Seasonal dynamics of bacterial meningitis: a time-series analysis

Juliette Paireau, Angelica Chen*, Helene Broutin, Bryan Grenfell, Nicole E Basta*

Summary

Background Bacterial meningitis, which is caused mainly by *Neisseria meningitidis*, *Haemophilus influenzae*, and *Streptococcus pneumoniae*, inflicts a substantial burden of disease worldwide. Yet, the temporal dynamics of this disease are poorly characterised and many questions remain about the ecology of the disease. We aimed to comprehensively assess seasonal trends in bacterial meningitis on a global scale.

Methods We developed the first bacterial meningitis global database by compiling monthly incidence data as reported by country-level surveillance systems. Using country-level wavelet analysis, we identified whether a 12 month periodic component (annual seasonality) was detected in time-series that had at least 5 years of data with at least 40 cases reported per year. We estimated the mean timing of disease activity by computing the centre of gravity of the distribution of cases and investigated whether synchrony exists between the three pathogens responsible for most cases of bacterial meningitis.

Findings We used country-level data from 66 countries, including from 47 countries outside the meningitis belt in sub-Saharan Africa. A persistent seasonality was detected in 49 (96%) of the 51 time-series from 38 countries eligible for inclusion in the wavelet analyses. The mean timing of disease activity had a latitudinal trend, with bacterial meningitis seasons peaking during the winter months in countries in both the northern and southern hemispheres. The three pathogens shared similar seasonality, but time-shifts differed slightly by country.

Interpretation Our findings provide key insight into the seasonal dynamics of bacterial meningitis and add to knowledge about the global epidemiology of meningitis and the host, environment, and pathogen characteristics driving these patterns. Comprehensive understanding of global seasonal trends in meningitis could be used to design more effective prevention and control strategies.

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See **Comment** page e345

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Introduction

Bacterial meningitis causes inflammation of the meninges, which leads to sudden onset of fever, headache, stiff neck, nausea, vomiting, and altered mental status, and can rapidly result in death. *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae* are the leading causes of bacterial meningitis worldwide.[1] All three pathogens are carried asymptomatically in the human nasopharynx and transmission occurs through respiratory droplets or saliva. Symptoms typically occur within 3–7 days after transmission. The relative contribution of these three pathogens to the incidence of bacterial meningitis differs over time, by location, and by characteristics such as patient age.[2] Although vaccination programmes have been implemented in many countries and have had a considerable impact on disease,[2] more than 1·2 million cases of bacterial meningitis are estimated to occur each year.[3] The case-fatality rate is high for all three pathogens (ranging from 5% to 50%) and neurological sequelae occur in up to 50% of survivors.[3]

Previous work has documented the substantial burden of meningitis worldwide[4–6] and identified prevention of meningitis as a priority.[7,8] However, the temporal dynamics of bacterial meningitis, including the seasonality, interannual variation, and secular trends are poorly characterised in many parts of the world. Thus, many questions remain about the ecology of the disease. Comprehensively assessing the temporal dynamics of bacterial meningitis is the first, key step towards understanding the complex interactions between environmental, demographic, social, immunological, and other factors that might drive these patterns of disease. In this Article, we specifically focus on investigating country-level patterns of the seasonality of bacterial meningitis. Comparing and contrasting the seasonality of infectious diseases across diverse settings can increase understanding of the interactions between host and pathogen biology and ecology; enhance the accuracy of surveillance systems; lead to the development of optimum prevention and control strategies; and improve ability to predict epidemics.[9,10]

Research in context

Evidence before this study

In 2014 we searched the literature to review the existing evidence on seasonality of bacterial meningitis. We searched PubMed for papers including the terms "season*" in Title/Abstract and "bacterial meningitis", "meningococcal meningitis", "pneumococcal meningitis" or "*Haemophilus* meningitis" in MeSH terms, with no language or date restrictions. We found several reports of seasonal trends from single countries, either at the country level or at a sub-country level such as a metropolitan area or a hospital. However, the evidence was sparse and no comprehensive global comparative analysis of the seasonality of bacterial meningitis had been undertaken. We aimed to build upon previous studies that have described the global burden of disease in terms of morbidity and mortality by undertaking an investigation of the country-level, intra-annual variation in incidence with the primary aim of assessing the seasonality of bacterial meningitis worldwide.

Added value of this study

We compiled the first global database of monthly bacterial meningitis incidence data as reported by country-level surveillance systems in 66 countries, including 47 countries outside the meningitis belt, and we performed the most comprehensive analysis of global bacterial meningitis seasonality thus far. Our study provides a unique and global perspective on bacterial meningitis seasonality with time-series data from all continents. Our findings confirm previous reports of seasonality in specific contexts and countries and present strong evidence that bacterial meningitis incidence exhibits persistent seasonal patterns across a wide geographic range. In addition, we have shown, for the first time, that the timing of the seasonal peak in bacterial meningitis incidence is correlated to the latitude of the country's most populous city.

Implications of all the available evidence

Characterising bacterial meningitis seasonality is crucial to advancing understanding of the epidemiology, ecology, and transmission dynamics of the disease and is key to designing and implementing optimum prevention and control strategies. Moreover, the latitudinal trend in seasonal timing that we observed provides a basis for developing hypotheses about the potential factors, such as host susceptibility, environment, and pathogen characteristics, driving bacterial meningitis dynamics across various geographic settings. These hypotheses could be investigated through further studies beyond the scope of this analysis. Understanding seasonal patterns of meningitis contributes to ensuring that public health officials can plan and implement the most effective disease mitigation efforts.

Bacterial meningitis is known to peak during the dry season in the African meningitis belt, a group of countries in sub-Saharan Africa that have the highest incidence of bacterial meningitis.[11] Previous epidemiological reports from individual countries outside the meningitis belt show various seasonal patterns of bacterial meningitis. For instance, increased incidences have been observed in May to October in Brazil;[12] December to March in the USA,[13] France,[14] and the UK;[15] and July to September in New Zealand.[16] Here, we compile a global database of reported bacterial meningitis incidence by country to assess whether a significant seasonal signature is detected across diverse geographic settings, to estimate the timing of the meningitis season when seasonality is present, and to determine whether synchrony exists between these three primary causes of bacterial meningitis.

Methods

Database compilation

In our database, we included country-level time-series data from reports of laboratory-confirmed cases of meningitis caused by *H influenzae*, *N meningitidis*, and *S pneumoniae* or reports of suspected or laboratory-confirmed cases of bacterial meningitis (when the pathogen responsible was not specified) that were collected by a national surveillance system serving the general population of an entire country (as opposed to sentinel surveillance or other methods for collecting data from select populations or subnational regions) with weekly or monthly temporal resolution. No age or patient-based restrictions were used.

We obtained data using three strategies. First, we searched public databases using general search terms such as "bacterial meningitis incidence data", "national meningitis surveillance", and "meningitis database", and additional country-specific queries. The databases searched were Google, Google Scholar, PubMed, EuroSurveillance, Global Infectious Diseases and Epidemiology Network (GIDEON), WHO Databases, and Centers for Disease Control and Prevention (CDC) Vital Statistics. Second, we wrote web-crawling Java data-scraping programs to automatically search for links to ministry of health websites, reports, and other databases. The Java scripts were designed to automate the process of locating and exporting data from these websites into Excel spreadsheets. Each result was manually reviewed by AC and evaluated using the inclusion criteria described above. Third, we actively corresponded with public health officials such as ministries of health and authors of papers in which relevant time-series were analysed. Only aggregate and anonymous data were obtained; permission to use the data was acquired from data owners whenever necessary.

We specified that confirmed cases were those confirmed with laboratory-based diagnostic tests, although the specific criteria differed between countries and methods included macroscopic or microscopic

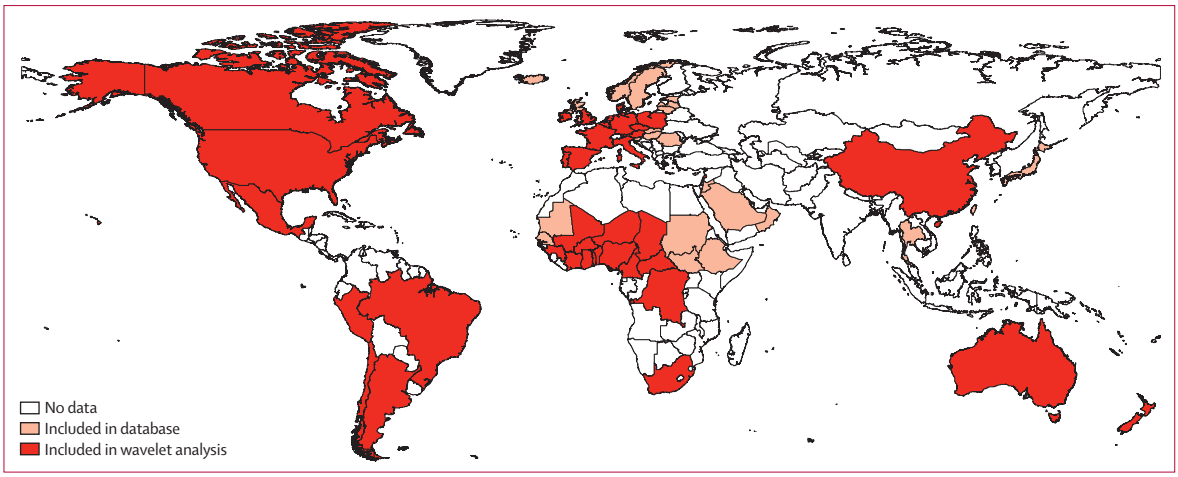

Figure 1: **Map of countries for which time-series data were available for inclusion in the bacterial meningitis database**
Monthly incidence data were obtained for the 66 countries highlighted in pink or red. The 38 countries in red met our inclusion criteria for the wavelet analyses for at least one pathogen.

examination of cerebrospinal fluid, antigen detection, culture, or PCR. Suspected cases (ie, defined by clinical criteria only) were sometimes the only available data from countries in which laboratory confirmation is a challenge, and therefore we included these in the database under a separate category and analysed them separately. Most data sources only reported aggregated number of cases per week or month, without any other information about age or sex of the patients. Information about serogroups or serotypes was rarely reported. We included case data in the database without modification, except we aggregated weekly data by month. Because we were interested in assessing seasonal patterns, rather than the magnitude of incidence, no specific efforts were undertaken to account for under-reporting.

	In the database	In wavelet analyses
Cases of unspecified bacterial meningitis	23	16
Cases caused by *Neisseria meningitidis*	65	25
Cases caused by *Haemophilus influenzae*	37	5
Cases caused by *Streptococcus pneumoniae*	37	5
Total (any aetiology)	66	38

Criteria for inclusion in wavelet analyses were countries with more than 5 years of non-missing data with more than 40 cases per year.

Table 1: **Number of countries included in database time-series and in wavelet analyses**

Time-series analyses

Our primary aim was to assess whether a significant seasonal signature was detected in bacterial meningitis time-series at country-level. To do this we used wavelet analyses to explore the periodicity in each time-series.[17] To ensure the highest quality data were included in the analysis and to avoid spurious results due to noise, we used only time-series that included at least 5 years of continuous data with at least 40 cases per year. A single country's surveillance system could contribute up to four time-series: reports of cases due to each of the three pathogens (laboratory confirmed) or due to suspected bacterial meningitis cases (undifferentiated aetiologies). For each time-series, we used the wavelet power spectrum to identify whether a 12 month periodic component (annual seasonality) was detected. We used the R package WaveletComp for the analyses. Additional technical details are provided in the appendix. As a supplementary analysis, we also examined whether the seasonal trends differed between pre-vaccine and post-vaccine introduction in those countries where one or more meningitis vaccines were introduced during the years for which time-series data were available (appendix).

Our secondary aim was to measure the mean timing of disease activity, for each time-series for which the wavelet analyses detected a significant seasonality that was persistent over at least 3 consecutive years. For this measure, we computed the centre of gravity of the monthly distribution of cases in a given country for each pathogen. We defined the centre of gravity as the mean month of the distribution, where each month is weighted by its number of cases. We henceforth referred to this as the seasonal timing or timing of disease activity. We used circular statistics to compute the centre of gravity and its 95% CI (based on 1000 bootstrap samples). For data where there is no true zero and the designation of high and low values is arbitrary (such as monthly data), circular statistics are better adapted than commonly used techniques. We used the R package circular to conduct these analyses. When significant seasonality was detected for at least two different pathogens within a single country, we compared the seasonal timing for these pathogens and determined whether they followed synchronous dynamics. We used Watson's

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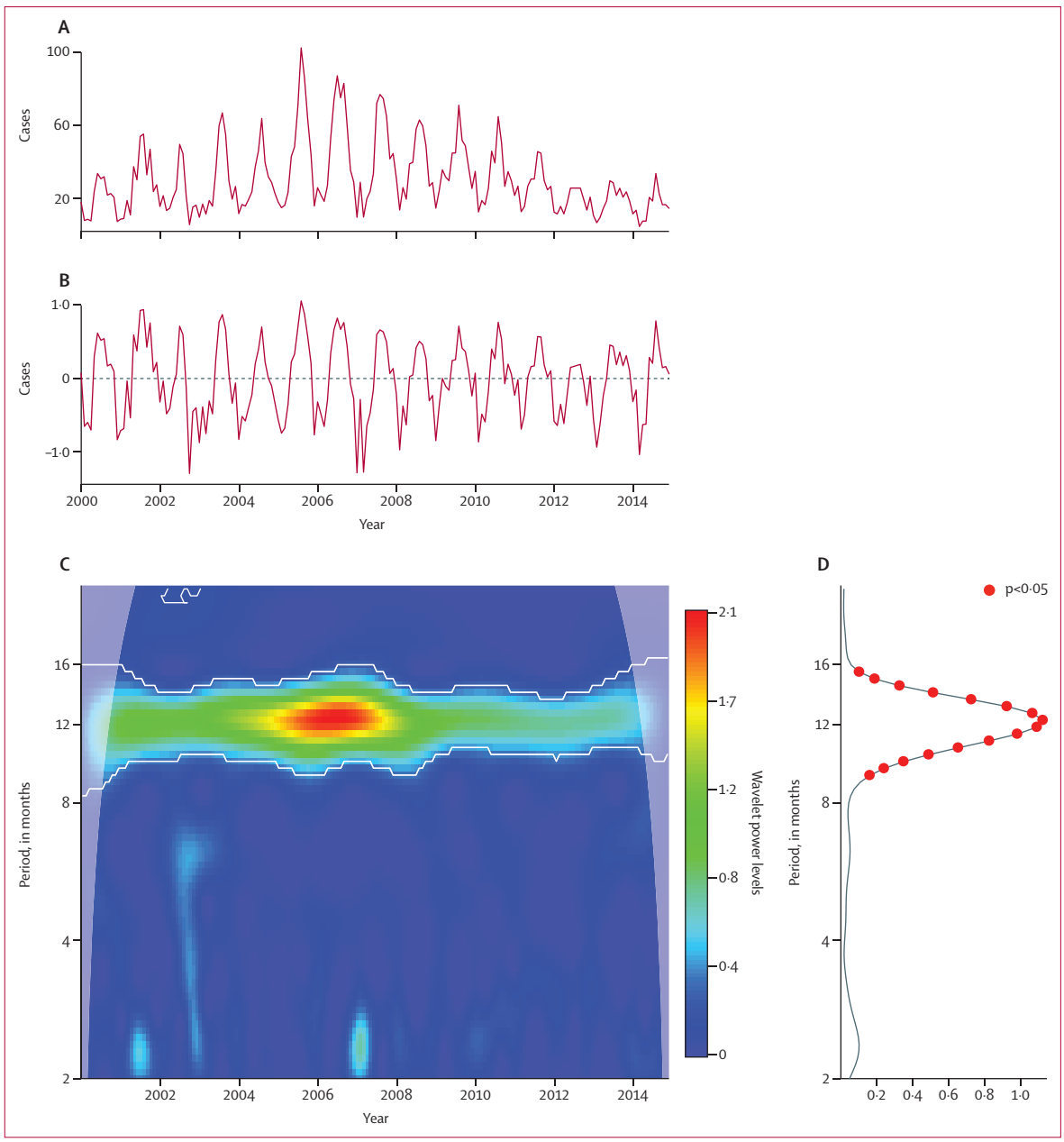

Figure 2: **Wavelet analysis for *Neisseria meningitidis* in South Africa, 2000–14**
(A) Raw time-series of reported cases. (B) Log-transformed, detrended, and standardised time-series used for wavelet analysis. (C) Wavelet power spectrum: wavelet power values increase from blue to red, and white contour lines indicate the 5% significance level. In this example, the time-series shows a significant 12 month periodicity over the entire time period. Shaded regions on either end delimit the cone of influence, where edge effects become important and spectral information is less robust. (D) Average wavelet power over time, with red dots indicating significant periods at the 5% level. Here the significant peak of power occurred at the 12 month period. Additional details and analyses for all other countries are available in the appendix.

non-parametric test to test the null hypothesis of a common centre of gravity for the two distributions of cases, with a 5% significance level.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Our database contained monthly bacterial meningitis incidence time-series from 66 countries: 27 in Europe, 20 in Africa (one outside the meningitis belt), six in east or southeast Asia, four in the Middle East, four in South

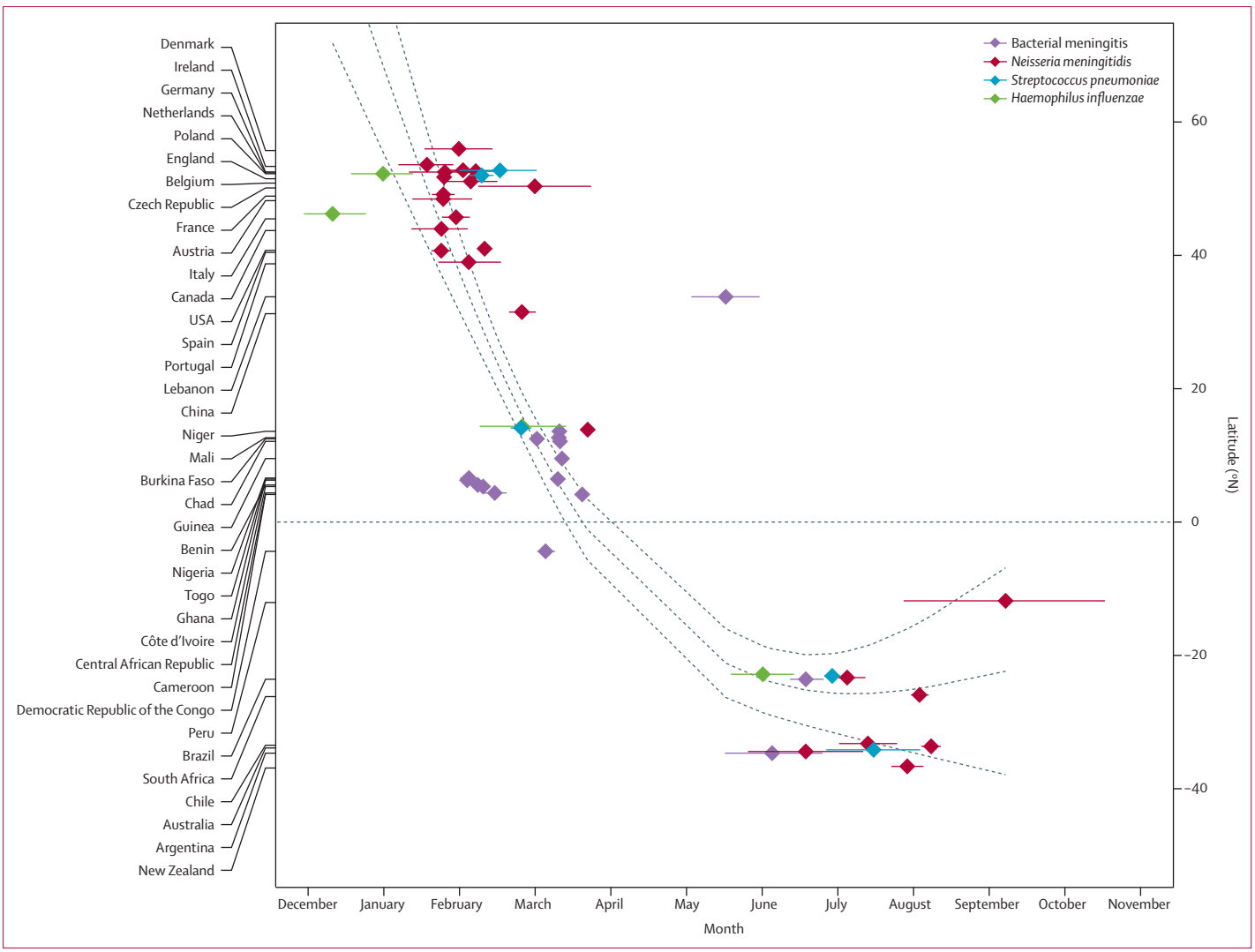

Figure 3: **Mean timing of bacterial meningitis season by country and aetiology**
Countries listed in order of mean latitude of their most populous metropolitan area. Dots represent the centre of gravity of the monthly distribution of cases. Horizontal segments show 95% CI. The dashed line shows a regression spline (weighted natural cubic spline with two degrees of freedom) with 95% CIs.

America, three in North America, and two in Oceania (figure 1, table 1). For each country, we report the data source, causative agents, time resolution, and time period of the time-series, and reported annual incidence ranges (appendix). About 700 000 cases of bacterial meningitis due to any cause were included in the database. The time-series had an average length of 9·7 years (range 0·3–32·5). Most time-series started in the late 1990s to the early 2000s.

51 time-series from 38 countries met the criteria to be included in the wavelet analyses (table 1, figure 1, appendix). As an illustration, figure 2 shows the wavelet power spectrum for *N meningitidis* in South Africa. The appendix shows all wavelet power spectra and corresponding time-series. All 25 countries included in the analyses for *N meningitidis* had a significant 12 month periodicity (ie, annual pattern). This pattern was detected over at least 3 years in all countries but Mexico. Five countries met our inclusion criteria for *S pneumoniae* (Argentina, Brazil, England, Niger, and Poland), and all had a significant 12 month periodicity. For *H influenzae*, a significant 12 month periodicity was detected in Brazil, England, Italy, and Niger, but not in Poland. Among the 16 countries for which their bacterial meningitis (unspecified aetiology) time-series were analysed, 13 were countries in the African meningitis belt, along with Argentina, Brazil, and Lebanon. A significant 12 month periodicity was detected in all of these countries. For any of the three pathogens, we did not observe the seasonal signal to be altered by vaccine introduction, as long as the incidence of disease remained sufficiently high to perform wavelet analysis (summary of trends included in appendix). Overall, 49 (96%) of the 51 time-series analysed showed a significant and persistent seasonality over at

	Centre of gravity			p values		
	Neisseria meningitidis	*Streptococcus pneumoniae*	*Haemophilus influenzae*	p_{Nm-Sp}	p_{Nm-Hi}	p_{Sp-Hi}
Poland	1·81 (0·87)	2·53 (0·86)	NA	0·034	..	..
England	1·80 (0·82)	2·29 (0·78)	0·99 (0·89)	<0·001	<0·001	<0·001
Italy	1·95 (0·71)	NA	0·32 (0·74)	..	<0·001	..
Niger	3·69 (0·21)	2·81 (0·47)	2·83 (0·74)	0·001	0·002	0·965
Brazil	7·12 (0·91)	6·92 (0·81)	6·01 (0·85)	0·129	<0·001	<0·001
Argentina	6·58 (0·87)	7·47 (0·84)	NA	0·066	..	..

Shows the centre of gravity in month numbers (1=January; 2=February, etc). Values in parentheses are variances. The p value shows comparisons of the centres of gravity of two pathogens within a country. p_{Nm-Sp}=p of *Neisseria meningitidis* versus *Streptococcus pneumoniae*. p_{Nm-Hi}=p of *Neisseria meningitidis* versus *Haemophilus influenzae*. p_{Sp-Hi}=p of *Streptococcus pneumoniae* versus *Haemophilus influenzae*. NA=not available.

Table 2: **Comparison of the seasonal timing of cases of bacterial meningitis in countries with available data**

least 3 years (all but *N meningitidis* in Mexico and *H influenzae* in Poland).

Figure 3 shows the mean timing of meningitis activity for the 49 seasonal time-series (from 37 different countries) against the mean latitude of the most populous metropolitan area in the country. Interestingly, an overall latitudinal trend could be observed in the seasonal timing, although a complete quantification of this trend is precluded by latitudinal gaps in our data. More specifically, three main groups of countries could be distinguished. First, in countries with latitudes above 30°N (Europe, North America, and China), the mean timing of *N meningitidis* activity (the pathogen most represented in the time-series) was located in winter, in January to February. Second, in all countries of the African meningitis belt (between –5°N and 20°N), the seasonal timing of bacterial meningitis was situated in February to March, during the dry season. Third, in countries below –20°N (South America, Oceania, and South Africa), the incidence of disease caused by any of the pathogens peaked June to July (winter season). Two outliers can be highlighted—the mean timing of bacterial meningitis in Lebanon was detected in May whereas its latitude is close to southern Europe and the meningococcal meningitis season in Peru occurred a bit later than in other South American countries, with a seasonal timing detected in September, but the confidence interval was large due to the small number of years and a mild seasonal signature.

The timing of the seasons for at least two different pathogens could be compared in six countries (table 2). Overall, the seasonal signatures in cases caused by the three pathogens were similar within each country. More specifically, the mean timing of meningitis activity was not different between *S pneumoniae* and *H influenzae* in Niger, and between *N meningitidis* and *S pneumoniae* in Brazil and Argentina. However, some differences were significant. Compared with *N meningitidis, S pneumoniae* occurred later in England and Poland, with a delay of 0·5–0·7 months, but occurred 0·9 months earlier in Niger. Interestingly, *H influenzae* cases systematically came before *N meningitidis* cases in the four countries in which these trends could be investigated, with lags ranging from 0·8 to 1·6 months.

Discussion

In this study, we compiled a database of country-level monthly time-series for bacterial meningitis incidence for 66 countries, and did the most detailed analysis of bacterial meningitis seasonality so far. Countries in the African meningitis belt were already known to feature a seasonal peak in incidence during the dry season. Here we show that bacterial meningitis also has significant seasonal patterns in the countries analysed outside the belt for the three primary causes of bacterial meningitis, *N meningitidis*, *S pneumoniae*, and *H influenzae*. We show that the timing of disease activity follows a latitudinal trend and that relatively higher incidences occur during winter in both the northern and southern hemispheres.

A significant 12 month periodicity was detected in all regions where the wavelet analyses could be performed—ie, mainly North America, South America, Europe, Africa, and Oceania. This striking result is consistent with and significantly builds upon previous studies of bacterial meningitis seasonality in individual countries or regions.[11–16,18–20] It is interesting to note that vaccine introduction, which occurred in different years depending on the country and vaccine, did not preclude detection of the seasonal trends as long as the number of cases, although sharply declining in some areas, remained relatively high (appendix). This suggests that, although reducing the incidence of disease and possibly shifting the seasonal timing, vaccine introduction has not eliminated a seasonal signal altogether.

We conducted an observational, time-series analysis to advance understanding of global seasonal trends in bacterial meningitis. Our results can be used to generate hypotheses about factors potentially involved in shaping disease seasonality, although further studies will be necessary to assess the relative role, if any, of these factors. Interestingly, we found evidence of a latitudinal trend in the timing of bacterial meningitis season worldwide: from January to March in European and North American countries, to February to April in countries in the African meningitis belt, to June to August for southern hemisphere countries. Although considering the host–pathogen–environment paradigm and acknowledging the complex and nuanced interaction between these factors, we could hypothesise that the latitudinal trend suggests a potential relationship between climate and the seasonality of bacterial meningitis, across a broad geographic range. An association between climate and meningitis has been suggested by previous research conducted within a much more limited geographic scope.[13,16,20,21] Whether environmental factors play a causal role in meningitis incidence remains unknown, but others have postulated that climatic conditions could facilitate pathogen invasion by damaging the nasopharyngeal mucosa.[11] The seasonal increase in

bacterial meningitis could also be triggered by a seasonal increase in respiratory virus infections (which are themselves likely related to climate) such as influenza, via an effect on transmission, colonisation, or invasion.[14,22–24] Others hypothesise that seasonal physiological changes in host susceptibility, possibly driven by changes in photoperiod, could explain the seasonality of the disease.[13] The key seasonal drivers are yet to be established and warrant further comprehensive studies that account for the role of host and pathogen characteristics, in addition to environmental factors, through laboratory-based research with new animal models and population-based epidemiological studies.[7] Population-based epidemiological studies investigating potential drivers of meningitis trends would benefit from a global and comparative perspective, such as the one adopted in the present study, to learn from similarities and differences in seasonal patterns across multiple, heterogeneous geographic contexts.

Although previous studies have investigated the synchrony between viral and bacterial pathogens,[14,23,24] less attention has been placed on evaluating the synchrony between multiple bacterial pathogens. Although our results were synthesised from a small sample of countries, they suggest that the three pathogens investigated here shared similar seasonality, but with slightly different time-shifts depending on the country. Previous work has suggested that these pathogens could share similar seasonal risks factors but might react slightly differently to them, due to different transmission, colonisation, or invasion capacity, and that multiple, varied country-specific drivers might interact with these risk factors.[25] Further studies are needed to investigate more broadly the combination of host, environment, and pathogen characteristics that could account for these differences.

Our study is limited by the completeness and quality of the data obtained. We undertook extensive efforts to obtain complete time-series data from established national surveillance systems and restricted our analyses to countries with the longest time-series data available. Although all data came from national surveillance systems, we had no information about the potential degree of under-reporting. However, as imperfect as the surveillance systems might be, there is no obvious reason why the seasonal peaks would be pure artifacts. Our results and conclusions are based on the relative seasonal increase in incidence and the peak timing, not on the absolute magnitude of the peak. Inherent to our analysis is the assumption that while the magnitude of incidence might be underestimated year round, the seasonal peaks are more likely due to the intrinsic dynamics of the disease than to systematic biases in the reporting systems. The consistency of the observed trends across a wide range of countries suggests that this assumption is reasonable.

Both northern and southern hemisphere countries are well represented in our database, suggesting broad generalisability of our results. However, few official statistics were available from east and southeast Asian countries and Middle East and north Africa countries.[26,27] For instance, India, a country regularly affected by meningococcal meningitis outbreaks, does not have a national surveillance programme for bacterial meningitis.[27] Surveillance in countries in the Middle East and north Africa is particularly important since the Hajj pilgrimage has been identified as a key factor in outbreaks and the regional spread of bacterial meningitis.[28] Our study thus highlights some important gaps where surveillance should be enhanced. Strengthening the capacity for laboratory confirmation of meningitis cases is needed across a wider range of countries as well. Knowledge of the aetiology of the reported disease burden is crucial for developing appropriate prevention and control strategies, especially given the potential for targeted vaccination strategies.

Our efforts to uncover global patterns of bacterial meningitis incidence constitute a first step towards generating hypotheses about how multiple factors interact to produce the complex dynamics exhibited by the disease. Ultimately, a better understanding of the seasonal dynamics of bacterial meningitis could help public health officials to effectively plan and implement prevention and control strategies in the future.

Contributors

NEB originally designed the study. JP, HB, and BG contributed to study design. JP, AC, HB, and NEB collected the data. JP and AC analysed the data. JP, AC, HB, BG, and NEB interpreted the data. JP, AC, and NEB wrote the manuscript. HB and BG substantially revised the manuscript. All authors approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

Acknowledgments

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