

The stubborn persistence of adult pneumococcal pneumonia as a public health problem

Rosalind Hollingsworth* and Raul Isturiz

¹Pfizer Inc; Specialty Care—Medicines Development Group; Collegeville, PA USA

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Sirs:

We appreciate the opportunity to respond to Dr Fedson's reply¹ to our letter² in which we stated that effectiveness of polysaccharide pneumococcal vaccines for the prevention of non-invasive pneumococcal pneumonia or all-cause community acquired pneumonia has not been established. We stand by that statement. We did not overlook any reviews or meta-analyses previously published; we cited two of the most recent^{3,4} because their methodology is sound. Furthermore, we contend that if the positive or negative effects of pneumococcal polysaccharide vaccines (PPSVs) were clear cut, we would not still be debating after nearly 30 y of worldwide use.

The impact of 23-valent PPSV (PPSV23) has been recently estimated in the United Kingdom.⁵ In England and Wales, the PPSV23 program was expanded over the years 2003–2005 to include all those aged 65 y and older. As a result, the proportion of those aged ≥ 65 y who received PPSV23 increased from approximately 30% to 75%. The impact of this program was evaluated by the Health Protection Agency (now Public Health England) using national invasive pneumococcal disease (IPD) surveillance data. Between 1998 and 2006, IPD incidence due to PPSV23 serotypes in the targeted age groups was unchanged. At an individual level, the case-control study reported PPSV23 vaccine effectiveness for prevention of IPD declined from 48% (95% CI; 32% to 60%) within two years of vaccination to 15% (-3% to 30%) after five years. Furthermore, vaccine efficacy varied significantly by serotype, ranging from -23% (-85% to 19%) for serotype 3 to 63% (29% to 81%) for 12F ($P = 0.005$).

Dr Fedson discusses his reference to the 7-valent pneumococcal conjugate vaccine (PCV7) rather than the 13-valent PCV (PCV13) data in the original review. Although the pivotal clinical immunogenicity studies that supported licensure for PCV13 for adults ≥ 50 y of age were not published in a peer-reviewed journal until July 2013,^{6,7} these data are presented in the package inserts for this product which, for example, has been publicly available in the United States since December 2011.⁸ They are also presented and discussed in the FDA briefing document that supported licensing discussions in the United States,⁹ as well as in the European Public Assessment Report, which was made

publicly available in September 2011.¹⁰ Referring to earlier studies of PCV7 that do not assess functional antibodies is misleading.

When appraising any vaccine, hyporesponsiveness must not be taken lightly. In immunocompetent individuals, absent or low responses to pneumococcal polysaccharide vaccine antigens 7F and 23F preceded cases of pneumococcal pneumonia due to these serotypes;¹¹ if re-vaccination results in lower antibody responses than the first vaccination, it appears likely that hyporesponsiveness will be the precursor of clinical failure.

Dr Fedson states, incorrectly, that the conclusions of the cost-effectiveness studies of Weycker et al.¹² and Smith et al.^{13,14} are unreliable because of their assumed levels of indirect effects. His argument relies on selective data from a single study,¹⁵ a retrospective evaluation of hospital administrative records (2005–2006 compared with 1997–1999); this is but one piece of evidence in an accumulating body of literature on herd effects due to conjugate vaccines.^{16–20} For example, for all-serotype IPD, Simonsen et al. reported a 36% reduction in cases among persons aged 40–64 y and 47% among persons aged ≥ 65 y from widespread PCV7 use in children.¹⁵ However, these estimates are higher (substantially so for younger adults), than those reported by Pilishvili et al.¹⁹ for laboratory-confirmed cases from the Centers for Disease Control and Prevention's (CDC) Active Bacterial Core (ABC) surveillance (2007 compared with 1998–1999), which report an 18% reduction among persons aged 50–64 y and a 37% reduction among persons aged ≥ 65 y. It is unlikely that studies utilizing healthcare utilization data are more accurate than studies describing the impact on laboratory-confirmed cases. The Weycker et al. evaluation was informed by the herd effects reported by the CDC's ABC data, with estimated reductions ranging from 26–32%, depending on age.¹² For non-bacteremic pneumococcal pneumonia, Simonsen et al.¹⁵ reported a 44% reduction in hospitalized cases among persons aged 40–64 y and 54% among persons aged ≥ 65 y. In the only other study that evaluated pneumococcal pneumonia, Grijalva et al. reported much smaller reductions in hospitalized cases (2004 compared with 1997–1999); 10% among persons aged 40–64 y and 20% among persons aged ≥ 65 y.¹⁷ Both of these studies operationally defined pneumococcal pneumonia based on the appearance of

*Correspondence to: Rosalind Hollingsworth; Email: Ros.Hollingsworth@pfizer.com

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Table 1.

	65–74 y (Cases/100 000)	75–84 y (Cases/100 000)	≥85 y (Cases/100 000)
All cause CAP	1208	2398	4396
PCV7-type CAP*	36	72	132
PCV13-type CAP*	133	264	484

*Derived from data presented by Sherwin et al.,²⁸ percentage of radiographically-confirmed confirmed CAP due to PCV7 serotypes is 3%, percentage of radiographically-confirmed CAP due to PCV13 serotypes is 11%.

the specific *International Classification of Disease, Ninth Revision* (ICD-9) code for this disease, but, given the diagnostic difficulty of ascertaining the etiologic pathogen for pneumonia, this code is unlikely to be totally accurate. Accordingly, both studies also evaluated reductions in all-cause pneumonia hospitalizations. Simonsen et al. reported reductions of 8% among persons aged 40–64 y and 12% among persons aged ≥65 y,¹⁵ which were smaller than those reported by Grijalva et al.—19% among persons aged 40–64 y and 15% among persons aged ≥65 y).¹⁷ We note that both Weycker et al. and Smith et al. assumed herd effects against all-cause pneumonia based on data from Grijalva et al., which appear to be largely consistent with those reported in another independent study.¹⁸

We therefore maintain that the Weycker et al. and Smith et al. studies employed reasonable estimates of expected herd effects from widespread childhood use of PCV13, and that corresponding estimates of the cost-effectiveness of PCV13 in older adults are based on sound underlying assumptions. However, while the data for IPD are sound, the pneumonia data are more opaque. Healthcare utilization data, as described above, clearly point to a sustained reduction in all cause pneumonia hospitalizations in some, but not all, adult age groups. However, with these data systems there is no granularity regarding the underlying trends in vaccine and non-vaccine serotypes contributing to such pneumonias. In addition, the burden of pneumococcal pneumonia overall is not well characterized due to challenges of diagnostic testing (lack of sensitivity and specificity), presumptive antibiotic treatment, and so on. Furthermore, chest X-rays as the confirmatory diagnostic criteria for pneumonia are of low sensitivity and low positive predictive value; the calculation of the incidence of adult pneumonia would improve considerably taking into account the additional numbers of cases detected by the addition of more sensitive imaging procedures such as CT or ultrasound.^{21–26} Therefore, we and others²⁷ see great value in the use of the serotype-specific urinary antigen detection (UAD) assay for determining the burden of specific serotypes responsible for noninvasive pneumococcal pneumonia.

Recognizing the limitations of currently available data, let's consider the incidence of hospitalized all-cause pneumonia reported by Griffin et al. for US adults aged 65 years of age and older in 2009,¹⁸ and the percentage of hospitalized radiographically-confirmed pneumonia due to the PCV7 and PCV13 serotypes reported by Sherwin et al.²⁸ over a similar time period. As presented in the table, the incidence of all cause pneumonia, stratified by age, is reported as 1208 cases/100 000 in those aged

65–74 y, rising to 4396 cases/100 000 in those aged 85 y and older. We can apply the percentage of radiographically-confirmed pneumonia due to the PCV7 and PCV13 serotypes reported by Sherwin et al. and generate an estimate of the incidence of PCV7- and PCV13-type community acquired pneumonia (CAP) (Table 1).

This approach provides a conservative estimate of the incidence of PCV7-type CAP at a time when this vaccine had already been in widespread use in the United States pediatric population for approximately 10 y. Therefore, whatever the magnitude of decline of the PCV7 serotypes in pneumonia has been, these data suggest that PCV7 serotypes continue to cause a notable amount of pneumonia in adults. Pfizer and others have ongoing work to confirm these findings and to better define the true incidence of all-cause and pneumococcal CAP in the older adult population in the United States.

The global impact of the CAPiTA study,²⁹ the largest randomized, controlled, double blind adult vaccine trial ever conducted, will be of worldwide importance irrespective of the results. Pediatric use of PCV7 in the Netherlands initially, and more recently the 10-valent PCV (PCV10), do not diminish but enhance the value of CAPiTA. The use of PCV7 for childhood immunization in the Netherlands and associated herd effects in adults were anticipated and considered in sample size calculations for the CAPiTA study. Furthermore, conducting this study in a population with high uptake of PCV will improve the real world interpretation of the data for those many countries similarly benefitting from indirect effects. Although published information on any herd effects in adults following implementation of PCV10 is not available, the effect would impact both study arms. Moreover, serotype 19A, contained in PCV13 but not in PCV10, is among the most common pneumococcal serotypes recovered from respiratory specimens in adults in the United States and other areas of the world including the Netherlands and other countries of Europe.^{30–32} If efficacy against non-bacteremic pneumococcal pneumonia translates into PCV13 cost-effectiveness even by the most stringent calculations^{12–14} it will warrant direct protection by vaccination of older adults even in those countries that have experienced the largest herd effects from childhood immunization. Future research incorporating real-world data on the direct and indirect effects of vaccination is needed, and this research will reveal the true cost-effectiveness of PCV13 use in adults.

Given the persistently high burden of pneumococcal pneumonia in adults, a strategy that combines direct immunization plus indirect effects from a conjugate vaccine would have a solid public health benefit by protecting both the individual and society. For adults, given that (1) the serotype specific efficacy of polysaccharide vaccine is unknown and must be researched further, and (2) the possibility that PPSV23 induces hyporesponsiveness, impacting an individual's ability to subsequently respond to vaccination or natural infection, the additional benefit against IPD

probably afforded by at least some of the additional serotypes in PPVS23 makes sequential use of these vaccines a reasonable option until higher valency PCVs are developed.

Disclosure of Potential Conflicts of Interest

R.H. and R.I. are employees of Pfizer Inc.

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