Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study

Nick J Andrews, Pauline A Waight, Polly Burbidge, Emma Pearce, Lucy Roalfe, Marta Zancolli, Mary Slack, Shamez N Ladhani, Elizabeth Miller, David Goldblatt

Summary

Background **Efficacy of the 13-valent pneumococcal conjugate vaccine (PCV13) was inferred before licensure from an aggregate correlate of protection established for the seven-valent vaccine (PCV7). We did a postlicensure assessment of serotype-specific vaccine effectiveness and immunogenicity in England, Wales, and Northern Ireland to derive the correlates of protection for individual serotypes.**

Methods **We assessed vaccine effectiveness against invasive pneumococcal disease using the indirect cohort method. We measured serotype-specific IgG concentration in infants after they were given two priming doses of PCV7 (n=126) or PCV13 (n=237) and opsonophagocytic antibody titre from a subset of these infants (n=100). We derived correlates of protection by relating percentage protection to a threshold antibody concentration achieved by an equivalent percentage of infants. We used multivariable logistic regression to estimate vaccine effectiveness and reverse cumulative distribution curves to estimate correlates of protection.**

Findings **For the 706 cases of invasive pneumococcal disease included in the study, PCV13 vaccine effectiveness after two doses before age 12 months or one dose from 12 months was 75% (95% CI 58–84). Vaccine effectiveness was 90% (34–98) for the PCV7 serotypes and 73% (55–84) for the six additional serotypes included in PCV13. Protection was shown for four of the six additional PCV13 serotypes (vaccine effectiveness for serotype 3 was not significant and no cases of serotype 5 infection occurred during the observation period). The vaccine effectiveness for PCV13 and PCV7 was lower than predicted by the aggregate correlate of protection of 0·35 µg/mL used during licensing. Calculated serotype-specific correlates of protection were higher than 0·35 µg/mL for serotypes 1, 3, 7F, 19A, 19F, and lower than 0·35 µg/mL for serotypes 6A, 6B, 18C, and 23F. Opsonophagocytic antibody titres of 1 in 8 or higher did not predict protection.**

Interpretation **PCV13 provides significant protection for most of the vaccine serotypes. Although use of the aggregate correlate of protection of 0·35 µg/mL has enabled the licensing of effective new PCVs, serotype-specific correlates of protection vary widely. The relation between IgG concentration after priming and long-term protection needs to be better understood.**

Funding **Public Health England and UK Department of Health Research and Development Directorate.**

Lancet Infect Dis 2014; 14: 839–46

Published Online July 18, 2014 http://dx.doi.org/10.1016/S1473-3099(14)70822-9

See Comment page 784

Statistics, Modelling, and Economics Department, Health Protection Services (N J Andrews PhD), **Immunisation, Hepatitis, and Blood Safety Department, Health Protection Services** (P A Waight BSc, S N Ladhani MD, E Miller FRCPath), **and Respiratory and Vaccine Preventable Bacteria Reference Unit, Microbiology Services** (M Slack FRCPath), **Public Health England, London, UK; and Immunobiology Section, UCL Institute of Child Health, London, UK** (P Burbidge BSc, E Pearce BSc, L Roalfe BSc, M Zancolli PhD, Prof D Goldblatt MB ChB)

Correspondence to: Prof David Goldblatt, UCL Institute of Child Health, London WC1N 1EH, UK **d.goldblatt@ucl.ac.uk**

Introduction

Since 2010, the seven-valent pneumococcal conjugate vaccine (PCV7) has been replaced in many countries by higher valency vaccines containing ten (PCV10, GlaxoSmithKline, Brentford, UK) or 13 (PCV13, Pfizer, New York, NY, USA) serotypes. This change in vaccine became necessary as a result of the change in serotypes causing invasive pneumococcal disease, partly driven by the use of PCV7. The high effectiveness of PCV7 at reducing vaccine-type invasive pneumococcal disease[1] has been partly offset by an increase in invasive pneumococcal disease caused by non-vaccine serotypes.[2,3] The serotypes that emerged as major causes of invasive pneumococcal disease after the widespread use of PCV7 include many of the additional serotypes in PCV10 and PCV13.

Assessment of vaccine effectiveness for the newer, extended-valency PCVs is of particular interest because, unlike PCV7, PCV10, and PCV13 were licensed on the basis of immunogenicity data alone. Head-to-head studies of PCV7 and the new vaccines with immunogenicity endpoints were deemed acceptable for licensing the new conjugates,[4] largely because of the existence of a correlate of protection for PCV7. An anticapsular polysaccharide antibody concentration of 0·35 µg/mL measured by ELISA aggregated across all the seven serotypes in PCV7 is regarded as predictive of protection against invasive pneumococcal disease.[5] This correlate was derived from three randomised trials of PCV7 or an experimental nine-valent conjugate (Wyeth, Collegeville, PA, USA) done in California, USA,[6] in an Indigenous American population,[7] and in South Africa,[8] by correlation of post-primary IgG concentrations aggregated across the three studies with aggregate efficacy against invasive pneumococcal disease.[5]

Individual serotype-specific correlates could not be derived from the efficacy trials because even the largest PCV7 trial showed significant serotype-specific efficacy

for only three of the seven serotypes, with wide CIs because of small numbers of cases of invasive pneumococcal disease.[9] Researchers therefore derived an aggregate estimate, although serotype-specific differences in the amount of antibody needed to protect against invasive pneumococcal disease and otitis media are now recognised.[10,11] Pooled data from the heterogeneous populations investigated in the efficacy trials[6–8] were used to narrow the confidence limits around the point estimate of efficacy, despite different levels of protection seen in these three populations. With effectiveness estimates for the additional serotypes in the extended-valency conjugates now available, the possibility exists to derive serotype-specific correlates of protection. More precise estimates will both aid decision making relevant to vaccine schedules and inform the licensure of next-generation extended-valency conjugates.

PCV13 replaced PCV7 in the UK on April 1, 2010. For both vaccines, a 2+1 schedule was used (at 2, 4, and 12 months). We previously reported on the effectiveness of PCV13 against vaccine-type invasive pneumococcal disease in the first 15 months after introduction in a case-control (indirect cohort) study.[12] Here, we extend the estimates of effectiveness to 3·5 years after introduction. Additionally, using data from immunogenicity studies of PCV13 and PCV7 in infants in the UK and previously published data for the effectiveness of PCV7,[13] we aimed to derive individual serotype-specific estimates of correlates of protection for the vaccine serotypes and to calculate the first serotype-specific functional correlates of protection based on opsonophagocytic killing.

For the **ELISA protocol** see http://www.vaccine.uab.edu/ELISA%20Protocol.pdf

Methods

Setting

We did a postlicensure indirect cohort study to investigate the serotype-specific effectiveness and correlates of protection for PCV13. We used cases of invasive pneumococcal disease (diagnosed in infants by culture of *Streptococcus pneumoniae* from a normally sterile site or by DNA detection in pleural fluid or cerebrospinal fluid) for which a serotype was identified. Cases were reported during a sufficiently long surveillance period (3·5 years and about 700 cases) to produce serotype-specific estimates of vaccine effectiveness that we could use to produce and assess correlates of protection based on antibody measurements from available clinical trial data (n=126 for PCV7 serotypes; n=237 for PCV13 serotypes).

Procedures

To assess vaccine effectiveness, we used all cases of invasive pneumococcal disease in the cohort eligible for PCV13 vaccination in England, Wales, and Northern Ireland identified up to Oct 31, 2013, through enhanced national surveillance by Public Health England (responsible for surveillance in these countries; formerly known as the Health Protection Agency until 2013) and in whom the serotype of the infecting isolate was known.[3] To enhance study power, individuals born on or after April, 2008, were included as long as the onset of invasive pneumococcal disease was on or after March 30, 2010, because they might have received PCV13 as a booster dose. We obtained vaccination history, clinical risk group, and prematurity status from general practitioners through a postal questionnaire and telephone calls. Only individuals aged at least 2·5 months were included, and those with serogroup information only were excluded. For the assessment of vaccine effectiveness against the extra serotypes in PCV13 (including 6C), PCV7 serotypes were excluded; for the assessment of PCV13 vaccine effectiveness against PCV7 serotypes, any child who received PCV7 was excluded.

To derive correlates of protection, we used serum samples from children who had received PCV7 or PCV13 in two immunogenicity studies (Findlow and colleagues[6] and EudraCT 2010-023865-22/NCT01425372) by the UK National Vaccine Evaluation Consortium (NVEC). These studies were done in two representative populations in the middle of England and on the outskirts of London that have been used consistently by NVEC for vaccine studies to inform UK immunisation policy. For PCV7 and PCV13 serology, serotype-specific IgG was measured at age 5 months after PCV7 (n=126)[6] or PCV13 (n=237; EudraCT 2010-023865-22/NCT01425372) administration at ages 2 months and 4 months.

We used ELISA to assay serum samples for antibodies to 13 vaccine-type capsular polysaccharides (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F) at the University College London Institute of Child Health (London, UK), a WHO reference laboratory for pneumococcal serology, as previously described.[14] We obtained prevaccination IgG titres from infants in the first year of life from historical data generated before the introduction of PCV7 in the UK.[15] In a random subset of serum samples (n=100), we measured functional antibodies to the 13 vaccine serotypes in a multiplexed opsonophagocytic assay, as previously described.[14] Values are expressed as an opsonophagocytic antibody titre equivalent to the reciprocal of the serum dilution needed to produce 50% killing of the relevant serotype.

Statistical analysis

We calculated vaccine effectiveness using a case-control design wherein the cases are individuals with vaccine-type invasive pneumococcal disease and controls are individuals with invasive pneumococcal disease caused by the non-PCV13 serotypes (Broome or indirect cohort method),[16] as described previously for UK PCV7 and PCV13 studies.[12,13] We used logistic regression to adjust for age (2·5–5, 6–12, 13–17, 18–23, 24–35, 36–47, and 48–56 months) and year of infection (2010, 2011, 2012, and 2013), and to examine the need to adjust for clinical risk group (since underlying comorbidities or prematurity might affect vaccine effectiveness).