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EXPLORING THE CLINICAL ASPECTS OF VACCINE-PREVENTABLE INVASIVE AND NON-INVASIVE BACTERIAL DISEASE WITHIN EUROPE

A. Vergison

ULB, Brussels, Belgium

Bacterial infections remain the most common cause of mortality and morbidity in children worldwide. Implementation of vaccination programmes has decreased the incidence of bacterial disease caused by *Haemophilus influenzae* type b¹ and group C meningococci;² however, invasive disease and mucosal respiratory tract infections due to Gram-positive bacteria, primarily *Streptococcus pneumoniae*, remain prevalent.³ Pneumonia remains a leading cause of morbidity and mortality in Europe, causing an estimated 300,000 hospitalisations and 31,500 child deaths annually.⁴

S. pneumoniae causes invasive pneumococcal disease (IPD), characterised by bacteraemia, septicaemia and bacterial meningitis. The consequences can be severe, resulting in hospitalisation, complications and death. Whilst non-invasive diseases are generally less severe than IPD, their higher incidence poses a significant healthcare and social burden, including promotion of antibiotic resistance.⁵ The introduction of pneumococcal conjugate vaccines has led to important decreases in the incidence of IPD,⁶ and to a lesser extent on pneumonia hospitalisations⁷ and on acute otitis media (AOM) visits.⁸

Although non-typeable *H. influenzae* (NTHi) has been increasingly recognised as a pathogen in invasive diseases,⁹ it is also a causative agent of mucosal disease, predominantly in association with *S. pneumoniae*. The role of NTHi is well established in AOM,¹⁰ still controversial in lobar pneumonia, and increasingly implicated in chronic bronchial inflammation in young children with persistent wheezing.¹¹

In Europe, the spectrum of invasive and non-invasive disease that could be prevented by vaccination remains significant, with potential immediate effects on morbidity and mortality, and long-term impact on indirect disease burden.

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SYNFLORIX™: WHAT HAVE WE LEARNED FROM IMMUNOGENICITY STUDIES?

J. Wysocki

Poznan University of Medical Sciences,
Poznan, Poland

Synflorix™ (10-valent pneumococcal conjugate vaccine; GlaxoSmithKline Biologicals, Belgium) has been investigated globally to evaluate immunogenicity, safety and reactogenicity with different vaccination schedules and routine co-administered vaccines.¹ As expected, population variability in immune responses following priming was observed between continents.^{2,3} In European studies, Synflorix™ was proven to be immunogenic post-primary and post-booster vaccination in terms of

-amount of antibody (ELISA) for the 10 serotypes and protein D (carrier for 8/10 serotypes) and

-functional antibodies (opsonophagocytic activity; OPA) for the 10 serotypes.¹ Furthermore, Synflorix™ induced similar immunological memory following the licensed 3+1 schedule or the investigational 2+1 schedule in Europe, with robust immune responses after a challenge dose 2 years post-booster.⁴

Although not indicated for non-vaccine-serotypes, in clinical trials, Synflorix™ has induced cross-reactive immune responses (ELISA and OPA) and immunological memory against serotypes 6A and 19A post-primary⁴ and post-booster vaccination.⁵ An 11-valent prototype vaccine included serotype 3; however, no efficacy or immune memory was observed⁶ and it was removed from the final formulation.¹ Synflorix™ decreased nasopharyngeal carriage of vaccine-serotypes in the second year of life by 23-35%.⁷ Whilst a trend towards increased carriage of non-vaccine-serotypes was observed,⁷

a trend towards decreased 6A carriage was noted in line with the cross-reactive immune response induced by Synflorix™.⁸ These data give the first indications of biological activity and effectiveness of Synflorix™. The efficacy of pneumococcal vaccines needs careful monitoring and ongoing trials (COMPAS⁹ and FinIP¹⁰) will evaluate efficacy and effectiveness, respectively, of Synflorix™ against invasive pneumococcal disease, pneumonia, acute otitis media and carriage.

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PREVENTING ACUTE OTITIS MEDIA THROUGH VACCINATION: WHAT MIGHT THE FUTURE HOLD

M. Knuf

Universal Medicine, Mainz, Mainz, Germany

Acute otitis media (AOM) constitutes a significant burden in children, in terms of clinical, psychological, social and economic costs.^{1,2} It is the most frequent reason for antibiotic prescriptions in children,³ thus contributing to the development of antibiotic resistance. Therefore, preventing AOM via

vaccination is a promising approach.⁴ The impact of vaccination with the 7-valent pneumococcal conjugate vaccine (PCV7) on AOM visits and episodes in the US has been reported in various studies. There is a broad range of reported impacts, with randomised controlled trials reporting 6-9% decreases and most observational studies reporting 13-26% decreases;⁵ however, one study reported a substantially higher decrease (43%).⁶ The 43% reduction was well outside the range reported in the other studies, possibly due to various methodological limitations.

Synflorix™ (10-valent pneumococcal conjugate vaccine; GlaxoSmithKline Biologicals, Belgium) is licensed in Europe for active immunisation against invasive disease and AOM caused by *Streptococcus pneumoniae* in infants and children from 6 weeks up to 2 years of age.⁷ Although not indicated for protection against AOM caused by non-typeable *Haemophilus influenzae* (NTHi) in Europe, there are data that support the hypothesis that this vaccine may also protect against AOM due to NTHi; these include data from the POET trial indicating efficacy of 33.6%, 51.5% and 35.3% for all-cause AOM, pneumococcal AOM and NTHi AOM, respectively;⁸ immunogenic bridging studies of Synflorix™ to the POET trial;⁹ and pre-clinical efficacy data in chinchillas.¹⁰ Importantly, clinical efficacy (COMPAS) and effectiveness (FinIP) trials are ongoing to evaluate potential indications for AOM and pneumonia.

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