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2Descriptive statistics80026016Inferential statistics80013113Heatmap1000001ANOVA0120003GLM101012014LOWESS8001009MEM2100003Fourier's analysis3000003Multiplicative decomposition1000001ACF/PACF190000019ARIMA/SARIMA210000021Wavelet analysis3000104Mathematical modelling120210016 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. Funding: Princeton University Health Grand Challenge, US National Institutes of Health (NIH), NIH Fogarty International Center Research and Policy for Infectious Disease Dynamics programme (RAPIDD), Bill & Melinda Gates Foundation. Assistant Professor Nicole BastaA new study from the School of Public Health shows bacterial meningitis cases vary by season and peak during the winter months around the world. Bacterial meningitis, which is highly fatal and caused by common bacterial infections like streptococcus, has an estimated 1.2 million cases annually.The study, which is the first world-wide analysis of the seasonal dynamics of bacterial meningitis, was recently published in the journalThe Lancet Global Health.To gather the results, the research team from the University of Minnesota, Princeton University, and the Institut de recherche pour le dveloppement created the first-ever bacterial meningitis global database, which was compiled from more than 700,000 cases reported by surveillance systems in 66 countries.We found a strong seasonal trend in nearly all countries analyzed, saysstudy senior author and Assistant Professor Nicole Basta. We also observed a strong latitudinal gradient in the timing of the seasonal peak, with bacterial meningitis seasons peaking during the dry, winter months in countries in both the northern and southern hemispheres.Interest in the seasonality of meningitis outbreaks stems from the previously observed annual dry season outbreaks of the disease occurring in the sub-Saharan area of Africa known as the Meningitis Belt.Our analysis of the seasonal dynamics of meningitis across diverse geographic settings is the first step towards understanding what factors drive these trends, saysBasta.The researchers believe their findings provide key insight into the global epidemiology of meningitis and can be used to develop hypotheses about the host, environment, and pathogen characteristics that may be driving these patterns. They also argue that understanding global seasonal trends in meningitis could be used to design more effective disease prevention and control strategies. As a library, NLM provides access to scientific literature. Inclusion in an NLM database does not imply endorsement of, or agreement with, the contents by NLM or the National Institutes of Health. Learn more: PMC Disclaimer | PMC Copyright Notice . Author manuscript; available in PMC: 2017 Jul 19. 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.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.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.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.Princeton University Health Grand Challenge, US National Institutes of Health (NIH), NIH Fogarty International Center Research and Policy for Infectious Disease Dynamics programme (RAPIDD), Bill & Melinda Gates Foundation.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 37 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 12 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.3Previous work has documented the substantial burden of meningitis worldwide46 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 environ mental, 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.9,10Bacterial 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.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 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.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 countrys 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 Watsons 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.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.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 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 97 years (range 03325). Most time-series started in the late 1990s to the early 2000s. 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.Number of countries included in database time-series and in wavelet analysesIn the databaseIn wavelet analysesCases of unspecified bacterial meningitis2316Cases caused by Neisseria meningitidis6525Cases caused by Haemophilus influenzae375Cases caused by Streptococcus pneumoniae375Total (any aetiology)6638 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 least 3 years (all but N meningitidis in Mexico and H influenzae in Poland). (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.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 30N (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 5N and 20N), the seasonal timing of bacterial meningitis was situated in February to March, during the dry season. Third, in countries below 20N (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 highlightedthe 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. 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.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 0507 months, but occurred 09 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 08 to 16 months.Comparison of the seasonal timing of cases of bacterial meningitis in countries with available dataCentre of gravityp valuesNeisseria meningitidisStreptococcus pneumoniaeHaemophilus influenzaepNmSppNmHipSpHiPoland181 (087)253 (086)NA0034England180 (082)229 (078)099 (089)