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Serotype Specific Invasive Capacity and Persistent Reduction in Invasive Pneumococcal Disease

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Abstract

Defining the propensity of *Streptoccocus pneumoniae (SP)* serotypes to invade sterile body sites following nasopharyngeal (NP) acquisition has the potential to inform about how much invasive pneumococcal disease (IPD) may occur in a typical population with a given distribution of carriage serotypes. Data from enhanced surveillance for IPD in Massachusetts children ≤7 years in 2003/04, 2006/07 and 2008/09 seasons and surveillance of SP NP carriage during the corresponding respiratory seasons in 16 Massachusetts communities in 2003/04 and 8 of the 16 communities in both 2006/07 and 2008/09 were used to compute a serotype specific "invasive capacity *(IC)*" by dividing the incidence of IPD due to serotype *x* by the carriage prevalence of that same serotype in children of the same age. A total of 206 IPD and 806 NP isolates of SP were collected during the study period. An approximate 50-fold variation in the point estimates between the serotypes having the highest (18C, 33F, 7F, 19A, 3 and 22F) and lowest (6C, 23A, 35F, 11A, 35B, 19F, 15A, and 15BC) IC was observed. Point estimates of IC for most of the common serotypes currently colonizing children in Massachusetts were low and likely explain the

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continued reduction in IPD from the pre-PCV era in the absence of specific protection against these serotypes. Invasive capacity differs among serotypes and as new pneumococcal conjugate vaccines are introduced, ongoing surveillance will be essential to monitor whether serotypes with high invasive capacity emerge (e.g. 33F, 22F) as successful colonizers resulting in increased IPD incidence due to replacement serotypes.

Keywords

Streptoccocus pneumoniae; serotype; invasive capacity

Introduction

The pathogenesis of invasive pneumococcal disease (IPD) begins with nasopharyngeal (NP) colonization that proceeds, often through local infection, to blood stream invasion. Although almost all children become colonized with *Streptococcus pneumoniae* repeatedly during the first few years of life, a very small fraction of these acquisitions results in invasive disease. Global surveillance demonstrates that a limited number of serotypes cause 80% of IPD, and serotypes vary in their contribution to invasive disease [1]. There are two components to this variation: (i) some serotypes are more commonly carried and thus have more temporal opportunity for invasion [2], and (ii) some serotypes are more likely to cause invasive disease with each carriage episode, perhaps because of their superior ability to overcome host defenses and penetrate the bloodstream [3].

Differences in invasive capacity of more than 90 known capsular serotypes have been assumed to depend primarily on the antiphagocytic properties of the capsular polysaccharides rather than surface proteins, although it is likely that each contributes to the capacity of specific strains to produce blood stream invasion or mucosal surface infection [4]. Support for this concept is derived from the observation that isolates lacking a capsule are rarely detected as a cause of invasive disease in patients or animal models [4-6]. Second, despite the antigenic diversity found among *S. pneumoniae,* 10 serotypes account for more than 80% of disease globally in the absence of vaccination [1, 7]. As vaccine serotypes (VST) are recovered less frequently from pneumococcal carriers, non-vaccine serotypes (NVST) may cause more IPD cases due to increasing prevalence in the community, or due to the enhanced capacity of some NVST for evading host defenses compared to other serotypes or due to acquisition of new genetic material that could potentially increase invasive capacity of existing NVST. Investigating the propensity for a specific serotype to invade sterile body sites once NP acquisition occurs can suggest how much IPD we may anticipate in a population with any particular distribution of serotypes in carriage.

Prior to universal immunization of infants and toddlers with the heptavalent pneumococcal conjugate vaccine (PCV7), the seven vaccine serotypes accounted for 80.5% of IPD in North American children under 5 [8]. Following introduction of PCV7 in the US, invasive disease due to vaccine serotypes declined greater than 99%, contributing to a 75% decline in total IPD [9]. While nearly complete elimination of NP carriage of the seven vaccine serotypes has occurred, these have been replaced by NVST as a result of both expansion of existing strains and emergence of new NVST strains, some of which represent capsule transformants from vaccine serotype strains [10]. In the United States, there has been little or no change in total carriage prevalence following PCV7 use and serotype replacement since 2000 [2, 11, 12]. Thus, the substantial ongoing reduction in IPD likely reflects a reduction in the mean invasiveness of currently colonizing strains compared to those that were colonizing prior to PCV introduction, and continued benefit from the vaccine may

depend on the success of colonization with less-invasive serotypes compared to the relatively more invasive non-vaccine strains in the community.

Expansion of serotype-specific NP carriage has coincided with a measurable increase in IPD incidence for some, but not all, serotypes. Surveillance studies of carriage and IPD in the same geographic area allows an estimate of serotype-specific invasive disease potential and may aid in predicting whether reductions in post-PCV7 IPD will persist. Several investigators have evaluated the propensity of various pneumococcal serotypes to cause IPD before PCV introduction, but invasive capacity in populations with widespread PCV7 use has not been reported. Ideally, invasive capacity would be measured as the probability of an invasive event occurring for each NP acquisition. Since the acquisition rates and duration of carriage for particular serotypes are hard to obtain, published studies to date have reported an odds ratio for invasive disease calculated as the odds of IPD following colonization with that serotype either: (i) compared to a selected reference serotype such as 14 [13], or (ii) compared to all other serotypes in the population [14-18]. Brueggemann et al [16] described this measure as the odds of disease due to a particular serotype or clone, compared with the odds of carriage of that serotype or clone. They also emphasized the need for more data on NVSTs to better anticipate the impact of PCVs and the potential for durable reduction in IPD.

The goal of this study was to estimate the relative propensity of “replacement” serotypes to cause invasive disease among Massachusetts children in the post-PCV7 era. We also sought to define a new measure for describing invasive disease probability that would permit comparison across different populations and sets of isolates.

Materials and methods

The serotype-specific propensity of *S. pneumoniae* to cause IPD was estimated using data on the incidence of IPD in children <7 years of age in the entire state of Massachusetts obtained during the 2003/04, 2006/07, and 2008/09 respiratory seasons (expressed as cases per person-year of children under 7) [19] and the prevalence of NP carriage isolates of the same serotype collected during the same time periods in similarly aged children from 16 Massachusetts communities in 2003/04 and 8 of the 16 communities in both 2006/07 and 2008/09 (for carriage isolates) [2, 11]. The majority of children (>95%) with IPD had received at least one dose of PCV7, and comprised mostly healthy children; co-morbid conditions associated with immunologic deficiency were present in less than 10%[20].

Isolates

Cases of IPD occurring in children <7 years were detected through enhanced laboratory surveillance in Massachusetts, which began in 2001. This surveillance system has been previously described in detail [19]. Briefly IPD is defined as isolation of *S. pneumoniae* from a normally sterile site. All clinical microbiology laboratories in Massachusetts submit isolates from cases of IPD to the Massachusetts Department of Public Health (MDPH). MDPH epidemiologists interview parents/guardians and/or primary care providers to obtain demographic and clinical information about each case, and the isolates are sent to the Maxwell Finland Laboratory for Infectious Diseases at Boston Medical Center for serotyping and evaluation of antimicrobial susceptibility.

Streptococcus pneumoniae carriage isolates were identified from a series of NP colonization studies conducted in 16 Massachusetts communities during respiratory virus season from November to April in 2003/04, and then a subset of 8 of these 16 from October to April in 2006/07 and 2008/09 [2, 11]. Nasopharyngeal swabs were collected from children 3 months to <7 years of age during well-child or sick visits at primary care practices. Parental consent

was obtained and swabs were taken by either trained study personnel or trained nurses in pediatric or family practice physician offices. The presence of *S. pneumoniae* was confirmed by optochin sensitivity and bile solubility using standard microbiological methods according to guidelines of Clinical and Laboratory Standards Institute and serotyped using antisera from Statens Serum Institute (Copenhagen, Denmark). One isolate per child was evaluated in any season. There were 987, 971 and 1011 participants and pneumococcal carriage was identified in 23%, 30% and 29% of kids in study periods 2003/04, 2006/07 and 2008/09, respectively.

Estimate of serotype-specific "invasive capacity"

The propensity of each serotype to cause IPD is estimated by using IPD incidence and NP prevalence and called invasive capacity (IC). "Invasive capacity *(IC)*" for each serotype *x* was calculated by dividing the incidence of IPD due to serotype *x* by the carriage prevalence of that same serotype in children of the same age [2, 11, 19]. Annual incidence of IPD (from October 1 through September 31 of 2003-4, 2006-7, and 2008-9) due to serotype x, I_x, was calculated as the number of newly diagnosed IPD cases of type *x*, N_x, divided by 3 years, which is the total study period for IPD, and divided by the number of Massachusetts children aged <7 years during the study period as determined from the 2000 US Census, which was 564,247. Prevalence of *S. pneumoniae* carriage, q_x, was calculated as the number of NP isolates of a given serotype divided by the number of children from whom NP swabs were collected during the three collection periods (*m*).

$$Invasive\ capacity\ (IC) = I_x / q_x$$

The natural logarithm of the estimate of IC_x is approximately normally distributed with variance [21]:

$$\frac{1}{N_x} + \frac{1 - q_x}{q_x m}$$

When no isolates of a serotype are observed, our estimate of the incidence of invasive disease, and therefore of the IC is 0. However, because we do not believe the true incidence is 0, we provide the 95% upper confidence limit for the IC. The "rule of three" states that the 95% upper limit for the true incidence rate, when 0 cases are observed, is 3 divided by the population size [22]. We calculate the 95% upper limit for the IC as the IC had the number of invasive isolates been 3; this accounts for variance from the incidence, which makes the major contribution to variance in IC, but not from the carriage prevalence.

Furthermore, to define whether the decrease in the incidence of IPD after 24 months is a result of decreased NP colonization seen in older children or to a reduced likelihood of invasive events among those colonized with a specific serotype, we compared serotype-specific IC for children less than 2 with that computed for children 2 through 7 years of age using the 2-tailed sign test.

Results

Serotype distribution

A total of 206 isolates of *S. pneumoniae* causing invasive disease in children <7 years of age were collected in Massachusetts during the study period, corresponding to a total incidence

of 15 IPD cases per 1000,000 per child-year; 56.3% (116) isolates were from children under 2 years of age, the majority of whom were otherwise healthy (data not shown). There were 29 different serotypes; 19A, 7F, 22F, 6A, and 33F were the most frequent (38.8%, 13.6%, 6.8%, 5.8% and 5.3% of all IPD isolates, respectively) (Figure 1). The proportion of isolates included in PCV7 was 16.9% in the 2004 respiratory season, whereas only one (1.1%) of the IPD cases in the 2009 season was due to a vaccine serotype (serotype 19F). Nasopharyngeal specimens were collected from 2,969 children, and a total of 806 isolates from 39 different serotypes were recovered; 408 were obtained from children under 2 years of age. Nonvaccine serotypes 19A, 15BC, 6C, 35B, 11A, and 23A were most common (14.0%, 9.2%, 8.1%, 8.1%, 7.8%, and 7.7% of all pneumococcal isolates respectively); 19F was the most common PCV7 vaccine serotype (3.8% of all NP isolates).

Serotype-specific invasive capacity (IC)

Serotype-specific IC computed from IPD incidence and NP colonization prevalence in Massachusetts differed by serotype: serotypes 18C, 33F, 7F, 19A, 3 and 22F exhibited significantly higher invasive capacity than serotypes 6C, 23A, 35F, 11A, 35B, 19F, 15A, and 15BC, as reflected by non-overlapping confidence intervals (Figure 2a). An approximate 50-fold variation in the point estimates was noted between the serotypes having the highest and lowest IC.

The point estimates of serotype specific IC for each particular serotype were lower in children over 24 months of age cohort except for serotypes 23B and 18C; however, few of the individual comparisons were statistically significant (Figure 2b). However, overall 13 of the 15 point estimates of IC were lower in children over 24 months, a finding which would be very unlikely to occur by chance if IC were the same between age groups (p=0.007).

Discussion

After the introduction of PCV7 in 2000, a significant decrease in the incidence of IPD in children has been observed, as well as an increase in cases caused by NVST [19, 23, 24]. PCV7 prevents VST IPD by eliciting type specific functional antibody that prevents new acquisition of serotype-specific NP colonization and enhances clearance of pneumococci from the blood stream [25-27]. The increase in IPD caused by any particular NVST reflects the increased colonization of that NVST and its capacity to produce invasive events. Both NP carriage and IPD due to serotype 19A increased between 2001 and 2007 in Massachusetts [11, 19]. In contrast, carriage of serotype 35B increased nearly 4 fold from approximately 2.5 % of children less than 7 years of age in 2001 to 9 % in 2007, while cases of IPD due to 35B remained infrequent with no cases identified in 2004 or 2007. In the absence of specific immunization against serotype 35B, the absence of an increase in IPD concomitant with exposure through carriage presumably reflects the relatively low invasive potential of this serotype. The same phenomenon appears with several other serotypes (Table 1).

Although prevalence of pneumococcal colonization among children less than 7 remained constant or slightly increased, the incidence of IPD has shown a sustained decline. By 2007, 96% of NP isolates in Massachusetts were NVST [11]. Hanage *et al.* have suggested that the increased incidence of some IPD cases with 19A, 15BC, and 33F resulted from the higher rate of carriage of these serotypes [17] and hence increased exposure to them. In the present study we studied the differences in the relative potential of pneumococcal serotypes to cause invasive disease by comparing carriage prevalence of individual serotypes in community samples with IPD due to those serotypes in the state as a whole.

The results of our study support the previous published data that serotypes differ considerably in their IC; we computed estimates ranging from 2.7×10^{-5} to 3.5×10^{-3} (Table 1). Moreover, some serotypes - such as 35B, 23A, and 6C, - were rarely, if ever, isolated from patients with IPD despite being frequently found in NP carriage, suggesting a very low propensity of these serotypes to cause invasive disease in this community. Several studies addressed this issue by computing serotype specific odds ratios (ORs) as a measure of invasive potential. Brueggemann *et al.* found the specific odds ratio for serotypes 1, 4, 14, 7F, and 18C were greater than 1 and concluded these serotypes were overrepresented among invasive disease isolates, whereas in comparison with other serotypes, 23F was overrepresented among NP carriage isolates [16]. Serotypes 4, 14, and 18C were also reported to be significantly positively associated with IPD by Lagos et al [15]. A third study demonstrated this association with serotypes 1, 5, and 12F [14]. Using the same approach, Hanage *et al.* reported that 14, 18C, 19A, and 6B were the most invasive serotypes [17]. Our calculations of relative IC are consistent with the results of these studies with a few differences; 33F was found to be highly invasive in our study, and 19A ranked in the middle in terms of invasive capacity, although it was the most common cause of colonization and IPD in all three years studied. The differences in the measures of serotype specific invasive potential may be due to differences in invasiveness between clones of the same serotype, and further evaluation is necessary [17]. The serotype specific IC that we have estimated enables comparisons across studies and overcomes the limitations of ORs which are based on serotype comparisons within a specific data set. Even when ORs relative to a serotype that is present in all samples (e.g. serotype 19A) are calculated, it is possible that specific strains within a serotype differ in invasive capacity, and hence differences in the specific strain composition would influence the estimate of the OR when related to that serotype.

The decrease in the incidence of IPD after 24 months could be the result of a change in exposure to pneumococci (reduced incidence of carriage) or changes in the propensity of each serotype to cause IPD (invasive capacity). We observed a lower IC estimate in children over 24 months, when compared with those less than 24 months, for 13 of 15 serotypes that had sufficient data in each age group. Our data are hence consistent with a reduction in IC with age. The comparable rates of pneumococcal colonization observed in both age cohorts combined with previous observations of large serotype-specific declines in invasive disease incidence after the first birthday [1, 26] support the observation that IC declines with increasing age for most serotypes, however within each age subdivision, serotypes maintain a hierarchy of IC. Larger data sets will be necessary to further evaluate the relationship of age and invasive capacity as we were limited by the case numbers and distribution of IPD cases in older children. Such data may contribute to our understanding of the decline in IPD incidence with increasing age.

A caveat of this study is that we have used NP prevalence as a surrogate measure of incidence (the acquisition of a new serotype). It is known that serotypes differ in their duration of carriage, and therefore a serotype with a low prevalence but a short carriage duration may be associated with a high IPD incidence (because it has undergone more acquisition events than a serotype with the same prevalence but a longer duration of carriage). It has been suggested that IPD typically follows acquisition of a new serotype [28] and if this is so, the differences in carriage duration (and hence number of acquisitions) may explain some of the differences in invasive capacity which we report here.

Analysis of whether invasive capacity for specific serotypes differs in children with comorbid illness would be valuable, but is beyond the scope of our current data set. We lack the power to determine whether our measure of invasive potential varied between 2004, 2007, and 2009 (year specific invasive capacity was not statistically different between years, but the confidence intervals are wide-data not shown). However, the similarities with

previously reported measurements for majority of the serotypes provide support for invasive capacity as biologically based and independent of community.

Our findings both confirm the previous observations that the propensity to cause IPD differs among serotypes and provide an explanation for the continued reduction in IPD in the absence of direct protection against current colonizing serotypes. Further studies are necessary to provide better insight into the invasive disease potential of the emerging nonPCV7-vaccine colonizers such as 19A, 15A, 15BC, 6C, 35B, 11A, 23A, 23B, and 10A. As new pneumococcal conjugate vaccines are introduced, changes in the distribution of carriage serotypes will continue to occur and increases in highly invasive serotypes would be alarming as they may potentially be associated with increased IPD. Ongoing surveillance of IPD will be essential to determine whether serotypes with high invasive potential emerge as successful colonizers.

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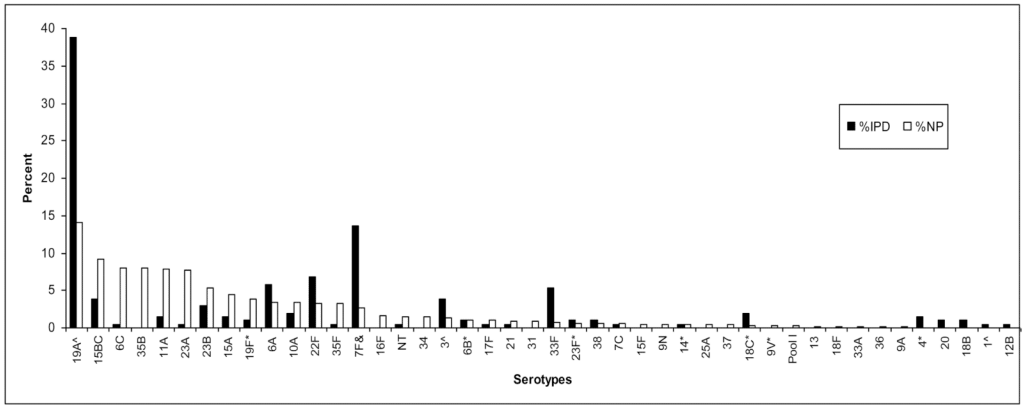

Figure 1.

Distribution of IPD and NP Isolates by Serotype from Massachusetts Children less than 7 years of age (2004, 2007 and 2009 combined)

* PCV7 serotypes, &PCV10 serotypes, ^ PCV13 serotypes

Figure 2a.

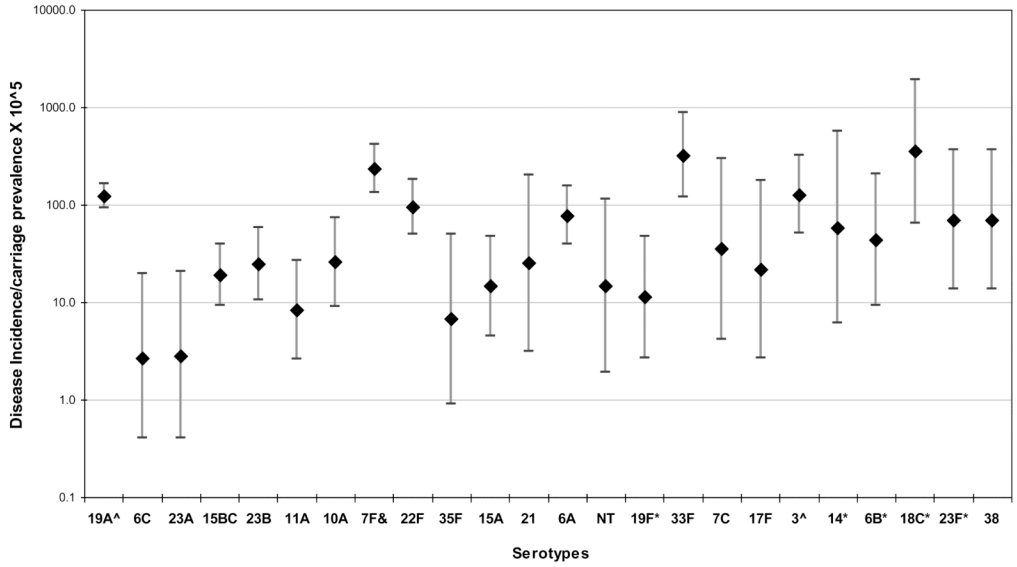

Figure 2b.

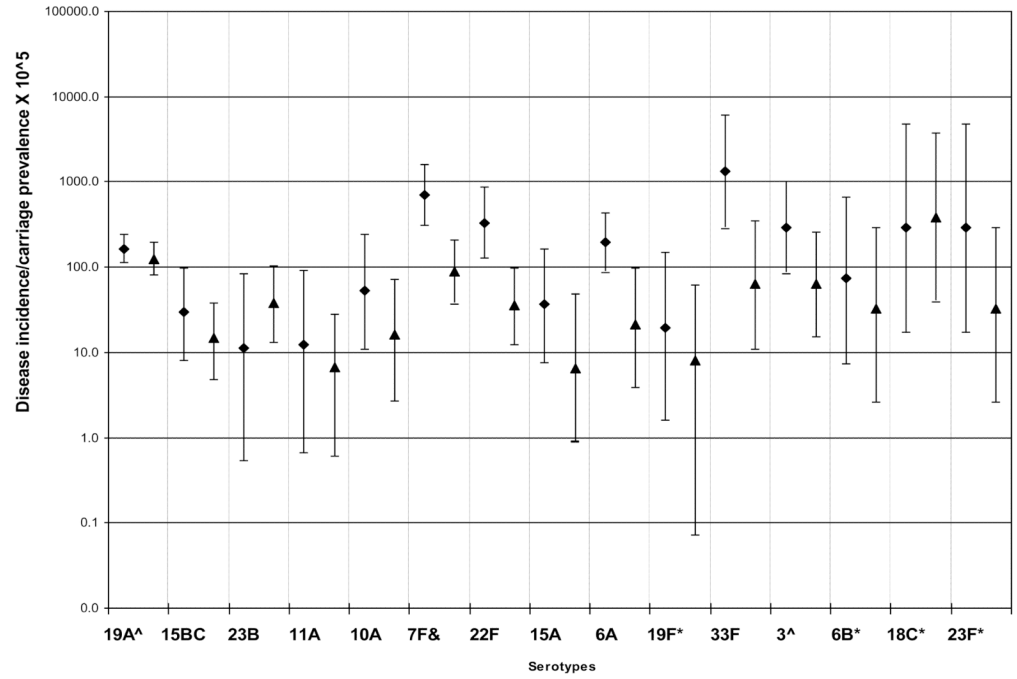

Figure 2.

Figure 2a. Estimate of Invasive Capacity of *Streptococcus pneumoniae* by Serotype for the 24 most Prevalent Serotypes Causing IPD in Children less than 7 years of age in Massachusetts (by order of decreasing frequency in 2009)[#]

[#]Y-axis is displayed on log-scale.

* PCV7 serotypes, [&]PCV10 serotypes, ^ PCV13 serotypes

Figure 2b. Estimate of Invasive Capacity of *Streptococcus pneumoniae* by Serotype in children less than 24 months vs. children 24 months to less than 7 years of age in Massachusetts (by order of decreasing frequency in 2009)[#]

[#]Children less than 24 months shown first. Y-axis is displayed on log-scale.

* PCV7 serotypes, &PCV10 serotypes, ^ PCV13 serotypes

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Table 1

Serotype specific invasive potential of *Streptococcus pneumoniae* in MA among children less than 7 years of age calculated as serotypes specific incidence of IPD divided by prevalence of serotypes specific carriage.

Serotype	Number of invasive isolates	Number of carriage isolates	Invasive potential (Disease incidence/carriage prevalence X 105)	95% CI**
18C*	4	2	350.8	64.3 - 1914.5
33F	11	6	321.6	119.0 - 868.9
7F&	28	21	233.9	133.0 - 411.3
3^	8	11	127.6	51.3 - 316.9
19A^	80	113	124.2	93.5 - 165.0
22F	14	26	94.4	49.4 - 180.7
6A	12	27	78.0	39.5 - 153.7
23F*	2	5	70.2	13.6 - 361.5
38	2	5	70.2	13.6 - 361.5
14*	1	3	58.5	6.1 - 561.9
6B*	2	8	43.8	9.3 - 206.4
7C	1	5	35.1	4.1 - 300.2
10A	4	27	26.0	9.1 - 74.2
21	1	7	25.1	3.1 - 203.6
23B	6	43	24.5	10.4 - 57.5
17F	1	8	21.9	2.7 - 175.2
15BC	8	74	19.0	9.2 - 39.3
15A	3	36	14.6	4.5 - 47.4
NT	1	12	14.6	1.9 - 112.4
19F*	2	31	11.3	2.7 - 47.3
11A	3	63	8.4	2.6 - 26.6
35F	1	26	6.7	0.9 - 49.7
23A	1	62	2.8	0.4 - 20.4
6C	1	65	2.7	0.4 - 19.4
35B	0	65	0.0	0.0 - 8.1#
13	0	1		

Serotype	Number of invasive isolates	Number of carriage isolates	Invasive potential (Disease incidence/carriage prevalence X 105)	95% CI**
15F	0	4		
16F	0	13		
18F	0	1		
25A	0	3		
31	0	7		
33A	0	1		
34	0	12		
36	0	1		
37	0	3		
9A	0	1		
9N	0	4		
9V*	0	2		
Pool I	0	2		
4*	3	0		
20	2	0		
18B	2	0		
1^	1	0		
12B	1	0		
TOTAL	206	806		

*PCV7 serotypes,

&PCV10 serotypes,

^PCV13 serotypes.

**95% CIs were calculated as 1.96 × the SE calculated as in methods.

#The estimated IC is 0; the upper bound is the 95% upper limit for the IC and the CI around that value, calculated by using “3” for Nx incorporating variability from the invasiveness incidence but not from prevalence in the formulae shown in the methods section [22].