Making sense of differences in pneumococcal serotype replacement

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Serotype replacement in invasive pneumococcal disease threatens to undermine the most costly vaccination programme currently undertaken. However, the effects of replacement on public health have varied geographically. Striking differences have emerged between the UK and USA, countries that otherwise often resemble each other epidemiologically. Similar to other European settings, the UK has had rising non-vaccine serotype invasive pneumococcal disease, most notably in older adults, since introducing a 13-valent pneumococcal conjugate vaccine to the paediatric immunisation schedule. Such impacts of serotype replacement have not been reported in the USA, where incidence of non-vaccine serotype invasive pneumococcal disease in young children and older people has been stable since the introduction of the same vaccine. Here, we explore factors that have been suggested to account for these differences, including surveillance practices, transmission dynamics, population risk factors, and pathogen evolution. We contend that none of these factors individually appears sufficient to account for the observed differences. Assessing the existing evidence, we define priorities for research and data collection to discern causes and inform future pneumococcal vaccine policy.

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Introduction

Serotype replacement is a concern in the use of vaccines that target a proportion of diverse antigenic types. Initially controversial and hard to distinguish from long-term trends, serotype replacement in pneumococcal carriage and disease after introduction of pneumococcal conjugate vaccines (PCVs) targeting seven, ten, and 13 serotypes from the more than 96 serotypes of *Streptococcus pneumoniae*, is now well established. However, the outcomes in terms of total morbidity have varied markedly. England and Wales reported 37% lower incidence of invasive pneumococcal disease since the period before PCV7 introduction; however, there was little or no reduction in disease among older people, owing to an increase in non-vaccine serotypes.[1] For reasons that remain unclear, the USA has not had similar increases in invasive pneumococcal disease caused by serotypes that are not targeted by vaccines (non-vaccine) among young children and older adults following PCV13 implementation.[2]

Because PCV scheduling is an evolving policy area, understanding the reasons for these differences is of paramount importance. The US Advisory Committee on Immunization Practices will soon revisit its 2014 recommendation for adults aged 65 years or older to receive PCV13.[3] Meanwhile, the UK Joint Committee on Vaccination and Immunisation has recommended a shift from the current 2+1 dose (two primary vaccines plus one booster) paediatric PCV13 series to a 1+1 series.[4] Studies of the effects of 1+1 schedules are underway for low-income and middle-income countries, where PCV10 and PCV13 use is supported by Gavi, the Vaccine Alliance.[5] Factors causing PCV7 and PCV13 implementation in the USA and Europe to bring about starkly different indirect effects on adult invasive pneumococcal disease should guide these decisions and the integration of next-generation pneumococcal vaccines into immunisation programmes.

We address possible explanations for the differences between the USA and Europe in serotype replacement and their implications, with the goal of defining a programme for research and data collection that could discriminate among hypotheses. Although we broadly seek to address the experiences of European settings, the availability of good quality invasive pneumococcal disease and carriage surveillance data from the UK allows us to highlight the British experience in greater depth.

Trends in serotype replacement

Although prelicensure PCV trials did not immediately indicate the risks of vaccine-induced serotype replacement in invasive pneumococcal disease among children,[6,7] trials with carriage[8,9] and otitis media[10] endpoints suggested that the niche vacated by PCVs could harbour other pneumococcal serotypes. Following PCV7 implementation, studies in the USA,[11] UK,[12] and other settings[13] reported that increases in the carriage of non-vaccine serotypes had offset reductions in the carriage prevalence of vaccine-targeted serotypes. The effect on non-vaccine serotype disease was initially controversial, given the variation in outcomes across settings, low statistical power in surveillance datasets, and the difficulties in distinguishing vaccine-driven phenomena from long-term trends.[14] However, nearly two decades' experience with programmatic use of PCV7, PCV10, and PCV13 has now supported the notion that paediatric vaccination increases the burden of non-vaccine serotype invasive pneumococcal disease in children and adults.[15,16]

Since the implementation of PCV13, conflicting observations have reignited the debate of how vaccination affects the incidence of disease caused by non-vaccine serotypes. Data from a nationwide cohort study of England and Wales showed rapid increases in non-vaccine serotype invasive pneumococcal disease immediately after PCV7 implementation in 2006, in both

children protected directly by vaccination and adults who were not vaccinated.[17] Whereas the switch to PCV13 in 2010 halted and reversed the rise in incidence of serotypes 1, 6A, and 7F in all age groups,[18] UK data[1] from 2018 indicate stark increases since 2013–14 in the incidence of all invasive pneumococcal disease in adults aged between 45 and 64 years and older than 65 years, together with more modest serotype replacement in vaccinated young children. The most notable serotypes were 8, 9N, 12F, and 15A, alongside those that had already been increasing since PCV7 was introduced in 2006.[1] By contrast, no increases in non-PCV13 serotype invasive pneumococcal disease were evident in US children younger than 5 years or adults aged 65 years or older, following the switch from PCV7 to PCV13.[2,19] Serotypes 8, 9N, and 15A are reported to be increasing in some US studies,[20] but they are minor contributors to disease burden in the USA, unlike in the UK. Most notably serotype 8, now causing 20% of invasive pneumococcal disease in England and Wales, has been isolated from less than 1% of US cases, and 12F is similarly rare.[19]

Studies from the USA are still more striking when compared with those from other settings. Increases in non-vaccine serotype invasive pneumococcal disease have negated reductions in vaccine-targeted disease in adults aged 65 years and older in Israel,[21] France,[22] Sweden,[23] and Canada;[24] in South Africa,[25] Italy,[26] and Spain, following PCV7 introduction;[27,28] and in Brazil where PCV10 has been implemented.[29] Although early increases in non-vaccine serotype disease in adults in Denmark[30] and Norway[31] did not fully offset pre-PCV13 disease burden, the pattern of replacement is more concordant with observations from elsewhere in Europe than in the USA (figure 1).

Explanation 1: differences in sampling

Pneumococcal serotypes vary in their association with invasive disease syndromes[32] and severity,[33] including risk of hospital admission and death. Consequently, variations in sampling criteria among countries might give rise to differing distributions of serotypes, and possibly incompatible estimates of invasive pneumococcal disease incidence. Whereas surveillance in the UK and Europe is essentially limited to hospital inpatients,[1,34] US surveillance includes both ambulatory and inpatient cases, resulting in a higher proportion of non-severe disease, such as occult bacteraemia. Precise differences between settings in the clinical threshold for taking cultures are difficult to define, but isolates collected from a sample of predominantly inpatients would generally be expected to come from more serious disease cases. Such factors have been suggested to explain historical differences in the incidence of serotype 1 disease in Europe and the USA.[34]

Although certainly important when comparing surveillance systems, it is hard to see how this explanation can fully account for the discrepant experience of the USA. Including less severe disease in the surveillance would be expected to increase reported disease incidence in the USA, but, in fact, since 2015 higher incidence has been reported in UK adults aged 65 years and above. Furthermore, although 35% of invasive pneumococcal disease isolates among surveilled US children aged 0–17 years come from ambulatory cases, the proportion in adults is only 6%.[19] Hence, sampling is more similar in the age group with the most notable difference in disease.

Explanation 2: transmission dynamics, age structure, and vaccine schedules

A second set of explanations concerns differential exposure to pneumococcal transmission. Differences in transmission dynamics could be caused by different PCV7–PCV13 schedules and uptake histories among countries, as well as sociodemographic factors. Independently or in combination, these factors could contribute to differences in how often various age groups encounter pneumococci.

The USA follows a 3+1 schedule for PCV13, whereas most European settings follow a 2+1 schedule. The choice of vaccine schedule could impart subtle differences on serotype replacement among vaccine recipients and those they come in contact with, with three primary doses being linked to a more immediate increase in the risk of carrying non-vaccine serotypes.[35] However, in one trial,[36] a long-term follow-up comparison of the 2+1 schedule with the 3+1 schedule found that the situation was reversed. In comparison with children who received a control vaccine, those who received the 2+1 schedule experienced a 72% increase in the rate at which they acquired non-vaccine serotype pneumococci, while children who received a 3+1 PCV series experienced only a 38% increase.[36] Such outcomes could reflect weaker natural protection against vaccine serotypes, owing to reduced carriage earlier in life among other factors. The expansion and distribution of vaccine coverage in the population might also influence serotype replacement. A focus on nationally aggregated data in most surveillance studies has tended to obscure the effects of considerable subnational heterogeneity in PCV coverage in some settings, historically due to vaccine supply issues[37] and increasingly due to vaccine hesitancy.[38] Although the contribution of local variation in coverage to rare outcomes like invasive pneumococcal disease is difficult to assess, analyses from the past 3 years have suggested that dose-specific coverage in children influences local maintenance of vaccine serotypes and determines indirect protection in adults.[39,40] However, considerations of schedule and coverage do little to explain the reasons for the differences in invasive pneumococcal disease, especially in older patients. The question remains: if replacement in carriage occurs, why is it followed by replacement disease in some settings and not others?

An alternative explanation, and one that is especially relevant for older adults, is that there are different contact

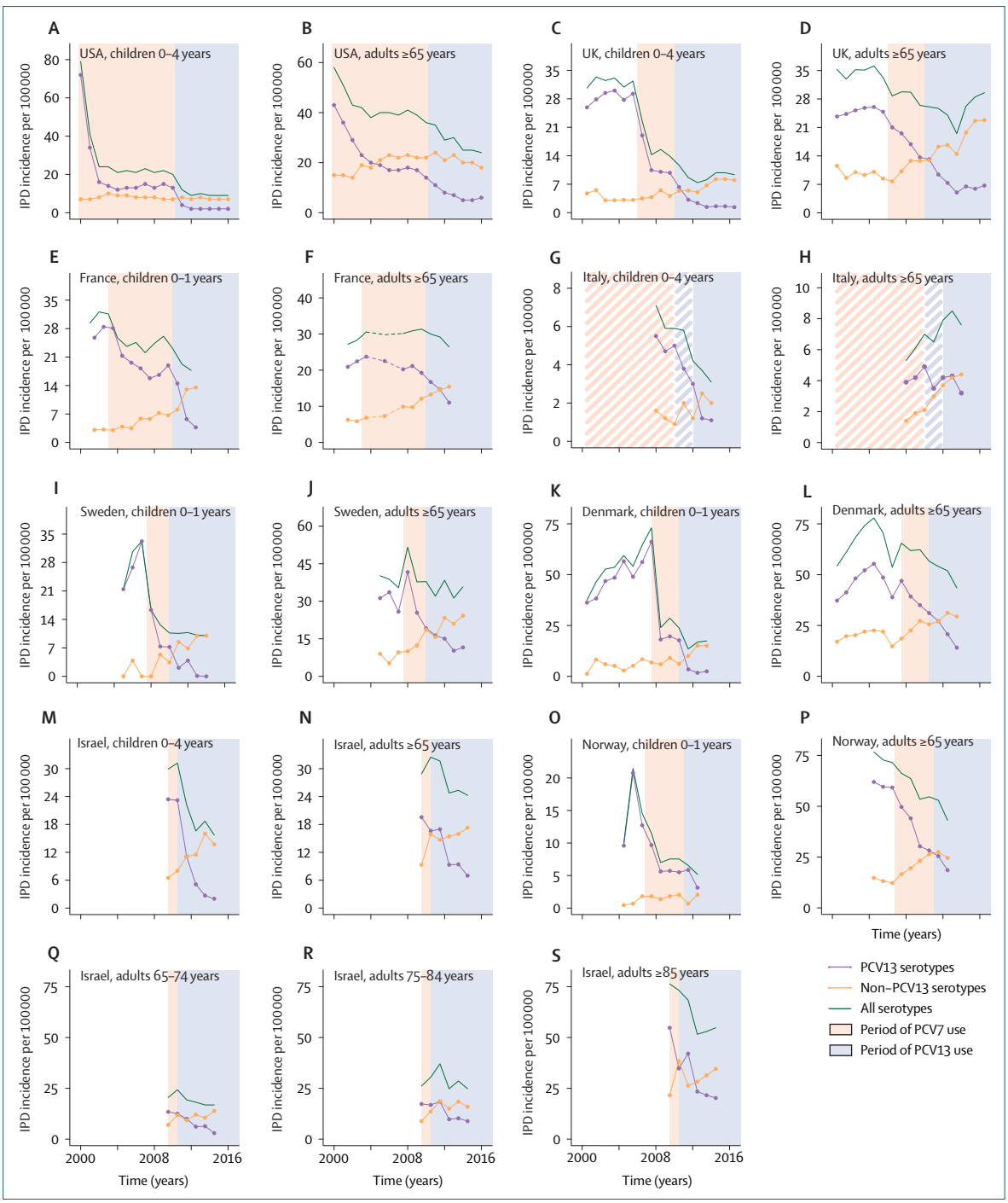

Figure 1: **Trajectories in non-vaccine and all-serotype invasive pneumococcal disease incidence amid PCV13 implementation per 100 000 individuals**
Trends in the incidence of invasive pneumococcal disease caused by PCV13-targeted and non-vaccine serotypes among children younger than 5 years and adults aged 65 years or older in each country using PCV13 for which a PubMed search of the terms "pneumococcal conjugate" AND "surveillance" identified data for pre-implementation and post-implementation invasive pneumococcal disease incidence.[1,2,21–24,26,30,31] Hatched lines are indicated for Italy, where vaccine recommendations were initially made at the regional level. IPD=invasive pneumococcal disease. PCV=pneumococcal conjugate vaccine.

patterns among generations and across settings. Increased exposure of older adults to the reservoir of pneumococci that colonise young children has been suggested to cause the well known spike in invasive pneumococcal disease in adults aged 65 years and older around the winter holiday season.[41] Whereas the 2014 recommendation from the US Advisory Committee on Immunization Practices[3] for adults aged 65 years or older

to receive PCV13 complicates comparisons of subsequent surveillance data, differences in serotype replacement in invasive pneumococcal disease in adults were evident well before this time, and can thus be assumed to stem largely from transmission among younger children.[42–46] There is little naturally acquired immunity against emerging non-vaccine serotypes in older adults in both settings; contact with children is probably their most important determinant of exposure. In earlier studies, household exposure to young children, in particular those who attend day care, was a risk factor for invasive pneumococcal disease in older adults.[47]

Anticipating the effects of factors that influence transmission intensity within and between generations is not straightforward. Contact patterns in the USA and Europe that could lead to observed differences in serotype replacement, including the potential for intergenerational spread, have not been systematically compared. However, census data indicate a roughly threefold higher prevalence of grandparent–grandchild co-residency in the USA compared with the UK.[48] Studies of geographical and age-structured mixing[49,50] at time scales beyond daily contact matrices[51] might help to model intergenerational transmission and implications for serotype replacement.

Explanation 3: risk factors

Although the USA, UK, and continental Europe are similar in many ways, they differ with respect to certain risk factors known to influence progression of pneumococcal carriage to invasive pneumococcal disease, such as age and demographics, cigarette smoking or exposure, alcohol misuse, and comorbidities such as chronic obstructive pulmonary disease, heart failure, asthma, cirrhosis, and diabetes.[52] Co-infecting viruses, whose incidence and transmission patterns vary across settings, further influence the risk of invasive pneumococcal disease and might account for differing seasonal patterns of pneumococcal disease across countries.[53] Even if vaccination led to identical changes in carriage, distinct trends over time in the distribution of such risk factors could result in contrasting trajectories in the incidence of invasive pneumococcal disease.

Several designs of epidemiological studies could provide straightforward answers for the role of these risk factors in changes in invasive pneumococcal disease incidence over the past decade. These designs range from ecological studies of co-occurring trends in invasive pneumococcal disease incidence and risk factor prevalence to case-control studies that measure changes in the fraction of invasive pneumococcal disease cases attributable to risk factors. However, it should be stated that at present no single risk factor is known to differ sufficiently between the USA and other settings to explain the discrepancy in pneumococcal disease trends. For example, the proportions of smokers in the USA and UK are actually similar (16·8% in the USA in 2014 *vs* 17·2% in the UK in 2015); in both cases, these numbers are lower than in most of western Europe.[54–56] The intensity of smoking, measured as numbers of cigarettes per smoker per day, has been consistently higher in the USA than these other settings since 1980.[57] Moreover, the countries are undergoing similar demographic transitions, with higher proportions of adults aged 65 years or older. However, data from Israel[21] have showed increasing disease rates within more narrowly defined strata of older people, suggesting that demographic change alone cannot explain the observations (figure 1).

In general, the societies of these developed areas are probably quite similar in terms of the risk factors for invasive pneumococcal disease, and it is not readily evident that their differing experiences with serotype replacement are associated with any particular risk factor.

Explanation 4: serotype interactions and molecular epidemiology

So far in this Personal View, we have paid little attention to the role played by serotypes themselves, including the differences among settings in their carriage distribution before and after PCV13 introduction and in their pathogenicity. Repeated cross-sectional carriage studies undertaken among children in Massachusetts, USA[11,58,59] and Hertford and Gloucestershire, UK[12,60,61] show differences in circulating non-vaccine serotypes amid the PCV7-to-PCV13 transition (figure 2), with higher PCV7-era prevalence of 23A and 35B in the USA, versus 21 and 22F in the UK. Serotype 15A expansion in UK carriage studies for the period 2013–15 mirrors its emergence as a major cause of disease. Nonetheless, serotype distributions in carriers in the two settings are somewhat similar, and the carriage data do little to clarify the greater invasive pneumococcal disease burden of serotypes 8, 9N, 12F, and 15A in the UK.

As serotype-specific invasiveness varies by orders of magnitude, even subtle differences in the prevalence of carried serotypes can produce stark differences in the total incidence of invasive pneumococcal disease caused by all serotypes. Notably, serotypes 8 and 12F were not detected by a 2018 UK carriage study,[60] despite being increasingly found in invasive disease. These serotypes are similarly absent from US pneumococcal carriage samples, and so it is possible that the increase in invasive pneumococcal disease due to 8 and 12F could reflect undetected changes in exposure for such vanishingly rare serotypes with an extremely high case-to-carrier ratio. When interpreting the available carriage data, the possibility that transmission of the emerging serotypes is clustered in space and time cannot be excluded. Serotypes causing even a substantial proportion of disease nationwide might not be captured in cross-sectional carriage samples from the particular communities where studies have been undertaken. This is not the case, however, for other serotypes such as 15B/C, which has reportedly been increasing in invasive pneumococcal disease in the UK, yet is already

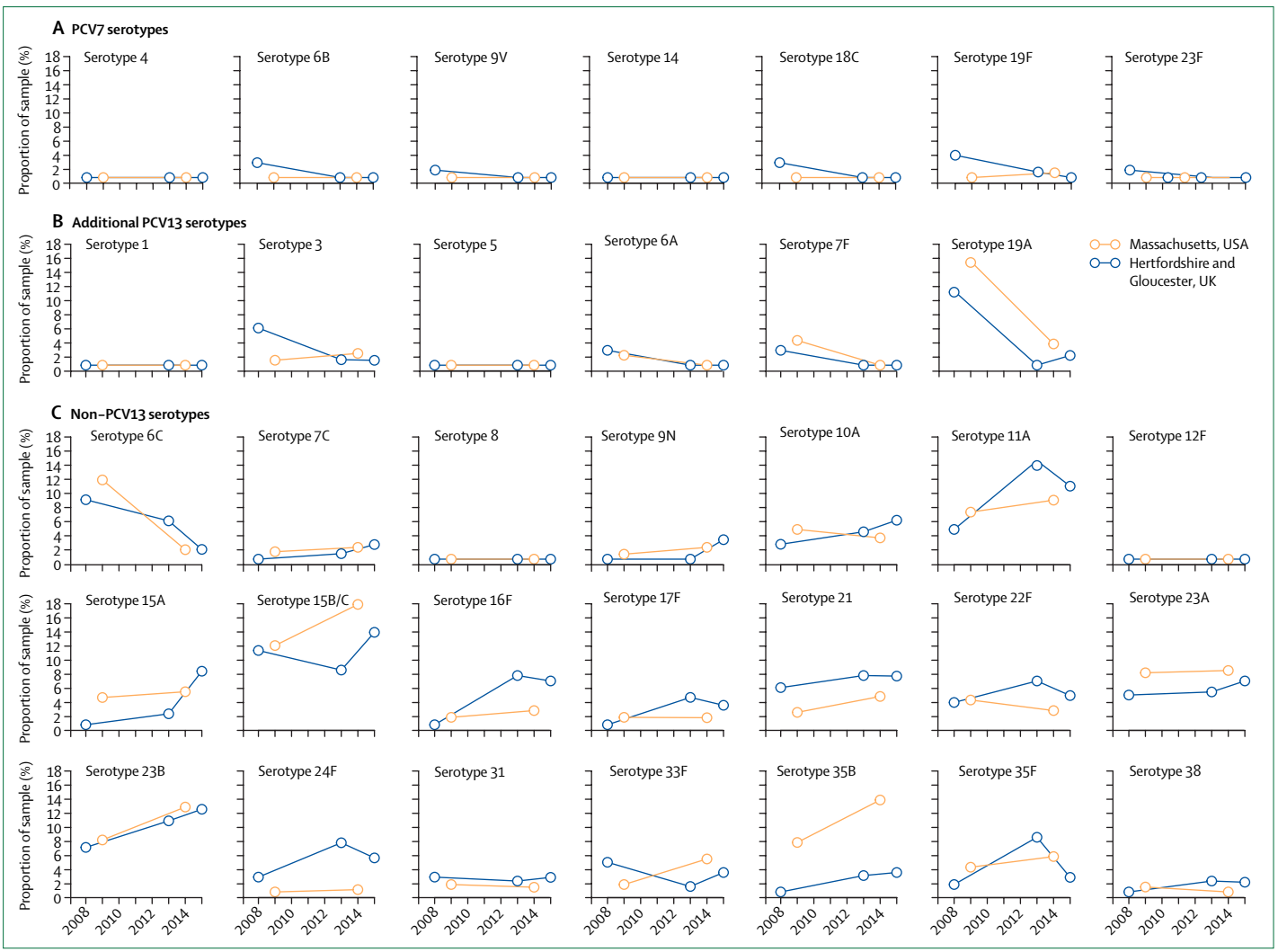

Figure 2: **Serotype-specific carriage in US and UK communities amid PCV7 and PCV13 implementation**
The proportion of colonisation of asymptomatic children younger than 5 years attributable to individual vaccine and non-vaccine serotypes in sequential cross-sectional studies undertaken in Massachusetts, USA[11,58,59] and Hertford and Gloucestershire, UK.[12,60,61] PCV=pneumococcal conjugate vaccine.

commonly carried in the USA with no similar increase in disease.

Variation in invasiveness has also been described among clonal lineages of the same serotype.[62,63] Case-to-carrier ratios have provided a useful way to measure the pathogenicity of pneumococcal lineages.[64–66] Although underpowered to determine changes within individual serotypes, data from the UK indicate a 54% overall increase in the case-to-carrier ratio of non-vaccine serotypes in 2015–16 relative to 2012–13.[60] Small changes in the composition of specific non-vaccine serotypes over the same period (figure 2) suggest that changes within lineages could in part be contributing to this increase. The high recombination rate of some pneumococci indeed permits rapid adaptive change.[67] However, for this effect to explain the increase in invasive pneumococcal disease in the UK, several conditions would have to be met. First, there would have to be large differences in case-to-carrier ratios between lineages of the same serotype. Second, increases in pathogenicity would have to be happening in parallel in multiple serotypes. Third, the affected serotypes would have to be only those not targeted by PCVs, with the possible exception of 3 and 19A. By contrast, long-term surveillance of carriage and disease in the USA among the Navajo and in Alaskan communities indicated no change in serotype-specific case-to-carrier ratios before and after PCV7 introduction.[42,68] It is uncertain whether serotype-specific case-to-carrier ratios have also remained consistent since PCV13 came into use in 2010. It is important to note that the case-to-carrier ratio for invasive pneumococcal disease in children could differ from that in older adults. However, this contrast is insufficient to explain the different epidemiology of invasive pneumococcal disease between the USA and other

settings because it raises the questions of why age-specific case-to-carrier ratios would vary across settings for a given serotype, and what evolutionary pressure might be selecting for higher case-to-carrier ratios only in Europe.

Other explanations

Although these explanations are a priori reasonable, it is an inescapable fact that none of them, independently, is especially plausible. Surveillance practices do vary, but it is hard to imagine they do so to the extent required for the USA to report stable incidence of non-vaccine serotype disease, whereas other countries report increases as those shown in figure 1. Similarly, although differences in risk factors or host contact networks might exist, they have oddly not produced differences in the epidemiology of diseases other than non-vaccine serotype invasive pneumococcal disease. Finally, the frequencies of distinct serotypes are somewhat different, but the great majority of lineages and serotypes in the USA are not absent from Europe and vice versa. For reasons that remain obscure, they are simply not causing as much disease in the USA. Thus, we must remain open to other possible explanations, featuring less well understood mechanisms.

Differences across countries in the microbiomes of individual hosts could be contributing to this effect. The pneumococcus is one of many streptococcal species that colonise the upper respiratory tract and some of these bacteria produce polysaccharide capsules that are serologically indistinguishable from certain pneumococcal capsules.[69,70] Could exposure to them alter host susceptibility to pneumococci that exhibit a similar antigen? Indeed, examples of these oral streptococci have been found colonising seniors in the USA[71] and interactions between them and pneumococci deserve attention. Understanding of the specificity of immune responses to structurally related capsules is only now beginning to emerge.[72] However, for these effects to explain the different experiences that follow PCV13, we would have to ask what prevented a similar effect following PCV7, and whether the oral microbiome in the USA is systematically different from that elsewhere.

Future directions

Establishing reasons for the differential extent of serotype replacement in invasive pneumococcal disease in the USA and UK, as well as most other countries, is crucial to mitigating future risks as policy makers weigh changes to PCV10 and PCV13 immunisation schedules, introduce PCVs to new settings, and plan to roll out next-generation pneumococcal vaccines. Several lines of investigation are needed to test the hypotheses above and to distinguish how these mechanisms influence the pneumococcal response to PCVs.

Characterising specific consistencies and inconsistencies surrounding serotype replacement in carriage and invasive pneumococcal disease in the USA, UK, and other countries is an immediate priority. Comparisons and discussions of replacement are made difficult by differences in practices of disease surveillance and reporting among countries and possibly over time. For instance, the UK has measured trends relative to historical incidence,[1,17,18] correcting for suspected changes in surveillance sensitivity, whereas the most recent analysis of US surveillance data[19] compares observations to the counterfactual incidence expected from continuing pre-PCV13 trends. There is also variation in the reporting of other important factors, including comorbidities, the exact serotypes that are being replaced, and their lineages and resistance characteristics. An agreed standard framework for reporting would be of great benefit.

Collaborative, side-by-side analysis of US and UK surveillance data is warranted. Clarifying consistencies and inconsistencies could itself streamline the identification and testing of hypotheses such as those we propose above, while at least giving a verdict on the considerations that we classify under Explanation 1. Although definitive comparisons are not straightforward, the explanations we offer are testable, provided appropriate data are collected.

Contributors

JAL and WPH contributed to the literature search, the collection and interpretation of data, the design of figures, and the writing of the manuscript.

Declaration of interests

JAL received grants and consulting fees from Pfizer, Inc to Harvard University and the University of California, Berkeley. WPH declares no competing interests.

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