próximo.

VII. LIMITACIONES

LIMITACIONES

EL trabajo que aquí se ha presentado tiene una serie de limitaciones que deben mencionarse. La primera de ellas hace referencia al cálculo de incidencia. Al no ser un estudio poblacional, las estimaciones de incidencia que se han realizado pueden no ser del todo correctas. Aun así este problema se ha intentado solventar colaborando con otros centros, lo que aumenta la fiabilidad de las estimaciones. Además, en dos de los estudios publicados se han presentado también la incidencia calculada por 1000 admisiones hospitalarias-año, obteniendo resultados idénticos al calculado respecto a la población de referencia. Por otro lado, dos de los estudios se realizaron en una misma área geográfica (Barcelona), por lo que sus resultados pueden no ser representativos de otras regiones en las que la distribución de serotipos puede diferir.

Otra de las limitaciones que se puede argumentar es que no se estudiado una serie de factores que pueden influenciar en la epidemiologia de la infección neumocócica así como en la presentación clínica de la enfermedad como son las co-infecciones virales, las propiedades genéticas del neumococo, la respuesta inflamatoria particular de cada individuo, etc. Por último, el número limitado de episodios causados por algunos serotipos en particular ha impedido realizar un análisis de posibles correlaciones con la presentación clínica.

VIII. CONCLUSIONES

CONCLUSIONES

Como conclusión, este trabajo muestra que tras la introducción de la VCP7 no tan solo se ha producido un cambio en la incidencia de la enfermedad neumocócica en el adulto sino que también su presentación clínica se ha modificado. La enfermedad afecta ahora a pacientes más jóvenes y con menos comorbilidades, presentándose de una forma más grave y con mayor tasa de complicaciones supuradas. Este fenómeno, aunque multifactorial, parece estrechamente relacionado con el reemplazo de serotipos y la emergencia de serotipos en particular.

Objetivo primero:

Estudiar si existen cambios en la el porcentaje de complicaciones en forma de empiema de la neumonía neumocócica así como variaciones en la incidencia global de empiema, en la población adulta entre el periodo prevacunal y postvacunal.

La incidencia de empiema, así como el porcentaje de neumonías que se complican con la misma, ha aumentado de forma significativa en el subgrupo de pacientes de adultos jóvenes en el periodo postvacunal. Los pacientes que padecen esta complicación son ahora más jóvenes y con menos comorbilidades. El aumento de las infecciones causadas por el serotipo 1, responsable de más del 40% de estos empiemas, parece ser la principal causa del incremento observado.

Objetivo segundo.

Estudiar si existen cambios en la gravedad de la presentación clínica y el pronóstico de la neumonía neumocócica, en la población adulta entre el periodo prevacunal y postvacunal.

La neumonía neumocócica en el periodo postvacunal se presenta de forma más grave, con mayores tasas de shock séptico y de requerimiento de ingreso en unidades de cuidados intensivos. La presentación en particular con shock séptico parece deberse al aumento de los casos producidos por el serotipo 3 y el 19 A.

Objetivo tercero.

Estudiar si existen cambios en la incidencia, en la presentación clínica y su pronóstico, y en las características microbiológicas de la enfermedad neumocócica

en una subpoblación de alto riesgo para ella como son los pacientes adultos con infección por VIH, entre el periodo prevacunal y postvacunal.

La incidencia de la enfermedad neumocócica en los pacientes con infección por VIH ha disminuido significativamente en el periodo de estudio, posiblemente debido a la mejora de la situación inmunológica conseguida con la generalización del tratamiento antirretroviral. Sin embargo la presentación clínica de la enfermedad se ha agravado con mayores tasas de insuficiencia respiratoria o de necesidad de intubación orotraqueal equiparándose al de la población no infectada por VIH de la misma edad. También se ha observado un reemplazamiento de serotipos, aunque diferente de la población no infectada por VIH.

IX. BIBLIOGRAFÍA

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X. ANEXOS

REVIEW

The increasing incidence of empyema

Joaquín Burgos, Vicenç Falcó, and Albert Pahissa

Purpose of review
The aim of this review is to highlight recent changes concerning the incidence of empyema. In this article we have focused on community-acquired empyema

Recent findings
The incidence of empyema seems to have been increasing both in children and adults worldwide in the past decades, mainly in healthy young adults and in older patients. The bacteriology of pleural infection is changing as well. In children, the most common microorganism that causes empyema continues to be *Streptococcus pneumoniae*. Interestingly, the widespread use of the seven valent conjugate vaccine has produced a replacement phenomenon with the emergence of some pneumococcal serotypes such as serotypes 1, 3 and 19A, which have a higher propensity to cause empyema. Moreover increases in the incidence of empyema due to *Staphylococcus aureus* have also been observed. In adults, increases in the rate of empyema due to *Streptococcus milleri* group and *S. aureus* have been reported.

Summary
Continued surveillance in the epidemiology of empyema is needed. Progress in new strategies of prevention, such as a new generation of conjugate pneumococcal vaccines and protein-based vaccines, could become an important step in the control of this important complication.

Keywords
empyema, pneumococcal conjugate vaccine, pneumococcal serotypes

INTRODUCTION

Empyema is an ancient disease that continues to be an important clinical problem nowadays. The earliest recorded description of a patient with empyema dates back to more than 5000 years ago in ancient Egypt [1]. Later, the first consistent description of its manifestations and treatment was attempted by Hippocrates over 2000 years ago [2]. However, despite the centuries of learned experience, the appearance of antibiotics and the use of different pneumococcal vaccines, empyema remains the most common complication of pneumonia and an important cause of morbidity worldwide [3]. Nowadays, over 65 000 patients suffer from pleural infection each year in the UK and USA [4]. Approximately 15% of these patients die, and another 30% require surgical drainage of the pleural space [5,6].

The incidence of pleural infections diminished significantly during the first half of the 20th century [7,8]. In the preantibiotic era, empyema was a complication of approximately 5% of cases of pneumonia, but with the development of antibiotics in the decade of the 1940s the rate of empyema declined to 2% [3]. In an interesting study over four decades, Weese *et al.* [7] found an incidence of empyema of 79 cases per 100 000 admissions in the preantibiotic era; this rate of incidence dropped to 52 cases per 100 000 by 1947–1948 and remained at about that level through 1967–1969. However, this trend changed at the end of the 20th century and, since the decade of the 1990s the incidence of empyema has tended to be increasing worldwide.

To understand the dynamics in the incidence of empyema, it is important to take into account the complex microbiology of pleural infection. A wide range of microorganisms have been cultured from empyema, and mixed infections do occur. The prevalence of different causative organisms differs depending on the source of infection (community vs. hospital-acquired empyema), the age (children

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Curr Opin Pulm Med 2013, 19:000–000
DOI:10.1097/MCP.0b013e3283606ab5

KEY POINTS

- The incidence of empyema is increasing both in children and adults.
- The number of cases of pneumococcal empyemas caused by serotypes not included in the PCV7 is increasing, and also cases of empyema caused by *Staphylococcus aureus*, other streptococci (nonpneumococci) and Gram-negative microorganisms.
- Explanations for these epidemiological changes in empyema are probably multifactorial and not entirely known.

vs. adults) and the host characteristics (immunocompetent vs. immunocompromised patients). In addition, in up to 40% cases of empyema a causal microorganism is not isolated in bacterial cultures [5,9,10].

The aim of this review is to highlight recent changes concerning the incidence of empyema, with special emphasis on community-acquired empyema. We will also review the possible clinical implications of these changes and discuss the possible causes of this phenomenon.

INCIDENCE OF EMPYEMA IN CHILDREN

The bacteriology of empyema in children is more homogeneous and has remained more stable over time than in the adult population. *Streptococcus pneumoniae* remains the most common causative microorganism of empyema in the pediatric population, accounting for more than 50% of cases [11,12].

Pneumococcal infections are the leading cause of death from vaccine-preventable illness in children aged below 5 years, causing around 11% of all deaths in this age group [13]. Since the mid-1980s, the polysaccharide pneumococcal vaccine, that contains purified capsular polysaccharide from 23 pneumococcal serotypes, is available. However, this vaccine is not efficacious for children aged below 2 years because of the immaturity of their immune system. At the beginning of the 21st century, the heptavalent protein–polysaccharide conjugate vaccine (PCV7), that conferred protection for seven of the most common pneumococcal serotypes (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F), was licensed for use in young children with the aim to prevent pneumococcal disease in this high risk population. After its implementation, PCV7 proved to be highly effective in reducing nasopharyngeal carriage by vaccine serotypes and also in preventing pneumococcal disease by vaccine serotypes [14–17]. A large active population surveillance study carried out in the USA from 1998 to 2007 found a striking reduction of invasive pneumococcal disease (IPD) in children aged below 5 years [16]. The incidence of IPD caused by vaccine serotypes decreased dramatically from 81.9 cases per 100 000 population in 1998–1999 to 0.4 cases per 100 000 in 2007. In this study the overall incidence of IPD decreased from 98.7 to 23.6 cases per 100 000 [16]. Nevertheless, despite the effectiveness of the PCV7, the incidence of complicated pneumonia not only did not decrease but seemed to increase around the world.

An increase in the incidence of empyema was already observed during the last years of the 20th century, before the implementation of PCV7, in several countries of Europe, America and Asia [18–28]. In England, a national study found an increase in admissions due to empyema from 1.4 per 100 000 population in 1995–1996 to 2.6 per 100 000 in 2002–2003 [23]. Another study carried out in Scotland also found an increase of hospitalizations due to empyema from 1.0 per 100 000 population in 1998 to 3.7 per 100 000 in 2005 [28]. These increases were related to a higher number of children with pneumococcal empyema, especially caused by pneumococcal serotype 1 which was responsible for 50% of cases [22,23,25]. In this prevaccine period, emergence of other microorganisms different from pneumococci was not observed.

After the introduction of PCV7, and despite the decreases observed in the rate of hospitalizations for pneumonia, the number of cases of pneumonia complicated with empyema continued to increase. Several regional studies performed in different geographic areas observed a two-fold rise from 15 to 30% in the rates of complicated pneumonia [29,30,31–42,43▪,44]. This increase was related in part to the emergence of pneumococcal serotypes not covered in the PCV7, especially serotypes 1, 3 and 19A [31–35,39,43▪,44]. Furthermore, an important increase in the role of other pathogens such as *Staphylococcus aureus* was described [37,40].

A recent important study by Grijalva *et al.* [40], using a large national database, analyzed the hospitalizations for pneumonia and empyema in children before (1996–1999) and after (2001–2007) the introduction of PCV7 in USA. After the implementation of the vaccine, the incidence of all-cause pneumonia for children younger than 2 years old decreased from 1267 cases per 100 000 to 852 cases per 100 000, which represented a 33% reduction. There was also a significant 61% reduction in hospitalizations for pneumococcal pneumonia. In contrast, there was a two-fold rise from 3.5 to 7 cases per 100 000 in hospitalized cases with empyema.

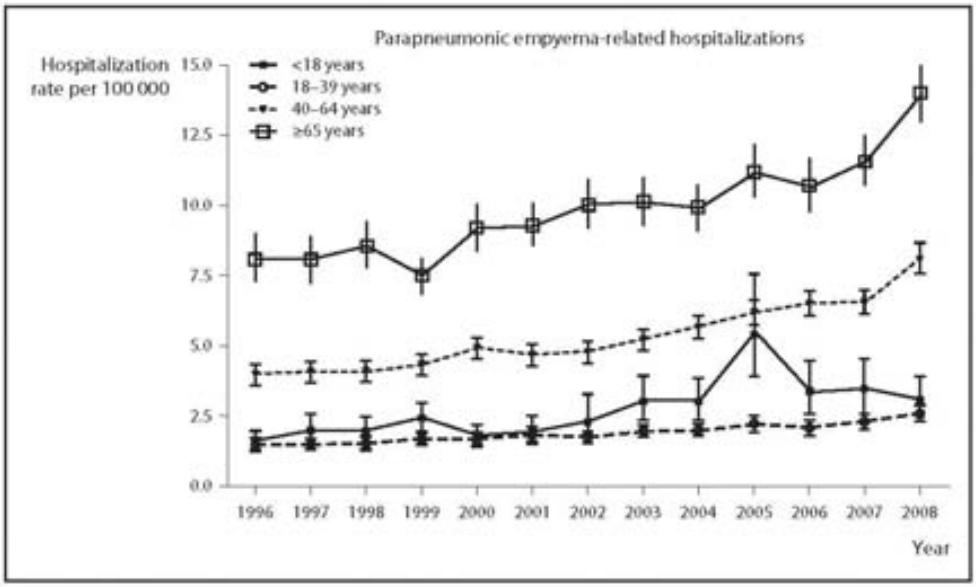

FIGURE 1. Trends in parapneumonic empyema-related hospitalizations in the USA, 1996–2008. Data from the Nationwide Inpatient Sample.

Concerning the causative agents, rates were stable for pneumococcal and streptococcal (nonpneumococci) empyema but increased more than four-fold for staphylococcal empyema and almost two-fold for other or unspecified causes [40]. Among children aged 2–4 years, whereas rates of pneumococcal pneumonia decreased by 26%, cases of pneumonia complicated with empyema increased from 3.7 to 10.3 cases per 100 000. In this age group significant increases in both pneumococcal and staphylococcal empyema were observed [40] (Fig. 1).

From an epidemiological point of view, the mean age of children who suffer from this suppurative complication has increased from less than 2 to 2–4 years old [31,44]. Regarding other clinical aspects, Mckee *et al.* [45▪] found an increase from 1% in 2002–2007 to 33% in 2008–2009 in the rates of bronchopulmonary fistula complicating empyema, which was accompanied by an increase in the surgical intervention rates. Fortunately, despite the higher rates of complications, the higher need of surgery and the longer hospital stay of patients, the case-fatality rate remains low and it seems not to have increased [31,45▪,46].

INCIDENCE OF EMPYEMA IN ADULTS

The causal microorganisms of empyema in adults have varied significantly over time. In the preantibiotic era, *S. pneumoniae* accounted for 60–70% of cases, *Streptococcus pyogenes* for 10–15% and *S. aureus* for 5–10% [5,8]. With the introduction of antibiotics in the 1940s, cases of empyema caused by hemolytic streptococci became infrequent and although pneumococcal empyema continued to occur frequently, its incidence declined. In contrast, empyemas caused by *S. aureus* and Gram-negative microorganisms were most frequent in originally mixed infections, hospital-acquired cases, and superinfections [3].

Interestingly, in the past decades causal microorganisms of empyema seem to be changing again. Some reports suggest a shift of traditional pathogens to the *Streptococcus milleri* group in community-acquired empyemas, especially in patients with comorbidities such as underlying malignancy or diabetes mellitus [6,9]. In the Multicenter Intrapleural Sepsis Trial (MIST-1) performed in 52 centers in the UK in 2005, the *S. milleri* group was recovered in 32% of community-acquired empyema cases with known cause, followed by *S. pneumoniae* (13%), *S. aureus* (11%) and enterobacteria (10%) [9]. Similar results were obtained in a large study from Canada where *S. milleri* group caused half of the episodes of empyema [6] (Fig. 2). Studies from Taiwan have showed a higher incidence of Gram-negative infections in patients with pneumonia complicated with empyema [47–49]. In the UK and Spain, higher rates of empyema caused by *S. aureus* have also been observed [50▪,51▪].

Beyond the variations in the cause of empyema, the increase in the incidence of the disease that has occurred in the past years is worrisome. In a hospital study focused on pneumococcal empyema in adults performed in our hospital, we found a significant increase in the incidence of empyema, mainly in

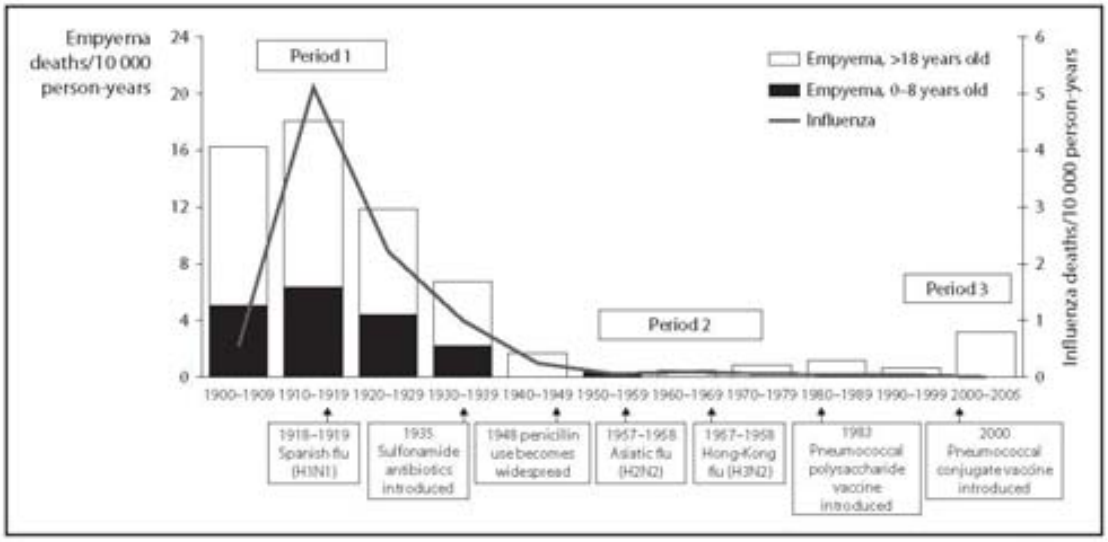

FIGURE 2. Average rates of deaths in Utah caused by parapneumonic empyema and influenza, by decade, 1900–2005.

young adults (aged 18–50 years). In this population the rate of pneumococcal pneumonia complicated with empyema increased from 7.6% in 1996–2001 to 14.9% in 2005–2011 [52▪]. These results are in concordance with those obtained in a national study from Canada in which there was a 23% increase in the rate of empyema in patients aged 40–54 years [30]. This increase in the incidence of pneumococcal empyema in young adults is associated with the emergence of serotypes 3, 19A and especially serotype 1, which nowadays causes more than 40% of pneumococcal empyema in adults [52▪,53▪].

The most recent data available regarding the incidence of empyema in adults is obtained from the study by Grijalva *et al.* [54▪▪]. The authors employed a robust design using a large national database that included approximately 1000 hospitals in the USA in the period from 1996 to 2008. In this study, the rates of hospitalizations because of empyema increased from 3.96 cases per 100 000 in 1996 to 8.10 per 100 000 in 2008 in adults aged 40–64 years, which represents a two-fold increase. Similarly, 1.8 and 1.7-fold increases among adults aged 18–39 years and above 65 years, respectively, were also reported [54▪▪].

The authors also observed variations in the cause of empyema. Whereas rates of pneumococcal empyema appeared to remain stable in adults, the incidence of streptococcal (nonpneumococcal) and especially staphylococcal empyema showed a significant increase over the study period, with a 1.9 and 3.3-fold increase, respectively. The proportion of empyema with unknown cause or caused by other agents, which occurred in 62.4% of cases, had a 2.1-fold increase [54▪▪]. It is important to highlight that a significant proportion of culture-negative empyema is found to be caused by pneumococci when molecular techniques for the diagnosis of empyema are used [29,55,56].

In summary, nowadays healthy young adults have a greater risk of developing empyema than years ago, especially that caused by *S. pneumoniae* [57▪]. Moreover, empyemas caused by Gram-negative bacteria and *S. aureus* have increased in the older population with serious underlying diseases. The mortality in these cases is high, around 20%. In fact, a six-fold increase of deaths attributable to empyema was observed in Utah in the past years in comparison with the period from 1950 through 1975, especially among persons above 65 years of age [58] (Fig. 3).

REASONS FOR EPIDEMIOLOGICAL CHANGES

Explanations for these epidemiological changes in empyema are complex and not entirely known. Probably the introduction of the PCV7 has played a key role in these changes [59]. Since its implementation, a replacement phenomenon has occurred. This process consists of a dynamic replacement of serotypes that are included in the PCV7 by serotypes not included in the vaccine as colonizers of the nasopharynx. In a second step, these serotypes have emerged not only as colonizers but also as causing disease in children [60]. The final step is the transmission of these new serotypes from colonized children to adults as a consequence of a 'herd effect' [60]. This phenomenon explains the increase

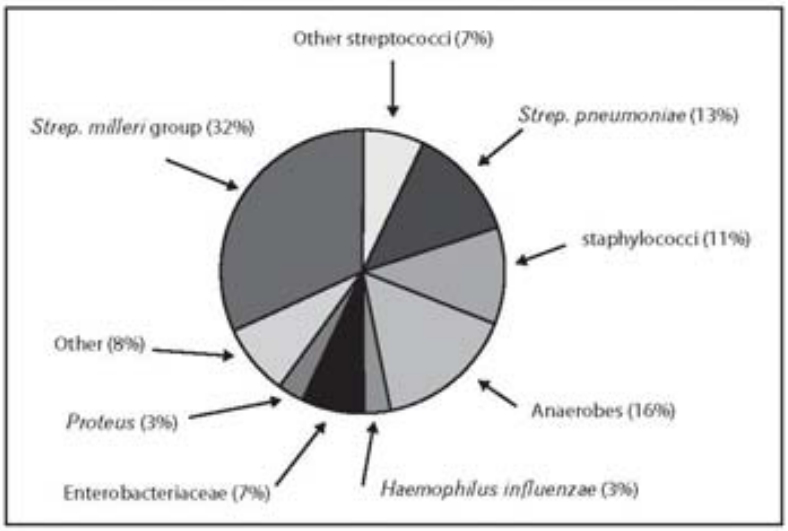

FIGURE 3. Cause of community-acquired empyema in adults. Data form MIST-1 trial.

in cases of pneumococcal infections caused by the nonvaccine serotypes 1, 3 and 19A.

Pneumococcal serotypes differ in properties such as resistance to phagocytosis, ability to penetrate into tissues and capacity to activate the inflammatory response [61–64]. It is plausible that the emerging 1, 3 and 19A pneumococcal serotypes contain virulence factors than confer an increased ability to invade the pleural space and to develop suppurative complications. On the other hand, the decrease in the colonization of the nasopharynx by pneumococci could facilitate the occupation of this ecological niche by other microorganisms, such as *S. aureus* [65▪]. We hypothesize that this colonization by new microorganisms could favor the subsequent infection.

Nevertheless the emergence of these new pneumococcal serotypes cannot easily be explained only by a vaccine effect. Temporal trends in pneumococcal serotype distribution have been described worldwide with epidemic increases in the frequency of pneumococcal infections caused by serotype 1 in the last years of the 20th century, before the implementation of PCV7 [66–68]. These fluctuations in the epidemiology of pneumococcal serotypes could be the reason why increases in the incidence of pneumococcal empyema in children had already been reported before the introduction of PCV7.

Other factors might also have influenced the epidemiology of pleural infections in the past years. Some authors argue that the spread of antibiotic-resistant bacteria, some of which are major empyema pathogens, may partly explain the observed increases [69]. In particular some studies found increases in empyema related to staphylococcal and Gram-negative resistance microorganisms [69]. *S. pneumoniae* is the major exception as the incidence of disease caused by resistant strains has decreased markedly following the introduction of PCV7 [70].

Influenza has historically been linked to increases in cases of pneumonia and suppurative complications. In this way Bender *et al.* [58] observed that deaths caused by empyema peaked during the Spanish influenza pandemic of 1918–1919. However, the increase in deaths by empyema that has occurred at the turn of the 21st century has taken place without the advent of an influenza pandemic [58]. Only one study in 2009 observed an increase in hospitalizations for empyema in children associated to an outbreak of H1N1 influenza [42].

The increase in the elderly population, with more patients suffering from comorbidities, has been argued by some authors as a factor directly related to the increased incidence of empyema, especially in those cases caused by Gram-negative microorganisms and *S. aureus* [47,48,50▪].

Finally, the increasing wide availability of new diagnostic techniques such as computed tomography scans undoubtedly has contributed to higher recognition of less severe cases of empyema [40,71].

CONCLUSION

Empyema remains an important healthcare problem, with rising incidence both in children and adults. Microbiology of empyema is complex and changing, with increases in the number of cases of

pneumococcal empyemas caused by serotypes not included in the PCV7. Cases of empyema caused by *S. aureus*, other streptococci (nonpneumococci) and Gram-negative microorganisms have also increased, linked to the more advanced age of the population and the higher proportion of adults with underlying diseases. Reasons to explain these epidemiological changes in empyema are probably multifactorial and not entirely known; nevertheless the introduction of the PCV7 seems to have played an important role. Progress in pneumococcal vaccine development with the new generation of conjugated vaccines and protein-based vaccines, which may prevent invasion and preserve colonization, might be an important step in the prevention of this important complication of pneumonias.

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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REVIEW

The Spectrum of Invasive Pneumococcal Disease in Adults in the XXI Century

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Abstract: *Streptococcus pneumoniae* is the most common cause of community-acquired pneumonia and bacterial meningitis in adults. Despite the availability of potent antibiotics and the development of different pneumococcal vaccines, the burden of pneumococcal infections in terms of morbidity, hospitalizations, mortality, and healthcare costs continues to be tremendous. The different pneumococcal serotypes play an important role in some aspects of pneumococcal epidemiology. The introduction of the 7-valent conjugate vaccine among children led to important changes not only in the epidemiology but also in the clinical outcomes and mortality of invasive pneumococcal disease in adults. Moreover, with the widespread use of immunosuppressive and immunomodulating therapies for different medical conditions, we may expect an increase in the number of patients at a high risk of pneumococcal infections in the following years. The influence of immunosuppression as a risk factor for invasive pneumococcal disease, the changes in the dynamics of pneumococcal serotypes, the influence of pneumococcal serotypes on the clinical presentation of pneumococcal invasive disease, and the role of pneumococcal vaccines are some of the important issues that are discussed in this review.

Key Words: *Streptococcus pneumoniae*, invasive pneumococcal disease, pneumococcal vaccines

(*Clin Pulm Med* 2013;00:000–000)

Streptococcus pneumoniae remains a leading cause of serious infections in humans. Despite its discovery more than 100 years ago, it continues to be the most common cause of community-acquired pneumonia (CAP) and bacterial meningitis in adults. It is estimated that about 1.6 million individuals die from pneumococcal disease each year worldwide, most of them in developing countries.[1] A recent active bacterial surveillance report in 2010 estimated an incidence of invasive pneumococcal disease (IPD) of 12.9 cases/100,000 individuals, with 4000 deaths in the United States each year because of pneumococcal infections, primarily among adults.[2] Moreover, the burden of pneumonia in terms of healthcare costs is considerable. Looking to data from the United States and the European Union, CAP is among the 2 diseases that had the highest impact on healthcare costs in these societies.[3] Because *S. pneumoniae* is the most common cause of CAP worldwide, we can estimate the importance of this microorganism in the healthcare system of different countries. Paradoxically, pneumococcal infections constitute the first cause of death that is preventable by vaccination in individuals of all ages. In this review, we focus on some important issues in terms of IPD in adults that, in our opinion, will be relevant in the future.

THE ROLE OF IMMUNOSUPPRESSION AS A RISK FACTOR FOR IPD

The most important risk factors for acquiring an IPD are summarized in Table 1. The incidence of IPD is clearly related to age. It is particularly high in children <1 year, with rates of 34.3 cases per 100,000 children-years, and later it progressively decreases to 2.2 cases in children aged 5 to 17 years. In adults, the incidence of invasive disease ranges from 3.8 cases per 100,000 among individuals aged between 18 and 34 years to 36.4 in those aged 65 years and older.[2] It is also well known that adults with cigarette smoking, alcohol abuse, or certain medical conditions are at an increased risk for IPD. Adults with diabetes, chronic heart disease, or chronic lung disease have a 3- to 6-fold increased risk of IPD, compared with healthy adults.[4]

The problem is especially important in patients with immunosuppressive conditions. In a recent study carried out in our hospital, about 35% of patients with IPD had an underlying immunosuppressive condition.[5] The conditions strongly associated with the occurrence of IPD are the presence of solid tumors (300.4 cases/100,000), human immunodeficiency virus (HIV) infection (422.9 cases/100,000), and hematological malignancies (503.1 cases/100,000).[4] Overall, the disease rates for adults in these groups can be more than 20 to 50 times higher than for adults without these high-risk medical conditions.

An interesting situation is the case of HIV-infected patients. Shortly after the introduction of highly active antiretroviral therapy, different studies reported a >50% decrease in the incidence of IPD in HIV-infected adults.[6–8] It seemed that it would occur as with other opportunistic infections that had shown a progressive decreasing tendency. Unfortunately, more recent reports show that, despite the widespread use of HAART, the incidence rates of IPD in HIV-infected patients remain significantly higher than those in non–HIV-infected population in developed countries.[9] As an example, in a recent study carried out in Spain, the overall incidence of IPD in HIV-infected patients decreased significantly from 781 episodes/100,000 patient-years in the period 1996 to 2001 to 378 in the years 2002 to 2004 and 369 episodes/100,000 patient-years in the most recent years (2005 to 2010). Compared with the first period, there was a 53% decrease of the incidence in the most recent period.[10] However, it is worth keeping in mind that the actual incidence of IPD in HIV-infected patients continues to be unacceptably high, with rates 50- to 100-fold higher than that in the uninfected population.

Patients with immune-mediated inflammatory diseases such as rheumatoid arthritis, spondyloarthropathies, inflammatory

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V.F. has received honoraria from Pzifer. The remaining authors declare that they have nothing to disclose.

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ISSN: 1068-0640/13/0000-0000
DOI: 10.1097/CPM.0b013e3182a2db89

TABLE 1. Risk Factors for Invasive Pneumococcal Disease (IPD)

Risk Factors	%
Age, older than 65 y	44.5
Smoking	51
History of alcohol abuse	19.1
Chronic lung disease	28.1
Chronic liver disease	15.7
Chronic heart disease	15.7
Chronic kidney disease	5.7
Diabetes mellitus	17.9
Any immunosuppressive condition	37.4
HIV infection	17
Splenectomy	3
Hematologic malignancy	10
Solid tumor	13.6
Bone marrow transplant	1.5
Solid organ transplant	1.2
Chronic immunosuppressive and/or immunomodulating therapies	5.3

Data represent proportion of patients with IPD who have any of the above risk factors.

Data were obtained from the database of Hospital Vall d'Hebron Barcelona (965 patients).

HIV indicates human immunodeficiency virus.

bowel disease, or psoriasis are at an increased risk of pneumococcal infections, partially because of the disease itself but mostly because of treatment with immunomodulatory or immunosuppressive drugs.[11] In fact, bacterial pneumonia is one of the most common opportunistic infections in patients receiving anti-TNF-α treatment. These patients are also considered to be at high risk for IPD.[12]

With advances in all fields of medicine that will lead to a widespread use of immunosuppressive and immunomodulating therapies for different medical conditions, we may expect an increase in the number of patients at high risk of pneumococcal infections in the following years. This is why pneumococcal vaccination strategies should become a priority in these high-risk groups of patients.

THE DYNAMICS OF PNEUMOCOCCAL SEROTYPES

The different pneumococcal serotypes play an important role in some aspects of pneumococcal epidemiology. The invasiveness of a serotype or the frequency with which it causes invasive disease per carriage episode is a stable property. There is an inverse relationship between the carriage prevalence of a serotype and its invasiveness and between disease severity and invasiveness.[13] Case series and experimental data have shown that the capsular serotype is involved in the pathogenesis of the infection and it may even be a determinant of disease outcome. Previous studies have shown that serotypes with a high polysaccharide content were generally more lethal in murine models of sepsis than serotypes with a lower polysaccharide content.[14]

The introduction of the 7-valent pneumococcal conjugate vaccine (PCV7) among children led to significant changes in the epidemiology of IPD in adults. After the introduction of this vaccine in 2000, the rates of IPD caused by serotypes included in the PCV7 (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F) among older adults decreased from 34.5 cases per 100,000 individuals per year to 8.2 cases per 100,000 individuals per year in 2004.[15] In contrast, the rates of IPD because of nonvaccine serotypes increased modestly. Nevertheless, in the United States, the overall effect of these changes was that the rate of IPD decreased in adults and this beneficial effect persisted in the United States 7 years after the introduction of the vaccine in all age groups.[16–18]

However, in other geographical areas, these changes in the burden of IPD in adults have not been so evident and marked inequalities in the geographical distribution of disease have been observed. In British Columbia, Canada, 7 years after the introduction of the PCV7, a 78% decrease in the incidence of IPD among children younger than 5 years was achieved. In contrast, in adults, gains in disease reduction were offset by increase in replacement serotypes, particularly among the age group older than 65, which resulted in no net change in adult IPD rates.[19] In the United Kingdom, over the period of 2002 to 2009, despite the fact that the 23-valent pneumococcal polysaccharide vaccine (PPV23) uptake increased from 49% to 70% and PCV7 uptake reached 98% by 2009, the overall incidence of IPD increased from 11.8/100,000 to 16.4/100,000.[20] Although a reduction in the proportion of IPD caused by PCV7 serotypes was observed, concurrent increases in PPV23 and nonvaccine serotype IPD contributed to an increased IPD burden overall.[20] In France, PCV7 was introduced in 2003 and by 2006 the incidence of IPD had not only not decreased but also increased significantly in adults of all age groups.[21] A similar situation has been observed in Spain.[5,22]

It is remarkable to note the increase in the incidence of infections caused by some nonvaccine serotypes. The nonvaccine serotype 19A has emerged as the most important cause of invasive disease worldwide, especially in the United States and in Europe; therefore, this serotype might be considered as an escape strain.[23] In our setting, we also observed a significant increase in infections caused by the nonvaccine serotype 1 and serogroup 7.[5] Similarly, in another study carried out in Utah, emerging serotypes 3, 7F, and 19A caused the majority of IPD in adults.[24]

THE INFLUENCE OF PNEUMOCOCCAL SEROTYPES ON THE CLINICAL PRESENTATION AND OUTCOME OF PNEUMOCOCCAL INVASIVE DISEASE

Experimental studies in animal models have shown that pneumococcal serotypes differ in properties such as resistance to phagocytosis, ability to penetrate into tissues, and capacity to activate the inflammatory response. These characteristics of each serotype could explain some differences in the clinical presentation of pneumococcal disease depending on the causal serotype.

Pneumococcal serotypes have been classified according to their capacity to produce invasive disease.[13] Serotypes 1, 5, and 7F have been grouped as highly invasive serotypes and have been associated with invasive disease in younger adults. These serotypes are hardly isolated as colonizers of the nasopharynx. However, serotypes 3, 6, 8, 15, 19, and 23 y 33, which are often found as colonizers of the nasopharynx in children, are considered to be low-invasive serotypes and have been related with illness in older patients with comorbidities.[25]

The influence of the different pneumococcal serotypes on clinical outcomes and mortality has been reported in several studies. A recent systematic review and meta-analysis of serotype-specific disease outcomes for patients with pneumococcal pneumonia and meningitis found a higher risk for mortality particularly for serotypes 3, 6A, 6B, 9N, and 19F. However, serotypes 1, 7F, and 8 were associated with lower

mortality.[26] This property of serotypes was especially important in patients with invasive pneumococcal pneumonia but not in those with meningitis.

The importance of these observations has emerged in the recent years because of the changes in serotype distribution that have been produced after the implementation of the PCV7 in children. In this way, some studies have found an increase in the proportion of healthy young adults who develop pneumococcal infections.[27,28] The question of why the disease is increasing in younger adults may be related to the emergence of the nonvaccine serotypes 1 and 7F, which are considered as primary pathogens with a high invasive potential.

The emergence of nonvaccine serotypes has also led to important changes in the clinical presentation of IPD, especially in patients with pneumococcal pneumonia. Some studies have observed that pneumococcal disease in the postvaccine era seems to be changing toward a more severe disease. In fact, in our cohort of adults with invasive pneumococcal pneumonia, we observed that an increased rate of patients who developed septic shock and serotypes 3 and 19A were independently associated with the development of this complication.[5] This observation is in agreement with a previous study that suggested that initial presentation with septic shock was associated with pneumonia caused by serotype 3.[29]

There are also intriguing and worrisome changes in the incidence of suppurative complications that have been described in recent years. After the implementation of the PCV7, a significant increase in the incidence of necrotizing pneumonia and empyema was observed in children.[30,31] These suppurative complications were associated with the emergence of the non-PCV7 serotypes 1 and 3. Recent reports have observed the same phenomenon in adults.[27,28,32] In a hospital study focused on pneumococcal empyema in adults, we found a significant increase in the incidence of empyema mainly in young adults.[28] In this population, the rates of pneumococcal pneumonia complicated with empyema increased from 7.6% between 1996 and 2001 to 14.9% between 2005 and 2011. This change was associated with the emergence of serotype 3 and especially serotype 1, which nowadays causes >40% of pneumococcal empyemas in adults.[28] Although the reason why these serotypes tend to cause suppurative complications is unknown, it is possible that they contain virulence factors that confer an increased ability to invade the pleural space.

EVOLVING ISSUES IN ANTIMICROBIAL RESISTANCE OF *S. PNEUMONIAE*

Trend analysis since 1994 to 1995 indicated that rates of resistance to β-lactams, macrolides, tetracyclines, trimethoprim/sulfamethoxazole, and multiple drugs had either plateaued or had even begun to decrease.[33] In fact, over the last several years, data from different surveillance studies, most of them carried out in the United States, have shown a reduction in the rates of penicillin nonsusceptible *S. pneumoniae* infections both in children and in adults.[34] A similar phenomenon has been observed with macrolide resistance. In settings where PCV7 has been widespread, there has been a distinct reduction in the overall prevalence of macrolide resistance among invasive isolates.[35] The most recent surveillance in the United States has shown rates of penicillin susceptibility of 90% with only 5.1% of resistant strains.[2] Similarly, only 1.8% of pneumococcal strains are resistant to cefotaxime and almost 100% of strains are susceptible to levofloxacin.[2]

Most studies suggest that the current levels of β-lactam resistance do not cause treatment failures for patients with CAP when appropriate agents and doses are used.[36,37] The reason why resistance to β-lactams does not affect the outcome of treating extrameningeal infections with these drugs would be that the drug levels attained at the doses used ordinarily are sufficient to overcome resistance. In contrast, in patients with meningitis, it is necessary to achieve adequate penicillin concentrations in the cerebrospinal fluid and if these concentrations are not achieved there is a considerable risk of clinical failure. For these reasons, the breakpoints for susceptibility to β-lactams have been updated according the site of infection. For pneumococcal infections other than meningitis, a strain is considered to be susceptible to parenteral penicillin if the minimum inhibitory concentration (MIC) value is $\leq 2\,\mu g/mL$, intermediate susceptible if the MIC = 4 μg/mL, and resistant at MIC values $\geq 8\,\mu g/mL$.[38] In contrast, for meningeal infections, the breakpoints for susceptibility were maintained as penicillin-susceptible ($MIC \leq 0.06\,\mu g/mL$), penicillin-intermediate (MIC = 0.12 to 1 μg/mL), or penicillin-resistant ($MIC \geq 2\,\mu g/mL$). Therefore, although antimicrobial resistance in *S. pneumoniae* remains a serious concern, we have to accept that in the clinics, we really do not see failures because of resistance, especially in invasive infections, because we can increase the daily dose of penicillin or β-lactams.

The problem is that the resistance profile of *S. pneumoniae* has a dynamic nature and we never know when a new mutant will appear. In fact, one of the main concerns of the changing epidemiology of *S. pneumoniae* after the introduction of the PCV7 is the emergence of serotypes with high resistance rates to antimicrobials. In this way, a recent population-based surveillance study carried out in the United States showed that the incidence of pneumococcal meningitis caused by isolates that were nonsusceptible to penicillin, cefotaxime, or meropenem decreased significantly between 1998-1999 and 2004-2005.[17] However, the emergence of some *S. pneumoniae* strains with multidrug resistance, such as nonvaccine serotypes 15A, 19A, and 35B, has been reported recently.[17,39,40]

All these data point out that the issue of antibiotic resistance is a dynamic process that may again become a matter of concern in the next few years, and it justifies the need for continued surveillance to monitor the pattern of antibiotic resistance.

THE ROLE OF NEW DIAGNOSTIC METHODS

Diagnosis of IPD is based on the isolation of *S. pneumoniae* from a normally sterile site. In cases of meningitis, arthritis, or peritonitis, the diagnostic yield of culture is high. However, only about 20% to 30% of pneumococcal pneumonias have positive blood cultures. In most cases of pneumococcal pneumonias, diagnosis relies on Gram staining and culture of a sputum sample, which has a limited sensitivity and specificity.

The detection of pneumococcal urinary antigen is based on an immunochromatographic membrane technique to detect the C-polysaccharide antigen of *S. pneumoniae*. This test has shown reasonable sensitivity and good specificity and positive predictive value to diagnose pneumococcal pneumonia, mainly in patients with invasive pulmonary disease.[41] A major limitation of the immunochromatographic technique to detect urinary antigen over bacterial culture is that it does not provide information on the antimicrobial susceptibility of pneumococcus. This limitation could be overcome by novel techniques such as nucleic acid detection with the use of real-time polymerase chain reaction (PCR). PCR detection of *S. pneumoniae* may offer some potential advantages in the near future. We

could identify the exact pneumococcal serotype causing the disease, its antimicrobial susceptibility, and also its potential to cause severe disease.

Another advantage of molecular diagnostics is the possibility of identifying pathogens in patients already receiving antibiotic treatment. The use of PCR technology in patients with CAP allows improving the etiological diagnosis in a higher number of cases. Using a real-time quantitative PCR, about 80% of cases of CAP of unknown etiology were found to be caused by *S. pneumoniae*.[42] These findings support earlier suggestions that pneumococci cause a majority of CAP cases in which negative test results were found using conventional methods.

The use of quantitative real-time PCR may provide additional information of great diagnostic value to distinguish colonization from infection when *S. pneumoniae* is identified in respiratory samples. In a study carried out in a population with a high prevalence of HIV infection, the mean real-time PCR copy number was 6.0 $\log_{10}$ copies/mL in patients with pneumococcal pneumonia compared with 0.8 $\log_{10}$ copies/mL in asymptomatic colonized controls.[43] In this study, a real-time PCR density of $\geq$ 8000 copies/mL had a sensitivity of 82.2% and a specificity of 92% for distinguishing community-acquired pneumococcal pneumonia from asymptomatic colonization.

Finally, detection of *S. pneumoniae* by a real-time quantitative PCR performed in whole-blood samples of patients with pneumococcal pneumonia may be a useful tool as an aid to clinical judgment to identify patients at risk for poorer outcomes. In a cohort of patients with CAP, a multivariate analysis adjusted for age, sex, comorbidities, and pneumonia severity index identified bacterial load as associated independently with septic shock and the need for mechanical ventilation.[44] In this study, a bacterial load of $\geq 10^3$ copies/mL was associated with a significantly higher risk for septic shock, need for mechanical ventilation, and hospital mortality. More studies are needed to define the exact role and the cost-effectiveness of this technique in the management of patients with IPD.

THERAPY OF PNEUMOCOCCAL INFECTIONS

Nowadays, the main problem we have to deal with when treating pneumococcal infections is probably not the lack of effective antibiotics but the need to improve adjuvant strategies to decrease mortality. Taking into account that prospective trials have been unable to associate discordant penicillin treatment with an adverse outcome and the lack of documentation of penicillin failures, particularly when aminopenicillins are administered at adequate dosages, it seems reasonable to consider penicillin and amoxicillin as the drugs of choice to treat pneumococcal pneumonia. In the same way, treatment of IPD in adults with currently used doses of ceftriaxone, cefotaxime, or cefepime should be effective against all but the most highly resistant isolates with MIC > 8 μg/mL. Fluorquinolones are an excellent alternative therapy for patients with pneumococcal pneumonia, even for those caused by highly resistant pneumococcal strains with MIC > 2 μg/mL to penicillin.[45]

Nevertheless, there are still several issues that deserve to be explored in the field of treatment of IPD. One question that should be defined is the role of combination therapy with macrolides. Some observational studies suggest that outcomes of patients with bacteremic pneumococcal pneumonia and severe sepsis or shock might be improved with combination therapy with β-lactams plus macrolides.[46] Despite some methodological limitations, the findings of most published clinical studies point to a trend that has to be explored more thoroughly by additional prospective clinical treatment studies. The interaction between antibiotic agents with respect to the modulation of the immune response to pneumococcal infection may play an important role and may be a plausible explanation for the observed benefit of macrolides.

The potential role of an inappropriate inflammatory response triggered by *S. pneumoniae* in the early deaths in patients with pneumococcal pneumonia has led to investigations of the utility of different anti-inflammatory agents to decrease the early mortality associated with pneumococcal pneumonia. Recent studies suggest that statins and angiotensin-converting enzyme inhibitors may have beneficial effects for some types of infections. Statins have potent anti-inflammatory effects in laboratory studies of pulmonary inflammation and some observational studies have suggested that they might have beneficial effects for some types of infections. However, a recent published multicenter cohort study of 1895 patients hospitalized with CAP did not find evidence of a protective effect for statin use on clinical outcomes.[47] The main problem with the interpretation of non-randomized studies is the possibility of bias that could affect the results. This is why randomized-controlled trials are needed to examine whether the use of adjunctive medications, such as statins and angiotensin-converting enzyme inhibitors, in patients hospitalized with pneumococcal infections may be beneficial.

Corticosteroids would theoretically be a good option as an adjunctive therapy for pneumococcal infections with the aim of reducing the excess systemic and pulmonary inflammation, which might translate to an improved outcome. However, in 2 recent well-designed placebo-controlled trials that involved more than 500 patients hospitalized with CAP, corticosteroids failed to show a relevant clinical efficacy.[48,49]

Further research not only for new antibiotics but also for adjuvant therapies should focus on patients with high predicted mortality. These patients should be predominant in clinical trials to assess new strategies for the treatment of severe IPD.

PNEUMOCOCCAL VACCINATION

Epidemiologic data indicate the need to improve vaccination policies and to achieve better control than we actually do with respect to overall pneumococcal disease prevention, especially among adults. Why is it mandatory to expand the use of the actual pneumococcal vaccines? There are several reasons that can be provided. First, pneumococcal infections, especially pneumococcal pneumonia, cause a high morbidity and mortality worldwide, especially in older patients and in those with underlying diseases or immunosuppression. Second, the average mortality has not changed significantly in the last 50 years despite advances in antimicrobial therapy. Third, pneumococcal infections are evolving infections with new emerging serotypes that cause new clinical patterns of infection. Finally, the emergence of new serotypes as a consequence of the replacement phenomenon caused by the widespread use of conjugate vaccines, with a limited number of serotypes included, may lead to the increase in the number of pneumococcal infections caused by serotypes with resistance to available antibiotics, and why is it important to encourage investigation on new vaccines and preventive strategies? We can answer this question with another question. If a replacement phenomenon was produced after the widespread use of

the PCV7 with the emergence of new serotypes, why cannot the same phenomenon be produced after the use of the 13-valent pneumococcal conjugate vaccine (PCV13)?

The history of pneumococcal vaccines is long. The first steps in this history were the development of the 6-valent and 14-valent polysaccharide vaccines, but it was not until 1983, with the approval of the current PPV23, that there was a significant impact on prevention of pneumococcal infections.[50] The second important step occurred in 2001 when the first PCV7 was licensed. The history of pneumococcal vaccines continued in 2009 with the 10-valent conjugate vaccine and today with the PCV13.

One of the main problems with polysaccharide vaccines is that polysaccharides are not good vaccine antigens because they trigger a limited immune response. It is only a B-cell response with a short durability and a lack of immunologic memory; thus, they have no booster effect to enhance the immune response with repeated vaccination. An additional drawback is that infants do not respond to polysaccharide vaccines because they do not have these specific B cells.

We have had the PPV23 almost for 30 years, but still there are no definite data on its effectiveness. Data on the effectiveness of PPV23 are conflicting and subject to personal interpretations. In response to the question of whether the PPV23 protects against pneumococcal disease, one author says yes, citing a 2008 Cochrane analysis, whereas another says no, citing another meta-analysis carried out in 2009.[50–53] Different studies have shown that the PPV23 reduces the risk of IPD in immunocompetent elderly patients, but neither observational studies nor clinical trials have shown consistent evidence for a reduction in the incidence of pneumonia in vaccinated adults.[51] Data on the utility of this vaccine in patients at higher risk for pneumococcal infections, such as those with immunosuppressive conditions, are even more scarce.[52]

Despite these doubts, in February 2012, the CDC recommended vaccination with PPV23 to all individuals with the following indications: individuals aged 65 years or older without a history of previous PPV23 administration. Adults younger than 65 years should be vaccinated if they have any of the following conditions: chronic lung disease (including asthma), chronic cardiovascular diseases, diabetes mellitus, chronic liver diseases, cirrhosis, chronic alcoholism, functional or anatomic asplenia, immunocompromising conditions, cochlear implants, and cerebrospinal fluid leaks. Residents of nursing homes or long-term care facilities and individuals who smoke cigarettes should also be vaccinated.[54] One-time revaccination after 5 years is recommended for individuals aged 19 through 64 years with chronic renal failure or nephrotic syndrome, functional or anatomic asplenia, and for individuals with immunocompromising conditions. For individuals aged 65 years and older, one-time revaccination is recommended only if they were vaccinated 5 or more years previously and were younger than 65 years of age at the time of primary vaccination.[54]

The basis of the conjugated vaccines is the combination of the capsular polysaccharide with specific carrier proteins. When the carrier proteins are linked to the polysaccharide, they will be able to induce a T-cell mediated response, thus leading to the potential for a memory response and a mucosal response. The advantages of conjugated vaccines over polysaccharide vaccines are as follows: (1) they induce an effective stimulation of antibodies in infants; (2) they are able to develop an immune memory stimulation, with a booster effect that leads to a prolonged duration of protection; and (3) they have the potential of reduction of nasopharyngeal carriage that will also contribute toward the herd effect.

The utility of the PCV7 in adults has been paradoxically devalued because of its success in children and the herd effect produced in adults. The reductions in the risk of disease in the elderly population after the widespread use of PCV7 in children were attributable to decreases in the transmission of vaccine strains in the population. As a consequence, the potential benefit derived from vaccination with the PCV7 has also decreased because older adults are now at lower risk of acquiring infections caused by the 7-valent vaccine serotypes.

The development of the PCV13 may solve part of this problem because it includes all the 7-valent vaccine serotypes and also some of the emergent serotypes (1, 3, 5, 6A, 7F, and 19A).

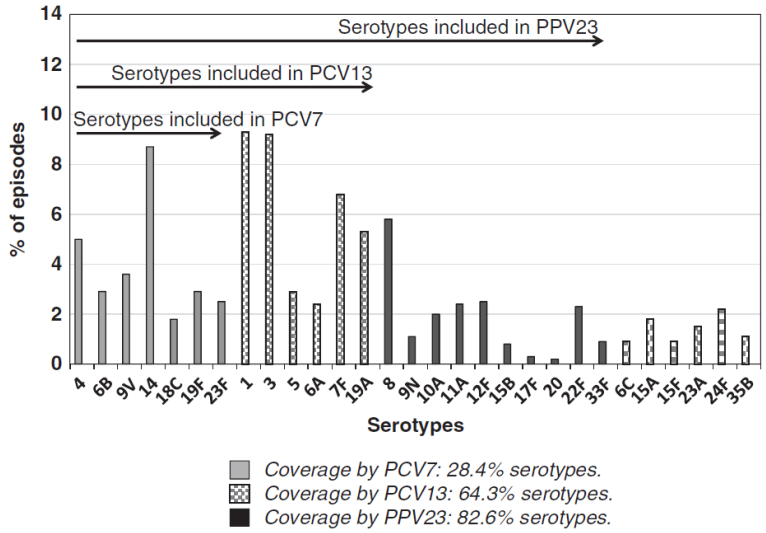

FIGURE 1. Serotype distribution in cases of IPD in adults. Data obtained from the database of Hospital Vall d'Hebron Barcelona (965 patients). IPD indicates invasive pneumococcal disease; PCV7, 7-valent pneumococcal conjugate vaccine; PCV13, 13-valent pneumococcal conjugate vaccine; PPV23, 23-valent pneumococcal polysaccharide vaccine.

PCV13 currently is recommended as a 4-dose series for children, starting at the age 2 months. Recently, the Food and Drug Administration also approved PCV13 for prevention of pneumonia and invasive disease caused by PCV13 serotypes among adults aged 50 years and older.[55] On June 20, 2012, the Advisory Committee on Immunization Practices recommended routine use of PCV13 for adults aged 19 years and older with immunocompromising conditions, functional or anatomic asplenia, cerebrospinal fluid leaks, or cochlear implants. PCV13 should be administered to eligible adults in addition to the PPV23.[56] However, these approvals were based mainly on studies that measured the antibody response against the vaccine.

The actual situation is that there are 2 pneumococcal vaccines available for adults, both recommended by the current guidelines. How should clinicians choose between them? Clinical efficacy measured by the reduction in disease incidence would be the argument to make this decision. PCV13 is actually the subject of a randomized clinical trial in adults from the Netherlands. Unfortunately, this study will not answer the question of whether PCV13 provides better protection than PPV23 in adults because this study does not include a control group of individuals who received the PPV23.[57]

An additional issue of concern arises from an epidemiological study of cases of IPD in older adults carried out in Spain. In this study, PCV13 serotypes accounted for only 59.3% of isolates.[58] The most frequent non-PCV13 serotypes were serotypes 16F (4.5%), 22F (3.6%), 24F (3.3%), and 6C (2.1%), and the incidence of IPD caused by 2 of the non-PCV13 serotypes increased compared with a previous period. The problem that arises with this observation is that the replacement phenomenon could emerge again after the widespread use of the PCV13. Figure 1 shows the serotype distribution in cases of IPD in adults in our hospital from 1996 to 2012.

In conclusion, prevention of pneumococcal infections continues to be a challenge. It is certain that we now have some answers, but undoubtedly, new questions have arisen. Because *S. pneumoniae* is an evolving microorganism, until we have an effective and universal vaccine with coverage against all pneumococcal serotypes, the replacement phenomenon may reappear.

GOALS FOR THE FUTURE

The most important goal should undoubtedly be to decrease mortality of patients with IPD. The average mortality rate of IPD and CAP was described to be around 12% in the 1950s.[59] Since then, we have not been able to change it. As an example, in a recently published observational study carried out in our institution of 653 adults with invasive pneumococcal pneumonia, the overall mortality was around 15% between 1996 and 2001 and continued to be 17% between 2005 and 2009.[5]

In the United States, it has been postulated that the objective for healthy individuals in 2020 is to decrease the incidence of IPD from 19 to 12 cases per 100,000 in individuals younger than 5 years of age and from 36 to 31 per 100,000 in individuals aged 65 and older.[2] Vaccination could probably be a new avenue if we have more effective vaccination strategies to change this. However, actually, we also have to deal with some economic and financial issues in terms of the opportunity to introduce novel vaccines into clinical practice.

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Enferm Infecc Microbiol Clin. 2011;29(4):247–249

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Editorial

Neumonía neumocócica: cambios epidemiológicos, diagnósticos y terapéuticos

Pneumococcal pneumonia: epidemiological, diagnostic and therapeutic changes

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A pesar de que fue descubierto hace más de 100 años y de que hace más de 50 que disponemos de un tratamiento antibiótico eficaz, *Streptococcus pneumoniae* continua siendo el agente causal de un gran número de infecciones, fundamentalmente neumonías, potencialmente graves que continúan provocando en la actualidad una elevada morbilidad y mortalidad incluso en países desarrollados. Prueba de ello se encuentra en los datos que proporciona el estudio realizado por Payeras et al[1] y que se publica en este número de la revista. En este estudio prospectivo realizado entre los años 2006-2009 se presentan datos de 346 episodios de neumonía neumocócica, 335 de los cuales se producen en adultos. Un primer aspecto importante de este estudio es que las cifras de mortalidad se acercan al 10%. Estas elevadas cifras de mortalidad, teniendo en cuenta que sólo el 37% de los pacientes tenían bacteriemia, reflejan la realidad de la gravedad de la neumonía neumocócica. En nuestro medio estas cifras de mortalidad llegan a ser superiores al 20% en determinados pacientes, como los ancianos o pacientes inmunodeprimidos, con neumonía neumocócica bacteriémica[2]. Todo ello a pesar de los indudables progresos que se han producido en el diagnóstico de la neumonía neumocócica, de los diversos antibióticos altamente eficaces de que disponemos y de las grandes mejoras que se han producido en las terapias de soporte intensivo. De hecho, ya en 1964 Austrian et al[3] observaron que la mortalidad precoz en la neumonía neumocócica no dependía de la instauración de un tratamiento antibiótico adecuado. Desgraciadamente, este hecho sigue siendo vigente en la actualidad. Probablemente, muchas de las muertes fulminantes que se producen en las primeras horas están en relación con una respuesta inflamatoria exuberante e inapropiada por parte del huésped desencadenada por el microorganismo más que a la propia acción virulenta del microorganismo. Por tanto, la lucha contra la infección neumocócica debe basarse en distintos frentes. En primer lugar, debemos utilizar de forma racional los distintos antibióticos de que disponemos. En segundo lugar debemos explorar e investigar en la utilización de medidas que permitan controlar y modular la respuesta inflamatoria inicial. Por último, y no por ello menos importante, debemos desarrollar nuevas estrategias adecuadas de prevención mediante programas de vacunación.

Precisamente, uno de los pilares básicos en la lucha contra la infección neumocócica invasiva debe basarse indudablemente en su prevención. Esta concienciación de prevención está muy arraigada en Estados Unidos, donde se calcula que aproximadamente el 67% de los adultos mayores de 65 años han recibido al menos una dosis de la vacuna neumocócica polisacárida 23-valente (VNPS-23 V). Sabemos que la vacuna actualmente recomendada en adultos, la VNPS-23 V, tiene importantes limitaciones. Probablemente, tiene un cierto grado de eficacia en la protección frente a la neumonía bacteriémica en personas inmunocompetentes de edad avanzada[4]. Sin embargo, no se ha demostrado que tenga un impacto significativo sobre el riesgo de neumonía en general, tanto en adultos jóvenes como ancianos con enfermedades de base. Por dicho motivo, las noticias que llegaban de Estados Unidos sobre un efecto protector de la vacuna neumocócica conjugada 7-valente (VNC-7 V) frente a la infección neumocócica resultaron inicialmente muy esperanzadoras. De hecho, tras la introducción de la VNC-7 V en Estados Unidos se produjo una disminución en la incidencia de infecciones neumocócicas invasivas tanto en niños como en adultos como consecuencia del efecto de inmunidad de grupo. A pesar de que se observó un aumento en la incidencia de infecciones causadas por serotipos no vacunales, la gran disminución en las infecciones causadas por serotipos incluidos en la VNC-7 V provocó una reducción significativa en la incidencia global de infección neumocócica invasiva en adultos en Estados Unidos en todos los grupos de edad incluso 7 años después de la introducción de la VNC-7 V[5].

Lamentablemente, y como sucede en otros ámbitos de la medicina, los fenómenos que se producen en Estados Unidos no pueden ni deben ser necesariamente extrapolados a otros medios como el nuestro. En Francia, la vacuna conjugada se introdujo en el año 2003 y en el año 2006 se constató un aumento significativo de la incidencia de bacteriemia neumocócica en adultos mayores de 16 años[6]. En Holanda y en España se han observado fenómenos similares. En Barcelona, entre los años 1997 y 2007 se produjo un significativo aumento del 40% en la incidencia de infección neumocócica invasiva en adultos, especialmente en adultos jóvenes. Ello se produjo fundamentalmente a expensas de un aumento del 81% en la incidencia de infección neumocócica invasiva causada por serotipos no vacunales en el período posvacunal tardío[7]. Posiblemente, el hecho de que la cobertura vacunal tanto en niños como en adultos sea sensiblemente inferior en nuestro medio explique en parte estas diferencias entre lo que sucede en Estados Unidos y Europa.

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doi:10.1016/j.eimc.2011.01.005

Desde el punto de vista del impacto clínico, se han publicado diversos artículos que indican que en los últimos años se está produciendo un aumento en el número de niños con neumonía neumocócica que desarrollan complicaciones supuradas, principalmente empiemas. Sin embargo, se conoce poco sobre las consecuencias clínicas en adultos del cambio que se está produciendo en los serotipos de neumococo causantes de neumonía. En este sentido, el trabajo realizado por Payeras et al[1] nos aporta una serie de datos interesantes. Es importante y necesario antes de comentar estos resultados mencionar que el estudio, tal como comentan ya los autores en la discusión, presenta algunas limitaciones que impiden generalizar sus conclusiones. Una de ellas es el bajo porcentaje de casos de los que se dispone del serotipo. Por otra parte, al ser un estudio realizado en la época en que ya se había implantado la VNC-7 V no permite realizar comparaciones que permitan conocer la importancia de los cambios clínicos con respecto a la época prevacunal. En este trabajo, igual que en otros estudios epidemiológicos más amplios ya publicados en nuestro medio, se comprueba una vez más que los serotipos no incluidos en la VCN-7 V son los que causan neumonía neumocócica con mayor frecuencia. Este cambio se produce incluso teniendo en cuenta que las tasas de vacunación, a pesar de que fueron aumentando anualmente, eran sólo de 246/1.000 niños menores de 5 años al final del período del estudio. El hecho de que se produzcan cambios microbiológicos y epidemiológicos a pesar de que un porcentaje importante de niños no están vacunados habla de la importancia que tiene la inmunidad de grupo.

Otro aspecto relevante a nuestro entender es que prácticamente el 45% de los episodios se produjeron en pacientes < 65 años. No sólo el número de casos en los adultos más jóvenes es elevado, sino que parece que los adultos jóvenes desarrollan más complicaciones supuradas. Así, la media de edad de los pacientes que desarrollaron empiema fue significativamente menor que la de los que no presentaron esta complicación, manteniéndose incluso estas diferencias al eliminar del análisis los pacientes pediátricos. Además, aunque sin alcanzar significación estadística, había una tendencia a presentar mayor riesgo de bacteriemia entre los pacientes < 65 años y el porcentaje de pacientes < 65 años que desarrollaron shock séptico fue mayor que en el grupo de más edad. De hecho, entre las variables asociadas al desarrollo de shock séptico en el análisis multivariado estaba la edad < 65 años.

¿Por qué parece que está aumentando la incidencia de infección neumocócica en adultos jóvenes? Una explicación podría estar en relación con la emergencia de infecciones causadas por serotipos no vacunales. Algunos de ellos, como los serotipos 1 y 7F, son serotipos más invasivos, con una mayor tendencia a afectar a población más joven previamente sana[8]. Otro aspecto que se debe considerar es que la vacuna polisacárida se ha administrado de manera más o menos generalizada entre los adultos > 65 años, con lo cual les ha ofrecido un cierto grado de protección frente a la infección neumocócica, mientras que los adultos < 65 años no han contado con esta protección.

Desde el punto de vista del tratamiento de la neumonía neumocócica queremos destacar la vigencia actual de los betalactámicos en general, y la penicilina o amoxicilina en particular, como tratamiento antibiótico de elección. A pesar de la numerosa literatura médica existente relativa a la resistencia de neumococo a la penicilina, lo cierto es que en la actualidad, especialmente tras la revisión de los puntos de corte que determinan la sensibilidad a la penicilina en el tratamiento de la neumonía neumocócica, podemos afirmar que la penicilina utilizada a las dosis adecuadas continua siendo el tratamiento de elección en la neumonía neumocócica[9]. Este aspecto también queda reflejado en el estudio de Payeras et al[1], en el que, utilizando los puntos de corte actualmente establecidos, prácticamente el 100% de los pacientes tenían una neumonía causada por un neumococo sensible a la penicilina.

Si bien parece que los cambios epidemiológicos y clínicos que se están produciendo en la infección neumocócica están en parte relacionados con el reemplazamiento en los serotipos de neumococo, sería un error no considerar otros fenómenos sociales, demográficos, epidemiológicos y microbiológicos que también se han producido en estos años. Desde el punto de vista sociodemográfico, se ha producido un gran incremento de la población inmigrante. Muchos de estos inmigrantes proceden de áreas, como África subsahariana, donde la incidencia de infección neumocócica es muy elevada, con lo que pueden haber contribuido en parte a estos cambios. Por otra parte, el incremento en el número de pacientes que tienen mayor riesgo de tener una infección neumocócica, como los que padecen enfermedades crónicas o los inmunodeprimidos, y el aumento en la esperanza de vida de la población condicionan tanto un aumento en la población sometida a riesgo de infección neumocócica como que estén en riesgo durante mayor tiempo. Por último, se han descrito oscilaciones epidémicas en los distintos serotipos que podrían contribuir a la existencia de cambios cíclicos en el espectro de los serotipos de neumococo causantes de infección.

A principios del 2010, tanto la Agencia Europea del Medicamento como la US Food and Drug Administration aprobaron la nueva vacuna neumocócica conjugada 13 valente para la prevención en lactantes y niños pequeños de la enfermedad neumocócica invasiva, así como la neumonía y otitis media aguda, causadas por los 13 serotipos de *Streptococcus pneumoniae* incluidos en ella. Esta vacuna incluye los 13 serotipos que causan con mayor frecuencia enfermedad neumocócica. Siete de estos serotipos (4, 6B, 9 V, 14, 18C, 19F y 23F) estaban ya incluidos en la VNC-7 V. Los seis serotipos adicionales (1, 3, 5, 6A, 7F y 19A) son causantes de la mayoría de infecciones en la actualidad, en particular el serotipo 19A, que es actualmente muy prevalente en varias regiones del mundo y que está generalmente asociado con resistencia a los antibióticos. La eficacia de esta vacuna para proteger a los niños de las infecciones causadas por serotipos incluidos en la vacuna está fuera de toda duda, pero su utilización generalizada abre la puerta a nuevos interrogantes. ¿Se producirá un nuevo reemplazamiento de los serotipos que colonizan la faringe de los niños apareciendo infecciones por serotipos que en la actualidad no tienen protagonismo?, ¿conllevará ello nuevos cambios en la presentación clínica tanto en niños como en adultos?, o bien ¿se producirá realmente un descenso en la colonización e infección por neumococo pero acompañado de un reemplazo por otros microorganismos?

En definitiva, parece claro que la lucha contra la infección neumocócica es un proceso dinámico. *Streptococcus pneumoniae* ha demostrado tener una gran capacidad de adaptación, tanto a la irrupción de los antibióticos desarrollando resistencias como a la de las vacunas dando lugar a cambios ecológicos en la distribución de los distintos serotipos causales de infección. En los últimos años hemos conseguido algunas victorias parciales como el reciclaje de la penicilina como tratamiento de elección. Sin embargo, en el campo de la prevención quedan todavía muchas batallas por librar. Sin duda, es imprescindible continuar y mejorar los programas de vigilancia activa epidemiológica, microbiológica y clínica para poder valorar el efecto en los adultos de la nueva vacuna conjugada.

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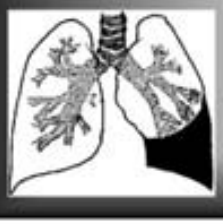

A Publication of the International Pleural Network

Volume 9 Issue 4
October 2011

Parapneumonic effusions

Pneumococcal Empyema

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Pneumococcal empyema is one of the most common complication of pneumococcal pneumonia as well as an important cause of morbidity and mortality worldwide. In the pre-antibiotic era, empyema involved 5% of pneumonia cases, but with the development of antibiotics the rate declined to 2%. In recent decades, the incidence of empyema has started increasing worldwide.

At the beginning of the 21st century, the heptavalent pneumococcal conjugate vaccine (PCV7), which protects against 7 of the most common pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), was introduced in practice to prevent pneumococcal infections in children, a high risk population for the disease. Its widespread use has been accompanied by substantial reductions in the occurrence of the disease caused by those serotypes. But, a dynamic process of replacement seems to have occurred and the incidence of pneumococcal infections caused by non-PCV7 serotypes has increased[1]. Although the vaccine was beneficial in decreasing the overall incidence of pneumococcal disease in children, such an effect was not observed for pneumococcal empyema. In fact, different studies have reported a 2 to 5-fold increase in rates of empyema in children after the introduction of PCV7[2,3]. This change was associated with the emergence of serotypes 1 and 3, none of which were included in the PCV7. Similarly, a striking increase

in the incidence of adult pneumococcal empyema has been reported, especially in those aged 18-50 years, from 7.6% in the pre-vaccine period to 14.9% in the post. The emergence of serotype 1 now causes more than 40% of empyemas in adults[4].

The reasons for the high tendency of pneumococcal serotypes 1 and 3 to develop empyema are not well understood. As *Streptococcus pneumoniae* strains differ in their abilities to cause invasive disease, it is possible that those strains which are isolated in cases of empyema contain virulence genes that confer an increased ability to invade the pleural space.

The increase in the incidence of pneumococcal empyema, in both children and adults, cannot be easily explained as just a vaccine effect. Temporal trends in pneumococcal serotype distribution were described worldwide, with epidemic increases of the frequency of serotype 1, before the implementation of PCV7[5,6].

In the future, information provided by the use of the 13-valent pneumococcal conjugated vaccine, which contains serotypes 1 and 3, may help us to better understand the exact role that PCV7 has played in the epidemiology of pneumococcal empyema, and could be an important step in the prevention of this complication.

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Chest Radiographs in Detecting Parapneumonic Effusions

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Bacterial pneumonia affects up to 4 million Americans annually in the community, with an additional 195,000 - 390,000 nosocomial infections[1]. One of the most frequent complications encountered amongst these patients is parapneumonic effusions (PPEs). Of the one million patients hospitalized with community-acquired pneumonia (CAP) each year, 44%-57% have an associated PPE[2]. Up to 10% of all patients with PPEs require operative intervention so it is important to quickly recognize this complication and treat it appropriately[3]. Physicians frequently rely on portable anteroposterior (AP) chest x-rays (CXRs), which can be of poor quality, to identify pneumonia and PPEs. It is unknown what percentage of significant effusions (those greater than 10 mm) is missed in patients having CAP by CXR alone.

A recent retrospective study performed at a single, large academic center evaluated the accuracy of CXRs in identifying PPEs[4]. Specifically, the authors studied lateral, postero-anterior (PA), and AP CXRs in patients with clinical and radiographic evidence of pneumonia that had had a chest CT (within 24 hours of their CXR) confirming the presence of a pleural effusion thought to be parapneumonic in nature. Interestingly, they found that all three views were equally poor in that they all missed more than 10% of PPEs. The sensitivity of lateral, PA, and AP CXRs was 85.7%, 82.1%, and 78.4%, respectively ($p = 0.749$); the specificity was 87.5%, 81.3%, and 76.4% ($p = 0.198$). As would be expected, the smaller effusions were missed more often that the larger in all three views. However, the three views combined missed 13% of effusions whose sizes were significant enough to warrant diagnostic thoracentesis. Individually, AP CXRs missed 12% of effusions > 10 mm, PA CXRs missed 16%, and lateral CXRs missed 12%.

One would have expected lateral CXRs to be more sensitive than PA and AP in detecting PPEs. The majority of effusions missed in each view were on films with lower lobe parenchymal consolidation adjacent to the hemidiaphragm, on the same side as the effusion. These results suggest that in the setting of pneumonia, the usual advantages of lateral and PA films in detecting pleural effusions[5,6] are lost if there is obscuration of the costophrenic angle from pulmonary consolidation. Since lower lobe pneumonia was present in the majority of CXRs that missed effusions in this study, it may be beneficial to obtain a thoracic ultrasound or chest CT in those patients. Thoracic ultrasound is increasingly being utilized to evaluate effusions given its bedside capability, lack of ionizing radiation, immediate return of information, superior sensitivity and specificity in identifying pleural effusions, and ability