Intrinsic Epidemicity of Streptococcus pneumoniae Depends on Strain Serotype and Antibiotic-Susceptibility Pattern

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Abstract

*Streptococcus pneumoniae* is a major cause of invasive diseases worldwide. It spreads through an interindividual transmission, followed by usually harmless colonization of the host. Possible transmission differences, reflecting intrinsic strain features (e.g. serotype, antibiotic susceptibility), have been little studied so far.

In this study, we used epidemiological data from an interventional trial on *S. pneumoniae* carriage among kindergartners and developed a mathematical model to estimate transmission parameters of the different strains isolated during that study.

We found small, but significant transmissibility differences between observed serotypes: serotypes 3, 6A and 19A were found to be the most epidemic, while serotypes 23F, 9V and 14 were the least epidemic. Further analysis indicated that, within a serotype, susceptible and resistant strains had different abilities to be transmitted. Susceptible-to-resistant transmission rate ratios were computed for five serotypes; susceptible strains were significantly more epidemic than resistant strains for serotypes 6A (mean 1.02) and 19F (1.05). Serotype 19A resistant strains were not out-competed by susceptible strains (0.97).

Non-significant trends were observed for serotypes 6B (1.01) and 15A (0.98).

Our results support the existence of heterogeneous abilities of the different serotypes for host-to-host transmission. They also suggest that antibiotic susceptibility within a serotype affects this transmissibility. We conclude that pneumococcal strains should not been considered as equally at-risk in terms of transmission. Further quantification of strain-specific epidemic potential is therefore needed, especially in a context of extensive use of conjugate vaccines with the aim of preventing pneumococcal infections.

241 words
Keywords: Streptococcus pneumoniae, serotype, resistance, epidemicity, mathematical model
**INTRODUCTION**

*S. pneumoniae* is a major pathogen, responsible for severe infections, and is currently the main cause of community-acquired infections worldwide (otitis media, sinusitis, bacteremia, pneumonia and meningitis) (10). *S. pneumoniae* resistance to antibiotics was first described >25 years ago, and has been a growing concern ever since, especially during the last 10 years, with the majority of clinical isolates now being commonly resistant or even multiresistant to antibiotics.

The rate at which resistant strains spread throughout the population is the result of complex interactions among several factors, reflecting pathogen, host and environmental characteristics. The association between antibiotic use and spread of *S. pneumoniae* resistant strains has been established for many antibiotic classes, namely beta-lactams, macrolides and fluoroquinolones (16). But it is generally thought that the balance between the volume of antibiotic consumption in the population and the magnitude of the bacterium’s fitness cost tied to resistance acquisition is predictive of resistance persistence within a population (17). Depending on whether their competitive disadvantage derived from resistance acquisition is offset by high-level antibiotic exposure, resistant strains are able to displace or not susceptible strains.

Concerning fitness cost, the authors of several studies observed that alterations of penicillin-binding proteins, the mechanism by which *S. pneumoniae* acquires resistance to beta-lactams, were associated with defective growth in drug-free medium and lower virulence than susceptible strains in mouse models (4, 23), even though the relationship between resistance and virulence appeared highly complex and dependent on the serotype. However, it remains unclear whether resistance affects the ability of *S. pneumoniae* to colonize, and, therefore, to be transmitted between hosts. Fernebro et al., using a murine
intranasal installation model, concluded that even large fitness defects did not impede *S. pneumoniae* colonization of the upper airways (11), whereas Trzcinski et al. observed diminished ability to colonize the upper airways among resistant strains, and deduced that antibiotic selective pressure was required to maintain resistance in the population (26). To our knowledge, no epidemiological study attempted to link these in vitro and/or experimental results to real data from human populations. Therefore, how those predictions apply to a human epidemiological setting is unknown.

Because nasopharyngeal colonization is the key event leading to cross-transmission, on the one hand, and infection, on the other (15, 20), it appears extremely important to analyze the factors responsible for *S. pneumoniae* transmission in the population, like the impact of resistance described below. These factors also comprise high antigenic diversity, with about 90 serotypes described to date, and the effects of public health measures, e.g. the introduction of the pneumococcal conjugate vaccine and antibiotic-use-restriction policies applied in some countries, including France.

That vaccine has successfully diminished invasive diseases caused by the serotypes it contains, with an additional and unexpected effect on colonization (15). However, the emergence of non-vaccine serotypes has raised concern about a possible phenomenon of serotype replacement, which could jeopardize vaccine efficacy. Accordingly, whether or not the epidemic success of *S. pneumoniae* depends on the serotype could become a crucial issue concerning the contents of future pneumococcal vaccines, and the choice of new serotypes to include.

Based on some evidence that decreasing antibiotic use can lower resistance rates (12), many countries have initiated public health programs to optimize antibiotic prescriptions in the community. Therefore, the way *S. pneumoniae* resistance affects the ability of the
strains to be transmitted is likely to have important consequences, when considering the
natural rise of susceptible strains, and the competition of resistant strains with them
subsequent to less antibiotic use in the population following antibiotic containment policies.

During our population-based study, we observed that less antibiotic exposure led to the
rapidly enhanced dissemination of antibiotic-susceptible strains in 3–6-year-old children
(12). That investigation provided unique epidemiological data to assess in real life how the
serotypes and antibiotic resistance affect the epidemic success of *S. pneumoniae*. Herein, we
estimated the transmission parameters of *S. pneumoniae* with the aim of examining how
those two factors might be able to account for transmissibility heterogeneity.

**MATERIALS AND METHODS**

Based on the epidemiological data from an interventional trial on *S. pneumoniae*
carriage in French kindergartners conducted in 2000, we explored hypothetical
transmissibility differences among *S. pneumoniae* serotypes, using a compartmental model
of *S. pneumoniae* transmission.

**Data**

The data had been obtained in a non-randomized, prospective, controlled, population-
based trial applying multidimensional interventions to reduce antibiotic use in the
community (12). That study compared two interventions with a control cohort of children.
The specific targeted intervention-population was 3–6-year-old kindergartners. Informed
consents were obtained from the parents prior to the study. Children were monitored for 5
months (January to May 2000), and screened thrice (January, March and May) for *S.
pneumoniae carriage, through oropharyngeal swabbing. For each swab, the dominant strain was selected and analyzed. Minimal inhibitory concentrations of penicillin G and erythromycin were determined with use of the micro-dilution method on ATB-pneumo strips (bioMérieux, Marnes-la-Coquette, France)(14) and strains were serotyped using latex particles coated with a complete panel of antisera and factor serum, able to identify the 90 known serotypes. Data on antibiotics taken by children were recorded in real time in the questionnaires prospectively distributed to parents, coupled with health-insurance reimbursement data. The follow-up period was similar for all children in a given school. Of the 36 serotypes observed during the interventional trial, only 14 were studied here, those for which at least 10 carriage events were observed during follow-up, to ensure of sufficient significance of the results. Figure 1 illustrates the frequencies of serotypes and antibiotic-susceptibility patterns of S. pneumoniae strains isolated during that investigation, including the serotypes analyzed herein.

Model description

Hypotheses were tested by means of a mathematical model (figure 2). The model takes into account two different antibiotic classes (BL: beta-lactams, M: Macrolides) and the resistance status of the strains to them (beta-lactam–resistant and macrolide-resistant strains, beta-lactam–resistant and macrolides-susceptible strains, beta-lactam–susceptible and macrolides-resistant strains, beta-lactam–susceptible and macrolides-susceptible strains, i.e. four possible phenotypes). Thus, the study population was divided into 15 possible situations, with respect to their antibiotic exposure: not exposed, beta-lactam–treated, macrolide-treated; and their colonization status: no carriage, carriage of a strain having one of the four profiles described above.
The model was then applied to simulate the transmission of a given *S. pneumoniae* serotype in the population, assuming that non-carriers of this serotype are not colonized by any *S. pneumoniae* strain whatsoever. Moreover, we assumed that individuals could not be exposed to beta-lactams and macrolides at the same time.

**Parameters**

Table 1 defines the parameters used in the model and their values. A first set of parameters was taken from the literature, namely, the natural duration of pneumococcal carriage (28 days (9)), the mean duration of beta-lactam and macrolide administration (7 days for both (1)) and the efficacy of the two antibiotics against susceptible strains (effective in 5 days (7)). Because our system was closed (no study population changes during follow-up), death and birth rates were null; in addition, at the time of the study (2000), the heptavalent vaccine was not yet available so the model does not take it into account.

Another set of parameters had to be computed from the observed data. Hence, the monthly antibiotic-consumption rate was estimated from the antibiotic exposure (questionnaires filled out by the parents and insurance-reimbursement data), it was the only time-dependent parameter in the model. Due to the closed system, colonization by a new serotype (i.e. one that had not been observed at the beginning of follow-up) could not append naturally in the simulation. However, children colonized by serotypes that had not been reported at the study onset were observed, probably acquired outside school in their households or missed in the first cultures. In order to model this serotype appearance, an additional parameter ($\chi$) was included in the model, allowing colonization by a new serotype. This parameter was computed as the probability of being colonized by each of the studied serotypes, and had the same parameter values for every serotype.
To assess and compare the transmissibility of the different strains, we chose to estimate the infectious contact rate (or transmission rate) $\beta$, a classical parameter of epidemiological models and to keep carriage duration constant among strains. We used a frequency-dependant assumption, in which the number of contacts per unit of time is independent of the size of the population $N$: hence $\beta/N$ represents the rate of transmission to each susceptible child per colonized child. The transmission rates were estimated from the data that had been collected during follow-up, using the method described below.

**Estimation**

For each serotype considered herein, we assigned a transmission rate for susceptible strains (defined as being susceptible to beta-lactams and macrolides) and another, possibly different one, to resistant strains (defined as being resistant to at least one of the considered antibiotics).

All transmission-rate values were tested in the interval [0–0.1] day$^{-1}$: model values were initialized with the results of the first sampling (January 2000), and simulation results were compared to the observed numbers of carriers at two times (second and third samplings in March and May 2000, respectively), using the likelihood function of Poisson’s law (see Appendix B). To perform the estimation and to ensure sufficient statistical power, observations made on all kindergartens were pooled in one sample. Finally, the two estimated transmission rates for each serotype were those maximizing the likelihood function.

**RESULTS**
First, transmission rates for each serotype were estimated without regard to antibiotic susceptibility, to determine whether *S. pneumoniae* transmissibility was a function of the carried serotype (figure 3). The estimate distribution was highly heterogeneous, with mean values ranging from 0.029 day$^{-1}$ (serotype 14) to 0.040 day$^{-1}$ (serotype 3). Significant transmissibility differences between carried serotypes were observed (no overlapping of the 95% Credibility Intervals (CrI)), especially for serotypes belonging to the same serogroup (serogroup 6, including serotypes 6A and 6B; serogroup 19, including serotypes 19A and 19F; serogroup 23, including serotypes 23A and 23F). The most transmissible serotypes were 3, 6A and 19A (estimates: 0.040, 0.039 and 0.038 day$^{-1}$, respectively), whereas the least transmissible were 23F, 9V and 14 (0.033, 0.032 and 0.029 day$^{-1}$, respectively).

Then, we tried to determine whether the carried strain’s antibiotic susceptibility affected the transmissibility of each *S. pneumoniae* serotype. To this end, a transmission rate was assigned to susceptible strains and another, possibly different, rate to resistant strains and values of both were thereafter estimated. Table 2 summarizes the results of this analysis. Again, the distribution of transmission rates was heterogeneous, with mean values ranging from 0.034 day$^{-1}$ (serotype 15A) to 0.039 day$^{-1}$ (serotype 11A) for carriage of susceptible strains, and from 0.029 day$^{-1}$ (serotype 14) to 0.038 day$^{-1}$ (serotype 6A and 19A) for carriage of resistant strains.

To test the hypothesis of a transmissibility difference between susceptible and resistant strains within a serotype, the susceptible-to-resistant transmission rate ratio ($\beta_s/\beta_r$ ratio) was computed for each serotype for which at least 10 carriage events each of susceptible strains and resistant strains had been observed during follow-up (table 2). Five serotypes were eligible (6A, 6B, 15A, 19A, 19F); their mean values ranged from 0.97 (serotype 19A) to 1.06 (serotype 19F). For serotypes 6B and 15A, the estimation intervals overlapped the null-
hypothesis value (1, same transmissibility for susceptible and resistant strains), which did not allow any conclusion to be drawn concerning the transmissibility of susceptible strains with respect to their resistant counterparts. Nevertheless, it can be noticed that the 15A $\beta_s/\beta_r$ ratio was <1, but it was >1 for 6B. For serotypes 6A and 19F, the estimated 95% CI were significantly higher than the null-hypothesis value, with no overlapping, indicating a higher transmissibility of susceptible strains. That estimation interval was significantly <1 for 19A, suggesting a higher transmissibility of resistant strains.

Finally, in order to test the accuracy of our simulation-derived results, we compared the rates of susceptible strain and resistant strain carriers predicted by our model to those observed during follow-up (Figure 4). Predicted rates of carriers matched very well the observations, indicating the model reproduced correctly the transmission dynamics during follow-up. A sensitivity analysis of the model was also undertaken to determine input parameters influencing the variability of the output-estimated rates (see Appendix C).

DISCUSSION

Our results support that *S. pneumoniae* transmissibility is determined by the capsular serotype, on the one hand, and its antibiotic susceptibility within a serotype on the other. Using the same data, Cauchemez et al. found no significant difference in transmission rates when grouping serotypes according to their inclusion or not in the conjugate vaccine (6). We showed that significant differences may exist between individual serotypes, independently to their vaccine inclusion or not. However, our transmissibility estimates lie within the same range (~0.03 day$^{-1}$) and were also consistent with those found by Melegaro et al for *S. pneumoniae* transmission in households (mean child-to-child transmission rate of
Our transmissibility estimates, 0.09 acquisitions per month and susceptible child on average, are also consistent with Auranen et al. findings in Danish day care centers (0.1 acquisition per month (3)). However, in the Danish study, serotype 23F was acquired at a high rate and serotype 19A at a low rate, contrary to our findings. This discrepancy may be due to ecological differences between the two countries, especially in light of the greater antibiotic consumption in France.

It was shown that carriage duration depended on the capsule, with significant differences among the serotypes (25). The mechanisms responsible for this capsular serotype-specific effect remain unclear, although the results of a recent study pointed out the possible existence of an *S. pneumoniae* serotype-specific immune response, mediated by the charge of anticapsular antibodies generated in response to the colonization by that serotype (27). If so, this specific immune response would be responsible for a lower risk of carriage, resulting in a diminished transmissibility depending on the serotype. An alternative explanation was provided in a recent study, where the authors found that serotype prevalence was correlated to the degree of encapsulation, most prevalent serotypes being more encapsulated and more resistant to neutrophil-mediated killing (28). Our findings are thereby consistent with those observations. As it was not possible, given the data, to differentiate in the analysis between differences in carriage duration and differences in transmissibility, we choose to fix common carriage duration for all serotypes and to allow transmissibility to vary. Fixing a common transmissibility rate and varying carriage duration could also have been done and would have resulted in the same conclusions regarding which serotypes were the most epidemic. Our aim here was to provide global epidemicity comparisons between strains, instead of estimating precise transmissibility rates for the different pneumococcal serotypes.
Seven serotypes (4, 6B, 9V, 14, 18C, 19F, 23F) were included in the first pneumococcal conjugate vaccine, chosen because they were the most frequently associated with resistant pneumococcal infections (15). Our results merely indicate that, among the 10 most epidemic serotypes, only two (6B and 19F) were contained in the initial vaccine (Figure 3). Vaccination pressure could induce the rapid dissemination of non-vaccine serotypes and their related invasive infections. Hence, because the composition of the pneumococcal vaccines will undoubtedly evolve, this finding may prove useful for the selection of other serotypes to include in an extended vaccine.

Our results also suggest that antibiotic susceptibility can affect the transmissibility of the strains within a serotype. For some serotypes, we found that susceptible strains were more transmissible than their resistant counterparts (6A, 6B and 19F), which is consistent with the common notion of a cost of resistance, herein found at a population level.

Intriguingly, we found for serotype 19A (and perhaps for 15A), that resistant strains were significantly more epidemic than susceptible strains. Since the conjugate vaccine was introduced, the non-vaccine serotype 19A has been identified as a (re-)emerging serotype (13), with increasing antibiotic-resistance and increased disease incidence described since 2000 (8). Capsular switch events from other serotypes predominating in the pre-vaccine era, e.g. serotypes 14, 6B, 23F, 19F or 9V, are a likely explanation for this rise (19, 21). Our results are in good agreement with those observations, as they highlighted the high transmissibility of this serotype, on the one hand (figure 3), while on the other, its resistant strains remain unimpaired at a population level (figure 4).

Considering the common concept that resistance acquisition might be associated with decreased fitness, we have no clear explanation for what we observed for serotype 19A (and perhaps 15A). Some investigators have supported that drug-resistant strains harboring low
or no-cost mutations are selected in hosts during treatment, and that these strains are more likely to spread in human populations, and also that compensatory mutations might occur and restore fitness (2). These possible outcomes might, in part, account for the seemingly counterintuitive results obtained for these serotypes. More generally, evidence is lacking concerning whether in vitro fitness costs are predictive of evolution and ecology of a given pathogen. This issue reflects the lack of an epidemiological definition of bacterial fitness at a population level, i.e. epidemic fitness. Herein, we developed a modest way to measure the competition between susceptible and resistant strains at the population level within a given serotype based on the ratio of reproductive numbers (a common parameter used in epidemiology to characterize epidemicity of a pathogen in a given population). We defined the susceptible-to-resistant transmissibility ratio $R_s/R_r = \beta_s\lambda_s/\beta_r\lambda_r$, where $R_s$ (respectively $R_r$) defines the reproductive number for susceptible strain (respectively for resistant strain). Further studies are needed to provide a satisfactory fitness equivalent at the population level so that an “intrinsic epidemicity” concept can be characterized.

Obviously, our analysis has some shortcomings. First, during the interventional study, swabbing samples were obtained from the oropharynx rather than the nasopharynx, which is the natural $S. pneumoniae$ reservoir. That choice is likely to have underestimated the number of carriers during the study and, in turn, estimated transmission rate values, as oropharyngeal swabbing is known to be less sensitive than nasopharyngeal swabbing (22). However, because we compared transmissibility between serotypes and that lack of sensitivity was uniform among them, this bias should not have affected our conclusions. Co-carriage information was not available from the data meaning that a few transmission events are likely to have been missed in the analysis. Co-colonisation might play an important role in the horizontal transfer of resistance in the nasopharynx (5) and for
between-serotype competition (15). Therefore, extending this analysis to more detailed data would prove very useful in the future. In addition, the interventional trial focused on 3–6-year-old children, so our results should only be interpreted for this population, as *S. pneumoniae* epidemiology varies with age. Second, the mathematical model included some over simplifications regarding pneumococcal epidemiology. In the model, the transmission dynamics of each serotype was not influenced by the presence of the others. As the overall prevalence of carriers was low during the study (about 10%), this condition should not have been too restrictive for our analysis. Serotype appearance, representing either serotypes acquired outside school or missed in the first swab cultures, was modeled here by using a simple serotype-independent parameter, as no additional data was available for this intervention trial. Household exposure is known to be important for pneumococcal transmission. Nevertheless, by giving to all the serotypes the same chance of appearing in the model, only those with high enough epidemicity could emerge and spread in the studied population. Although such a hypothesis may not be realistic in the case of a big epidemic of a specific strain happening in the adult population during the study period, it can otherwise be considered realistic. Due to the scarcity of the data for some serotypes, we had to limit our analysis to the most prevalent serotypes observed during the study, but similar differences in epidemicity may exist for serotypes which were not considered here as well.

Last, due to the pooling of kindergartens, our population did not constitute a single-host population in which the transmission fitness could have been better evaluated. This pooling was possible here, because our aim here was to fit trends of serotypes dynamics rather than transmission events on an individual basis.

The interventional trial from which the data were drawn was carried out in 2000, and the spread of *S. pneumoniae* strains has changed since then, due to two major public health
measures. First, a successful campaign aimed at reducing the use of antibiotics was launched in France in 2000, which led to a 25% decrease of antibiotic prescriptions and a simultaneous decline of resistance rates (24). Second, the pneumococcal conjugate vaccine was introduced in France in 2002 and was recommended for all children aged <2 years in 2006, resulting in a marked decrease of vaccine-targeted–serotype carriage, and their associated invasive diseases.

The method presented in this paper allows one to compare epidemicities among different strains of the same species. It could be easily adapted and applied to other data to investigate *S. pneumoniae*-serotype transmission after the introduction of the heptavalent vaccine. Indeed, that vaccine has greatly modified *S. pneumoniae* epidemiology, with unexpected effects on colonization and a phenomenon of serotype replacement of vaccine serotypes by those not included (15). Our method could contribute to identifying re-emerging serotypes and, hence, which serotypes should be included in future pneumococcal vaccines, thereby extending the valence of the current one.

Making allowance of the study limitations, we think that our results provide new insights into the comprehension of *S. pneumoniae* spread, and may help manage and control the transmission of this pathogen.
Table 1. Parameters Used in the Model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Mean</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\delta_{P_s}$</td>
<td>Beta-lactam/macrolides efficacy against susceptible strains</td>
<td>6.0</td>
<td>(7)</td>
</tr>
<tr>
<td>$\delta_{P_r}$</td>
<td>Beta-lactam efficacy against resistant strains</td>
<td>2.5</td>
<td>(7)</td>
</tr>
<tr>
<td>$\delta_{M_r}$</td>
<td>Macrolide efficacy against resistant strains</td>
<td>1.0 (no efficacy)</td>
<td>(7)</td>
</tr>
<tr>
<td>$1/\lambda$</td>
<td>Natural duration of <em>S. pneumoniae</em> carriage</td>
<td>28 days</td>
<td>(9)</td>
</tr>
<tr>
<td>$1/\gamma_P$</td>
<td>Duration of beta-lactam treatment</td>
<td>7 days</td>
<td>(1)</td>
</tr>
<tr>
<td>$1/\gamma_M$</td>
<td>Duration of macrolide treatment</td>
<td>7 days</td>
<td>(1)</td>
</tr>
<tr>
<td>$\chi_s$</td>
<td>Probability of susceptible-strain appearance for each serotype</td>
<td>$3.2 \times 10^{-6} \text{ day}^{-1}$</td>
<td>Calibrated</td>
</tr>
<tr>
<td>$\chi_r$</td>
<td>Probability of resistant-strain appearance for each serotype</td>
<td>$1.2 \times 10^{-6} \text{ day}^{-1}$</td>
<td>Calibrated</td>
</tr>
<tr>
<td>$\alpha_{P}$</td>
<td>Frequency of beta-lactam treatment</td>
<td>January: $10.5 \times 10^{-3} \text{ day}^{-1}$</td>
<td>Computed from the data</td>
</tr>
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<td></td>
<td></td>
<td>February: $8.2 \times 10^{-3} \text{ day}^{-1}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>March: $6.4 \times 10^{-3} \text{ day}^{-1}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>April: $5.2 \times 10^{-3} \text{ day}^{-1}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>May: $3.3 \times 10^{-3} \text{ day}^{-1}$</td>
<td></td>
</tr>
<tr>
<td>$\alpha_{M}$</td>
<td>Frequency of macrolide treatment</td>
<td>January: $3.9 \times 10^{-3} \text{ day}^{-1}$</td>
<td>Computed from the data</td>
</tr>
<tr>
<td></td>
<td></td>
<td>February: $2.7 \times 10^{-3} \text{ day}^{-1}$</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>March: $2.3 \times 10^{-3} \text{ day}^{-1}$</td>
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<td></td>
<td></td>
<td>April: $1.5 \times 10^{-3} \text{ day}^{-1}$</td>
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<td></td>
<td></td>
<td>May: $1.1 \times 10^{-3} \text{ day}^{-1}$</td>
<td></td>
</tr>
</tbody>
</table>

$\beta$, $\beta_s$, $\beta_r$: Transmission rates for each serotype, and for susceptible and resistant strains of each serotype. Estimated from the data.
Table 2. Estimated Transmission Rates ($\beta$) of Susceptible (s) and Resistant (r) for Each Serotype.

<table>
<thead>
<tr>
<th>Serotype</th>
<th>$\beta_s$ (day$^{-1}$)</th>
<th>$\beta_r$ (day$^{-1}$)</th>
<th>$\beta_s/\beta_r$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean 95% CrI</td>
<td>Mean 95% CrI</td>
<td>Mean 95% CrI</td>
</tr>
<tr>
<td>3</td>
<td>0.0388 0.0385, 0.0391</td>
<td>0.0383 0.0380, 0.0387</td>
<td>1.02 1.01, 1.03</td>
</tr>
<tr>
<td>6A</td>
<td>0.0392 0.0389, 0.0395</td>
<td>0.0389, 0.0387</td>
<td></td>
</tr>
<tr>
<td>6B</td>
<td>0.0355 0.0348, 0.0363</td>
<td>0.0352 0.0349, 0.0355</td>
<td>1.01 0.99, 1.03</td>
</tr>
<tr>
<td>9V</td>
<td>0.0316 0.0310, 0.0322</td>
<td>0.0310, 0.0322</td>
<td></td>
</tr>
<tr>
<td>11A</td>
<td>0.0394 0.0389, 0.0400</td>
<td>0.0389, 0.0387</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>0.0290 0.0287, 0.0294</td>
<td>0.0287, 0.0294</td>
<td></td>
</tr>
<tr>
<td>15A</td>
<td>0.0337 0.0327, 0.0348</td>
<td>0.0346 0.0340, 0.0351</td>
<td>0.98 0.95, 1.01</td>
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<tr>
<td>15B</td>
<td>0.0345 0.0337, 0.0354</td>
<td>0.0337, 0.0354</td>
<td></td>
</tr>
<tr>
<td>17F</td>
<td>0.0378 0.0373, 0.0384</td>
<td>0.0373, 0.0384</td>
<td></td>
</tr>
<tr>
<td>18C</td>
<td>0.0338 0.0334, 0.0343</td>
<td>0.0334, 0.0343</td>
<td></td>
</tr>
<tr>
<td>19A</td>
<td>0.0371 0.0364, 0.0378</td>
<td>0.0380, 0.0386</td>
<td>0.97 0.95, 0.99</td>
</tr>
<tr>
<td>19F</td>
<td>0.0381 0.0377, 0.0385</td>
<td>0.0358, 0.0364</td>
<td>1.06 1.04, 1.07</td>
</tr>
<tr>
<td>23A</td>
<td>0.0357 0.0349, 0.0364</td>
<td>0.0349, 0.0364</td>
<td></td>
</tr>
<tr>
<td>23F</td>
<td>0.0327 0.0324, 0.0330</td>
<td>0.0324, 0.0330</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: CrI, credibility interval.
Figure legends

Figure 1 – Intervventional trial results. Distributions of the isolated strains are represented for the first (January 2000) and last sampling (May 2000). The n values indicate the total number *S. pneumoniae* colonized children. Serotypes marked with an * are those considered in the analysis.

Figure 2 – Schematized model structure. The model is structured according to: antibiotic exposure: Untreated U, treated with beta-lactams BL and treated with macrolides M; colonization status: nc: not colonized and resistance phenotype of the carried strain: beta-lactam–susceptible and macrolide-susceptible strain carriers (ss); beta-lactam–susceptible and macrolide-resistant strain carriers (sr); beta-lactam–resistant and macrolide-susceptible strain carriers (sr) and beta-lactam–resistant and macrolide-resistant strain carriers (rr).

Figure 3 – Estimated transmission rates for each serotype. Mean values (●) and 95% confidence intervals (T-bars) are depicted for each serotype.

Figure 4 – Model fitting to the data. Predicted (dashed lines, ● mean value, T-bars: 95% confidence interval) based on simulation and observed (solid lines, × antibiotic-susceptible strain carriers’ rate, ◊ antibiotic-resistant strain carriers’ rate) carriers’ rates are represented at three times during follow-up.
References


