Serotype replacement in disease after pneumococcal vaccination

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Vaccination with heptavalent pneumococcal conjugate vaccine (PCV7) has significantly reduced the burden of pneumococcal disease and has had an important public health benefit. Because this vaccine targets only seven of the more than 92 pneumococcal serotypes, concerns have been raised that non-vaccine serotypes (NVTs) could increase in prevalence and reduce the benefits of vaccination. Indeed, among asymptomatic carriers, the prevalence of NVTs has increased substantially, and consequently, there has been little or no net change in the bacterial carriage prevalence. In many populations, pneumococcal disease caused by NVT has increased, but in most cases this increase has been less than the increase in NVT carriage. We review the evidence for serotype replacement in carriage and disease, and address the surveillance biases that might affect these findings. We then discuss possible reasons for the discrepancy between near-complete replacement in carriage and partial replacement for disease, including differences in invasiveness between vaccine serotypes. We contend that the magnitude of serotype replacement in disease can be attributed, in part, to a combination of lower invasiveness of the replacing serotypes, biases in the pre-vaccine carriage data (unmasking), and biases in the disease surveillance systems that could underestimate the true amount of replacement. We conclude by discussing the future potential for serotype replacement in disease and the need for continuing surveillance.

Introduction

Widespread use of heptavalent pneumococcal conjugate vaccine (PCV7; Prevnar, Wyeth, Madison, NJ, USA) has significantly reduced the burden of pneumococcal disease in many populations.[1–8] PCV7 targets seven of the more than 92 serotypes (so-called "vaccine types") of *Streptococcus pneumoniae* (serotypes 4, 6B, 9V, 14, 18C, 19F, and 23F), whereas the newly available PCV13 covers these seven serotypes as well as serotypes 1, 3, 5, 6A, 7F, and 19A. PCV7 has greatly reduced the incidence of disease caused by these serotypes both in vaccinated young children and among non-vaccinated groups due to herd immunity, and has led to public health benefits throughout the developed world where it has been used. In light of this evidence and of clinical trials done in developing countries that show substantial benefits,[9–11] conjugate vaccines are being introduced more widely throughout the world. However, the epidemiological effect of broad-scale use of conjugate vaccines in new settings can be difficult to predict, so careful monitoring of disease burden will be needed to assess the initial and long-term effects of mass vaccination in each region where the vaccine is introduced.

The pneumococcal population has changed since the widespread introduction of PCV7. Non-vaccine types (NVTs) have increased among asymptomatic carriers in a process dubbed "serotype replacement",[12,13] and to a lesser extent, NVTs have increased as causes of invasive pneumococcal disease (IPD). In nasopharyngeal carriage, we define serotype replacement as an increase in the proportion of individuals in a population who harbour NVTs in their nasopharynx after vaccine introduction. For IPD, serotype replacement is defined as an increase in the incidence of IPD caused by NVTs after vaccine introduction. Although the reported magnitude of this increase in disease among NVTs has been relatively modest in most countries, such changes have the potential to dampen the overall public-health benefit of the vaccine.

A key question is why does serotype replacement seem to be complete among asymptomatic carriers whereas replacement in disease seems incomplete? In other words, why has the vaccine successfully reduced the burden of pneumococcal disease whereas the prevalence of bacterial carriage has not changed? Understanding this issue will be crucial to enable us to predict the effects of future pneumococcal vaccination programmes, particularly in developing countries where pneumococcal epidemiology differs from that in Europe and the USA. We therefore review the evidence for serotype replacement in carriage and disease, assess potential biases in the data and reasons for heterogeneity between studies, discuss the biological and epidemiological features of the serotypes, and address the relative contributions of vaccination and other factors to the increases in NVTs. We also discuss the potential effects

Search strategy and selection criteria

We identified relevant studies on serotype replacement in disease with a comprehensive search of PubMed (by use of combinations of the search terms "pneumococ*", "Streptococcus pneumoniae", "PCV7", "conjugate", and "serotype") and the reference lists of selected articles. Because we were interested in the question of population-wide serotype dynamics, we included only studies that reported the incidence of vaccine-type and NVT disease in the general population (ie, nationwide or hospital-based surveillance systems or vaccine trials on otherwise healthy individuals) and excluded studies that focused exclusively on high-risk groups. Additionally, we excluded studies that only reported changes in proportions of serotypes, rather than absolute numbers of cases or incidence, because proportions do not give an indication of the effect of replacement on disease burden.

In instances in which multiple publications resulted from the same study, we extracted data from the most recently available publication. Some additional studies that were too small to infer changes in the serotype distribution, but that might be of interest to readers, have been included. We also discuss publicly available surveillance data from England and Wales, but do not include these in our comparisons because the methods for their collection and analysis have not been published.

of serotype replacement after the introduction of conjugate vaccines in diverse settings.

Nasopharyngeal carriage: the precursor to IPD

The first reports of serotype replacement came from a double-blind, randomised placebo-controlled trial (RCT) from The Gambia that showed that carriage of vaccine types significantly declined in vaccinated infants, while carriage of NVTs significantly increased.[14] As a result of this change, the net effect on carriage prevalence in the trial was small. An Israeli vaccine trial did not show a significant effect of serotype replacement in carriage among vaccinated children,[15] but a subsequent trial in Israel did show evidence of replacement.[16] Additionally,

	Study location (population)	Surveillance period	Year vaccine introduced	Study details	Age (years)	Change in incidence		
						Periods compared	NVT	IPD (net)
North America								
Kaplan et al[37]	USA	1994–2008	2000	8 hospitals nationwide	Paediatric	1994–99 *vs* 2007–08	..	−53%
Kaplan et al[37]	USA	1994–2008	2000	8 hospitals nationwide	Paediatric	2001 *vs* 2007–08	+100%*	−16%*
Techasaensiri et al[38]	Dallas, TX, USA	1999–2008	2000	Single hospital	≤18	1999 *vs* 2005–08	+177%	−22% (among serotyped cases [−38% among all IPD cases])
Bettinger et al[4]	Canada	2000–07	2001 (regional), 2005 (nationwide)	Active, nationwide	<5	2000–01 *vs* 2006–07	+90%	−61%
Jacobs et al[39]	Cleveland, OH, USA	1999–2007	2000	Hospital laboratory (invasive isolates only)	≤18 and >18	1999 *vs* 2005–07	≤18 years: +200%; >18 years: +88%	≤18 years: −69%; >18 years: −27%
Pilishvili et al[2]	USA	1998–2007	2000	Active, nationwide	<5 and ≥65	1998–99 *vs* 2006–07	<5 years: +32% (+102% hospitalised only); ≥65 years: +32% (36% hospitalised only)	<5 years: −77% (−60% hospitalised only); ≥65 years: −36% (−35% hospitalised only)
Wenger et al[40]	Alaska, USA	1996–2007	2000	Population-based laboratory	<5	1996–2000 *vs* 2005–07	Alaska native (Yukon): +185%; non-native rural: +321%; non-native urban: +240%	Alaska native (Yukon): −22%; non-native rural: −29%; non-native urban: −48%
Lacapa et al[41]	USA (Apache)	1991–2006	2000	Active surveillance	<1 and ≥18	1991–97 *vs* 2004–06	<1 year: −7%; ≥18 years: +32%	<1 year: −68%; ≥18 years: +4%
Weatherholtz et al[42]	USA (Navajo)	1995–2006	2000	Active surveillance	<5 and >18	1995–97 *vs* 2004–06	<5 years: −8%; >18 years: +6%	<5 years: −60%; >18 years: −2%
Black et al[43]	California, USA	1996–2005	2000	Laboratory cases in Northern California Kaiser system	<5	1996–2000 *vs* 2003–05	−5%	−78%
Messina et al[44]	Texas, USA	1999–2005	2000	Prospective, hospital	<18	1999 *vs* 2005	+171%†	−31%
Steenhoff et al[45]	Philadelphia, PA, USA	1999–2005	2000	Single hospital	<18	1999–2000 *vs* 2001–05	+75%	−57%
Byington et al[46]	Western USA	1996–2003	2000	Intermountain healthcare system‡	<2 and <18	1997–99 *vs* 2001–2003	<18 years: +125%§	<2 years: −40%; <18 years: +13%
Europe								
Foster et al[47]	Oxfordshire, UK	1995–2009	2006	Regional laboratory surveillance	<2 and ≥2	1995–2005 *vs* 2006–08	<2 years: +56%; ≥2 years: +18%	<2 years: −48%; ≥2 years: −16%
Maraki et al[48]	Crete, Greece	2000–09	2006	Single hospital	≤14	2000–04 *vs* 2005–09	+21%	−38%
Doit et al[49]	France	2001–08	2002/2003	Single hospital	<16	2001-04 *vs* 2005–08	+85%	−8%
Harboe et al[1]	Denmark	2000–08	2007	Nationwide surveillance	<2 and ≥5	2000–07 *vs* 2008	<2 years: −10%; ≥5 years: 0	<2 years: −56%; ≥5 years: −9%
Rodenburg et al[8]	Netherlands	2004–08	2006	Hospital sentinel surveillance	<2¶ and ≥65	2004–06 *vs* 2006–08	<2 years: +71%; ≥65 years: +6%	<2 years: −44%; ≥65 years: +2%
Rückinger et al[7]	Germany	1997–2008	2006	Nationwide hospital and laboratory surveillance	<2	1997–2003 *vs* 2007–08	+3%	−56%
Vestrheim et al[3]	Norway	2004–08	2006	Nationwide, mandatory reporting	<5 and ≥65	2004–05 *vs* 2008	<5 years: −5%; ≥65 years: +22%	<5 years: −72%; ≥65 years: −15%

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	Study location (population)	Surveillance period	Year vaccine introduced	Study details	Age (years)	Change in incidence		
						Periods compared*	NVT	IPD (net)
(Continued from previous page)								
Adranuy et al[5]	Barcelona, Spain	1997–2007	2001 (low coverage)	Single hospital (invasive isolates only)	≥65	1997–2001 *vs* 2005–07	+66%	+23%
Fenoll et al[50]	Spain	1979–2007	2001 (variable coverage)	Nationwide hospitals, passive (adjusted for ascertainment bias)	All ages	1996–2000 *vs* 2004–05	+38%	+2%
Guevara et al[51]	Navarre, Spain	2001–07	..	Active surveillance	<5 and ≥65	2001–02 *vs* 2006–07	<5 years: +47%; ≥65 years: +46%	<5 years: −12%; ≥65 years: +4%
Pérez-Trallero et al[52]	Spain (Basque)	1996–2007	..	Single hospital (adjusted for population size)	<5 and ≥65	1996–2000 (<5 years) or 1998–2000 (≥65 years) *vs* 2005–07	<5 years: +93%; ≥65 years: +32%	<5 years: −11%; ≥65 years: −3%
Muñoz-Almagro et al[53]	Barcelona, Spain	1997–2006	2001 (low coverage)	Single hospital	<2	1997–2001 *vs* 2002–06	+531%	+58%
Bingen et al[54]	France	2001–05	2002/2003	Nationwide hospital laboratory (meningitis only), among serotyped cases	<2‖	2001–02 *vs* 2005	+44%	−21%
Dias and Caniça[55]	Portugal	1999–2004	2002	Population/laboratory surveillance	<1	2002–04	+29%	−18%
Aristegui et al[56]	Basque and Navarro, Spain	1998–2003	..	Retrospective (pre-vaccination), prospective (post-vaccination) in several hospitals‡	<2 and 2–5	1998–01 *vs* 2002–03	<2 years: −3%; 2–5 years: +6%	<2 years: −27%; 2–5 years: +10%
Australia								
Hanna et al[57]	Queensland, Australia	1999–2007	2001	Laboratory-based (indigenous population only)	<5 and ≥15	1999–2001 *vs* 2005–07	<5 years: −3%; ≥15 years: +39%	<5 years: −61%; ≥15 years: +7%
Lehmann et al[58]	Western Australia	1997–2007	2001/2005	Enhanced	<2 and 15–29	1997–2001 vs 2005–07	Aboriginal, <2 years: +33%; non-aboriginal, <2 years: +53%; aboriginal, 15–29 years: +166%	Aboriginal, <2 years: −46%; non-aboriginal, <2 years: −67%; aboriginal, 15–29 years: +88%

We have summarised the findings of each study by presenting both net percentage changes in pneumococcal disease before and after vaccination and the percentage change among NVTs. In many instances, these numbers depend on which years were included before and after vaccination and which age-groups are reported. We have reported the years and age-groups that were used for the comparisons and noted other factors that might influence the calculations.[14-73] Note that this list of studies is not exhaustive and we have excluded publications that repeat data from the same study. Additional studies were excluded for the following reasons: lacked pre-vaccine baseline data; reported relative, rather than absolute, serotype frequencies; lacked a pre-vaccine baseline period; size was too small to infer changes in serotype distribution. Excluded studies came from France,[49,59,60] Spain,[6,61-64] Canada,[65-68] USA,[69-71] Taiwan,[72] and South Korea.[73] Additional studies that overlapped those listed were also excluded. NVT=Non-vaccine types. IPD=Invasive pneumococcal disease. *Adjusted for changes in annual admissions. †Probably affected by missing isolates from 1999. ‡By serogroup, not serotype. Serotype 19A included with the vaccine serogroup. §Not adjusted for population size. ¶Children born after April 1, 2006 compared with age-matched pre-vaccine cohort. ‖2–24 months.

Table: **Selected studies of changes in serotype distribution in disease**

RCTs from South Africa,[17] Netherlands,[18] the US Navajo population,[19] and a subsequent trial in The Gambia[20] have shown replacement in carriage. Because these were RCTs, they implicate vaccination rather than other factors as the cause of the increase in NVT carriage.

Since the licensure of PCV7, several observational studies have reported changes in the pneumococcal serotypes present in carriage. A paediatric cross-sectional study from Massachusetts, USA, has shown that, in the first 7 years of universal vaccination, PCV7 serotypes have been almost totally eliminated from carriage in young children.[21] However, carriage of NVTs has increased markedly, so the overall carriage prevalence is similar between the pre-vaccine and post-vaccine eras.[22] Additionally, serotype replacement has been observed in carriage studies from Norway,[23] France,[24,25] Portugal, Greece,[26] and Texas and Alaska, USA.[27,28]

The increase in carriage of NVT in these studies could be partly due to the artifact of "unmasking",[29] in which the reduction in prevalence of vaccine types has made it easier to detect NVTs present in the population but undetected in the absence of vaccination. Because the commonly used serotyping methods require that only one or two colonies be assessed, investigators are

unlikely to detect co-colonisation with multiple serotypes. Reducing the prevalence of vaccine types by vaccination could lead to an increase in the detection of NVTs, even in the absence of any real increase in the acquisition of NVTs. If unmasking were to play an important part, one would not necessarily expect that an increase in the detection of NVTs in carriage would be followed by a concomitant increase in disease. However, whereas unmasking might partially account for the increase in the detection of NVTs among carriage isolates, it is unlikely to fully explain it, as an analysis of the South African trial has suggested.[29] Estimates of multiple carriage range from less than 10% to 30% of individuals in unvaccinated populations, with many studies reporting multiple carriage on the lower end of that range.[22,30–33] Generally, if the overall prevalence of carriage did not change after vaccination, but the composition shifted from a mix of vaccine types and NVTs to almost pure NVTs, then implausibly high levels of multiple carriage would have to be invoked to attribute the entire observed effect to unmasking.[29]

In reality, increased acquisition of new serotypes and unmasking are both likely to contribute to the increase in NVTs in carriage.[34] There may be some contribution from a phenomenon that resembles unmasking but is biologically similar to true replacement: if vaccination reduces the proportion of individuals co-colonised with vaccine types and NVTs, and co-colonised individuals have a lower density of colonisation with NVTs than singly colonised hosts, then there could be both an increase in detection probability (the artifact of unmasking) and an increase in the density of NVTs, which could lead to an increased probability of IPD or transmission to new hosts (increased acquisition rate). One study has addressed this question, and although the point estimate suggested higher NVT colonisation density in vaccinated individuals, the effect was not significant.[35]

Theoretically, one would expect that large-scale use of a vaccine would result in a greater increase in NVT carriage than is observed in an individually randomised trial,[36] because mass vaccination changes the exposure of all individuals in the community (due to indirect effects) as well as the susceptibility of vaccinated individuals to NVT carriage. Indeed, complete disappearance of vaccine-type carriage and large increases in NVT carriage have been observed only in highly vaccinated populations,[21] whereas RCTs showed only partial reductions in vaccine types and smaller concomitant increases in NVT carriage.

In summary, there is strong evidence that colonisation with NVTs increases in vaccinated populations. RCTs implicate vaccination as the cause of these increases, and observational evidence is consistent with theoretical predictions that both larger reductions in vaccine-type carriage and larger increases in NVT carriage should occur after mass vaccination.

Invasive pneumococcal disease

Background

Many studies have assessed serotype-specific IPD incidence before and after the introduction of PCV7 (table), but the measured effect of vaccination on NVT disease has been inconsistent. In classic, individually randomised trials, only a small proportion of the population is typically vaccinated. Therefore, such trials have a small effect on the overall bacterial population by contrast with what will occur with mass vaccination. For this reason, individually randomised trials are not designed to detect the long-term effect of replacement.[36,74,75] Moreover, these trials are not powered to detect replacement disease. The largest RCT of a PCV (total 37 000 children) had only three cases of NVT IPD in the vaccinees and six cases in the controls.[76] The next largest trial, from The Gambia, was not powered for the detection of changes in NVT disease, and there was a trend in the other direction, with 15 cases of IPD in the vaccinated group and nine among the controls.[9] For these reasons, data from RCTs are inconclusive about serotype replacement in disease. Consequently, most data regarding replacement in IPD come from observational studies.

Observational studies of IPD after vaccine introduction are subject to ecological and sampling biases. However, these post-licensure observational studies more accurately indicate the population-wide effect of mass vaccination. As with carriage, disease caused by NVT is expected to increase more in a well-vaccinated population than among vaccine recipients in an RCT.[73] Additionally, studies of IPD are not susceptible to unmasking because a case of IPD is thought to be caused by a single clone.[77] As a result, increases in NVT IPD are likely to represent true serotype replacement if biases in the surveillance systems can be properly controlled. We will describe the methodological issues of these observational studies and then summarise their findings.

Overview of surveillance systems and potential sources of bias

With any surveillance system, the possibility for bias exists if either clinical practices or case reporting changes over time. Two reports from North America indicate that the proportion of febrile patients who have blood samples taken from culture decreases after vaccine introduction.[41,42] Additionally, the Emergency Department at Boston Children's Hospital stopped doing routine blood cultures in febrile, well-appearing 6–36-month-old children for the detection of pneumococcal occult bacteraemia 3 years after the introduction of PCV7 (Malley R, unpublished). The widespread use of routine blood cultures for febrile children in the USA before vaccination and the subsequent reduction of this practice could make it seem that the disease incidence was artificially high before the introduction of PCV7. As a result, the

apparent decline in disease in children several years into the nationwide vaccination campaign would be inflated, and the detection of replacement disease caused by NVTs would be reduced. Due to clinical practice, this issue would be most pronounced in studies of young children in emergency departments, and less pronounced, although perhaps still relevant, in studies of hospital inpatients. By contrast, reports from Spain have indicated that both the rate of blood-culturing and reporting of IPD have increased since the introduction of the vaccine, and if not properly accounted for, could make replacement seem to be more significant than it is.[54,78]

Passive surveillance systems, which rely on laboratories to report cases, could potentially be prone to reporting biases and changes in blood-culturing practices. Active surveillance systems, which review clinical records and try to identify all cases in participating clinics, should be less prone to the issues of reporting bias. However, such active surveillance systems might be more likely to detect cases of occult bacteraemia, and these might be more prone to changes in blood-culturing practices than severe diseases such as invasive pneumonia, sepsis, or meningitis. Finally, several studies have reported data from single hospitals (table). Such studies are prone to all of the above biases, and may also be more likely to indicate short-term local fluctuations in serotype patterns. One way to minimise biases due to changes in surveillance systems would be to focus on well-defined severe diseases such as meningitis for which the diagnostic criteria are unlikely to change significantly over time. However, reports of meningitis could still be biased by changes in reporting rates in passive surveillance systems.

Estimates of disease incidence in all of the above systems will be affected by natural fluctuations in overall IPD incidence. Depending on the years used to measure the pre-vaccine and post-vaccine disease incidence, such fluctuations could either magnify or dampen the effect of the vaccine. For instance, Foster and colleagues[47] showed a multi-year increase in IPD incidence that occurred in the late 1990s and early 2000s. Inclusion of these years in the calculation of pre-vaccine incidence makes it seem that there was a larger decline in disease incidence than could be detected if only the years in the mid 2000s were used in the calculation.

Likewise, the length of the post-vaccine follow-up period can affect the reported magnitude of changes in disease incidence. Carriage studies suggest that the relative prevalence of serotypes in the nasopharynx is in flux for the first few years of vaccination and then reaches a steady state.[79] Consequently, there seems to be a lag between vaccine introduction and the increase in IPD caused by NVTs in some populations.[37,39] This could be attributed to the amount of time required to reach full vaccine coverage and for vaccine serotypes to be eliminated, especially in the general population through herd effects. Additionally, changes in the bacterial population, such as serotype switching, could have a delayed effect on disease incidence. Studies reporting less than a few years of post-vaccine incidence data may thus underestimate replacement.

Evidence of serotype replacement in disease

PCV7 was first introduced in the USA in 2000. The active bacterial core surveillance system in the USA has shown a clear drop in vaccine-type disease and a modest increase in NVT disease, most notably caused by serotype 19A, although other serotypes have also increased.[2] The increase in NVTs in this population is most apparent among hospitalised cases.[2,80] This difference could be explained if blood-culturing had remained routine for patients ill enough to be admitted to hospital, but declined in frequency for less severe cases. Indeed, the incidence of bacteraemia without foci caused by NVTs has decreased in all age groups between the pre-PCV7 and post-PCV7 eras, whereas invasive pneumonia and meningitis caused by NVTs has increased in incidence in all age-groups.[2] However, despite the increases in NVTs, the overall rate of IPD in the paediatric population is still significantly lower than in the pre-vaccine era, even if only considering hospitalised cases.[2] Additionally, the same study reported a 64% decline in paediatric pneumococcal meningitis cases, which is unlikely to be biased by changes in clinical practice. This decline in IPD is further confirmed by a fall in the number of children younger than 2 years with all-cause pneumonia who are admitted to hospital.[81]

Other studies from North America show varied results (table). These data include both hospital-based laboratory surveillance and active population-based surveillance systems. Most studies from North America report some degree of serotype replacement, although one study reported no detectable increase in NVTs.[43]

Elsewhere, a study of Aboriginal people in Western Australia[58] found that PCV7 reduced the incidence of IPD in young children and older people, but there was a significant net increase in IPD in young adults driven by an increase in NVTs. In another population, there was no evidence of replacement in vaccinated children, but there was a significant increase in NVTs in adults, which offset the herd-immunity benefits of the vaccine.[57]

In Europe, reports on serotype replacement also give varied results. Several studies from Spain have examined the issue, with some areas reporting complete serotype replacement with no net effect of the vaccine on IPD incidence,[5,50,53] whereas another study reported no increase in NVTs.[56] The Spanish data are further complicated by regional differences in blood-culturing practices and by increases in blood-culturing and reporting since the introduction of PCV7.[52,78,82] In France, the vaccine had no overall effect in the most recent national study of paediatric pneumococcal meningitis in

children aged under 5 years, although it showed a benefit in those aged under 2 years.[83] The overall effect on IPD in France was modest.[49,60] Interpretation of the data from Spain and France is also difficult because of the relatively low initial vaccine coverage in these countries, the gradual introduction of the vaccine, and regional differences in vaccine uptake.

Elsewhere in Europe, a study from the Netherlands showed a 44% increase in NVT IPD in children younger than 2 years.[8] Studies from Norway and Denmark have found modest increases in specific serotypes, but which did not result in a net increase in NVT.[3,84] In Germany, no evidence of serotype replacement has been reported as of 2008.[85] In England, the incidence of NVTs more than doubled in children younger than 2 years after vaccine introduction, but there was still a 48% net decline in disease.[47,80,86] Data from the Health Protection Agency in England and Wales also show a net decline in disease incidence in children despite significant serotype replacement, but in older people, the increase in NVTs completely offsets the decline in vaccine types, so there was no herd-immunity effect in this population.[80,86]

In summary, most locations have reported a net decline in the incidence of IPD in young children, especially those aged under 2 years. Many, but not all, studies also report a substantial increase in NVT in young children. By contrast with the overall decline in IPD reported elsewhere, data from France, Spain, and Alaska natives show little net benefit of vaccination in children, especially in those aged 2 years and older. Among non-vaccinated age groups, there is substantial heterogeneity in the reported magnitude of the indirect benefits of vaccination, with some studies reporting complete replacement resulting in no net indirect benefit, whereas others report relatively little replacement. Further analysis of these data will be required to determine how much of the heterogeneity is due to true differences in serotype replacement and how much is due to surveillance artifacts.

Causes of observed replacement in disease

Background

Now that we have reviewed the evidence for serotype replacement in carriage and disease, we return to the questions of why serotype replacement has been complete in carriage but not in disease, how much the incidence of IPD has truly been affected by vaccination and replacement, and what factors are likely to be responsible for the increase in NVTs.

Discrepancy in magnitude of replacement between carriage and disease

The incidence of IPD caused by a particular serotype is the product of the incidence rate of new carriage episodes with that serotype, and the proportion of carriage episodes that results in a case of IPD—often referred to as invasiveness or the case–carrier ratio. The carriage prevalence and the invasiveness of a serotype are probably affected by the microbiological properties of the strains. The capsular polysaccharides play an important part in evading host immune responses. More heavily encapsulated serotypes tend to be carried more frequently,[87] and capsular polysaccharides vary in their ability to prevent complement deposition,[88] which might affect the invasiveness of a serotype.[89] Additionally, other microbial factors such as adhesins, toxins, and proteins that allow the bacterium to avoid host immune effectors probably influence the carriage prevalence of a serotype and its invasiveness.[90] Interestingly, there is an inverse correlation between the carriage prevalence of a serotype and its invasiveness.[91]

Invasiveness in children varies between serotypes, but the invasiveness of a given serotype is similar in different populations.[92–95] One would therefore expect that, if a serotype increases in carriage and invasiveness does not change, there should be a proportional increase in disease. Therefore, if the NVTs that increase in carriage are less invasive than the vaccine serotypes that they replace, there should be a decrease in disease burden. Conversely, if the replacement serotypes are more invasive, there should be a net increase in disease. The NVTs that have increased in carriage do tend to be less invasive than the serotypes targeted by PCV7.[96] This is particularly true if the highly invasive, yet rarely carried, serotypes 1 and 5 are excluded. Recent estimates from our group suggest that due solely to invasiveness differences between serotypes, we would have expected approximately a 30% decline in IPD in the USA after the introduction of PCV7.[97]

Given these points, the apparent discrepancies in serotype replacement between carriage and disease might be attributable to several factors. First, the lower invasiveness of the replacement serotypes compared with the vaccine serotypes could contribute to the net decline in disease incidence. Second, biases in the detection of NVT serotypes in pre-vaccine studies of pneumococcal carriage (so-called "masking") might have resulted in NVTs seeming to increase in carriage prevalence more than they actually did. Finally, biases in the pre-vaccine and post-vaccine disease incidence measurements caused by changes in surveillance methods or secular trends could have resulted in inaccurate comparisons between these two periods.

True magnitude of the increase of NVTs in disease

Some studies probably under-report serotype replacement, whereas other studies over-report it. In both cases, this is due to changes in blood-culturing, clinical practices, or reporting over the course of data collection. Despite these issues, we believe two conclusions can be reached: (1) nearly all studies indicate that there is a net positive benefit of vaccination with PCV7 that is apparent at least during the first 3 years of use; and (2) evidence for serotype replacement in disease is apparent in most populations. Most studies report a net decline in disease

of 40–60% in children even after accounting for replacement, although many of these studies have a short post-vaccine follow-up period. However, as previously noted, substantial heterogeneity exists between studies, and it is not yet clear how much of this variation can be attributed to true differences or to surveillance artifacts. The data from Alaska, in which the benefits of vaccination were smaller among rural Alaskan natives than in the rest of the population, suggest that there might be real differences in the magnitude of replacement between populations. These differences could depend on differences in the proportions of serotypes present before vaccination, the coverage of the vaccines, and socioeconomic differences between the groups.[40] As such, care must be taken when predicting the benefits of mass vaccination in new settings.

Finally, although we have focused on reported changes in serotype incidence and distributions in the general population, the patterns and magnitude of replacement could be different among those with immunodeficiencies and other comorbidities.[98] Particularly, the greater susceptibility of these high-risk groups to pneumococcal disease could lead to a higher level of replacement disease than that seen in the general population. Thus, the prevalence of such comorbidities could affect the overall magnitude of serotype replacement in a population.

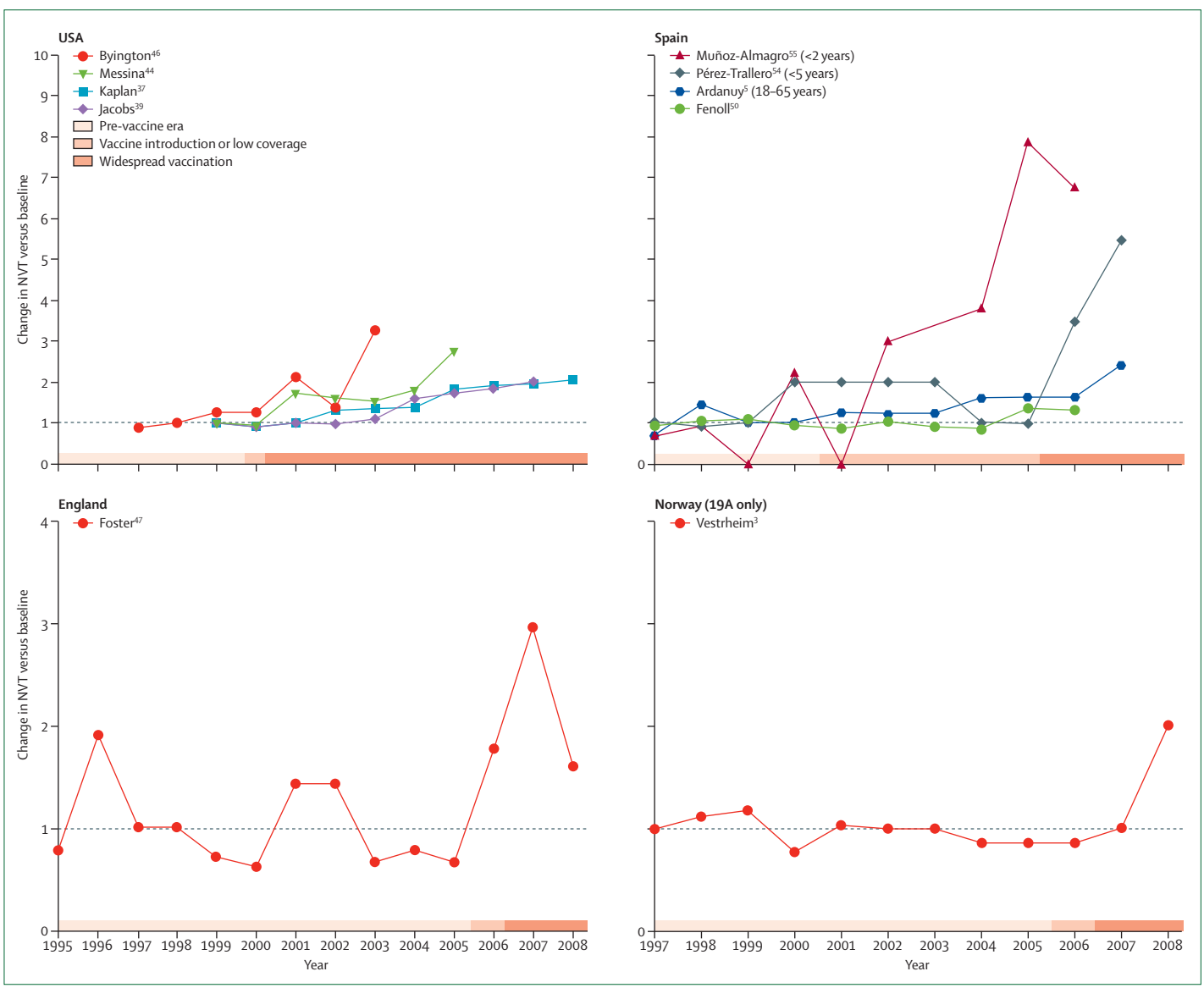

Figure: **Timing of the increase in the incidence of NVTs relative to vaccine introduction in selected studies that report serotype replacement**
Change in NVT versus baseline is calculated by dividing the incidence in each year by the mean pre-PCV7 incidence (table). Data from the USA and Spain represent changes in all NVTs, whereas data from England exclude the vaccine-related types (6A and 19A), and data from Norway are just serotype 19A. The data for Jacobs[39] include both invasive and non-invasive disease isolates. There was no net increase among NVTs in Norway as of 2008. NVT=Non-vaccine types.

Relative contribution of vaccination to the increase in NVTs in carriage and disease

Assessing whether PCV7 has a causal role in the increase in NVT disease following vaccine introduction has implications for the introduction of future pneumococcal vaccines. If the increase in NVTs is caused simply by factors not related to vaccination,[99] one would not necessarily expect additional serotype replacement when the new vaccine is introduced. However, if serotype replacement in carriage or disease is attributable to vaccination, one might expect that other serotypes will increase as the strains targeted by a new vaccine are eliminated. Patterns of antibiotic use or long-term secular trends have been suggested to affect changes in serotypes.[100,101] Indeed, serotype 19A has increased in some areas where the vaccine has not been introduced,[102,103] and certain serotypes (ie, serotype 1) do show long-term fluctuations in prevalence.[50,84] Such patterns unquestionably occur, but just as RCTs show for carriage, vaccination changes serotype prevalence more rapidly and to a greater extent than occurs from natural fluctuations.

Multiple mechanisms may contribute to the overall serotype patterns. The vaccine could create an open niche that could be filled by NVTs. However, which of the NVTs will increase could be affected by antibiotic use and resistance and other general biological properties of the strains.[21,87] The open niche created by vaccination could amplify these secular trends. However, antibiotic use and resistance are unlikely to be the sole causes of increasing IPD incidence from NVTs. Before vaccination in the USA, selection pressure for antibiotic resistance resulted in regional differences in the prevalence of resistance within serotypes, but not in regional differences in the serotype composition of IPD isolates.[104] This finding suggests that antimicrobial use may not be capable of changing serotype patterns appreciably. Most compelling are data from Norway, where there was a sharp rise in serotype 19A IPD about 1 year after the introduction of the vaccine.[3] This increase came despite low antibiotic pressure, and the serotype 19A clone that emerged was susceptible to penicillin.

Together, the evidence from RCTs, cross-sectional carriage studies, and population-based disease surveillance make it almost certain that a substantial proportion of observed replacement in disease has been caused by vaccination. Because IPD typically follows colonisation, one of the following, unlikely scenarios would have to be true for the vaccine not to have caused replacement in disease: (1) the observed increase in NVT carriage was entirely attributable to unmasking, hence there was no true serotype replacement in carriage; or (2) the invasiveness (ratio of IPD cases to carriers) of NVT declined since vaccination, fully compensating for any increase in carriage. Scenario 1 is unlikely because it would imply that every vaccine-type carrier before vaccination had both vaccine-type and NVT strains, and the NVT strains have just been unmasked. It would also imply that the unmasking is not followed by an increase in the density of NVT strains, a claim that seems biologically unlikely and contradicts animal studies of strain competition.[105] Scenario 2 is implausible because we know of no mechanism by which vaccination should reduce the invasiveness of NVTs, and the data on invasiveness from many different populations have been strongly consistent.[92–95] Finally, the temporal relation between the introduction of PCV7 in various countries and the rise of NVTs is unlikely to be due to coincidence because the vaccine was introduced at different times in different countries (figure). A study from England shows that although NVTs were increasing in disease before the introduction of PCV7, they increased significantly more rapidly after vaccination.[47]

Vaccination in developing countries

The studies reviewed here show that despite the increased incidence of NVTs that cause IPD in many populations, PCV7 has had a significant positive benefit on paediatric disease, especially in children younger than 2 years, in whom it is in widespread use. The measured benefit clearly varies across populations; some of this variation is real, and indicates host and pathogen population characteristics. The epidemiology of IPD in developing countries differs from that in other parts of the world.[106] The high carriage prevalence, co-infections, and different serotype distributions in these populations add uncertainty to efforts to extrapolate evidence from developed countries. The extent of serotype replacement could possibly be different—either larger or smaller—in a setting where the vaccine covers fewer of the serotypes responsible for IPD and the composition of serotypes differs. RCTs from The Gambia and South Africa[9,11,14,17,20] suggest that the vaccines could provide a significant benefit in these areas. However, as noted earlier, both the reduction in vaccine serotype disease and the increase in NVT disease are expected to be larger under mass vaccination than in a clinical trial.

The rapid introduction of PCVs in developing countries has much support. We believe that the incidence of disease in these new areas should be monitored after vaccine introduction to confirm effectiveness. Due to resource limitations, comprehensive laboratory-based surveillance systems, such as those used in the USA and parts of Europe, are unlikely to be used in many developing countries. However, existing pneumococcal research sites, such as those in South Africa, The Gambia, and East Africa (ie, Network for Surveillance of Pneumococcal Disease in the East African Region) could serve as sentinel sites for the rest of Africa. Because pneumonia, both bacteraemic and non-bacteraemic, constitutes the largest burden of pneumococcal disease, changes in pneumonia incidence could be the focus of

For more on **Network for Surveillance of Pneumococcal Disease in the East African Region** see http://www.netspear.org

surveillance. A significant and sustained drop in all-cause pneumonia incidence, as has been seen in the USA,[81] could be used as an indicator of vaccine effectiveness. Finally, the serotype composition among carriers should be monitored, if possible, to ensure that vaccine serotypes are being eliminated as expected, and to detect whether there is an increase in any especially invasive serotypes. Carriage surveys are relatively inexpensive and more feasible than population-based IPD surveillance. Use of carriage data with known invasiveness data could serve as an indirect way to monitor serotype replacement.[107]

Future prospects for serotype replacement in disease

The evidence presented here strongly support the notion that serotype replacement has occurred in IPD in most populations and is caused by the vaccine. We should assume that the introduction of new conjugate vaccine formulations in the future will again be met with complete serotype replacement among carriers and some amount of replacement in disease that will partly depend on the invasiveness of the colonising serotypes. The recently introduced 13-valent vaccine has the potential to have significant and sustained effects on disease, particularly in developing countries. Serotypes 1 and 5, which are covered by this vaccine, are rarely carried but cause a lot of disease in many areas. As a result, the elimination of these two specific serotypes is unlikely to be followed by substantial replacement.[12,36] Although it is difficult to predict how the composition of NVTs will change after the introduction of PCV13, or whether the characteristics of the serotypes will change, projections based on the invasiveness of the serotypes suggest that this new vaccine will result in additional reductions in disease incidence.[97] Such projections are valuable for defining likely scenarios, but limitations of our biological knowledge and of the formalisation of that knowledge in theoretical models mean that model predictions are no substitute for careful monitoring.[108] Long-term surveillance of both IPD, carriage, and non-bacteraemic pneumonia, which constitutes a major portion of disease burden, will be crucial to ascertain whether the vaccines are having the desired effect of reducing the incidence of disease over the long term.

Contributors

DMW reviewed the literature and DMW, RM, and ML wrote the manuscript.

Conflicts of interest

DMW has no conflicts of interest to declare. RM is a member of the Scientific Advisory Board of Genocea Biosciences. ML has accepted honoraria or consulting fees from Pfizer and Novartis.

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