

CONCLUSIONES

1. Los pacientes con infección por VIH con un recuento de linfocitos T CD4+ superior a 200 elementos/ml presentan globalmente una respuesta serológica de anticuerpos específicos IgG frente a la vacuna neumocócica inferior a la de los controles sanos de forma significativa. Sin embargo, un tercio de los pacientes producen una respuesta adecuada totalmente superponible a la de los controles sanos independiente del número de linfocitos T CD4+.
2. A pesar de que la respuesta serológica es inferior en los pacientes con infección por VIH, en el seguimiento realizado durante 5 años, no se ha constatado ningún episodio de infección neumocócica. Por lo tanto, creemos que, dada la elevada incidencia de la enfermedad y la inocuidad de la vacuna neumocócica, ésta se debe recomendar a los pacientes con infección por VIH.
3. Hemos observado que se produce un rápido descenso de los títulos de anticuerpos específicos antineumocócicos, de modo que a los 3 años, y de forma global, los títulos han retornado a los niveles basales. Por ello creemos que se debería considerar la revacunación en un periodo no superior a los 3 años.

RESUMEN

Los pacientes con infección por VIH presentan una inmunodepresión debida en su mayor parte a una deficiencia cuantitativa y cualitativa de sus linfocitos T CD4+ aunque también se observan alteraciones en la respuesta de los linfocitos B y en el funcionamiento de monocitos y neutrófilos. De todo ello se deriva una mayor susceptibilidad a las infecciones neumocócicas. Así, la incidencia de neumonía neumocócica es 6 veces mayor a la población normal y con mayor propensión a la bacteriemia y a la recurrencia, y la incidencia de bacteriemia aumenta hasta 100 veces. La distribución por serotipos es similar a la de la población normal aunque existe una mayor frecuencia de cepas con resistencia elevada a la penicilina lo cual influye en un peor pronóstico. Más del 80% de los serotipos que causan enfermedad en esta población están contenidos en la vacuna 23-valente polisacárida.

Un reducido número de estudios indican que la intensidad de la respuesta a la vacuna y el número de pacientes respondedores es inferior a la población adulta sana y que el título de anticuerpos desciende con el paso del tiempo. Además se han comunicado casos de pacientes vacunados que posteriormente han desarrollado una enfermedad neumocócica provocada por uno de los serotipos contenidos en la vacuna. Se ha observado que los pacientes que reciben tratamiento antirretroviral pueden mejorar su respuesta inmunitaria, si bien, por otra parte la vacunación se ha asociado con incrementos transitorios de la carga viral. Finalmente, ni la revacunación ni la utilización de vacunas conjugadas han supuesto una mejoría de la respuesta en este tipo de pacientes.

Dado que existen escasos estudios que evalúen la respuesta serológica en estos pacientes a largo plazo y que sigan la aparición de enfermedades neumocócicas creímos de interés diseñar un estudio clínico y serológico prospectivo con los objetivos de:

- comparar la respuesta inmunitaria de los pacientes con infección por VIH frente a la población sana,
- evaluar la persistencia de la misma a lo largo del tiempo, y
- valorar la aparición de infecciones neumocócicas en los pacientes vacunados.

Para ello constituimos un grupo de estudio de 60 pacientes con infección por VIH con un recuento de linfocitos T CD4+ superior a 200 elementos/ml y un grupo control constituido por 39 individuos sanos que fueron vacunados con la vacuna 23-valente polisacárida. Se extrajeron muestras de sangre previo, al mes, seis, y treinta y seis meses de la vacunación. El seguimiento clínico se realizó a través de la historia clínica proveniente de la consulta ambulatoria. Para la medición de la respuesta serológica se utilizó una técnica de ELISA modificada estandarizada en nuestro centro. Se consideró a un paciente como respondedor a aquél que desarrolló una respuesta serológica adecuada según unos parámetros previamente establecidos.

Los principales resultados obtenidos los podemos resumir de la siguiente manera:

1. Al mes los controles sanos presentaban una respuesta global significativamente superior a los pacientes con infección por VIH, a pesar de lo cual un tercio desarrollaban una respuesta serológica similar a los controles sanos.
2. La respuesta serológica a la vacunación no se relacionaba con la cifra de linfocitos T CD4+ ni con el nivel de IgG2 basal entre los pacientes con infección por VIH respondedores o no respondedores.
3. A los 6 meses el título de anticuerpos era significativamente superior al basal pero también significativamente inferior respecto a las 4 semanas en los pacientes con infección por VIH.
4. A los 3 años los títulos de anticuerpos en los pacientes con infección por VIH eran similar a los valores basales.
5. Se presentaron 6 casos de neumonía. En los primeros 2 años de seguimiento sólo se objetivó una neumonía y fue debida a *H. influenzae*. En ningún caso se pudo demostrar la etiología neumocócica ni por hemocultivo ni por cultivo de esputo.

En resumen, y como conclusiones de nuestro estudio podemos decir:

1. Los pacientes con infección por VIH presentan globalmente una respuesta serológica de anticuerpos específicos IgG frente a la vacuna neumocócica inferior a la de los controles sanos. Sin embargo, un tercio de los pacientes con infección por VIH producen una respuesta adecuada totalmente superponible a la de los controles sanos.
2. En nuestro seguimiento realizado durante 5 años no se ha constatado ningún episodio de infección neumocócica. Por lo tanto, creemos que, dada la elevada incidencia de la enfermedad y la inocuidad de la vacuna neumocócica, ésta se debe recomendar a los pacientes con infección por VIH.
3. También hemos observado que se produce un rápido descenso de los títulos de anticuerpos de modo que a los 3 años los títulos han retornado a los niveles basales. Por ello creemos recomendada la revacunación en un periodo no superior a los 3 años.

Estudios futuros deberán determinar cuál es la respuesta en los pacientes con infección por VIH que reciben TARGA (terapia antirretroviral de gran actividad) e intentar dilucidar previamente a la administración de la vacuna que pacientes serán aquéllos que responderán correctamente a la vacunación de cara a plantear la revacunación.

BIBLIOGRAFIA

1. Watson DA, Musher DM, Jacobson JB, Verhoef J. A brief history of the pneumococcus in biomedical research: a panoply of scientific discovery. *Clin Infect Dis* 1993;17:913-924.
2. Winkelstein JA, Tomasz A. Activation of the alternative complement pathway by pneumococcal cell wall teichoic acid. *J Immunol* 1978;120:174-178.
3. Musher DM, Watson DA, Baughn RE. Does naturally acquired IgG antibody to cell wall polysaccharide protect human subjects against pneumococcal infection?. *J Infect Dis* 1990;161:736-740.
4. Watson DA, Musher DM, Verhoef J. Pneumococcal virulence factors and host immune responses to them. *Eur J Clin Microbiol Infect Dis* 1995;14:479-490.
5. Bruyn GA, Zegers BJ, van Furth R. Mechanisms of host defense against infection with *Streptococcus pneumoniae*. *Clin Infect Dis* 1992;14:251-262.
6. Paton JC. The contribution of pneumolysin to the pathogenicity of *Streptococcus pneumoniae*. *Trends Microbiol* 1996;4:103-106.
7. Austrian R. The Quellung reaction: a neglected microbiologic technique. *Mount Sinai Med J* 1976;43:699-709.
8. Henrichsen J, Robbins JB. Production of monovalent antisera by induction of immunological tolerance for capsular typing of *Streptococcus pneumoniae*. *FEMS Microbiol Lett* 1992;72:89-93.
9. Scott JAG, Hall AJ, Dagan R, et al. Serogroup-specific epidemiology of *Streptococcus pneumoniae*: associations with age, sex and geography in 7,000 episodes of invasive disease. *Clin Infect Dis* 1996;22:973-981.

10. Hedlund J. Should pneumococcal infections continue to be classified as a single disease? *Lancet* 1997;349:371-372.
11. Johnston RB Jr. Pathogenesis of pneumococcal pneumonia. *Rev Infect Dis* 1991;13(suppl 6):S509-S517.
12. Tuomanen EI, Austrian R, Masur HR. Pathogenesis of pneumococcal infections. *N Engl J Med* 1995;332:1280-1284.
13. Cundell D, Masur HR, Tuomanen EI. The molecular basis of pneumococcal infection: a hypothesis. *Clin Infect Dis* 1995;21:S204-S212.
14. Cohn DA, Schiffman G. Immunoregulatory role of the spleen in antibody responses to pneumococcal polysaccharide antigens. *Infect Immunol* 1987;55:1375-1380.
15. Siber GR, Schur PH, Aisenberg AC, Weitzman SA, Schiffman G. Correlation between serum IgG2 concentrations and the antibody response to bacterial polysaccharide antigens. *N Engl J Med* 1980;303:178-182.
16. Musher DM, Groover JE, Watson DA, et al. Genetic regulation of the capacity to make immunoglobulin G to pneumococcal capsular polysaccharides. *J Invest Med* 1997;45:57-68.
17. Musher DM, Groover JE, Rowland JM, et al. Antibody to capsular polysaccharides of *Streptococcus pneumoniae*: prevalence, persistence, and response to revaccination. *Clin Infect Dis* 1993;17:66-73.
18. Ekdahl K, Ahlinder I, Hansson H, et al. Duration of nasopharyngeal carriage of penicillin-resistance *Streptococcus pneumoniae*: experiences from the South Swedish pneumococcal intervention project. *Clin Infect Dis* 1997;25:1113-1117.

19. Ambrosino DM, Schiffman G, Gotschlich EC, et al. Correlation between G2m(n) immunoglobulin allotype and human antibody response and susceptibility to polysaccharide encapsulated bacteria. *J Clin Invest* 1985;75:1935-1942.
20. Subdirección general de prestaciones y evaluación de tecnologías sanitarias. Ministerio de Sanidad y Consumo. Informe sobre vacuna neumocócica. *Med Clin (Barc)* 1994;102:383-386.
21. García de Lomas J. Grupo Español para Vigilancia de Patógenos Respiratorios. Situación epidemiológica actual y resistencia de los patógenos respiratorios en España. *Med Clin (Barc)* 1998;110(Supl. 1):44-51.
22. Anonymous. Guidelines for the initial management of adults with community-acquired pneumonia: diagnosis, assesment of severity and initial antimicrobial therapy. *Am Rev Respir Dis* 1993;198:1418-1426.
23. Boersma WG, Lowenberg A, Holloway Y, et al. The role of antigen detection in pneumococcal carriers: a comparison between cultures and capsular antigen detection in upper respiratory tract secretions. *Scand J Infect Dis* 1993;25:51-56.
24. Sánchez F, Prats G, Garau X, et al. Vacuna antineumocócica. En: Salleras, L (Ed.). *Vacunaciones preventivas. Principios y aplicaciones*. Masson, Barcelona 1997;259-286.
25. Hansman D, Morris S. Pneumococcal carriage amongst children in Adelaide, South Australia. *Epidemiol Infect* 1988;101:411-417.
26. Gray BM, Dillon HC Jr. Natural history of pneumococcal infections. *Pediatr Infect Dis J* 1989;8:S23-S25.

-
27. Macfarlane JT, Ward MJ, Finch RG, et al. Hospital study of adult community-acquired pneumonia. *Lancet* 1982;2:255-258.
 28. Del Beccaro MA, Memdelman PM, Inglis AF, et al. Bacteriology of acute otitis media: a new perspective. *J Pediatr* 1992;120:81-84.
 29. Kim P, Musher DM, Glezen WP, et al. Association of invasive pneumococcal disease with season, atmospheric conditions, air pollution, and the isolation of respiratory viruses. *Clin Infect Dis* 1996;22:100-106.
 30. Centers for Disease Control. Recommendations of the Advisory Committee on Immunization Practices (ACIP). Prevention of Pneumococcal Diseases. *MMWR* 1997;46 (RR 8):1-24.
 31. Klein JO. Epidemiology of otitis media. *Pediatr Infect Dis J* 1989;8:S91.
 32. Berman S. Otitis media in developing countries. *Pediatrics* 1995;96:126-131.
 33. Jokinen C, Heiskanen L, Juvonen H, et al. Incidence of community-acquired pneumonia in the population of four municipalities in eastern Finland. *Am J Epidemiol* 1993;137:977-988.
 34. Falcó V. Estudio clínico de las neumonías extrahospitalarias en un hospital universitario. Tesis doctoral. Universidad Autónoma de Barcelona. 1992.
 35. Vaqué J, Roselló J, Trilla A, et al. Nosocomial infections in Spain: results of five nationwide serial prevalence surveys (EPINE project, 1990-1994). *Infect Control Hosp Epidemiol* 1996;17:293-297.
 36. Pallares R, Liñares J, Vadillo M, et al. Resistant to penicillin and cephalosporin and mortality from severe pneumococcal pneumonia in Barcelona, Spain. *N Engl J Med* 1995;333:474-480.

-
37. Breiman RF, Spika JS, Navarero VJ, et al. Pneumococcal bacteremia in Charleston County, South Carolina: a decade later. *Arch Intern Med* 1990;150:1401-1405.
 38. Dagan R, Engelhard D, Piccard E, Engelhard DC. Epidemiology of invasive childhood pneumococcal infections in Israel. *JAMA* 1992;268:3328-3332.
 39. Takala AK, Jero J, Kela E, et al. Risk factors for primary invasive pneumococcal disease among children in Finland. *JAMA* 1995;273:859-864.
 40. Gowda R, Razvi FM, Summerfield GP. Risk of pneumococcal septicaemia in patients with chronic lymphoproliferative malignancies. *BMJ* 1995;311:26-27.
 41. Molrine DC, George S, Tarbell N, et al. Antibody responses to polysaccharide and polysaccharide-conjugate vaccines after treatment of Hodgkin disease. *Ann Intern Med* 1995;123:828-834.
 42. Styrt BA. Risks of infection and protective strategies for the asplenic patient. *Infect Dis Clin Pract* 1996;5:94-100.
 43. Cullingford GL, Watkins DN, Watts AD, Mallon DF. Severe late postsplenectomy infection. *Br J Surg* 1991;78:716-721.
 44. Wong WY, Overturf GD, Powars DR. Infection caused by *Streptococcus pneumoniae* in children with sickle cell disease: epidemiology, immunologic mechanisms, prophylaxis, and vaccination. *Clin Infect Dis* 1992;14:1124-1136.
 45. García-Arenzana JM, Alcorta M, Díaz de Tuesta JL, Idigoras P, Pérez-Trallero E. Indicación de la vacuna antineumocócica en España. *An Med Interna (Madrid)* 1993;10:116-118.

-
46. Fainstein V, Musher DM, Cate TR. Bacterial adherence to pharyngeal cells during viral infection. *J Infect Dis* 1980;141:172-176.
47. Nuorti JP, Butler JC, Farley MM, et al. Cigarette smoking and invasive pneumococcal disease. *N Engl J Med* 2000;342:681-689.
48. Lipsky BA, Boyko EJ, Inui TS. Risk factors for acquiring pneumococcal infections. *Arch Intern Med* 1986;146:2179-2185.
49. Hansman D, Bullen MM. A resistant pneumococcus. *Lancet* 1967;2:264-265.
50. Jacobs MR, Koornhof HJ, Robins-Browne RM, et al. Emergence of multiply resistant pneumococci. *N Engl J Med* 1978;299:735-740.
51. Appelbaum PC. World-wide development of antibiotic resistance in pneumococci. *Eur J Clin Microbiol* 1987;6:367-377.
52. Pallares R, Gudiol F, Lanares J. Risk factors and response to antibiotic therapy in adults with bacteremic pneumonia caused by penicillin-resistant pneumococci. *N Engl J Med* 1987;317:18-22.
53. Heffelfinger JD, Dowell SF, Jorgensen JH, et al. Management of community-acquired pneumonia in the era of pneumococcal resistance: a report from the Drug-Resistance *Streptococcus pneumoniae* Therapeutic Working Group. *Arch Intern Med* 2000;160:1399-1408.
54. Latorre C, Sierra M, Lite J. Estudio prospectivo de las cepas invasivas de *Streptococcus pneumoniae* aisladas en 16 hospitales de Cataluña durante 1996. *Enferm Infecc Microbiol Clin* 1999;17:286-291.

-
55. Fenoll A, Jado I, Vicioso D, Pérez A, Casal J. Evolution of *Streptococcus pneumoniae* serotypes and antibiotic resistance in Spain: update (1990 to 1996). *J Clin Microbiol* 1998;36:3447-3454.
56. Smith AM, Klugman KP, Coffey TJ, Spratt BG. Genetic diversity of penicillin-binding protein 2b and 2x genes from *Streptococcus pneumoniae* in South Africa. *Antimicrob Agents Chemother* 1993;37:1938-1944.
57. Tomasz A. Antibiotic resistance in *Streptococcus pneumoniae*. *Clin Infect Dis* 1997;24:S85-S88.
58. Liñares J, Alonso T, Perez JL, et al. Decreased susceptibility of penicillin resistant pneumococci to twenty four betalactam antibiotics. *J Antimicrob Chemother* 1992;30:279-288.
59. Crewe-Brown HH, Karstaedt AS, Saunders GL, et al. *Streptococcus pneumoniae* blood culture isolates from patients with and without human immunodeficiency virus infection: alterations in penicillin susceptibilities and in serogroups or serotypes. *Clin Infect Dis* 1997;25:1165-1172.
60. Bédos JP, Chevret S, Chastang C, Geslin P, Régnier B, and the French Cooperative Pneumococcus Study Group. Epidemiological features of and risk factors for infection by *Streptococcus pneumoniae* strains with diminished susceptibility to penicillin: findings of a french survey. *Clin Infect Dis* 1996;22:63-72.
61. Appelbaum PC. Antimicrobial resistance in *Streptococcus pneumoniae*: an overview. *Clin Infect Dis* 1992;15:77-83.
62. Butler JC, Hofmann J, Cetron MS, et al. The continued emergence of drug-resistant *Streptococcus pneumoniae* in the United States: an update from the

-
- Centers for Disease Control and Prevention's Pneumococcal Sentinel Surveillance System. *J Infect Dis* 1996;174:986-993.
63. Nava JM, Bella F, Garau J, et al. Predictive factors for invasive disease due to penicillin-resistant *Streptococcus pneumoniae*: a population-based study. *Clin Infect Dis* 1994;19:884-890.
64. Givon-Lavi N, Dagan R, Fraser D, Yagupsky P, Porat N. Marked differences in pneumococcal carriage and resistance patterns between day care centers located within a small area. *Clin Infect Dis* 1999;29:1274-1280.
65. Musher DM. *Streptococcus pneumoniae*. In: Mandell, Douglas, Bennett, eds. Principles and practice in Infectious Diseases, Fifth edition. Churchill Livingstone, 1999:2128-2147.
66. Wright AE, Morgan W, Colbrook L, Dodgson RW. Observations on prophylactic inoculations against pneumococcus infection, and on the results which have been achieved by it. *Lancet* 1914;1:1-10, 87-95.
67. Butler JC, Shapiro ED, Carlone GM. Pneumococcal vaccines: history, current status, and future directions. *Am J Med* 1999;107(1A):S69-S76.
68. MacLeod CM, Hodges RG, Heidelberger M, Bernhard WG. Prevention of pneumococcal pneumonia by immunization with specific capsular polysaccharides. *J Exp Med* 1945;82:445-465.
69. Bruyn GAW, van Furth R. Pneumococcal polysaccharide vaccines: indications, efficacy and recommendations. *Eur J Clin Microbiol Infect Dis* 1991;10:897-910.
70. Austrian R, Gold J. Pneumococcal bacteremia with especial reference to bacteremic pneumococcal pneumonia. *Ann Intern Med* 1964;60:759-776.

-
71. Austrian R, Douglas RM, Schiffman G, et al. Prevention of pneumococcal pneumonia by vaccination. *Trans Assoc Am Phys* 1976;89:184-194.
 72. Austrian R. Pneumococcal infection and pneumococcal vaccine. *N Engl J Med* 1977;297:938-939.
 73. Riley ID, Tarr PI, Andrews M, et al. Immunization with a polyvalent pneumococcal vaccine: reduction of adult respiratory mortality in a New Guinea highlands community. *Lancet* 1977;1:1338-1341.
 74. Cano FR, Query MV, Tarrant CJ, Ritchey MB, Schiffman G. Antibody responses after immunization with polyvalent pneumococcal vaccine containing 10, 25, or 50 micrograms of 14 polysaccharide types per dose. *Proc Soc Exp Biol Med* 1983;173:57-82.
 75. Baltimore RS. New challenges in the development of a conjugate pneumococcal vaccine. *JAMA* 1992;268:3366-3367.
 76. Robbins JB, Austrian R, Lee CJ, et al. Considerations for formulating the second generation pneumococcal capsular polysaccharide vaccine with emphasis on the cross-reactive types within groups. *J Infect Dis* 1983;148:1136-1159.
 77. Nichol KL, MacDonald RM, Hauge M. Side effects associated with pneumococcal vaccination. *Am J Infect Control* 1997;25:223-228.
 78. De Stefano F, Goodman RA, Noble GR, et al. Simultaneous administration of influenza and pneumococcal vaccines. *JAMA* 1982;247:2551-2554.
 79. Monddd JJ, Vos Q, Lees A, Snapper CM. T cell independent antigens. *Curr Opin Immunol* 1995;7:349-354.

-
80. Baker PJ. Regulation of magnitude of antibody response to bacterial polysaccharide antigens by thymus-derived lymphocytes. *Infect Immun* 1990;58:3465-3468.
81. Kehrl JH, Fauci AS. Activation of human B lymphocytes after immunization with pneumococcal polysaccharides. *J Clin Invest* 1983;71:1032-1040.
82. Griffioen AW, Toebes EA, Rijkers GT, et al. The amplifier role of T cells in the human in vitro B cell response to type 4 pneumococcal polysaccharide. *Immunol Lett* 1992;32:265-272.
83. Tvede N, Heilmann C, Christensen LD. Interleukin 2 receptor expression by human blood lymphocytes after vaccination with pneumococcal polysaccharides. *Clin Exp Immunol* 1989;76:404-411.
84. Rijkers GT, Dollekamp EG, Zegers BJ. The in vitro B-cell response to pneumococcal polysaccharides in adults and neonates. *Scand J Immunol* 1987;25:447-452.
85. Talesnik E, Vial PA, Labarca J, Méndez C, Soza X. Time course of antibody response to tetanus toxoid and pneumococcal capsular polysaccharides in patients infected with HIV. *J Acquir Immune Defic Syndr* 1998;19:471-477.
86. Granoff DM, Suarez B, Pandey JP, Shackelford PG. Genes associated with the G2m (23) immunoglobulin allotype regulate the IgG subclass responses to *Haemophilus influenzae* type b polysaccharide vaccine. *J Infect Dis* 1988;157:1142-1149.
87. Ambrosino DM, Barrus VA, DeLange GG, Siber GR. Correlation of the Km(1) immunoglobulin allotype with anti-polysaccharide antibodies in Caucasian adults. *J Clin Invest* 1986;78:361-365.

-
88. Musher DM, Groover JE, Watson DA, et al. IgG responses to protein-conjugated pneumococcal capsular polysaccharides in persons who are genetically incapable of responding to unconjugated polysaccharides. *Clin Infect Dis* 1998;27:1487-1490.
89. Musher DM, Chapman AJ, Goree A, Jonsson S, Briles D, Baughn RE. Natural and vaccine-related immunity to *Streptococcus pneumoniae*. *J Infect Dis* 1986;154:245-256.
90. Fedson DS, Musher DM, Eskola J. Pneumococcal vaccine. In: Plotkin SA, Orenstein WA, eds. *Vaccines*, 3rd ed. Philadelphia: WB Saunders: 1998;553-607.
91. Musher DM, Luchi MJ, Watson DA, Hamilton R, Baughn RE. Pneumococcal polysaccharide vaccine in young adults and older bronchitics: determination of IgG responses by ELISA and the effect of adsorption of serum with non-specific cell wall polysaccharide. *J Infect Dis* 1990;161:728-735.
92. Mufson MA, Hughey D, Lydick E. Type-specific antibody responses of volunteers immunized with 23-valent pneumococcal polysaccharide vaccine. *J Infect Dis* 1985;151:749-750.
93. Mufson MA, Krause HE, Schiffman G, Hughey DF. Pneumococcal antibody levels one decade after immunization of healthy adults. *Am J Med Sci* 1987;293:279-284.
94. Go ES, Ballas ZK. Anti-pneumococcal antibody response in normal subjects: a meta-analysis. *J Allergy Clin Immunol* 1996;98:205-215.
95. Mufson MA, Hughey DF, Turner CE, Schiffman G. Revaccination with pneumococcal vaccine of elderly persons 6 years after primary vaccination. *Vaccine* 1991;9:403-407.

-
96. Lue C, Tarkowski A, Mestecky J. Systemic immunization with pneumococcal polysaccharide vaccine induces a predominant IgA2 response of peripheral blood lymphocytes and increases of both serum and secretory anti-pneumococcal antibodies. *J Immunol* 1988;140:3793-3780.
 97. Rijkers GT, Sanders EAM, Breukels MA, Zegers BJM. Responsiveness of infants to capsular polysaccharides: implications for vaccine development. *Rev Med Microbiol* 1996;7:3-12.
 98. Douglas RM, Paton JC, Duncan SJ, Hansman DJ. Antibody response to pneumococcal vaccination in children younger than five years of age. *J Infect Dis* 1983;148:131-137.
 99. Ammann AJ, Schiffman G, Austrian R. The antibody responses to pneumococcal capsular polysaccharides in aged individuals. *Proc Soc Exp Biol Med* 1980;164:312-316.
 100. Musher DM, Groover JE, Graviss EA, Baughn RE. The lack of association between aging and postvaccination levels of IgG antibody to capsular polysaccharides of *Streptococcus pneumoniae*. *Clin Infect Dis* 1996;22:165-167.
 101. Fattal-German M, Taillandier J, Mathleu D, Bizzini B. Pneumococcal vaccination of elderly individuals. *Vaccine* 1991;9:542-544.
 102. Konradsen H, Henrichsen J. Antibody response to pneumococcal vaccination in the elderly. *Int J Med Microbiol* 1991;275:94-99.
 103. Sankilampi U, Honkanen PO, Bloigu A, Herva E, Leinonen M. Antibody response to pneumococcal capsular polysaccharide vaccine in the elderly. *J Infect Dis* 1996;173:387-393.

104. Sankilampi U, Honkanen PO, Bloigu A, Leinonen M. Persistence of antibodies to pneumococcal capsular polysaccharide vaccine in the elderly. *J Infect Dis* 1997;176:1100-1104.
105. Davis AL, Aranda CP, Schiffman G, Christianson LC. Pneumococcal infection and immunologic response to pneumococcal vaccine in chronic obstructive pulmonary disease. *Chest* 1987;92:204-212.
106. Kraus C, Fischer S, Ansorg R, Hütemann U. Pneumococcal antibodies (IgG, IgM) in patients with chronic obstructive lung disease 3 years after pneumococcal vaccination. *Med Microbiol Immunol* 1985;174:51-58.
107. Hidalgo H, Moore C, Leiva LE, Sorensen RU. Preimmunization and postimmunization pneumococcal antibody titers in children with recurrent infections. *Ann Allergy Asthma Immunol* 1996;76:341-346.
108. Shapiro ED, Clemens JD. A controlled evaluation of the protective efficacy of pneumococcal vaccine for patients at high risk of serious pneumococcal infections. *Ann Intern Med* 1984;101:325-330.
109. Beam TR, Crigler ED, Goldman JK, Schiffman G. Antibody response to polyvalent pneumococcal polysaccharide vaccine in diabetics. *JAMA* 1980;244:2621-2624.
110. Lindblad R, Kaijser b, Magnusson B, et al. Pneumococcal vaccination in splenectomized patients with hematological disorders. *Acta Med Scand* 1988;224:467-471.
111. Konradsen HB, Henrichsen J. The need for revaccination 10 years after primary pneumococcal vaccination in splenectomized adults. *Scand J Infect Dis* 1991;23:397.

-
112. Rutherford EJ, Livengood J, Higginbotham M, et al. Efficacy and safety of pneumococcal revaccination after splenectomy for trauma. *J Trauma* 1995;39:448-452.
 113. Weintrub PS, Schiffman G, Adiego JE Jr, et al. Long-term follow-up and booster immunization with polyvalent pneumococcal polysaccharide in patients with sickle cell anemia. *J Pediatr* 1984;105:261-263.
 114. Rao SP, Rajkumar K, Schiffman G, et al. Anti-pneumococcal antibody levels three to seven years after first booster immunization in children with sickle cell disease, and after a second booster. *J Pediatr* 1995;127:590-592.
 115. Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. *N Engl J Med* 1986;314:1593-1599.
 116. Schmid GP, Smith RP, Baltch AL, Hall CA, Schiffman G. Antibody response to pneumococcal vaccine in patients with multiple myeloma. *J Infect Dis* 1981;143:590-597.
 117. Linnemann CC Jr, First MR, Schiffman G. Revaccination of renal transplant and hemodialysis recipients with pneumococcal vaccine. *Arch Intern Med* 1986; 146:1554-1556.
 118. Cashland TM, Preheim LC, Gentry-Nielsen MJ. Pneumococcal vaccine response in cirrhosis and liver transplantation. *J Infect Dis* 2000;181:757-760.
 119. Ammann AJ, Addiego J, Wara DW, et al. Polyvalent pneumococcal-polysaccharide immunization of patients with sickle cell anemia and patients with splenectomy. *N Engl J Med* 1977;297:897-900.

-
120. Simberkoff MS, Cross AP, Al-Ibrahim M, et al. Efficacy of pneumococcal vaccine in high-risk patients: results of a Veterans Administration cooperative study. *N Engl J Med* 1986;315:1318-1327.
 121. Spika JS, Fedson DS, Facklam RR. Pneumococcal vaccination: controversies and opportunities. *Infect Dis Clin North Am* 1990;4:11-27.
 122. Shapiro ED. Pneumococcal vaccine failure. *N Engl J Med* 1987;316:1272-1273.
 123. Schwartz JS. Pneumococcal vaccine: clinical efficacy and effectiveness. *Ann Intern Med* 1982;96:208-220.
 124. Forrester HL, Jahnigen DW, LaForce FM. Inefficacy of pneumococcal vaccine in a high-risk population. *Am J Med* 1987;83:425-430.
 125. Smit P, Oberholzer D, Hayden-Smith S, Koornhof HJ, Hilleman MR. Protective efficacy of pneumococcal polysaccharide vaccines. *JAMA* 1977;238:2613-2616.
 126. Sims RV, Steinmann WC, McConville JH, King LR, Zwick WC, Schwartz JS. The clinical effectiveness of pneumococcal vaccine in the elderly. *Ann Intern Med* 1986;108:653-657.
 127. Shapiro ED, Berg AT, Austrian R, et al. The protective efficacy of polyvalent pneumococcal polysaccharide vaccine. *N Engl J Med* 1991;325:1453-1460.
 128. Butler JC, Breiman RF, Campbell JF, Lipman HB, Broome CV, Facklam RR. Polysaccharide pneumococcal vaccine efficacy: an evaluation of current recommendations. *JAMA* 1993;270:1826-1831.

-
129. Farr BM, Johnston BL, Cobb DK, et al. Preventing pneumococcal bacteremia in patients at risk: results of a matched case-control study. *Arch Intern Med* 1995;155:2336-2340.
 130. Bolan G, Broome CV, Facklam RR, et al. Pneumococcal vaccine efficacy in selected populations in the United States. *Ann Intern Med* 1986;104:1-6.
 131. Smit P, Oberholzer D, Hayden-Smith S, Koornhof HJ, Hilleman MR. Protective efficacy of pneumococcal polysaccharide vaccines. *JAMA* 1977;238:2613-2616.
 132. Kaufman P. Pneumonia in old age: active immunization against pneumonia with pneumococcus polysaccharide-results of a 6-year study. *Arch Intern Med* 1947;79:518-531.
 133. Broome CV. Efficacy of pneumococcal polysaccharide vaccines. *Rev Infect Dis* 1981;8:S82-S96.
 134. Hirschmann JV, Lipsky BA. The pneumococcal vaccine after 15 years of use. *Arch Intern Med* 1994;154:373-377.
 135. Simberkoff MS. Pneumococcal vaccination in the prevention of community-acquired pneumonia: a skeptical view of cost-effectiveness. *Semin Respir Infect* 1993;8:294-299.
 136. Örtqvist A, Hedlund J, Burman LA, et al. Randomised trial of 23-valent pneumococcal capsular polysaccharide vaccine in prevention of pneumonia in middle-aged and elderly people. *Lancet* 1998;351:399-403.
 137. Gaillat Z, Zmiron D, Mallaret MR, et al. Clinical trial of pneumococcal vaccine among institutionalized elderly. *Rev Epidemiol Sante Publique* 1985;33:437-444.

138. Koivula I, Sten M, Leinonen M, Makela PH. Clinical efficacy of pneumococcal vaccine in the elderly: a randomized, single-blind population-based trial. *Am J Med* 1997;103:281-290.
139. Nuorti JP, Butler JC, Crutcher JM, et al. An outbreak of multi-drug resistant pneumococcal pneumonia and bacteriemia among unvaccinated nursing home residents. *N Engl J Med* 1998;338:1861-1868.
140. Austrian R. Surveillance of pneumococcal infection for field trials of polyvalent pneumococcal vaccines. Bethesda. Md: National Institute of Allergy and Infectious Diseases:1980:1-59. National Institutes of Health publication DAB-VDP-12-84; Contract N01 A13257.
141. Klastersky J, Mommen P, Cantraine F, Safary A. Placebo controlled pneumococcal immunization in patients with bronchogenic carcinoma. *Eur J Cancer Clin Oncol* 1986;22:807-813.
142. Leech JA, Gervais A, Ruben FL. Efficacy of pneumococcal vaccine in severe chronic obstructive pulmonary disease. *Can Med Assoc J* 1987;136:361-365.
143. Fine MJ, Smith MA, Carson CA, et al. Efficacy of pneumococcal vaccination in adults: a metaanalysis of randomized controlled trials. *Arch Intern Med* 1994;154:2666-2677.
144. Sisk JE, Riegelman RK. Cost-effectiveness of vaccination against pneumococcal pneumonia: an update. *Ann Intern Med* 1986;104:79-86.
145. Sisk JE, Moskowitz AJ, Whang W, et al. Cost-effectiveness of vaccination against pneumococcal bacteremia among elderly people. *JAMA* 1997;278:1333-1339.

-
146. Gable CB, Botteman M, Savage G, Joy K. The cost effectiveness of pneumococcal vaccination strategies. *Pharmacoeconomics* 1997;12:161-174.
 147. Plans P, Garrido O, Salleras L. Coste-efectividad de la vacunación neumocócica en Cataluña. *Rev Esp Salud Pública* 1995;69:409-417.
 148. Jiménez FJ, Guallar P, Rubio C, Villasante P, Guallar E. Cost-effectiveness analysis of pneumococcal vaccination in the elderly population. *Br J Med Econ* 1996;10:193-202.
 149. Salleras L, Urbiztondo L, Parron I, et al. Programa de vacunación antineumocócica en la tercera edad en Cataluña. *Vacunas* 2000;1:91-94.
 150. Centers for Disease Control and Prevention. Influenza and pneumococcal vaccination coverage levels among persons aged 65 or more in the United States, 1973-1993. *MMWR* 1995;44:506-507, 513-515.
 151. Centers for Disease Control and Prevention. Pneumococcal and influenza vaccination levels among adults aged ≥ 65 años. United States 1995. *MMWR* 1997;46:913-919.
 152. Fedson D. Pneumococcal vaccination in the United States and 20 other countries, 1981-1996. *Clin Infect Dis* 1998;26:1117-1123.
 153. Klein RS, Adachi N. An effective hospital-based pneumococcal immunization program. *Arch Intern Med* 1986;146:327-329.
 154. Fedson DS, Baldwin JA. Previous hospital care as a risk factor for pneumonia. Implications for immunization with pneumococcal vaccine. *JAMA* 1982;248:1989-1995.

155. Borgoño JM, McLean AA, Vella PP, et al. Vaccination and revaccination with polyvalent pneumococcal polysaccharide vaccines in adults and infants. *Proc Soc Exper Biol Med* 1978;157:148-154.
156. Jackson LA, Sneller V-P, Kvartrskhava T, et al. Safety of revaccination with pneumococcal polysaccharide vaccine. *JAMA* 1999;281:243-248.
157. Hilleman MR, Carlson AJ Jr, McLean AA, Vella PP, Weibel RE, Woohour AF. *Streptococcus pneumoniae* polysaccharide vaccine: age and dose responses, safety, persistence of antibody, revaccination, and simultaneous administration of pneumococcal and influenza vaccine. *Rev Infect Dis* 1981;3(suppl):S31-S42.
158. Konradsen HB. Quantity and avidity of pneumococcal antibodies before and up to five years after pneumococcal vaccination of elderly persons. *Clin Infect Dis* 1995;21:616-620.
159. Davidson M, Bulkow LR, Grabman J, et al. Immunogenicity of pneumococcal revaccination in patients with chronic disease. *Arch Intern Med* 1994;154:2209-2214.
160. Shahid NS, Steinhoff MC, Hoque SS, et al. Serum, breast milk, and infant antibody after maternal immunization with pneumococcal vaccine. *Lancet* 1995;346:1252-1257.
161. Garg M, Subbarao B. Immune responses of systemic and mucosal lymphoid organs to Pnu-Immune vaccine as a function of age and the efficacy of monophosphoryl lipid A as an adjuvant. *Infect Immun* 1992;60:2329-2336.
162. Nohria A, Rubin RH. Cytokines as potential vaccine adjuvants. *Biotherapy* 1994;7:261-269.

-
163. Robbins JB, Schneerson R. Polysaccharide-protein conjugates. A new generation of vaccines. *J Infect Dis* 1990;161:821-832.
 164. Anderson EL, Kennedy DJ, Geldmacher KM, Donnelly J, Mendelman PM. Immunogenicity of heptavalent pneumococcal conjugate vaccine in infants. *J Pediatr* 1996;128:649-653.
 165. Dagan R, Muallem M, Melamed R, et al. Reduction of pneumococcal nasopharyngeal carriage in early infancy after immunization with tetravalent pneumococcal vaccines conjugated to either tetanus toxoid or diphtheria toxoid. *Pediatr Infect Dis J* 1997;16:1060-1064.
 166. King JC Jr, Vink PE, Farley JJ, Smilie M, Parks M, Lichenstein R. Safety and immunogenicity of three doses of a five-valent pneumococcal conjugate vaccine in children younger than two years with and without human immunodeficiency virus infection. *Pediatrics* 1997;99:575-580.
 167. Powers DC, Anderson EL, Lottenbach K, Mink CM. Reactogenicity and immunogenicity of a protein-conjugated pneumococcal oligosaccharide vaccine in older adults. *J Infect Dis* 1996;173:1014-1018.
 168. Shelly MA, Jacoby H, Riley GJ, et al. Comparison of pneumococcal polysaccharide and CRM197-conjugated pneumococcal oligosaccharide vaccine in young and elderly adults. *Infect Immun* 1997;65:242-247.
 169. Chan CY, Molrine DC, George S, et al. Pneumococcal conjugate vaccine primes for antibody responses to polysaccharide pneumococcal vaccine after treatment of Hodgkin's disease. *J Infect Dis* 1996;173:256-258.
 170. Amdahl BM, Rubins JB, Daley CL, Gilks CF, Hopewell PC, Janoff EN. Impaired natural immunity to pneumolysin during human immunodeficiency

-
- virus infection in the United States and Africa. *Am J Respir Crit Care Med* 1995;152:2000-2004.
171. Alexander JE, Lock RA, Peeters CC, et al. Immunization of mice with pneumolysin toxoid confers a significant degree of protection against at least nine serotypes of *Streptococcus pneumoniae*. *Infect Immunol* 1994;62:5683-5688.
172. Tart RC, McDaniel LS, Ralph BA, Briles DE. Truncated *Streptococcus pneumoniae* PspA molecules elicit cross-protective immunity against pneumococcal challenge in mice. *J Infect Dis* 1996;173:380-386.
173. McDaniel LS, Loechel F, Benedict C, et al. Immunization with a plasmid expressing pneumococcal surface protein A (PspA) can elicit protection against fatal infection with *Streptococcus pneumoniae*. *Gene Ther* 1997;4:375-377.
174. Shurin PA, Rehmus JM, Johnson CE, et al. Bacterial polysaccharide immune globulin for prophylaxis of acute otitis media in high-risk children. *J Pediatr* 1993;123:801-810.
175. Buckley RH, Schiff RI. The use of intravenous immune globulin in immunodeficiency disease. *N Engl J Med* 1991;325:110-117.
176. Schiffman G, Douglas RM, Bonner MJ. A radioimmunoassay for immunologic phenomena in pneumococcal disease and for the antibody response to pneumococcal vaccine. Method for radioimmunoassay of the anticapsular antibodies and comparison with other techniques. *J Immunol Methods* 1980; 33:133-144.
177. Giebink GS, Le CT, Spika JS. Summarized vs. type-specific analysis of antibody to pneumococcal capsular polysaccharides. *Rev Infect Dis* 1981;3(suppl):S43-S46.

-
178. Katz MA, Schiffman G. Comparison of an enzyme-linked immunosorbent assay with radioimmunoassay for the measurement of pneumococcal capsular polysaccharide antibodies. *Mol Immunol* 1985;22:313-319.
179. Siber GR, Priehs C, Madore DV. Standardization of antibody assays for measuring the response to pneumococcal infection and immunization. *Pediatr Infect Dis J* 1989;8(suppl):S84-S91.
180. Nieuwhof WN, Hodgen AN. An enzyme-linked immunoabsorbent assay suitable for the routine estimation of specific immunoglobulin G responses to polyvalent pneumococcal polysaccharide vaccine in humans. *J Immunol Methods* 1985;84:197-202.
181. Verheul AF, Versteeg AA, Westerdaal NA, Van Dam GJ, Jansze M, Snippe H. Measurement of the humoral immune response against *Streptococcus pneumoniae* type 14-derived antigens by an ELISA and ELIS-POT assay based on biotinavidin technology. *J Immunol Methods* 1990;126:79-87.
182. Rudolph KM, Parkinson AJ. Measurement of pneumococcal capsular polysaccharide serotype-specific immunoglobulin G in human serum, a method for assigning weight-based units to proposed reference sera. *Clin Diagn Lab Immunol* 1994;1:526-530.
183. Musher DM, Johnson B Jr, Watson DA. Quantitative relationship between anticapsular antibody measured by enzyme-linked immunoabsorbent assay or radioimmunoassay and protection of mice against challenge with *Streptococcus pneumoniae* serotype 4. *Infect Immunol* 1990;58:3871-3876.
184. Vitharsson G, Jonsdottir I, Jonsson S, Valdimarsson H. Opsonization and antibodies to capsular and cell wall polysaccharides of *Streptococcus pneumoniae*. *J Infect Dis* 1994;170:592-599.

-
185. Pantaleo G, Fauci AS. Immunopathogenesis of HIV infection. *Annu Rev Microbiol* 1996;50:825-854.
 186. Cohen O, Cicala C, Vaccarezza M, Fauci A. The immunology of human immunodeficiency virus infection. In: Mandell, Douglas, Bennett, eds. *Principles and practice in Infectious Diseases*, Fifth edition. Churchill Livingstone, 1999:1374-1397.
 187. Müller F, Froland SS, Hvatum M, Radl J, Brandtzaeg P. Both IgA subclasses are reduced in parotid saliva from patients with AIDS. *Clin Exp Immunol* 1991;83:203-209.
 188. Janoff EN, Breiman RF, Daley CL, Hopewell PC. Pneumococcal disease during HIV infection. Epidemiologic, clinical and immunologic perspectives. *Ann Intern Med* 1992;117:314-324.
 189. Parkin JM, Helbert M, Hughes CL, Pinching AJ. Immunoglobulin G subclass deficiency and susceptibility to pyogenic infection in patients with AIDS-related complex and AIDS. *AIDS* 1989;3:37-39.
 190. Bender BS, Frank MM, Lawley TJ, Smith WJ, Brickman CM, Quinn TC. Defective reticuloendothelial system Fc-receptor function in patients with acquired immunodeficiency syndrome. *J Infect Dis* 1985;152:409-412.
 191. Ellis M, Gupta S, Galant S, et al. Impaired neutrophil function in patients with AIDS or AIDS-related complex: a comprehensive evaluation. *J Infect Dis* 1988;158:1268-1276.
 192. Glesby MJ. Immunization during HIV infection. *Curr Opin Infect Dis* 1998;11:17-21.

-
193. Rosok B, Voltersvik P, Bjerknes R, et al. Dynamics of HIV-1 replication following influenza vaccination of HIV+ individuals. *Clin Exp Immunol* 1996;104:203-207.
194. Lane CH, Masur H, Edgar LC, Whalen G, Rook AH, Fauci AS. Abnormalities of B-cell activation and immunoregulation in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1983;309:453-458.
195. Janoff EN, Douglas JM Jr, Gabriel M, et al. Class-specific antibody response to pneumococcal capsular polysaccharides in men infected with human immunodeficiency virus type 1. *J Infect Dis* 1988;158:983-990.
196. Janoff EN, O'Brien J, Thompson P, et al. *Streptococcus pneumoniae* colonization, bacteremia, and immune response among persons with human immunodeficiency virus infection. *J Infect Dis* 1993;167:49-56.
197. Rodriguez-Barradas MC, Musher DM, Lahart C, et al. Antibody to capsular polysaccharides of *Streptococcus pneumoniae* after vaccination of human immunodeficiency virus-infected subjects with 23-valent pneumococcal vaccine. *J Infect Dis* 1992;165:553-556.
198. Hibbs JR, Douglas JM Jr, Judson FN, Mc Gill WL, Rietmeijer CA, Janoff EN. Prevalence of human immunodeficiency virus infection, mortality rate, and serogroup distribution among patients with pneumococcal bacteremia at Denver General Hospital, 1984-1994. *Clin Infect Dis* 1997;25:195-199.
199. Nuorti JP, Butler JC, Gelling L, Kool JL, Reingold AL, Vugia DJ. Epidemiologic relation between HIV and invasive pneumococcal disease in San Francisco County, California. *Ann Intern Med* 2000;132:182-190.
200. Frankel RE, Virata M, Hardalo C, Altice FL, Friedland G. Invasive pneumococcal disease: clinical features, serotypes and antimicrobial

- resistance pattern in cases involving patients with and without human immunodeficiency virus infection. *Clin Infect Dis* 1996;23:577-584.
201. García-Leoni ME, Moreno S, Rodeño P, Cercenado E, Vicente T, Bouza E. Pneumococcal pneumonia in adult hospitalized patients infected with the human immunodeficiency virus. *Arch Intern Med* 1992;152:1808-1812.
202. Opstad NL, Daley CL, Thurn JR, et al. Impact of *Streptococcus pneumoniae* bacteremia and human immunodeficiency virus type 1 on oral mucosa immunity. *J Infect Dis* 1995;172:566-570.
203. Rodriguez-Barradas MC, Tharapel RA, Goover JE, et al. Colonization by *Streptococcus pneumoniae* among human immunodeficiency virus-infected adults: prevalence of antibiotic resistance, impact of immunization, and characterization by polymerase chain reaction with BOX primers of isolates from persistent *S. pneumoniae* carriers. *J Infect Dis* 1997;175:590-597.
204. Polsky B, Gold JWM, Whimbey E, et al. Bacterial pneumonia in patients with the acquired immunodeficiency syndrome. *Ann Intern Med* 1986;104:38-41.
205. Selwyn P, Feingold A, Hartel D, et al. Increased risk of bacterial pneumonia in HIV-infected intravenous drug users without AIDS. *AIDS* 1988;2:267-272.
206. Mientjes GH, Spijkerman IJ, van Ameijden EJ, vanden Hoek JA, Coutinho RA. Incidence and risk factors for pneumonia in HIV infected and non infected drug users. *J Infect* 1996;32:181-186.
207. Burns DN, Hillman D, Neaton JD, et al. Cigarette smoking, bacterial pneumonia, and other clinical outcomes in HIV-1 infection: Terry Beinr Community programs for Clinical Research on AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol* 1996,13:374-383.

-
208. Witt DJ, Craven DE, McCabe WR. Bacterial infections in adult patients with the acquired immune deficiency syndrome (AIDS) and AIDS-related complex. *Am J Med* 1987;82:900-906.
209. Jones N, Huebner R, Khoosal M, Crewe-Brown H, Klugman K. The impact of HIV on *Streptococcus pneumoniae* bacteremia in a South African population. *AIDS* 1998;12:2177-2184.
210. Redd SC, Rutherford GW III, Sande M, et al. The role of human immunodeficiency virus infection in pneumococcal bacteremia in San Francisco residents. *J Infect Dis* 1990;162:1012-1017.
211. Falcó V, Fernández de Sevilla T, Alegre J, et al. Bacterial pneumonia in HIV-infected patients: a prospective study of 68 episodes. *Eur Respir J* 1994;7:235-239.
212. Pesola GR, Charles A. Pneumococcal bacteremia with pneumonia. Mortality in acquired immunodeficiency syndrome. *Chest* 1992;101:150-155.
213. Miller RF, Foley NM, Kessel D, Jeffrey AA. Community acquired lobar pneumonia in patients with HIV infection and AIDS. *Thorax* 1994;49:367-368.
214. Earhart KC, Wallace MR. The changing epidemiology of pneumococcal bacteremia in human immunodeficiency virus infection. *J Infect Dis* 1996;174:242-243.
215. Tumbarello M, Tacconelli E, de Gaetano K, et al. HIV-associated bacteremia: how it has changed in the highly active antiretroviral therapy (HAART) era. *JAIDS* 2000;23:145-151.

-
216. Almirante B, Saballs M, Ribera E, et al. Favorable prognosis of purulent meningitis in patients infected with human immunodeficiency virus. *Clin Infect Dis* 1998;27:176-180.
217. Wallace JM, Hansen N, Lavange L, et al. Respiratory disease trends in the pulmonary complications of HIV infection study cohort. *Am J Respir Crit Care Med* 1997;155:72-80.
218. Edge MD, Rimland D. Community-acquired bacteremia in HIV-positive patients: protective benefit of co-trimoxazole. *AIDS* 1996;10:1635-1639.
219. Gebo KA, Moore RD, Keruly JC, Chaisson RE. Risk factors for pneumococcal disease in human immunodeficiency virus-infected patients. *J Infect Dis* 1996;173:857-862.
220. Scott JAG, Hall AJ, Hannington A, et al. Serotype distribution and prevalence of resistance to benzylpenicillin in three representative populations of *Streptococcus pneumoniae* isolates from the coast of Kenya. *Clin Infect Dis* 1998;27:1442-1450.
221. Meynard JL, Barbut F, Blum L, et al. Risk factors for isolation of *Streptococcus pneumoniae* with decreased susceptibility to penicillin G from patients infected with human immunodeficiency virus. *Clin Infect Dis* 1996;22:437-440.
222. Turett GS, Blum S, Fazal A, Justman JE, Telzak EE. Penicillin resistance and other predictors of mortality in pneumococcal bacteremia in a population with high human immunodeficiency virus seroprevalence. *Clin Infect Dis* 1999;29:321-327.
223. Janoff EN, Fasching C, Ojoo JC, O'Brien J, Gilks CF. Responsiveness of human immunodeficiency virus type 1-infected Kenyan women with or without

- prior pneumococcal disease to pneumococcal vaccine. *J Infect Dis* 1997;175:975-978.
224. Klein RS, Selwyn PA, Maude D, Pollard C, Freeman K, Schiffman G. Response to pneumococcal vaccine among asymptomatic heterosexual partners of persons with AIDS and intravenous drug users infected with human immunodeficiency virus. *J Infect Dis* 1989;160:826-831.
225. Vandenbruaene M, Colebunders R, Mascart-Lemone F, et al. Equal IgG antibody response to pneumococcal vaccination in all stages of human immunodeficiency virus disease. *J Infect Dis* 1995;172:551-553.
226. Ballet JJ, Sulcebe G, Couderc LJ, et al. Impaired anti-pneumococcal antibody response in patients with AIDS-related persistent generalized lymphadenopathy. *Clin Exp Immunol* 1987;68:479-487.
227. Ragni MV, Ruben FL, Winkelstein A, Spero JA, Bontempo FA, Lewis JH. Antibody responses to immunization of patients with hemophilia with and without evidence of human immunodeficiency virus (human T-lymphotropic virus Type III) infection. *J Lab Clin Med* 1987;109:54-549.
228. Ochs HD, Junker AK, Collier AC, Virant FS, Handsfield HH, Wedgwood RJ. Abnormal antibody responses in patients with persistent generalized lymphadenopathy. *J Clin Immunol* 1988;8:57-63.
229. French N, Gilks CF, Mujugira A, Fasching C, O'Brien J, Janoff EN. Pneumococcal vaccination in HIV-1-infected adults in Uganda: humoral response and two vaccine failures. *AIDS* 1998;12:1683-1689.
230. Ammann AJ, Schiffman G, Abrams D, Volberding P, Ziegler J, Conant M. B-cell immunodeficiency in acquired immune deficiency syndrome. *JAMA* 1984;251:1447-1449.

-
231. Kroon FP, van Dissel JT, de Jong JC, van Furth R. Antibody response to influenza, tetanus and pneumococcal vaccines in HIV-seropositive individuals in relation to the number of CD4+ lymphocytes. *AIDS* 1994;8:469-476.
232. Weiss PJ, Wallace MR, Oldfield III EC, O'Brien J, Janoff EN. Response of recent human immunodeficiency virus seroconverters to the pneumococcal polysaccharide vaccine and *Haemophilus influenzae* type b conjugate vaccine. *J Infect Dis* 1995;171:1217-1222.
233. Mascart-Lemone F, Gérard M, Libin M, et al. Differential effect of human immunodeficiency virus infection on the IgA and IgG antibody responses to pneumococcal vaccine. *J Infect Dis* 1995;172:1253-1260.
234. Rodriguez-Barradas MC, Groover JE, Lacke CE, et al. IgG antibody to pneumococcal capsular polysaccharide in human immunodeficiency virus-infected subjects: persistence of antibody in responders, revaccination in non-responders and relationship of immunoglobulin allotype to response. *J Infect Dis* 1996;173:1347-1353.
235. Carson P, Schut R, Simpson M, O'Brien J, Janoff EN. Antibody class and subclass responses to pneumococcal polysaccharides following immunization of human immunodeficiency virus infected patients. *J Infect Dis* 1995;172:340-345.
236. Loeliger AE, Rijkers GT, Aerts P, et al. Deficient antipneumococcal polysaccharide responses in HIV-seropositive patients. *FEMS Immunol Med Microbiol* 1995;12:33-41.
237. Willocks LJ, Vithayathil K, Tang A, Noone A. Pneumococcal vaccine and HIV infection: report of a vaccine failure and reappraisal of its value in clinical practice. *Genitourin Med* 1995; 71:71-72.

-
238. Hirschfeld S, Schiffman G, Tudor-Williams G, Pizzo PA. Pneumonia and bacteremia by pneumococcal serotype 16 in a human immunodeficiency virus-infected child with a normal serum antibody response to 23-valent Pneumovax vaccine. *J Infect Dis* 1995;171:761-762.
239. Simberkoff MS, El Sadr WE, Schiffman G, Rahal Jr JJ. *Streptococcus pneumoniae* infection and bacteremia in patients with acquired immunodeficiency syndrome, with report of a pneumococcal vaccine failure. *Am Rev Respir Dis* 1984;130:1174-1176.
240. Unsworth D, Rowen D, Carne C, et al. Defective IgG2 response to Pneumovax in HIV-seropositive patients. *Genitourin Med* 1993;69:373-376.
241. Glaser JB, Volpe S, Aguirre A, Simpkins H, Schiffman G. Zidovudine improves responses to pneumococcal vaccine among persons with AIDS and AIDS-related complex. *J Infect Dis* 1991;164:761-764.
242. Nielsen H, Krinesdal B, Benfilld TL, Lundgren JA, Konradsen HB. Rapid loss of specific antibodies after pneumococcal vaccination in patients with human immunodeficiency virus-1 infection. *Scand J Infect Dis* 1998;30:597-601.
243. Brichacek B, Swindells S, Janoff EN, Pirucello S, Stevenson M. Increased plasma human immunodeficiency virus type 1 burden following antigenic challenge with pneumococcal vaccine. *J Infect Dis* 1996;174:1191-1199.
244. Vigano A, Bricalli D, Trabattoni D, et al. Immunization with both T cell-dependent and T-cell independent vaccines augments HIV viral load secondarily to stimulation of tumor necrosis factor alpha. *AIDS Res Hum Retroviruses* 1998;14:727-734.

-
245. Katzenstein TL, Gerstoff J, Nielsen H. Assessments of plasma HIV RNA and CD4 cell counts after combined Pneumovax and tetanus toxoid vaccination: no detectable increase in HIV replication 6 weeks after immunization. *Scand J Infect Dis* 1996;28:239-241.
246. Janoff EN, Tasker SA, Stevenson M, et al. Immune activation and virologic response to immunization in recent HIV type 1 seroconverters. *AIDS Res Hum Retroviruses* 1999;15:837-845.
247. Kroon FP, van Dissel JT, Ravensbergen E, Nibbering PH, van Furth R. Antibody response to tetravalent conjugate vaccine in HIV-infected adults. *Int Conf AIDS* 1996;11:2, 18 (abstract no. We.B.115).
248. Ahmed F, Steinhoff M, Rodriguez-Barradas M, et al. Effect of human immunodeficiency virus type 1 infection on the antibody response to a glycoprotein conjugate pneumococcal vaccine: results from a randomized trial. *J Infect Dis* 1996;173:83-90.
249. Breiman RF, Keller DW, Phelan MA, et al. Evaluation of effectiveness of the 23-valent pneumococcal capsular polysaccharide vaccine for HIV-infected patients. *Arch Intern Med* 2000;160:2633-2638.
250. French N, Nakiyingi J, Carpenter LM, et al. 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet* 2000;355:2106-2111.
251. Keller DW, Breiman RF. Preventing bacterial respiratory tract infections among persons infected with human immunodeficiency virus. *Clin Infect Dis* 1995;21(Suppl 1):S77-S83.
252. Wortley PM, Farizo KM. Pneumococcal and influenza vaccination levels among HIV-infected adolescents and adults receiving medical care in the United

-
- States. Adult and Adolescent Spectrum of HIV Disease Project Group. *AIDS* 1994;8:941-944.
253. USPHS/IDSA Prevention of Opportunistic Infections Working Group. 1999 USPHS/IDSA guidelines for the prevention of opportunistic infections in persons infected with human immunodeficiency virus. *MMWR* 1999;48(RR10):1-59.
254. Berenguer J, Laguna F, López-Aldeguer J, Moreno s. Prevención de las infecciones oportunistas en pacientes adultos y adolescentes infectados por el virus de la inmunodeficiencia humana en la era del tratamiento antirretrovírico de gran actividad. *Enferm Infec Microbiol Clin* 2000;18:457-468.
255. Rodrigo MJ, Miravittles M, Cruz MJ, et al. Characterization of specific immunoglobulin G (IgG) and its subclasses (IgG1 and IgG2) against the 23-valent pneumococcal vaccine in a healthy adult population: proposal for response criteria. *Clin Diag Lab Immunol* 1997;4:168-172.
256. Opravil M, Fierz W, Matter L, Blaser J, Lüthy R. Poor antibody response after tetanus and pneumococcal vaccination in immunocompromised HIV infected patients. *Clin Exp Immunol* 1991;84:185-189.
257. Huang KL, Ruben FL, Rinaldo CR Jr, Kingsley L, Lyter DW, Ho M. Antibody responses after influenza and pneumococcal immunization in HIV-infected homosexual men. *JAMA* 1987;257:2047-2050.
258. Kroon FP, van Dissel JT, Ravensbergen E, Nibbering PH, van Furth R. Antibodies against pneumococcal polysaccharides after vaccination in HIV-infected individuals: 5-year follow-up of antibody concentrations. *Vaccine* 1999;18:524-530.

-
259. Baker PJ, Amsbaugh DF, Stashak PW, Caldes G, Prescott B. Regulation of the antibody response to pneumococcal polysaccharide thymus-derived cells. *Rev Infect Dis* 1981;3:332-341.
260. Koskela M. Serum antibodies to pneumococcal C polysaccharide in children: response to acute pneumococcal otitis media or to vaccination. *Pediatr Infect Dis* 1987;6:519-526.
261. De Velasco A, Dekker BA, Verheul AF, Feldman RG, Verhoef J, Snippe H. Antipolysaccharide immunoglobulin isotype levels and opsonic activity of antisera: relationships with protection against *Streptococcus pneumoniae* infection in mice. *J Infect Dis* 1995;172:562-565.
262. Landesman SH, Schiffman G. Assessment of the antibody response to pneumococcal vaccine in high-risk populations. *Rev Infect Dis* 1981;3(suppl):S184-S196.
263. Jain A, Jain S, Gant V. Should patients positive for HIV infection receive pneumococcal vaccine?. *Br Med J* 1995;310:1060-1062.
264. Rose DN, Schechter CB, Sacks HS. Influenza and pneumococcal vaccination of HIV infected patients: a policy analysis. *Am J Med* 1993;94:160-168.
265. Sax P, Singer M. Routine immunization in HIV: helpful or harmful? *AIDS Clin Care* 1996;8:11-3,15