Unraveling the seasonal epidemiology of pneumococcus
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Infections caused by Streptococcus pneumoniae—including invasive pneumococcal diseases (IPDs)—remain a significant public health concern worldwide. The marked winter seasonality of IPDs is a striking, but still enigmatic aspect of pneumococcal epidemiology in nontropical climates. Here we confronted age-structured dynamic models of carriage transmission and disease with detailed IPD incidence data to test a range of hypotheses about the components and the mechanisms of pneumococcal seasonality. We find that seasonal variations in climate, influenza-like illnesses, and interindividual contacts jointly explain IPD seasonality. We show that both the carriage acquisition rate and the invasion rate vary seasonally, acting in concert to generate the marked seasonality of IPDs. We also find evidence that influenza-like illnesses increase the invasion rate in an age-specific manner, with a more pronounced effect in the elderly than in other demographics. Finally, we quantify the potential impact of seasonally timed interventions, a type of control measures that exploit pneumococcal seasonality to help reduce IPDs. Our findings shed light on the mechanisms of pneumococcal seasonality and may have notable implications for the control of pneumococcal infections.

Significance
The pneumococcus, a bacterium frequently carried in the nasopharynx, is responsible for a wide spectrum of infections in humans, including severe invasive pneumococcal diseases (IPDs). In nontropical climates, IPDs typically display a marked winter seasonality, a striking but still enigmatic aspect of pneumococcal epidemiology. Here we used dynamic models of carriage transmission and disease, confronted with detailed IPD incidence data, to elucidate the components and the mechanisms underlying the seasonality of IPDs. We find that temporal variations in climate, influenza-like illnesses, and interindividual contacts explain most of the seasonal variability in IPDs. We quantify the potential impact of seasonally timed interventions, a type of control measures that exploit pneumococcal seasonality to help reduce IPDs.

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ILI Data.ILI incidence data were available from the French Sentinelles network, a nationwide surveillance system based on a sample of general practitioners across France (17). An ILI case was defined clinically as sudden onset of fever (≥39 °C), associated with myalgia and respiratory symptoms (e.g., cough and sore throat). According to previous evidence, this specific case definition makes ILI a good proxy for influenza infection (5). As for the IPD data, the ILI data consisted of weekly, age-stratified time series of cases during wk 27/2000 to wk 26/2010 (Fig. 1B). Correction factors were applied to account for the age-specific pattern of health-seeking behavior observed in France, in particular the high probability of consulting a physician for an ILI infection in young children (SI Appendix, Table S1).

Meteorological Data. Daily meteorological records from nine weather stations located near the most populated cities across France were provided by Météo-France, the French national meteorological service. The following variables were considered, based on previous associational evidence (6, 7, 10): daily average temperature (measured in degrees Celsius), hours of sunshine, average relative humidity (in %), and average vapor pressure (a measure of absolute humidity, measured in hPa). Before analysis, the data were preprocessed in two steps. First, the data were averaged temporally and spatially to create weekly time series representing the average climatic conditions in mainland France. Second, because these variables were markedly correlated, we conducted a principal component analysis to summarize them (SI Appendix, Figs. S2 and S3). The first two components, displayed in Fig. 1C, captured about 97% of the variability and were used instead of the individual meteorological variables in all of the analyses.

Interindividual Contact Data. Data on age-specific contact rates were available from an empirical study of self-reported contacts in France (ref. 18 and SI Appendix, Fig. S1), comparable to the POLYMOD study in other European countries (19). The POLYMOD contact matrix from Great Britain was also tested in a sensitivity analysis (SI Appendix, Fig. S7 and Table S5).

Demographic Data. Annual birth rates and age-specific annual population estimates in France were available from the French National Institute of Statistics and Economic Studies. The smoothed estimates were used to calculate age-specific migration rates, so that the simulated population sizes approximately equaled the observed population sizes (SI Appendix, Supplementary Data).

Model and Hypotheses Formulation. To identify the mechanisms underlying the seasonal variations of IPDs, we formulated an age-structured, semi-mechanistic model of pneumococcal transmission, carriage, and subsequent invasive disease (20, 21). A feature of this model was the inclusion of two stages of carriage (early and late) to test the hypothesis that disease risk was not uniform over the duration of carriage (22). To analyze pneumococcal seasonality, the model further incorporated seasonal variations of ILIs (Fig. 1A), climate (Fig. 1C), and interindividual contact rates. The impact of ILIs was modeled mechanistically, by means of a pneumococcus–ILI coinfection model that integrated different mechanisms of interaction (21, 23). Specifically, we examined three different hypotheses of interaction: an individual carrying pneumococcus and infected with ILI was assumed (i) to contribute more to pneumococcal transmission or (ii) to be at higher risk of contracting an IPD; an individual not carrying pneumococcus but infected with ILI was assumed (iii) to have a higher risk of acquiring pneumococcal carriage. In contrast to ILIs, and in the absence of information to inform a fully mechanistic model, the impact of climate was modeled semimechanistically. Specifically, we considered four meteorological variables identified in previous ecological studies (6, 7, 10), summarized—via a principal component analysis (PCA)—by two principal components to bypass collinearity issues (Fig. 1C). We then constructed a background seasonal function that incorporated these two components, in addition to annual and semiannual harmonic terms representing a potentially unexplained seasonality. The model also incorporated seasonal variations of contacts between schoolchildren, timed according to the calendar of summer and Christmas holidays in France. Finally, we also considered a potential increase of contacts between children and the elderly during Christmas school holidays, a hypothesis previously put forth to explain the early-winter peaks of IPDs (24). In sum, our model incorporated most of the seasonal factors thought to contribute to pneumococcal epidemiology.

Because pneumococcal carriage precedes disease, the seasonal variations of IPDs can be ascribed to seasonality in the carriage acquisition rate or in the rate of progression from carriage to disease, i.e., the invasion rate. To identify the source of IPD seasonality, we formulated five hypotheses about the seasonalties of the acquisition and the invasion rates. The first and second hypotheses proposed that either the acquisition rate or the invasion rate varied seasonally. The third hypothesis proposed that both rates varied seasonally with a similar timing, but a possibly lower amplitude [e.g., as a result of bacterial population bottlenecks during transmission (25)] for the acquisition rate. The fourth hypothesis proposed that both the invasion and the acquisition rates varied seasonally, but the latter rate as a result of differences of contacts between school terms and school holidays in children. Finally, the fifth hypothesis combined the third and the fourth hypotheses.

Model Implementation and Estimation. The model was represented as a set of deterministic differential equations, completed by a negative-binomial stochastic observation model to correct for underreporting of IPD cases. To test our different hypotheses about pneumococcal seasonality, we conducted maximum likelihood estimation via trajectory matching using the R pomp package (26). For every hypothesis, the estimation was completed in several steps, starting from a broad search of parameter space, followed by a refined search to pinpoint the maximum likelihood estimate. The convergence
Dissecting Pneumococcal Seasonality. According to the best model’s estimates, the background seasonal function included a climate-associated component that gradually increased from summer to winter and an unexplained component that displayed a shallow trough during early summer and a peak in early November (Fig. 2A, Top). As a result, the estimated invasion rate displayed large-amplitude oscillations over the year (approximately ±40% around the seasonal mean, Fig. 2A, Bottom). Despite some seasonality, the background seasonality in the invasion rate displayed smaller-amplitude variations over the year (approximately ±10% around the seasonal mean, Fig. 2A, Bottom). In addition to this background seasonality, the acquisition rate incorporated seasonal variations of contact rates, resulting from reduced contacts between schoolchildren during school holidays and increased contacts between children and the elderly during Christmas holidays (SI Appendix, Table S5). The overall effect of the seasonal ingredients composing the acquisition rate is apparent in model simulations of age-specific carriage prevalence (Fig. 2B). In schoolchildren, the predicted carriage prevalence was stable during winter and spring; it gradually decreased during summer holidays and reincreased from school resumption until the end of the year. In contrast, carriage prevalence was more uniform in adults, except for a marked, but transient increase in the elderly during Christmas and the start of the new year. This pattern of seasonal carriage prevalence, combined with the seasonally varying invasion rate, resulted in large-amplitude variations of IPDs (Fig. 2C). Hence, our results demonstrated that both the acquisition rate and the invasion rate varied seasonally and acted in concert to produce the pronounced seasonality typical of IPDs.

Predicted Impact of a Seasonally Timed Intervention. In addition to the hypothetical interventions targeted at ILIs or climate described above, the seasonality in the carriage acquisition rate suggests that targeting interindividual contact rates over the year might be an effective way to control IPDs. The success of such an intervention, however, will hinge on the pattern of age-specific contacts and the identification of core transmitter age groups. To examine this, we performed numerical experiments in which contacts from a target age group were reduced (e.g., by enhancing barrier precautions, such as improving hand hygiene or using protective masks) during a specific week of the year, throughout the study period. The predicted effect of such a seasonally timed intervention on young children and the elderly—the two demographics most at risk for IPDs—is shown in Fig. 3C. To control IPDs in young children (Fig. 3C, Top), the predicted best strategy was to reduce the frequency of same-age contacts during fall and winter. By contrast, targeting other age groups was predicted to have much lower impact, except for a transient effect of reducing contacts from the elderly during Christmas holidays. A different picture emerged regarding the control of IPDs in the elderly (Fig. 3C, Bottom). Although the best strategy remained to reduce same-age contacts during winter and fall, the predicted impact of other age groups was more pronounced. In particular, young children were the second most impactful age group, with a seasonally varying effect of reducing their contacts highest during fall and winter, particularly during Christmas holidays. Similar results were obtained in other age groups (SI Appendix, Fig. S9), with indication of a seasonal impact of the timed intervention, highest when targeted, first, at same-age contacts and, second, at contacts involving young children. We
found these results to be robust with an alternative contact matrix, derived from the POLYMOD study in Great Britain (SI Appendix, Fig. S10). These results emphasize the assortative nature of pneumococcal transmission, in addition to the key role of young children as core transmitters to other age groups. Furthermore, they provide a proof of concept of the potential usefulness of interventions that exploit seasonality to control IPDs.

Discussion

The main goal of this study was to elucidate the mechanisms of pneumococcal seasonality, by leveraging detailed IPD incidence data in France. To do so, we developed semimechanistic models of pneumococcal transmission, carriage, and disease that incorporated seasonal variations of ILIs, climate, and interindividual contact rates—all seasonal factors previously proposed to contribute to pneumococcal epidemiology. Using likelihood-based statistical inference methods, we systematically evaluated the support of multiple hypotheses about the components and the mechanisms of pneumococcal seasonality. We found that pneumococcal seasonality was best explained by a conjunction of all of the seasonal factors considered. In addition, we found evidence that both the invasion rate and the carriage acquisition rate varied seasonally and acted in concert to generate the marked seasonality typical of IPDs in France. Finally, we explored the impact of seasonally timed interventions, which aim at exploiting pneumococcal seasonality to control IPDs.

Our results indicated that a substantial part of IPD variability was explained by seasonal variations of climate. These results are broadly consistent with previous ecological studies that estimated an association between IPDs and climatic drivers, such as temperature (7, 10), humidity (6), UV radiation (6, 10), or sunshine duration (7). Also in keeping with our findings in France, a recent modeling study found evidence of higher pneumococcal trans-

duration (7). Also in keeping with our findings in France, a recent association between IPDs and climatic drivers, such as tem-

rate and the carriage acquisition rate varied seasonally and considered. In addition, we found evidence that both the invasion rate and the carriage acquisition rate varied seasonally and acted in concert to generate the marked seasonality typical of IPDs in France. Finally, we explored the impact of seasonally timed interventions, which aim at exploiting pneumococcal seasonality to control IPDs.

Regarding influenza viruses, a number of experimental studies have examined their interaction with pneumococcus (12). The evidence garnered from these studies consistently demonstrated that influenza viruses have a facilitatory effect on pneumococcus, by increasing acquisition, bacterial load, transmission, or disease severity. Understanding how these individual-level mechanisms in animal models translate into population-level patterns in humans, however, is not straightforward. Indeed, population-based studies have estimated an at most modest contribution of influenza to IPDs (Refs. 5, 7, 8, and 33, reviewed in ref. 11.). As proposed by Shrestha et al. (23), this discrepancy may be explained by the fact that a large individual-level interaction results in a much lower population-level effect, whose identification depends on the interannual variability of influenza peaks. Our results, which also point to a disconnect between the individual- and population-level scales, entirely support this view. Unlike Shrestha et al., however, we found little evidence that ILIs affected pneumococcal acquisition, but two differences are worth noting. First, we explicitly modeled pneumococcal carriage, in addition to disease, so that our estimates may not be directly comparable. Second, our study focused on two disease outcomes (pneumococcal meningitis and bacteremia) whose epidemiology may differ from that of pneumococcal pneumonia. Indeed, a US study documented differences of seasonality between pneumonia and nonpneumonia IPDs and suggested the existence of different mechanisms leading to the two disease outcomes (33). To further test this hypothesis, a natural follow-up would be to apply our models to pneumococcal pneumonia data. Regarding the specific outcomes considered here, our results are consistent with those of Opatowski et al. (21), although a more pronounced effect on pneumococcal carriage transmission was found in that study. In addition, our estimate of the relative risk of carriage acquisition in ILI-infected individuals (1.0 [1.02, 4.69], ref. 34).

Our results have public health implications. First, we found that the population-level effect of ILIs on pneumococcal
circulation—via either increased transmission or acquisition—was minor. Importantly, therefore, interventions targeted at ILIs are not expected to produce marked indirect effects on pneumococcal carriage. Second, in keeping with previous studies (7, 8), we estimated that the overall fraction of IPDs due to ILIs was modest. Considering the severity and the high incidence of IPDs in certain regions, however, interventions that aim at reducing ILIs could still prevent a large number of IPDs, in particular in the context of influenza pandemics (35). Our results suggest that such interventions should be directed to individuals aged 5–20, in whom the burden of ILIs and its subsequent direct impact on IPDs are highest. Third, our results confirmed the key role of young children as core transmitters of pneumococcus, who should therefore be the prime target of control efforts that aim to reduce pneumococcal carriage. Finally, our findings support the concept of a senescence of the immune system in the elderly (36), which may help explain the high burden of IPDs in that age group. Hence, interventions targeted at the elderly are another important component of control efforts, although we predict they will have limited indirect effects.

To interpret our results more generally, we point out that both ILIs and climate were estimated to have a much higher effect on invasion than on either acquisition or transmission. Seconding a previous study (33), we propose that seasonal variations in pneumococcal carriage density may explain these results. Indeed, we expect such variations to have a much higher effect on invasion than on transmission, because bottlenecks (i.e., reductions in bacterial population size) are presumably tighter during between-host transmission than during within-host invasion. Because we did not explicitly model carriage density, this interpretation is speculative. However, previous experimental (25) and epidemiological (37) studies have suggested that carriage density is an important factor in transmission and invasion.

Several limits of our study are worth noting. First, in the absence of longitudinal carriage data, we made pragmatic assumptions based on available evidence. Specifically, we calibrated our models to reproduce a decrease of carriage prevalence with age, a robust signature of pneumococcal epidemiology (38). Regarding the seasonality of carriage prevalence in high-income countries, most [but not all (13)] longitudinal studies reported small-amplitude variations of carriage over the year (39–41). Our model-based hindcasts (Fig. 2B) of carriage prevalence are broadly consistent with those observations. However, our result regarding the increase of contact rates and of carriage prevalence in the

Fig. 3. Predicted impact of different interventions. (A) Fraction of IPDs attributable to ILIs according to age (x axis), calculated during the whole study period (blue boxplots) or the ILI epidemic periods (defined as ±6 wk around the ILI peak week every year, red boxplots). For every epidemiological year, ILIs were set to 0 in a given age group; the resulting number of IPDs in that age group during that year was calculated and compared with that of the base model (with ILIs). The attributable fraction represents the relative decrease (compared with the base model) in the number of IPDs. Each boxplot shows the year-to-year variation in the attributable fraction. (B) Relative excess of IPDs due to climate, according to week number (x axis). For every epidemiological year, the climate covariates of the best model were set to 0; the resulting overall number of IPDs during that year was calculated and compared with that of the base model. The fraction represents the relative decrease (if positive) or increase (if negative) in the number of IPDs, compared with the base model. For every week number, year-to-year variability is summarized by the median (blue line), the interquartile range (dark blue ribbon), and the range (blue ribbon). (C) Predicted impact of a seasonally timed intervention. We simulated the impact of reducing the contacts of a target age group (y axis) during a target week number (x axis) throughout the study period. The heatmap shows the predicted relative decrease (in %) of IPDs in 0–5 (Top) and 60+ (Bottom), the two age groups most at risk for IPDs. For visual clarity, the color scale is square-root transformed. See SI Appendix, Supplementary Results for complete details of the simulation protocol and SI Appendix, Fig. S9, showing the predicted impact in all of the age groups.
elderly during Christmas holidays should be confronted with new empirical data. Importantly, the estimate of the risk of disease during early carriage was sensitive to this transient effect, as evidenced by the fact that the information about that parameter was lost after removing data during Christmas holidays (95% confidence interval [0, 1]). Acknowledging these limitations, our results nevertheless demonstrate that IPD incidence data contain dynamic information about the transmission of pneumococcal carriage. Second, different types and subtypes of influenza can vary in transmissibility and virulence and may have a different impact on pneumococcus (11). Future work could therefore extend the models proposed here to incorporate more detailed information on influenza viruses, if available. Third, other co-circulating pathogens, considered here, have been proposed to interact with pneumococcus (42). Incorporating additional candidate pathogens may help further understand pneumococcal seasonality, in particular the part that remained unexplained by our models (Fig. 24).

In SI Appendix, we present preliminary evidence suggesting that the respiratory syncytial virus [quantified as the number of visits to emergency departments for bronchiolitis in children <5 y (SI Appendix, Fig. S8)] may also interact with pneumococcus. Finally, our model ignores a number of complexities associated with pneumococcal epidemiology, foremost the differences of fitness between the different serotypes (43). Previous studies, however, indicated that IPD seasonality changed little after the introduction of conjugate vaccines, despite substantial serotype replacement (5, 8), suggesting that the seasonal drivers act comparably on the different serotypes.

In conclusion, we systematically dissected the seasonality of pneumococcus, building on detailed IPD incidence data in France. Our results bring together a number of previous lines of evidence and add significant knowledge of the mechanisms that govern transmission, carriage, and disease. We anticipate that dynamic models, such as those presented here, will prove to be valuable tools to further elucidate the seasonality of pneumococcus and, it is likely, of other bacterial respiratory pathogens.

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