

The Transforming *Streptococcus Pneumoniae* in the 21st Century

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Streptococcus pneumoniae, an important pathogen causing sepsis, sinusitis, otitis media, bacterial meningitis and bacterial pneumonia, results in global morbidity and mortality each year. The burden of pneumococcal disease is highest in children and the elderly. Treatment of pneumococcal infection has been hampered by the complexity of the host immune response. In recent decades, the increase of *S. pneumoniae* strains' resistance to β -lactam antibiotics and other classes of antimicrobials has made treatment even more complicated. Fortunately, the advent of heptavalent conjugate vaccine confers a high degree of protection against pneumococcal disease and colonization caused by vaccine serotype strains. After the introduction of conjugate pneumococcal vaccine, invasive pneumococcal disease caused by vaccine serotypes and antibiotic-resistant isolates has been reduced. However, naturally transformable pneumococci may escape vaccine-induced immunity by switching their capsular genes to non-vaccine serotypes. Development of cheaper, serotype-independent vaccines based on a combination of protein antigens should be pursued. (*Chang Gung Med J* 2008;31:117-24)



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Streptococcus pneumoniae, a pathogen discovered more than one hundred years ago, remains a leading cause of bacteremia, sinusitis, otitis media, bacterial meningitis and pneumonia. This bacterium is present worldwide, and is associated with substantial illnesses and deaths in humans.⁽¹⁾ Historically, study of the biology of *S. pneumoniae* led to the identification of the nature of genetic material, the phenomenon of quorum sensing, the use of polysaccharide-based vaccine and the recognition of bacterial resis-

tance to antimicrobial drugs.^(2,3) Since the complete genome of *S. pneumoniae* was decoded in 1997, much has been discovered about the bacterial proteins involved in pneumococcal disease, the regulation of virulence and the regulation of DNA uptake.⁽⁴⁾ Recently, the landscape of pneumococcal infection has been changed by two major events, namely, availability of conjugate pneumococcal vaccine and more aggressive behavior of pneumococcal pneumonia.^(5,6) It is now a good time to review our under-

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standing of the biology and clinical behavior of *S. pneumoniae*.

***S. pneumoniae* virulence factors**

Capsule

Polysaccharide capsule is the earliest known *S. pneumoniae* virulence factor, and serves as a paradigm for studies of immune responses and polysaccharide biochemistry. Capsular polysaccharide is composed of multiple sugars that help pneumococci fight against phagocytosis. The amount of capsule expression in the microbe changes during replication in the host, a phenomenon known as phase variation.⁽⁷⁾ Reduced capsule expression (transparent variant) in the nasopharynx is instrumental in exposing the adhesins necessary for colonization, whereas increase in capsule expression (opaque variant) is essential for avoiding complement-mediated opsonophagocytosis during invasive disease. Several factors such as BOX elements, capsule locus A (CpsA), CpsB, CpsC and CpsD, and spontaneous sequence duplication contribute to the complex regulation of capsule synthesis.⁽⁸⁻¹²⁾

Choline-binding proteins

S. pneumoniae possesses several choline-binding proteins on its surface that serve as a way of attaching it to the cell surface. The most well-known choline-binding proteins in pneumococci are autolysin, pneumococcal surface protein C (PspC) and pneumococcal surface protein A (PspA). Autolysin (LytA amidase) degrades peptidoglycan of the pneumococcal cell wall and separates daughter cells. Lysis of pneumococci by autolysin leads to release of the pneumococcal cell wall and pneumolysin, which in turn induce inflammatory responses and cause tissue damage.⁽¹³⁾ PspA is a protective antigen of *S. pneumoniae*, and is able to inhibit complement deposition and activation.^(14,15) It contributes to pneumococcal virulence in both bacteremia and sepsis models.⁽¹⁶⁾ PspC, also referred to as choline-binding protein A (CbpA), acts as an adhesin, and interacts with the polymeric immunoglobulin receptor (pIgR) on mucosal epithelial cells to facilitate adhesion and invasion.⁽¹⁷⁾

Pneumolysin and other virulence factors

The role of pneumolysin in pneumococcal infec-

tion has been well studied. Pneumolysin belongs to the family of pore-forming toxins, which can lyse cell membranes containing cholesterol. This toxin also activates the complement system, induces the production of proinflammatory mediators, recruits inflammatory cells and causes cell apoptosis.^(18,19) Other proteins, including LPXTG-anchored protein (hyaluronidase, neuraminidase and serine protease), lipoprotein, hydrogen peroxide, superoxide dismutase, NADH (nicotinamide adenine dinucleotide, reduced form) oxidase, as well as zinc metalloprotease (immunoglobulin A protease, ZmpB and ZmpC), also contribute to the virulence of *S. pneumoniae*. A pneumococcal pilus encoded by the *rlrA* pathogenicity islet, consisting of LPXTG-containing surface proteins and sortases, enhances adherence and stimulates the host inflammatory response.⁽²⁰⁾ Pneumococcal neuraminidases cleave sialic acid-containing substrates. Neuraminidase A and B both have essential roles in respiratory tract infection and sepsis. Neuraminidase C may contribute to the ability of pneumococci to cause meningitis.⁽²¹⁾

Capsular type or clonal type determine the invasive capacity of *S. pneumoniae*

S. pneumoniae can be divided into more than 91 distinct types according to capsular polysaccharides but only 20 to 30 types are associated with human diseases. Hence, there is an association between serotype and the potential of pneumococci to cause invasive disease. Certain serotypes, such as serotype 1 are highly invasive, mostly due to the specific chemical composition of their capsules. Serotype 3 can evade the immune system, readily resulting in a fatal disease.⁽²²⁾ Further studies of the population biology of *S. pneumoniae* found that, even within the same serotype, some individual clones (such as ST9 and ST124) were significantly overrepresented in invasive diseases compared with carriage.⁽²³⁾ So far, the exact mechanisms of why some serotypes can go beyond colonization to cause invasive disease remain unclear but it appears that the capsule is not sufficient to determine invasive potential or inflammatory response.^(24,25) The genetic background of the host, in addition to the capsule, also plays a critical role in dictating virulence. Understanding the underlying mechanism of virulent genotypes becomes a priority in the era of the pneumococcal conjugate vaccine.

Innate immunity

S. pneumoniae infection is countered by a robust inflammatory reaction in the host. Complement, C-reactive proteins (CRP), surfactant protein, Toll-like receptors (TLR) and T cells comprise the major components of the immune response against *S. pneumoniae*. Studies using mice deficient in specific genes indicated that both the classical and alternative complement pathways were vital in host defense against pneumococcal infection.⁽²⁶⁾ CRP specifically binds to phosphocholine residues of C-polysaccharide (PnC) in the cell wall of *S. pneumoniae* to activate the classical pathway of complement in human serum.⁽²⁷⁾ Lung surfactant protein-D (SP-D) facilitated the early clearance of pneumococci in a murine model of bronchopneumonia and bacteremia.⁽²⁸⁾ TLR2 recognizes pneumococcal lipoteichoic acid (LTA) and cell wall peptidoglycan to initiate an inflammatory response. TLR2 also had a protective role in systemic infection and nasopharyngeal colonization in a murine model.^(29,30) TLR4 recognizes pneumococcal pneumolysin to limit pneumococcal proliferation in the nasopharynx.⁽³¹⁾ TLR4 also interacts with pneumolysin to induce mammalian cell apoptosis against pneumococcal infection.⁽³²⁾ CD4 (cluster of differentiation 4) T cells were found to contribute to early protective immunity to *S. pneumoniae* based on studies using mice lacking the major histocompatibility complex II (MHCII) gene.⁽³³⁾ However, how CD4⁺ T cells function in this aspect remains unclear.

In addition, Nod1 and Nod2 are cytosolic proteins of the pathogen recognition receptor within host cells that respond to pneumococci.⁽³⁴⁾ The myeloid differentiation factor (MyD88) is an adaptor molecule in the signaling of the host inflammatory cascade against pneumococcal infection.⁽³⁵⁾

Pneumococcal colonization

The first step leading to pneumococcal disease is nasopharyngeal colonization. *S. pneumoniae* spreads through respiratory droplets. Following exposure, the pathogen may establish itself in the nasopharynx of the new host. The human nasopharynx is the only known natural reservoir for *S. pneumoniae*. Invasive pneumococcal disease occurs when pneumococci gain access into deep human tissues, which might be facilitated by prior virus infection, especially influenza virus infection.⁽³⁶⁾ *S. pneumoniae* invades human nasopharyngeal epithelial cells

through a process termed reverse endocytosis mediated by pIgR. Nasopharyngeal colonization is dynamic, and influenced by overcrowding, smoking, ethnicity and socioeconomic status.⁽³⁷⁾ Colonization rates vary from 3% to 70% in healthy children in different countries and gradually decline with age up to adulthood.⁽³⁸⁻⁴⁰⁾ One way to reduce invasive pneumococcal disease is prevention of colonization. However, this may lead to replacement by other bacterial species in the nasopharynx, such as *Staphylococcus aureus* and *Haemophilus influenzae*.⁽⁴¹⁾ Hence, a protein-based pneumococcal vaccine to prevent the invasive disease without disturbing the bacterial ecology in the nasopharynx may be considered for controlling pneumococcal disease.⁽⁴¹⁾

Evolution of *S. pneumoniae*

S. pneumoniae was the first pathogen to demonstrate the phenomenon of transformation. In 1944, Avery et al. proved that the genetic material in bacterial cells was DNA by using a transformation model in *S. pneumoniae*.⁽⁴²⁾ Natural competence for genetic transformation in *S. pneumoniae* is mediated by a quorum sensing-regulated system. CSP, a heptadecapeptide pheromone, induces competence in growing cells at a critical cell density by activating the 2-component signal transduction system comDE.⁽³⁾ Due to the ability to undergo horizontal gene transfer, *S. pneumoniae* easily adapts to environmental changes, which leads to substantial genetic heterogeneity as well as genomic plasticity (Fig. 1). The first example is the presence of divergent mosaic blocks in penicillin binding protein (PBP) genes in penicillin-resistant *S. pneumoniae* under the selective pressure of

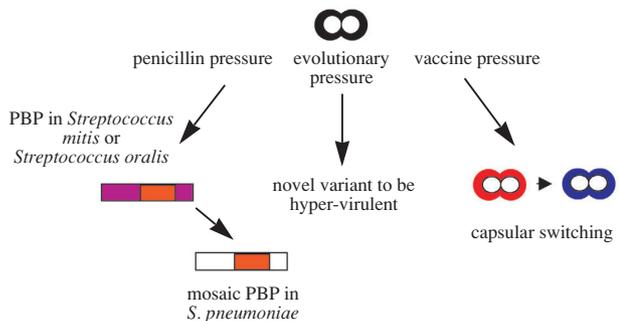


Fig. 1 Evolution of naturally transformable *Streptococcus pneumoniae*.

penicillin. Mosaic PBP genes evolve to be penicillin-resistant via acquiring PBP from other *Streptococcus* species.⁽⁴³⁾ The second example is the evolution to greater virulence via recombination. Serotype 6B causes more invasive diseases than serotype 6A. By using multilocus sequence typing, serotype 6B clones evolved almost exclusively by recombination, whereas serotype 6A evolved by mutation.⁽⁴⁴⁾ The third example is capsular switching under a large-scale vaccination program.⁽⁴⁵⁾ Although the current introduction of conjugate pneumococcal vaccine has successfully reduced invasive pneumococcal disease caused by the vaccine serotypes and effectively decreased the spread of antimicrobial drug-resistant isolates, pneumococcal infection remains a major issue. At least two consequences have been noted since the use of heptavalent conjugate vaccine. First, serotypes not covered by the conjugate vaccine have increased both in nasopharyngeal colonization and clinical illness.⁽⁴⁵⁾ Second, serotype switching can occur through recombination in naturally transformable clones and result in the acquisition of a non-vaccine capsule to escape vaccine-induced immunity.⁽⁴⁵⁾ Furthermore, the ability of different serotypes to be transformed affected the evolutionary biology and genetic diversity of each serotype. Serotype competence accounts for why the reported serotypes that underwent *in vivo* capsular transformation were also antibiotic-resistant. Gene transfer has been a powerful tool in the evolution of *S. pneu-*

moniae.

Emerging disease: complicated pneumonia

S. pneumoniae is the most common pathogen of pyogenic pneumonia in children. Previous studies have shown that the lungs return to normal after pneumococcal pneumonia, regardless of the severity at the peak stage of the disease. This is for two reasons. First, *S. pneumoniae* usually induces granulocyte apoptosis, which tends to limit tissue injury and promotes the complete resolution of pneumonia.⁽⁴⁶⁾ Second, *S. pneumoniae* produces few exotoxins capable of inducing lung damage, in contrast to other organisms such as *Staphylococcus aureus* and *Streptococcus pyogenes*, which produce a variety of tissue-damaging substances causing lung necrosis and destructive lung injury.⁽⁴⁷⁾ Since the advent of the use of penicillin, *S. pneumoniae* infection has rarely developed into empyema or lung necrosis.

However, an increase of complicated pneumococcal pneumonia, including necrotizing pneumonia, lung abscess and empyema, has been observed in children since the 1990s^(5,48,49) (Table 1). The occurrence of complicated pneumonia was associated with longer durations of fever, longer oxygen requirement and longer hospital stays.^(5,48) Older age, white race, presence of immature polymorphonuclear leukocytes in peripheral blood, high CRP levels, no underlying disease or chest pain on presentation were predictors of lung necrosis and/or abscess.^(5,48) This increase of

Table 1. Studies of an Increase in Complicated *Pneumococcal Pneumonia*

Reference	Country	Year	Pattern of complicated pneumonia	Prevalent serotype
(5)	U.S.A.	1993-2000	necrotizing pneumonia, pleural effusion, empyema and lung abscess	14, 1, 19, 6, 3
(50)	U.S.A.	1996-2000 (pre-PCV7)	empyema	1, 14, 6B, 19F
		2001-2005 (post-PCV)	empyema	1, 3, 19A
(51)	U.K.	1997-2001	empyema	1, 14, 3
(54)	U.K.	1997-2003	cavitary disease	1, 3, 14, 9V
(48)	Taiwan	1995-2003	necrotizing pneumonia, empyema	14, 23, 19, 9
(49)	Israel	1986-1997	pleural effusion, empyema, pneumothorax, pneumatocele and/or atelectasis	Not done
(55)	Singapore	1997-1999	cavitary necrosis, abscess formation, empyema	Not done
(56)	Spain	1993-2003	parapneumonic pleural effusion	Not done

Abbreviation: PCV: heptavalent conjugate vaccine.

complicated pneumonia is not directly related to the increase in penicillin-resistant *S. pneumoniae*.^(5,48,49) In the U.S., serotype 14 was the most common serotype causing complicated pneumonia, whereas serotype 1 and serotype 3 significantly caused complicated pneumonia compared to those serotypes causing lobar pneumonia in children before the widespread use of heptavalent pneumococcal conjugate vaccine.⁽⁵⁾ After the utilization of conjugate vaccine, serotype 1 remained prevalent, and serotypes 3 and 19A were increasingly detected.⁽⁵⁰⁾ In the U.K., serotype 1 was also the dominant serotype causing pneumococcal empyema.⁽⁵¹⁾ Clonal spread of pneumococcal serotype 1 is speculated to contribute to the increased complicated pneumonia in the U.S. and U.K. Interestingly, serotype 1 *S. pneumoniae* was rare in the nasopharynx but had a high clinical incidence. This serotype was common in both Northern Europe and North America in the early 20th century, and now has become more prevalent in developing countries such as Rwanda, Egypt and Africa. Poverty, overcrowding and decreased availability of antibiotics all contribute to the spread of serotype 1.⁽⁵²⁾ In view of the rare carriage of serotype 1 *S. pneumoniae*, it is mysterious as to how it is transmitted among humans. In most cases of culture-negative parapneumonic pleural effusion or empyema, serotype 1 was the frequent etiology.^(51,53) Surprisingly, several studies failed to identify serotype 1 in clinical samples in Taiwan. Instead, the major clone associated with complicated pneumonia in Taiwan was serotype 14.⁽⁴⁸⁾ Since serotype 1 is difficult to culture, whether there is real serotype difference in complicated pneumonia is worth further study in Taiwan.

Conclusion

Given the proclivity of horizontal gene transfer, current advances in antimicrobial therapy and serotype-limited conjugate vaccine are inadequate to combat pneumococcal diseases. In the future, better understanding of molecular interaction at the cellular level could provide insight into the development of protein vaccine and new modulation therapy.

REFERENCES

1. Hausdorff WP, Bryant J, Paradiso PR, Siber GR. Which pneumococcal serogroups cause the most invasive disease: implications for conjugate vaccine formulation and use, part I. *Clin Infect Dis* 2000;30:100-21.
2. Austrian R. Pneumococcus: the first one hundred years. *Rev Infect Dis* 1981;3:183-9.
3. Havarstein LS, Coomaraswamy G, Morrison DA. An unmodified heptadecapeptide pheromone induces competence for genetic transformation in *Streptococcus pneumoniae*. *Proc Natl Acad Sci USA* 1995;92:11140-4.
4. Campbell EA, Choi SY, Masure HR. A competence regulon in *Streptococcus pneumoniae* revealed by genomic analysis. *Mol Microbiol* 1998;27:929-39.
5. Tan TQ, Mason EO Jr, Wald ER, Barson WJ, Schutze GE, Bradley JS, Givner LB, Yogev R, Kim KS, Kaplan SL. Clinical characteristics of children with complicated pneumonia caused by *Streptococcus pneumoniae*. *Pediatrics* 2002;110:1-6.
6. Whitney CG, Farley MM, Hadler J, Harrison LH, Bennett NM, Lynfield R, Reingold A, Cieslak PR, Piliushvili T, Jackson D, Facklam RR, Jorgensen JH, Schuchat A; Active Bacterial Core Surveillance of the Emerging Infections Program Network. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med* 2003;348:1737-46.
7. Weiser JN, Markiewicz Z, Tuomanen EI, Wani JH. Relationship between phase variation in colony morphology, intrastrain variation in cell wall physiology, and nasopharyngeal colonization by *Streptococcus pneumoniae*. *Infect Immun* 1996;64:2240-5.
8. Morona JK, Paton JC, Miller DC, Morona R. Tyrosine phosphorylation of CpsD negatively regulates capsular polysaccharide biosynthesis in *Streptococcus pneumoniae*. *Mol Microbiol* 2000;35:1431-42.
9. Saluja SK, Weiser JN. The genetic basis of colony opacity in *Streptococcus pneumoniae*: evidence for the effect of box elements on the frequency of phenotypic variation. *Mol Microbiol* 1995;16:215-27.
10. Waite RD, Struthers JK, Dowson CG. *Spontaneous sequence* duplication within an open reading frame of the pneumococcal type 3 capsule locus causes high-frequency phase variation. *Mol Microbiol* 2001;42:1223-32.
11. Guidolin A, Morona JK, Morona R, Hansman D, Paton JC. Nucleotide sequence analysis of genes essential for capsular polysaccharide biosynthesis in *Streptococcus pneumoniae* type 19F. *Infect Immun* 1994;62:5384-96.
12. Bender MH, Yother J. CpsB is a modulator of capsule-associated tyrosine kinase activity in *Streptococcus pneumoniae*. *J Biol Chem* 2001;276:47966-74.
13. Lock RA, Hansman D, Paton JC. Comparative efficacy of autolysin and pneumolysin as immunogens protecting mice against infection by *Streptococcus pneumoniae*. *Microb Pathog* 1992;12:137-43.
14. Ren B, Szalai AJ, Thomas O, Hollingshead SK, Briles DE. Both family 1 and family 2 PspA proteins can inhibit

- complement deposition and confer virulence to a capsular serotype 3 strain of *Streptococcus pneumoniae*. *Infect Immun* 2003;71:75-85.
15. Tu AH, Fulgham RL, McCrory MA, Briles DE, Szalai AJ. Pneumococcal surface protein A inhibits complement activation by *Streptococcus pneumoniae*. *Infect Immun* 1999;67:4720-4.
 16. McDaniel LS, Yother J, Vijayakumar M, McGarry L, Guild WR, Briles DE. Use of insertional inactivation to facilitate studies of biological properties of pneumococcal surface protein A (PspA). *J Exp Med* 1987;165:381-94.
 17. Luo R, Mann B, Lewis WS, Rowe A, Heath R, Stewart ML, Hamburger AE, Sivakolundu S, Lacy ER, Bjorkman PJ, Tuomanen E, Kriwacki RW. Solution structure of choline binding protein A, the major adhesin of *Streptococcus pneumoniae*. *EMBO J* 2005;24:34-43.
 18. Cockeran R, Durandt C, Feldman C, Mitchell TJ, Anderson R. Pneumolysin activates the synthesis and release of interleukin-8 by human neutrophils in vitro. *J Infect Dis* 2002;186:562-5.
 19. Zysk G, Bejo L, Schneider-Wald BK, Nau R, Heinz H. Induction of necrosis and apoptosis of neutrophil granulocytes by *Streptococcus pneumoniae*. *Clin Exp Immunol* 2000;122:61-6.
 20. Barocchi MA, Ries J, Zogaj X, Hemsley C, Albiger B, Kanth A, Dahlberg S, Fernebro J, Moschioni M, Masignani V, Hultenby K, Taddei AR, Beiter K, Wartha F, von Euler A, Covacci A, Holden DW, Normark S, Rappuoli R, Henriques-Normark B. A pneumococcal pilus influences virulence and host inflammatory responses. *Proc Natl Acad Sci USA* 2006;103:2857-62.
 21. Pettigrew MM, Fennie KP, York MP, Daniels J, Ghaffar F. Variation in the presence of neuraminidase genes among *Streptococcus pneumoniae* isolates with identical sequence types. *Infect Immun* 2006;74:3360-5.
 22. Ling E, Feldman G, Dagan R, Mizrahi-Nebenzahl Y. Cytokine mRNA expression in pneumococcal carriage, pneumonia, and sepsis in young mice. *J Infect Dis* 2003;188:1752-6.
 23. Brueggemann AB, Griffiths DT, Meats E, Peto T, Crook DW, Spratt BG. Clonal relationships between invasive and carriage *Streptococcus pneumoniae* and serotype- and clone-specific differences in invasive disease potential. *J Infect Dis* 2003;187:1424-32.
 24. Sa-Leao R, Tomasz A, Sanches IS, Nunes S, Alves CR, Avo AB, Saldanha J, Kristinsson KG, de Lencastre H. Genetic diversity and clonal patterns among antibiotic-susceptible and -resistant *Streptococcus pneumoniae* colonizing children: day care centers as autonomous epidemiological units. *J Clin Microbiol* 2000;38:4137-44.
 25. Mohler J, Azoulay-Dupuis E, Amory-Rivier C, Mazoit JX, Bedos JP, Rieux V, Moine P. *Streptococcus pneumoniae* strain-dependent lung inflammatory responses in a murine model of pneumococcal pneumonia. *Intensive Care Med* 2003;29:808-16.
 26. Brown JS, Hussell T, Gilliland SM, Holden DW, Paton JC, Ehrenstein MR, Walport MJ, Botto M. The classical pathway is the dominant complement pathway required for innate immunity to *Streptococcus pneumoniae* infection in mice. *Proc Natl Acad Sci USA* 2002;99:16969-74.
 27. Kaplan MH, Volanakis JE. Interaction of C-reactive protein complexes with the complement system. I. Consumption of human complement associated with the reaction of C-reactive protein with pneumococcal C-polysaccharide and with the choline phosphatides, lecithin and sphingomyelin. *J Immunol* 1974;112:2135-47.
 28. Kadioglu A, Andrew PW. The innate immune response to pneumococcal lung infection: the untold story. *Trends Immunol* 2004;25:143-9.
 29. Khan AQ, Chen Q, Wu ZQ, Paton JC, Snapper CM. Both innate immunity and type 1 humoral immunity to *Streptococcus pneumoniae* are mediated by MyD88 but differ in their relative levels of dependence on toll-like receptor 2. *Infect Immun* 2005;73:298-307.
 30. van Rossum AM, Lysenko ES, Weiser JN. Host and bacterial factors contributing to the clearance of colonization by *Streptococcus pneumoniae* in a murine model. *Infect Immun* 2005;73:7718-26.
 31. Malley R, Henneke P, Morse SC, Cieslewicz MJ, Lipsitch M, Thompson CM, Kurt-Jones E, Paton JC, Wessels MR, Golenbock DT. Recognition of pneumolysin by Toll-like receptor 4 confers resistance to pneumococcal infection. *Proc Natl Acad Sci USA* 2003;100:1966-71.
 32. Srivastava A, Henneke P, Visintin A, Morse SC, Martin V, Watkins C, Paton JC, Wessels MR, Golenbock DT, Malley R. The apoptotic response to pneumolysin is Toll-like receptor 4 dependent and protects against pneumococcal disease. *Infect Immun* 2005;73:6479-87.
 33. Kadioglu A, Coward W, Colston MJ, Hewitt CR, Andrew PW. CD4-T-lymphocyte interactions with pneumolysin and pneumococci suggest a crucial protective role in the host response to pneumococcal infection. *Infect Immun* 2004;72:2689-97.
 34. Philpott DJ, Girardin SE. The role of Toll-like receptors and Nod proteins in bacterial infection. *Mol Immunol* 2004;41:1099-108.
 35. Yamamoto M, Takeda K, Akira S. TIR domain-containing adaptors define the specificity of TLR signaling. *Mol Immunol* 2004;40:861-8.
 36. Muller HE. Lethal synergism between influenza virus and *Streptococcus pneumoniae*. *J Infect Dis* 2003;187:1674-5.
 37. Hoge CW, Reichler MR, Dominguez EA, Bremer JC, Mastro TD, Hendricks KA, Musher DM, Elliott JA, Facklam RR, Breiman RF. An epidemic of pneumococcal disease in an overcrowded, inadequately ventilated jail. *N Engl J Med* 1994;331:643-8.
 38. Vives M, Garcia ME, Saenz P, Mora MA, Mata L, Sabharwal H, Svanborg C. Nasopharyngeal colonization in Costa Rican children during the first year of life. *Pediatr Infect Dis J* 1997;16:852-8.

39. Coles CL, Kanungo R, Rahmathullah L, Thulasiraj RD, Katz J, Santosham M, Tielsch JM. Pneumococcal nasopharyngeal colonization in young South Indian infants. *Pediatr Infect Dis J* 2001;20:289-95.
40. Chiou CC, Liu YC, Huang TS, Hwang WK, Wang JH, Lin HH, Yen MY, Hsieh KS. Extremely high prevalence of nasopharyngeal carriage of penicillin-resistant *Streptococcus pneumoniae* among children in Kaohsiung, Taiwan. *J Clin Microbiol* 1998;36:1933-7.
41. Bogaert D, De Groot R, Hermans PW. *Streptococcus pneumoniae* colonisation: the key to pneumococcal disease. *Lancet Infect Dis* 2004;4:144-54.
42. Avery OT, MacLeod CM, McCarty M. Studies on the chemical nature of the substance inducing transformation of pneumococcal types. *J Exp Med* 1944;79:137-58.
43. Dowson CG, Hutchison A, Brannigan JA, George RC, Hansman D, Linares J, Tomasz A, Smith JM, Spratt BG. Horizontal transfer of penicillin-binding protein genes in penicillin-resistant clinical isolates of *Streptococcus pneumoniae*. *Proc Natl Acad Sci USA* 1989;86:8842-6.
44. Robinson DA, Briles DE, Crain MJ, Hollingshead SK. Evolution and virulence of serogroup 6 pneumococci on a global scale. *J Bacteriol* 2002;184:6367-75.
45. Kaplan SL, Mason EO Jr, Wald ER, Schutze GE, Bradley JS, Tan TQ, Hoffman JA, Givner LB, Yogev R, Barson WJ. Decrease of invasive pneumococcal infections in children among 8 children's hospitals in the United States after the introduction of the 7-valent pneumococcal conjugate vaccine. *Pediatrics* 2004;113:443-9.
46. Haslett C. Granulocyte apoptosis and its role in the resolution and control of lung inflammation. *Am J Respir Crit Care Med* 1999;160:S5-11.
47. Spreer A, Lis A, Gerber J, Reinert RR, Eiffert H, Nau R. Differences in clinical manifestation of *Streptococcus pneumoniae* infection are not correlated with in vitro production and release of the virulence factors pneumolysin and lipoteichoic and teichoic acids. *J Clin Microbiol* 2004;42:3342-5.
48. Hsieh YC, Hsueh PR, Lu CY, Lee PI, Lee CY, Huang LM. Clinical manifestations and molecular epidemiology of necrotizing pneumonia and empyema caused by *Streptococcus pneumoniae* in children in Taiwan. *Clin Infect Dis* 2004;38:830-5.
49. Wexler ID, Knoll S, Picard E, Villa Y, Shoseyov D, Engelhard D, Kerem E. Clinical characteristics and outcome of complicated pneumococcal pneumonia in a pediatric population. *Pediatr Pulmonol* 2006;41:726-34.
50. Byington CL, Korgenski K, Daly J, Ampofo K, Pavia A, Mason EO. Impact of the pneumococcal conjugate vaccine on pneumococcal parapneumonic empyema. *Pediatr Infect Dis J* 2006;25:250-4.
51. Eastham KM, Freeman R, Kearns AM, Eltringham G, Clark J, Leeming J, Spencer DA. Clinical features, aetiology and outcome of empyema in children in the north east of England. *Thorax* 2004;59:522-5.
52. Dagan R, Gradstein S, Belmaker I, Porat N, Siton Y, Weber G, Janco J, Yagupsky P. An outbreak of *Streptococcus pneumoniae* serotype 1 in a closed community in southern Israel. *Clin Infect Dis* 2000;30:319-21.
53. Obando I, Arroyo LA, Sanchez-Tatay D, Moreno D, Hausdorff WP, Brueggemann AB. Molecular typing of pneumococci causing parapneumonic empyema in Spanish children using multilocus sequence typing directly on pleural fluid samples. *Pediatr Infect Dis J* 2006;25:962-3.
54. Ramphul N, Eastham KM, Freeman R, Eltringham G, Kearns AM, Leeming JP, Hasan A, Hamilton LJ, Spencer DA. Cavitary lung disease complicating empyema in children. *Pediatr Pulmonol* 2006;41:750-3.
55. Tan Kendrick AP, Ling H, Subramaniam R, Joseph VT. The value of early CT in complicated childhood pneumonia. *Pediatr Radiol* 2002;32:16-21.
56. Deiros Bronte L, Baquero-Artigao F, Garcia-Miguel MJ, Hernandez Gonzalez N, Pena Garcia P, del Castillo Martin F. Parapneumonic pleural effusion: an 11-year review. *An Pediatr (Barc)* 2006;64:40-5.

二十一世紀轉化中的肺炎雙球菌

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肺炎雙球菌是造成敗血症、鼻竇炎、中耳炎、細菌性腦膜炎的重要病因之一，每年都造成相當大的發病率及死亡率。這個疾病特別容易發生在兒童及老年人身上。當宿主受肺炎雙球菌感染時，複雜的免疫反應使得治療效果受限。近幾年來，抗藥性肺炎雙球菌的產生使得肺炎雙球菌的治療更為困難。幸運的是，由於7價結合型肺炎雙球菌疫苗的使用，成功的降低了疫苗型侵襲性肺炎雙球菌疾病的發生，也減少了抗藥性肺炎雙球菌的散播。雖然如此，由於肺炎雙球菌具有自然勝任能力，能夠將原本的疫苗型莢膜轉換成非疫苗型莢膜。宿主由於疫苗的保護，不會被疫苗型肺炎雙球菌感染，但有可能會受到非疫苗型肺炎雙球菌的侵襲。在未來，發展一個更經濟實惠，不受莢膜型限制的蛋白疫苗，將是努力的目標。(長庚醫誌2008;31:117-24)

關鍵詞：肺炎雙球菌，結合型疫苗，轉化的

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