Vaccine xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Commentary

# What is the heterogeneity in the impact seen with pneumococcal conjugate vaccines telling us?

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ARTICLE INFO

*Article history:*
Received 20 March 2017
Received in revised form 26 May 2017
Accepted 31 May 2017
Available online xxxx

*Keywords:*
Pneumococcus
Effectiveness
Acute otitis media
Invasive disease
Herd
Protection

ABSTRACT

Pneumococcal conjugate vaccines have proven highly effective in decreasing invasive disease and pneumonia in young children. However, there is considerable geographic variability in the impact of these vaccines on other disease endpoints and in other age groups. Investigation of the possible causes of this variability would greatly improve our understanding of pneumococcal pathophysiology and stimulate the effort to design more broadly effective vaccines.



## 1. Background

The fundamental premise of meta-analyses of vaccine impact is that there is a single "true" effectiveness value that should translate into similar vaccine impacts, regardless of setting. Sometimes the results are truly impressive.

For example, introduction of pneumococcal conjugate vaccines (PCVs) into pediatric immunization programs has consistently resulted in profound decreases in vaccine-type disease in both the target populations as well as in all other age groups through herd effects [1,2]. In the case of young children, this has resulted in a sustained decrease of 50–60% in rates of invasive pneumococcal disease (IPD) regardless of serotype [1]. These findings, as well as evidence of a significant impact on pediatric pneumonia rates and even on overall mortality [3,4] have justified the widespread use of PCVs in childhood immunization programs around the world, including many of the poorest countries.

In contrast, meta-analyses and systematic reviews have struggled to find a simple answer regarding the impact of pediatric PCV programs on two other important public health endpoints, acute otitis media (AOM) in children and the overall rate of IPD in older adults. Widely varying measurements of vaccine impact have been reported from different settings, ranging from quite substantial to virtually absent.

Yet to a surprising extent, most studies and reviews have downplayed this heterogeneity, often reflexively attributing it to differences in study design or methodology--if it's commented on at all. Rarely is consideration given to the possibility that PCV impact against these endpoints may truly vary by setting.

We briefly describe these examples, and then discuss why this heterogeneity may be overlooked.

## 2. Example 1: Variable impact of PCVs on AOM

Following introduction of the original 7-valent formulation (PCV7) into infant immunization programs, impact estimates have ranged widely from a 7% increase to a 48% decrease in AOM, even within the same setting (the US) over overlapping time periods [5].

Perhaps this variability shouldn't be surprising, as AOM is a polymicrobial disease, its clinical diagnosis is notoriously inaccurate, and AOM rates are subject to a wide variety of epidemiological and societal influences.

Because of AOM's high frequency, its association with antibiotic use and resistance [6] and its large economic impact, it is precisely in this murky area where rigorous critical evaluation is most in demand. Unfortunately, with few exceptions [5], original reports and reviews have glossed over the wide disparity in results.

For example, investigators reporting a 43% decrease in AOM visits in children <2 after PCV7 introduction [7], while terming it

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http://dx.doi.org/10.1016/j.vaccine.2017.05.089
0264-410X/

"more than expected" compared to the 6–9% decreases found in the double blind randomized controlled efficacy trials [5], curiously found it "consistent" with a 20% decrease reported in a similar study. A recent review of PCVs and AOM summarized this broad range of values as comprising a "substantial" reduction of the overall AOM burden [6].

Instead of being ignored, this variability should prompt a closer look at other factors and potential confounders that could be at work. One egregious example comes from a widely and uncritically cited [6,8,9] Greek hospital study that reported a 38% decrease in pediatric emergency room visits due to spontaneously draining otorrhoea [10] following PCV7 introduction. While an effect seems plausible based on efficacy trial results, considerable evidence indicates the decrease in this case likely PRECEDED population-level PCV introduction [5].

In fact, in most studies AOM rates were steadily declining in the years prior to PCV7 introduction [5]. That alone should give researchers pause. Indeed, investigators at Harvard [11], examining hospital discharge rates for AOM after PCV7, concluded that the decrease seen was most likely attributable not to the vaccine, but rather "the increasing trend in smoke-free households."

Yet this well-analyzed study, published 5 years ago and discussed at the biannual pneumococcal congress, has been cited by only a handful of papers in the PCV field. This may suggest a bias against citing studies that do not support one's beliefs.

## 3. Example 2: Variable herd impact of PCVs on overall IPD in older adults

A comprehensive meta-analysis [1] revealed a consistently positive effect of PCV7 on decreasing overall IPD in children. Three years after PCV7 introduction, 14/14 studies reported a decrease of at least 24% in overall IPD in <5 year olds, with a mean impact of 56% (95% CI: 45–65%); in those studies with longer experience, IPD rates remained low for at least 7 years.

The story in older adults ≥50 years of age is clearly more complex. On the one hand, the US Centers for Disease Control (CDC) convincingly documented an important herd impact on overall IPD in American adults following PCV7 introduction in children [12], with a larger number of cases prevented in non-vaccinees than in the target population [13].

On the other hand, only 5 of the 12 other studies included in the meta-analysis showed signs of any reduction in overall IPD in this age group, whether 3, 4, 5, or 6 years after introduction. Virtually all studies did describe profound decreases in vaccine type IPD within a few years of vaccine introduction, but these were negated by rises in non-vaccine type IPD.

A statistically significant point estimate for the mean effect was seen 7 years after PCV7 introduction. Yet by that time point, only 5 studies had sufficient follow-up time to remain in the meta-analysis, and the weighted results were heavily influenced by the large CDC study. Only year 7 values are mentioned in the abstract, and used to justify the authors' conclusions that "overall IPD decreased" in adults [1].

In fairness, the authors did highlight study variability and discuss potentially underlying methodological and societal factors. A more recent meta-analysis [2] by different investigators also revealed visually striking study-to-study variability in the change in IPD rates in older adults [Fig. 1], even 8–12 years after vaccine introduction. This, however, was not commented on; instead, these authors emphasized that their mathematical model came up with, in aggregate, a statistically significant decrease in IPD.

Neither meta-analysis mentioned the possibility that the magnitude—and even the existence—of an overall herd effect of PCV7 on IPD in older adults may depend on the specific epidemiological setting, driven perhaps by different degrees of non-vaccine type replacement disease [14].

## 4. Lessons from other vaccines

It is generally accepted that vaccines can show different levels of efficacy/effectiveness in different socio-economic settings. Classic examples include the geographical variability in efficacy of BCG against tuberculosis [15], of oral polio vaccine especially in South Asia [16] and more recently of rotavirus vaccines [17].

The variable results for each of these live vaccines, once viewed with skepticism, are since well accepted, and likely translate into the variable impact of the vaccines seen in real life.

Evidence exists from well-conducted clinical trials that highly immunogenic PCVs, which obviously are not live, also show setting-specific variability in their efficacy even against the highly specific outcome of VT invasive pneumococcal disease in children [18]. In addition, there have long been indications of country-specific epidemiological differences in serotype distribution that would likely affect vaccine impact. These differences were initially presumed to fall strictly along "developing" vs "developed" country lines [19], despite clear evidence of significant serotype differences even among developed country populations [20]. There is thus some biological plausibility that the variable impact of PCVs may be founded, at least in part, in variable efficacy or effectiveness against pneumococcal disease in different settings.

## 5. The biases we all have

We suggest that any number of "soft" biases, seen with other vaccines as well, could be causing investigators to ignore between study variability and overestimate the value of PCVs [Table 1].

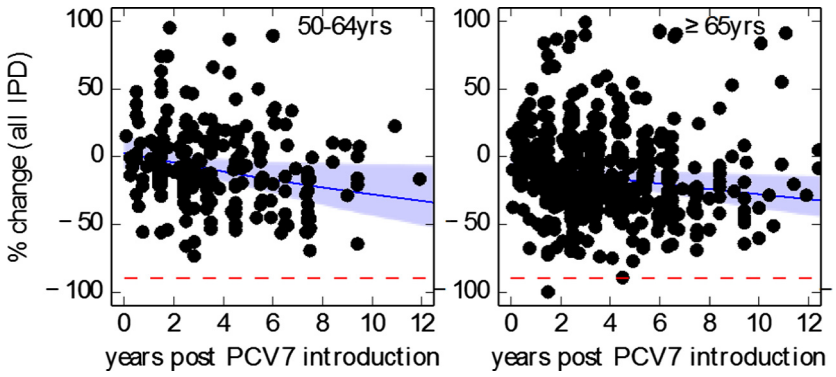


**Fig. 1.** Changes in overall IPD after the introduction of PCV7 into national immunization programs, stratified by age. (Reprinted from Fig. S4 of Shiri et al. [2] under the Creative Commons user license).

Please cite this article in press as: Hausdorff WP, Black S. What is the heterogeneity in the impact seen with pneumococcal conjugate vaccines telling us? Vaccine (2017), http://dx.doi.org/10.1016/j.vaccine.2017.05.089