Trends in invasive bacterial diseases during the first 2 years of the COVID-19 pandemic: analyses of prospective surveillance data from 30 countries and territories in the IRIS Consortium

David Shaw, Raquel Abad, Zahin Amin-Chowdhury, Adriana Bautista, Desiree Bennett, Karen Broughton, Bin Cao, Carlo Casanova, Eun Hwa Choi, Yiu-Wai Chu, Heike Claus, Juliana Coelho, Mary Corcoran, Simon Cottrell, Robert Cunney, Lize Cuypers, Tine Dalby, Heather Davies, Linda de Gouveia, Ala-Eddine Deghmane, Walter Demczuk, Stefanie Desmet, Mirian Domenech, Richard Drew, Mignon du Plessis, Carolina Duarte, Helga Erlendsdóttir, Norman K Fry, Kurt Fuursted, Thomas Hale, Desiree Henares, Birgitta Henriques-Normark, Markus Hilty, Steen Hoffmann, Hilary Humphreys, Margaret Ip, Susanne Jacobsson, Christopher Johnson, Jillian Johnston, Keith A Jolley, Aníbal Kawabata, Jana Kozakova, Karl G Kristinsson, Pavla Krizova, Alicja Kuch, Shamez Ladhani, Thiên-Trí Lâm, María Eugenia León, Laura Lindholm, David Litt, Martin C J Maiden, Irene Martin, Delphine Martiny, Wesley Mattheus, Noel D McCarthy, Mary Meehan, Susan Meiring, Paula Mölling, Eva Morfeldt, Julie Morgan, Robert Mulhall, Carmen Muñoz-Almagro, David Murdoch, Joy Murphy, Martin Musilek, Alexandre Mzabi, Ludmila Novakova, Shahin Oftadeh, Amaresh Perez-Argüello, Maria Pérez-Vázquez, Monique Perrin, Malorie Perry, Benoit Prevost, Maria Roberts, Assaf Rokney, Merav Ron, Olga Marina Sanabria, Kevin J Scott, Carmen Sheppard, Lotta Siira, Vitali Sintchenko, Anna Skoczyńska, Monica Sloan, Hans-Christian Slotved, Andrew J Smith, Anneke Steens, Muhamed-Kheir Taha, Maija Toropainen, Georgina Tzanakaki, Anni Vainio, Mark P G van der Linden, Nina M van Sorge, Emmanuelle Varon, Sandra Vohrnova, Anne von Gottberg, Jose Yuste, Rosemeire Zanella, Fei Zhou, Angela B Brueggemann

Summary

Background The Invasive Respiratory Infection Surveillance (IRIS) Consortium was established to assess the impact of the COVID-19 pandemic on invasive diseases caused by *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria meningitidis*, and *Streptococcus agalactiae*. We aimed to analyse the incidence and distribution of these diseases during the first 2 years of the COVID-19 pandemic compared to the 2 years preceding the pandemic.

Methods For this prospective analysis, laboratories in 30 countries and territories representing five continents submitted surveillance data from Jan 1, 2018, to Jan 2, 2022, to private projects within databases in PubMLST. The impact of COVID-19 containment measures on the overall number of cases was analysed, and changes in disease distributions by patient age and serotype or group were examined. Interrupted time-series analyses were done to quantify the impact of pandemic response measures and their relaxation on disease rates, and autoregressive integrated moving average models were used to estimate effect sizes and forecast counterfactual trends by hemisphere.

Findings Overall, 116 841 cases were analysed: 76 481 in 2018–19, before the pandemic, and 40 360 in 2020–21, during the pandemic. During the pandemic there was a significant reduction in the risk of disease caused by *S pneumoniae* (risk ratio 0·47; 95% CI 0·40–0·55), *H influenzae* (0·51; 0·40–0·66) and *N meningitidis* (0·26; 0·21–0·31), while no significant changes were observed for *S agalactiae* (1·02; 0·75–1·40), which is not transmitted via the respiratory route. No major changes in the distribution of cases were observed when stratified by patient age or serotype or group. An estimated 36 289 (95% prediction interval 17 145–55 434) cases of invasive bacterial disease were averted during the first 2 years of the pandemic among IRIS-participating countries and territories.

Interpretation COVID-19 containment measures were associated with a sustained decrease in the incidence of invasive disease caused by *S pneumoniae*, *H influenzae*, and *N meningitidis* during the first 2 years of the pandemic, but cases began to increase in some countries towards the end of 2021 as pandemic restrictions were lifted. These IRIS data provide a better understanding of microbial transmission, will inform vaccine development and implementation, and can contribute to health-care service planning and provision of policies.

Funding Wellcome Trust, NIHR Oxford Biomedical Research Centre, Spanish Ministry of Science and Innovation, Korea Disease Control and Prevention Agency, Torsten Söderberg Foundation, Stockholm County Council, Swedish Research Council, German Federal Ministry of Health, Robert Koch Institute, Pfizer, Merck, and the Greek National Public Health Organization.

Diseases, Institute of
Respiratory Medicine, Chinese
Academy of Medical Sciences,
Peking Union Medical College,
Beijing, China (Prof B Cao MD,
F Zhou PhD); Swiss National
Reference Center for Invasive
Pneumococci, Institute for
Infectious Diseases, University
of Bern, Bern, Switzerland
(C Casanova PhD, M Hilty PhD);
Department of Pediatrics,
Seoul National University
College of Medicine, Seoul,
South Korea
(Prof E Hwa Choi MD);
Department of Health,
Microbiology Division, Public
Health Laboratory Services
Branch, Centre for Health
Protection, Hong Kong Special
Administrative Region, China
(Y-W Chu PhD); University of
Würzburg, Institute for
Hygiene and Microbiology,
National Reference Centre for
Meningococci and
Haemophilus influenzae,
Würzburg, Germany
(H Claus PhD, T-T Lâm MD);
Department of Microbiology,
Royal College of Surgeons in
Ireland, Dublin, Ireland
(R Cunney, M Corcoran, R Drew,
Prof H Humphreys MD); Public
Health Wales, Cardiff, Wales,
UK (S Cottrell PhD,
C Johnson PhD, M Perry MSc,
M Roberts BSc(Hons)); National
Reference Centre for
Streptococcus pneumoniae,
University Hospitals Leuven,
Leuven, Belgium
(L Cuypers PhD, S Desmet PhD);
Department of Microbiology,
Immunology and
Transplantation, KU Leuven,
Leuven, Belgium (L Cuypers,
S Desmet); Statens Serum
Institut, Department of
Infectious Disease
Epidemiology & Prevention,
Copenhagen, Denmark
(T Dalby PhD); Meningococcal
Reference Laboratory, Institute
of Environmental Science and
Research, Porirua, New Zealand
(H Davies NZCS); Centre for
Respiratory Diseases and
Meningitis, National Institute
for Communicable Diseases,
Division of the National Health
Laboratory Service,
Johannesburg, South Africa
(L de Gouveia NatDipMedTech,
M du Plessis PhD,
Prof A von Gottberg PhD);
Institut Pasteur, Univeristé
Paris Cité, Invasive Bacterial
Infections Unit and National
Reference Centre for

Research in context

Evidence before this study

We searched PubMed, bioRxiv, and medRxiv for articles written in English and published before Dec 31, 2019, that reported on large-scale containment measures implemented during a pandemic. Search terms included "pandemic" AND "microbial transmission" OR "transmission" AND "containment". Overall, 262 papers were identified, but none met our inclusion criteria. In the early stages of the COVID-19 pandemic (ie, January–May, 2020), the Invasive Respiratory Infection Surveillance (IRIS) Consortium reported a significant reduction in invasive disease due to bacterial pathogens transmitted via the respiratory route. In particular, infections due to *Streptococcus pneumoniae* decreased by 68% at 4 weeks after COVID-19 containment measures were imposed (incidence rate ratio 0·32 [95% CI 0·27–0·37]), and by 82% at 8 weeks (0·18 [0·14–0·23]). This reduction in disease was found to be associated with the implementation of COVID-19 stringency measures and changes in human social behaviour. All 26 countries and territories participating in IRIS reported a substantial reduction in infections during this period compared with the previous 2 years.

Added value of this study

These new data from the expanded IRIS Consortium (which comprises 30 countries and territories as of 2021) showed a sustained reduction in invasive disease throughout the first 2 years of the COVID-19 pandemic. Using time-series modelling, we estimated that more than 36 000 cases of invasive bacterial disease were averted in 2020–21 among the countries participating in IRIS; however, minor increases in disease cases in the latter half of 2021 require close monitoring to understand the nature of and possible reasons for re-emerging cases.

Implications of all the available evidence

Future epidemics and pandemics will occur and, although it is essential to understand the pathogen that is directly responsible for the pandemic, we need to understand that overall human health and the transmission of other microbes are also broadly affected by population-level responses to an epidemic or pandemic. Data from IRIS provide evidence of the effects of such public health responses on severe invasive bacterial infections across many countries during the COVID-19 pandemic.

Introduction

Three of the most common causes of invasive bacterial disease are *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Neisseria meningitidis*; young children, adolescents, and older adults are at greatest risk of disease. All three bacterial species colonise the oropharynx or nasopharynx of healthy individuals and all three bacteria are transmitted person to person via respiratory droplets.

The Global Burden of Diseases, Injuries, and Risk Factors Study estimated that, in 2019, *S pneumoniae* was the leading bacterial cause of death among children younger than 5 years worldwide (225 000 deaths; 95% uncertainty interval [UI] 180 000–281 000).[1] It was also the leading cause of deaths due to lower respiratory infections (653 000; 95% UI 553 000–777 000) and meningitis (44 500; 34 700–59 800) among people of all ages, and led to 40·3 million (32·8–50·0) years of life lost globally.[1] The same report estimated that 101 000 deaths (95% UI 82 800–124 000) worldwide were due to *H influenzae*, the majority of which were due to lower respiratory infections, and an estimated 141 000 deaths (96 800–203 000) were from bloodstream infections and meningitis caused by *N meningitidis*. *N meningitidis* is a global pathogen but a particular public health problem in Africa since it is a cause of meningitis epidemics, both within and outside the meningitis belt.[2] *S pneumoniae* and *H influenzae* are also among the most common causes of deaths associated with infections caused by bacteria that are resistant to antibiotics.[3]

The Invasive Respiratory Infection Surveillance (IRIS) Consortium, an international network of microbiology laboratories in 30 countries and territories, was established early in 2020 in response to the COVID-19 pandemic and concerns about the potential for increased post-viral secondary bacterial infections.[4] The main aim of the IRIS Consortium is to investigate the incidence of invasive diseases caused by *S pneumoniae*, *H influenzae*, and *N meningitidis*. Invasive infections due to these bacterial species are legally notifiable to public health registries in the majority of countries participating in IRIS.[4]

Previously, we reported significant reductions in the incidence of diseases caused by all three bacteria early in the COVID-19 pandemic and showed that these reductions were associated with the timing and stringency of COVID-19 containment measures.[4–9] A subset of laboratories also submitted data for cases of disease caused by *Streptococcus agalactiae*, a major cause of invasive disease across all age groups but especially neonates, and which is not transmitted via the respiratory route.[1,10] *S agalactiae* was included as a comparator organism to assess the stability of routine disease surveillance during the pandemic. There was no change in the incidence of invasive *S agalactiae* infections in the early months of the pandemic, suggesting that any disruptions to routine laboratory surveillance during the COVID-19 pandemic were minor and did not explain the observed reductions in diseases caused by *S pneumoniae*, *H influenzae*, and *N meningitidis*.[4]

We conducted an expanded prospective analysis of surveillance data for four bacterial species (*S pneumoniae*, *H influenzae*, *N meningitidis*, and *S agalactiae*) in the 2 years before COVID-19 (2018–19)

and the first 2 years of the pandemic (2020–21). Four countries were added to the IRIS Consortium since our first publication in 2021,[4] which expanded the geographical coverage of IRIS to 30 countries and territories across six continents. We collected data on patient age and bacterial serotype or group to assess epidemiological changes that might have implications for disease burden and vaccination programmes. We quantified the effect of COVID-19 restrictions on the four pathogens under investigation, utilised time-series modelling techniques to analyse changes in disease during the first 2 years of the pandemic, and estimated the number of cases averted. We also assessed the incidence of disease by patient age and serotype or group, to investigate whether the epidemiology of invasive disease had changed during 2020–21 compared to the pre-pandemic years.

Methods

Study design and participants

For this prospective analysis, national reference and expert microbiology laboratories in 30 countries and territories submitted data on confirmed cases of invasive infections (within a normally sterile site) caused by one or more of the four bacteria under investigation. Australia, Colombia, Greece, and Paraguay joined IRIS after the initial establishment of the consortium. All IRIS-participating laboratories provided national reference data apart from Australia (New South Wales only) and China (one Beijing hospital only). Data were collected for patients of all ages except in South Korea, where only data from patients aged younger than 16 years were available for analyses.

Data collection

No patient-identifiable data were submitted to IRIS. In the originating laboratories, bacteria from clinical samples were primarily recovered and identified by standard microbiological culture methods and occasionally by PCR testing. Invasive disease cases identified from Jan 1, 2018, to Jan 2, 2022 (the end of ISO [International Organization for Standardization] week 52 for 2021), were included in the current analyses. The PubMLST suite of databases was used to collect and manage IRIS data, and a private project only accessible to IRIS participants was used for each of the four organisms. At a minimum, information about the specimen sampling date, patient age, and serotype or group was submitted for each case except where data protection rules in a country prevented the submission of data on patient age. Study data were entered by IRIS participants or the database curators (ABB, KAJ, and DS). Automated data integrity checks were applied before data upload, and all IRIS data were manually checked by the curators for data consistency; any discrepant or missing data were queried and resolved with the submitting laboratory.

Google COVID-19 Community Mobility Reports (CCMRs) are anonymised, within-country mobile device location history data that capture the movement of people in six categories, including time spent in workplaces and residential areas. Google CCMR data are calculated as a daily percentage change from the baseline day, which was the median value between Jan 3 and Feb 6, 2020. In our previous study we used Google CCMR data to estimate the week when each country first implemented COVID-19 containment measures. We used the same estimates in the current analyses, and for the four additional countries the week of implementation was calculated as described previously.[4]

The stringency of each country's COVID-19 containment measures was quantified with the Oxford Blavatnik COVID-19 Government Response Tracker (OxCGRT).[11] This stringency index combines nine indicators that are tracked daily: school, workplace, and public transport closures; public event cancellations; gathering restrictions; stay at home requirements; internal movement restrictions; international travel controls; and public information campaigns. A composite stringency index variable between 0 and 100 is calculated and is available for download on the OxCGRT website. For our analyses, the daily stringency index was converted into an ISO weekly index by taking the mean stringency index metric for that week. Cumulative weekly case counts for each organism were plotted against the weekly stringency index for each country and organism.

Time-series analysis and decomposition

Case counts were summed by month to generate country-specific and organism-specific time series for 2018–21. Monthly case totals were used to improve the overall model fit and accommodate the 2020 leap year (ie, 53 weeks). A second time-series analysis was done for

Meningococci and Haemophilus influenzae, Paris, France (A-E Deghmane PhD, Prof M-K Taha MD); National Microbiology Laboratory, Public Health Agency of Canada, Winnipeg, MB, Canada (W Demczuk BSc, I Martin BSc); National Center for Microbiology and CIBER of Respiratory Research, Instituto de Salud Carlos III, Madrid, Spain (M Domenech PhD, J Yuste PhD); Clinical Innovation Unit, Rotunda, Dublin, Ireland (R Drew); Department of Clinical Microbiology, Landspitali, The National University Hospital of Iceland, Reykjavik, Iceland (Prof H Erlendsdóttir MSc, Prof K G Kristinsson MD); Immunisation and Vaccine Preventable Diseases Division and Respiratory and Vaccine Preventable Bacteria Reference Unit, UK Health Security Agency, London, UK (N K Fry PhD); Statens Serum Institut, Department of Bacteria, Parasites & Fungi, Copenhagen, Denmark (K Fuursted MD, S Hoffmann MD, H-C Slotved DMSc); Blavatnik School of Government, University of Oxford, Oxford, UK (Prof T Hale PhD); Microbiology Department, Institut Recerca Sant Joan de Déu, Hospital Sant Joan de Deu, Barcelona, Spain (Prof C Muñoz-Almagro MD, D Henares PhD, A Perez-Argüello MLT); CIBER of Epidemiology and Public Health, Madrid, Spain

	Streptococcus pneumoniae	Haemophilus influenzae	Neisseria meningitidis	Streptococcus agalactiae
2018				
Number	30 553	3510	2302	1702
Median (IQR)	2405 (1824–3162)	282 (248–360)	192 (162–207)	147 (130–155)
2019				
Number	30 606	3697	2228	1883
Median (IQR)	2574 (2018–3050)	323 (273–342)	182 (164–196)	154 (144–171)
2020				
Number	15 501	2120	976	1886
Median (IQR)	834 (627–1258)	115 (102–169)	40 (36–81)	157 (145–168)
2021				
Number	15 306	2117	550	1904
Median (IQR)	1160 (1003–1391)	158 (128–194)	40 (35–56)	156 (149–170)

Data shown are numbers of isolates per year. The year corresponds to the International Organization for Standardization year. IRIS=Invasive Respiratory Infection Surveillance.

Table 1: **Overall number of invasive disease cases submitted to IRIS-participating laboratories before (2018–19) and during (2020–21) the COVID-19 pandemic**
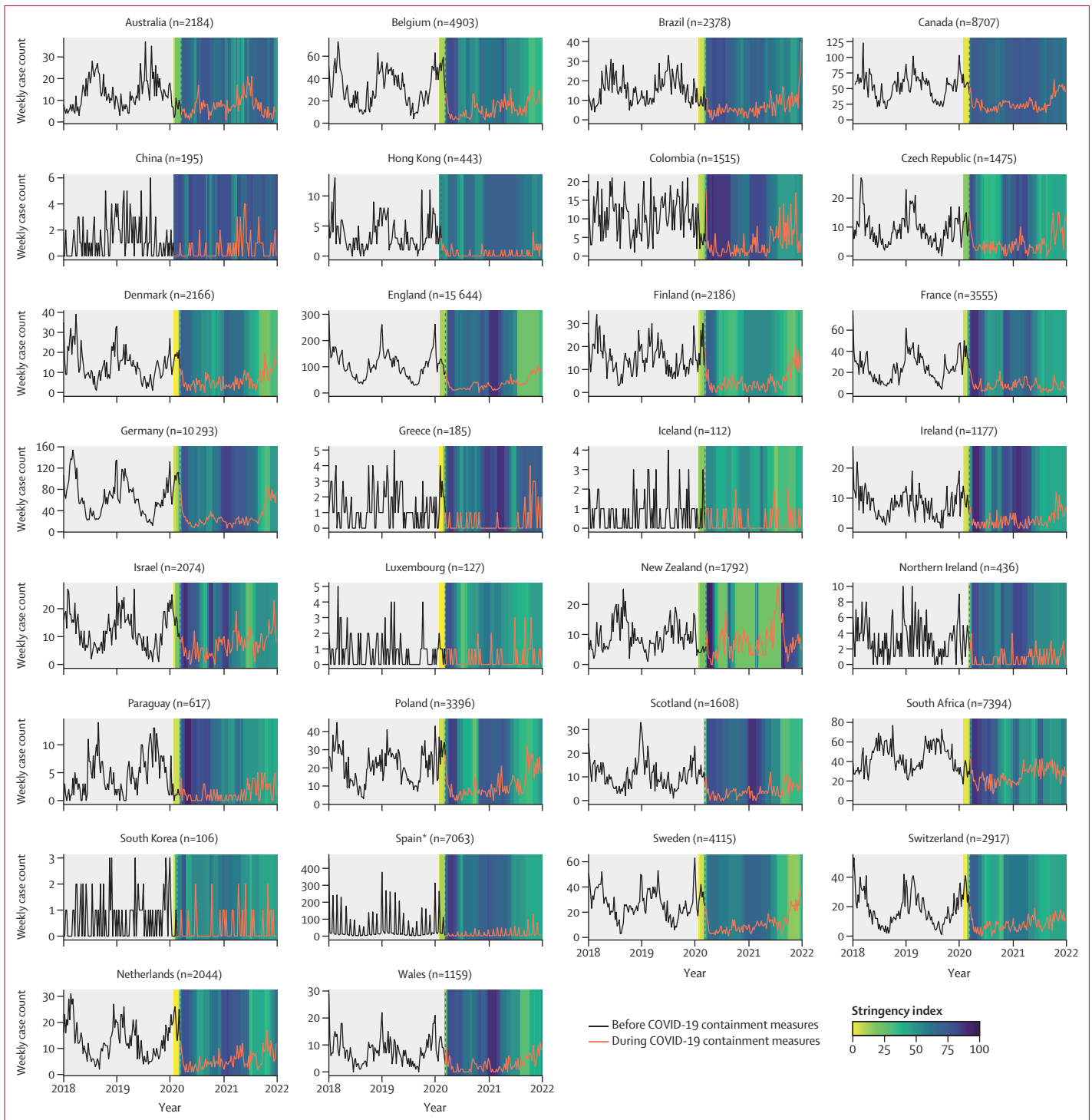
Figure 1: *Streptococcus pneumoniae* invasive disease case counts
For each country or territory, weekly invasive disease cases from Jan 1, 2018, to Jan 2, 2022 (four complete International Organization for Standardization years), were plotted against the weekly Oxford COVID-19 Government Response Tracker stringency index value in 2020–21. The vertical dashed line indicates the week in which pandemic response measures were initiated in each country. *Many of the Spanish sampling dates were submitted only by month and not day of sampling, so the sampling date was entered as the first day of the month if the actual sampling day was unavailable.
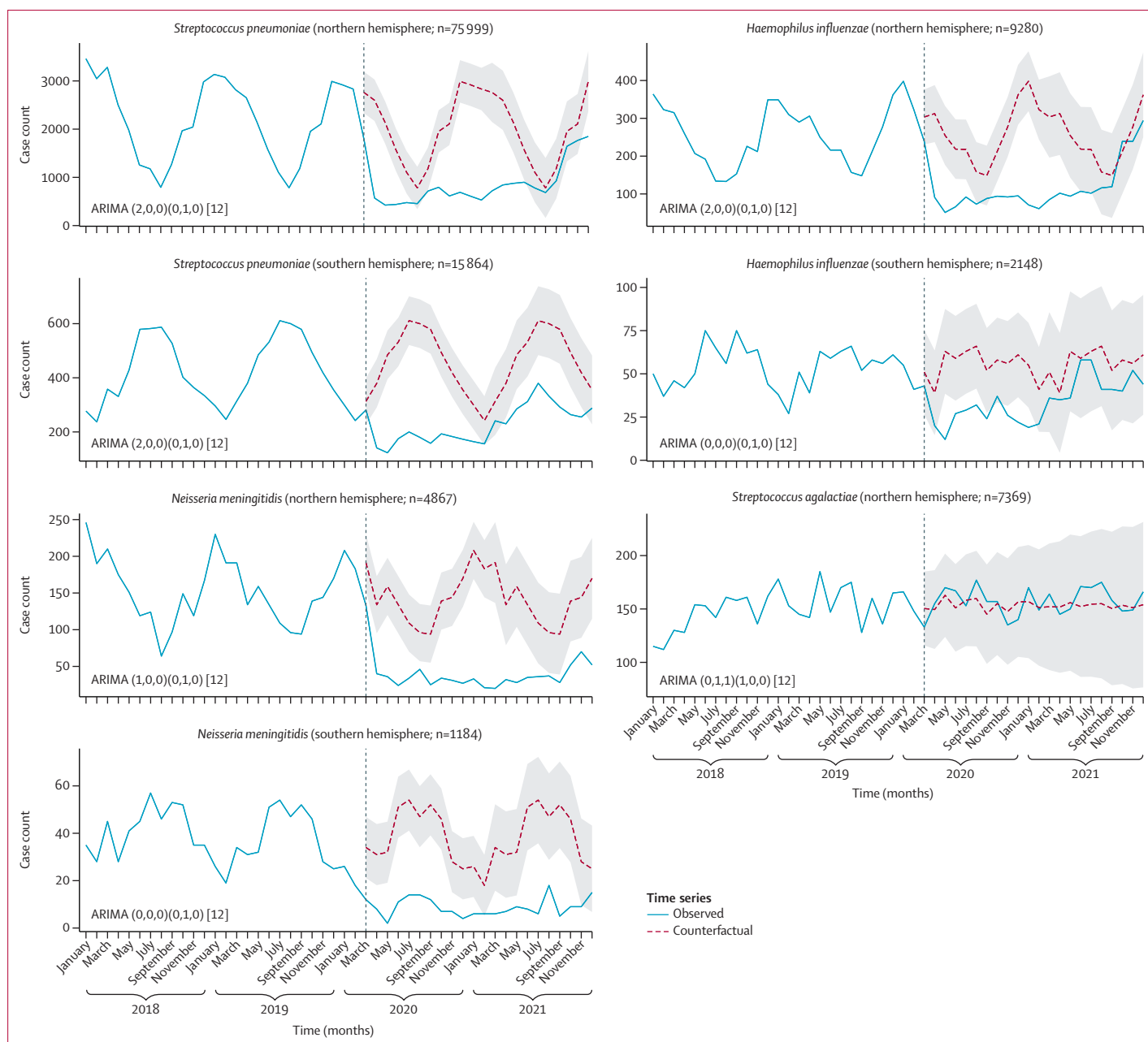
Figure 2: Interrupted time-series analyses of invasive disease data in the northern and southern hemispheres

Observed cases of invasive disease for each bacterial species (blue solid lines) were plotted against the counterfactual weekly number of cases predicted by the ARIMA models (red dashed lines) if the COVID-19 pandemic had not occurred. The black vertical dashed line indicates the modal month (ie, the most common month when containment measures were put in place). The grey shading depicts 95% prediction intervals. *Streptococcus agalactiae* data were only collected in the northern hemisphere, and data are plotted by weeks in the calendar year rather than International Organization for Standardization year. The numbers next to ARIMA in the first set of parentheses indicate which components have been included to generate the counterfactual (p,d,q), while the second set of parentheses provides an indication of the seasonal model used (P,D,Q). The square brackets indicate that the model is generated using monthly data (12 months in a year). Please see text for details. ARIMA=autoregressive integrated moving average.

the *S pneumoniae*, *H influenzae*, and *N meningitidis* datasets to account for potential seasonal differences, whereby case counts were pooled by countries residing in the northern or southern hemispheres, respectively. *S agalactiae* data were only collected from countries in the northern hemisphere.

Interrupted time-series analysis

Seasonal autoregressive integrated moving average (ARIMA) models were used to quantify the impact of COVID-19 containment measures on the incidence of invasive bacterial disease, and to generate counterfactual trends with 95% prediction intervals (PIs) for each of the

(Prof C Muñoz-Almagro, D Henares)**; Karolinska Institutet, Karolinska University Hospital, Public Health Agency of Sweden, Stockholm, Sweden** (Prof B Henriques-Normark MD)**;**
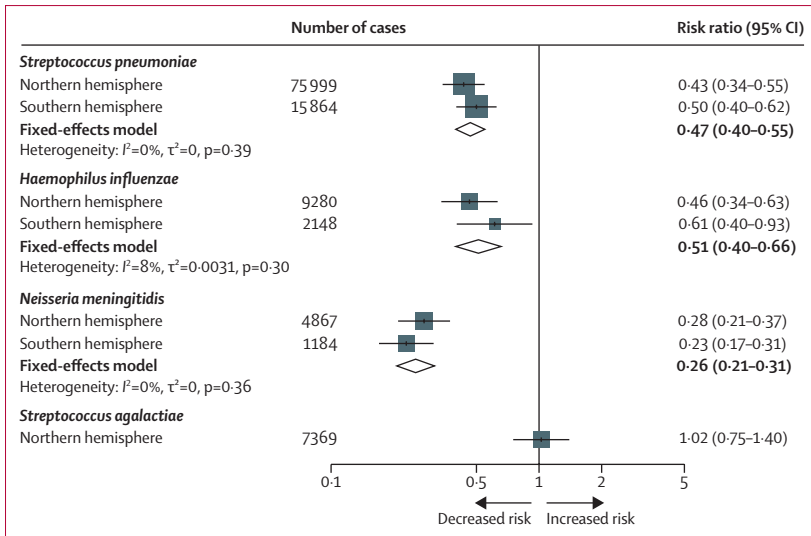
Figure 3: Risk of invasive disease during the pandemic for each bacterial species by hemisphere
Results of the meta-analysis are shown as fixed-effects model estimates for each bacterial species.

Department of Clinical Microbiology, Beaumont Hospital, Dublin, Ireland (Prof H Humphreys); Department of Microbiology, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong Special Administrative Region, China (Prof M Ip MSc); National Reference Laboratory for *Neisseria meningitidis*, Department of Laboratory Medicine, Clinical Microbiology, Faculty of Medicine and Health, Örebro University, Örebro, Sweden (S Jacobsson PhD, P Mölling PhD); Public Health Agency, Belfast, UK (J Johnston MBBS, J Murphy BA Hons, M Sloan); Department of Biology, University of Oxford, Oxford, UK (K A Jolley PhD, Prof M C J Maiden PhD); Laboratorio Central de Salud Pública, Asunción, Paraguay (A Kawabata, M Eugenia León MSc); National Reference Laboratory for Streptococcal Infections (J Kozakova MD, S Vohrnova MD) and National Reference Laboratory for Meningococcal Infections (P Krizova MD, M Musilek PhD), Centre for Epidemiology and Microbiology, National Institute of Public Health, Prague, Czech Republic; National Reference Centre for Bacterial Meningitis, Department of Epidemiology and Clinical Microbiology,

	Cases averted (95% PI)
Streptococcus pneumoniae	
Northern hemisphere	24 893 (13 377 to 36 410)
Southern hemisphere	5067 (2726 to 7409)
Haemophilus influenzae	
Northern hemisphere	3027 (966 to 5089)
Southern hemisphere	479 (–162 to 1120)
Neisseria meningitidis	
Northern hemisphere	2258 (1240 to 3275)
Southern hemisphere	649 (312 to 986)
Streptococcus agalactiae	
Northern hemisphere	–84 (–1314 to 1145)

Overall, 36 289 (95% PI 24 229 to 48 349) cases were averted. PI=prediction interval.

Table 2: Estimated number of invasive disease cases averted during the COVID-19 pandemic (2020–21), by hemisphere

four pathogens. Although it would have been desirable to fit separate ARIMA models by country, the dataset in most countries was too small for this to be implemented, and residual autocorrelation and negative case counts produced after model fitting precluded this approach.

ARIMA models took the simplified form of:

$$ARIMA\ (p,d,q)\ (P,D,Q)_s$$

where p=non-seasonal autoregressive (AR) order, d=non-seasonal differencing, q=non-seasonal moving average (MA) order, P=seasonal AR order, D=seasonal differencing, Q=seasonal MA order, and s=time span of repeating seasonal pattern (number of observations in a year), 12 months.

Box-Jenkins methodology was applied when building the ARIMA model and both manual and automated

methods were used to select the final models.[12] Each time series was assessed for stationarity with the augmented Dickey-Fuller unit root test, which tested the null hypothesis of non-stationarity.[12] None of the individual time series analysed in this study was non-stationary so no adjustments were required.

Manual model identification and coefficient estimation were performed, and we accounted for any seasonal pattern in the time series. We utilised the autocorrelation function and the partial autocorrelation function to decide on the potential inclusion of and number of autoregressive or moving average components (order selection), or both. The final ARIMA models were selected with a combination of unit root tests, maximum likelihood estimation, and minimised corrected Akaike information criterion values.[12,13]

To measure the impact of COVID-19 containment measures, step and slope variables were included as regressors in the final ARIMA models: step (0 before containment measure implementation, 1 thereafter); and slope (0 before containment measure implementation, +1 for each month thereafter). Based on Google CCMR data, the step variable switched from 0 to 1 from March, 2020, onwards for all countries.[4] These changes reflect the change in personal behaviour in response to the pandemic as well as the containment measures initiated across the 30 countries and territories in our cohort. The final ARIMA models were used to produce a counterfactual prediction that assumed the COVID-19 pandemic did not occur, based on disease data from the two pre-pandemic years, which generated a mean monthly case estimate and 95% PI. The relative risk (RR) of invasive disease, and number of cases averted, from March, 2020 (when the pandemic was officially declared by WHO), were estimated as follows: RR=number of cases observed / number of counterfactual cases. The major threats to internal validity as described by Penfold and Zhang[14] (history, instrumentation, and selection bias) were rigorously assessed and mitigated, and all model assumptions were met.

Meta-analysis
The RR estimates of disease and 95% CIs in the northern and southern hemispheres were combined with an inverse-variance weighted, fixed-effects meta-analysis to generate a pooled RR and 95% CI estimate. These models used a restricted maximum likelihood approach

Figure 4: *Streptococcus pneumoniae* invasive disease cases by serotype and patient age
(A) Distribution of serotypes responsible for 90% of all reported cases between 2018 and 2021, listed by case count, increasing or decreasing trend year by year, and percentage change of each serotype recovered in 2018–19 compared to 2020–21 (average number of cases each year, pre-pandemic *vs* during the pandemic). (B) Heat map depicting the number of cases of each serotype recovered per year and by age group. ND=not determined.

A *Streptococcus pneumoniae*

B Case count by serotype and year, stratified by age group (in years)
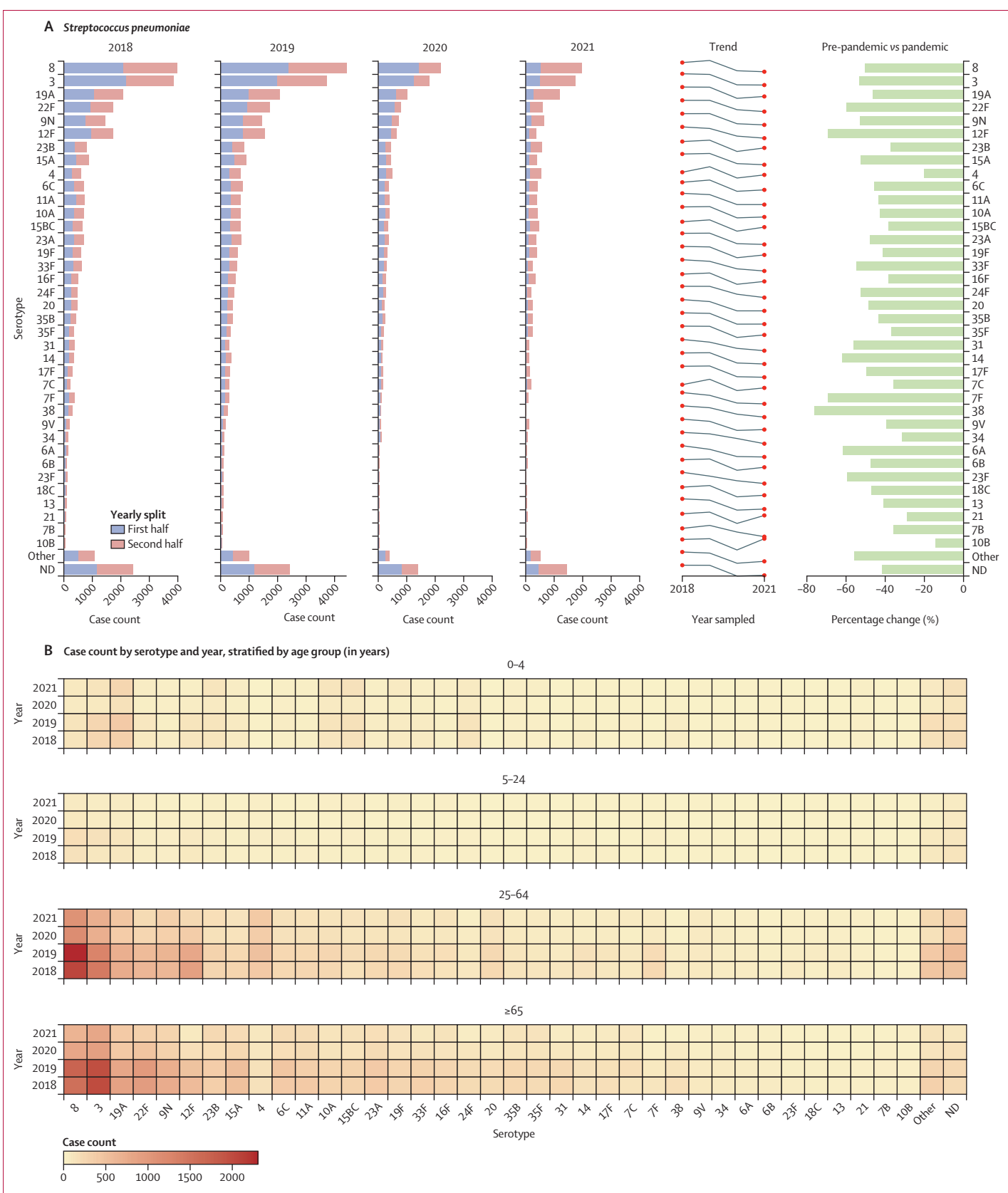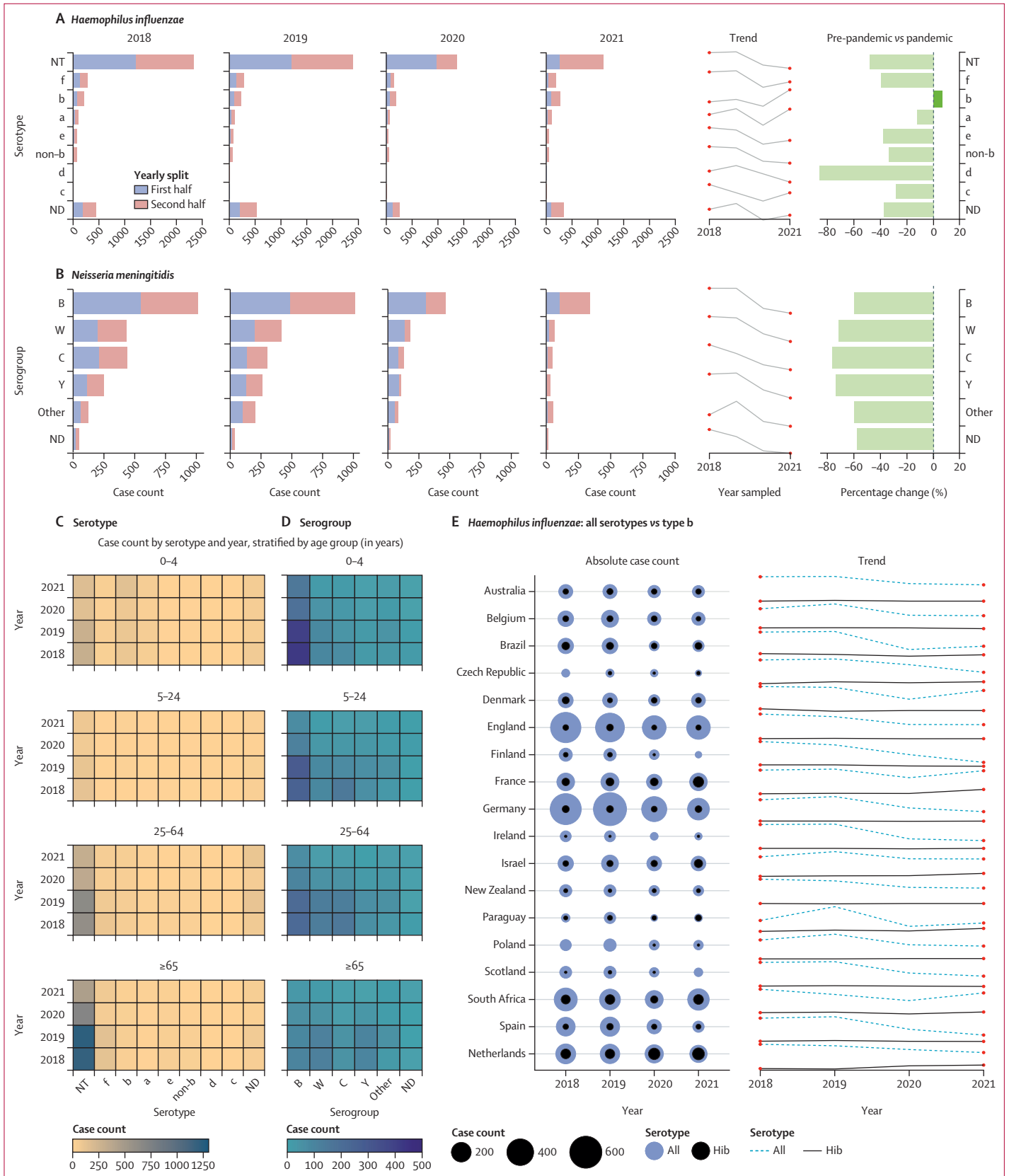
for coefficient estimates.[15] This approach was also applied to pool the results of the various sensitivity analyses.

Sensitivity analysis

For each of the four pathogens, segmented regression models were fitted to each country, stratified by age group and serotype or group. Negative binomial and quasi-Poisson generalised linear models were fitted to account for overdispersion of data, using population size as an offset and adjusting for seasonality, using month as a factor variable and Fourier terms.[13] These models included a step change variable for implementation of containment measures, as described above. We also included models that extrapolated a counterfactual trend from pre-pandemic data. Further details are provided in the appendix (pp 1–2) and have been published previously.[4]

Role of the funding source

The funders had no role in data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit the manuscript for publication.

Results

All 30 countries participating in the IRIS Consortium submitted data on cases of *S pneumoniae* invasive disease, as represented by bacterial isolates or case reports, or both, submitted to each of the IRIS laboratories. Most countries also submitted invasive disease data on *H influenzae* (n=24) and *N meningitidis* (n=21), and nine countries submitted invasive disease data on *S agalactiae*. Overall, 116 841 cases were analysed: 76 481 in 2018–19, before the pandemic, and 40 360 in 2020–21, during the pandemic. The number of *S pneumoniae*, *H influenzae*, and *N meningitidis* cases during 2020–21 was approximately half the expected number each year compared to pre-pandemic totals, but the number of *S agalactiae* cases was similar each year (table 1).

There was an association between the stringency of COVID-19 containment measures implemented in each country and the number of *S pneumoniae* cases reported to laboratories (ie, as the stringency of containment measures decreased during 2021 in many countries,

Figure 5: *Haemophilus influenzae* and *Neisseria meningitidis* invasive disease cases by serotype, capsule group, country, and age

Distribution of serotypes between 2018 and 2021 for *Haemophilus influenzae* (A) and *Neisseria meningitidis* (B) are shown, listed by case count, increasing or decreasing trend year by year, with percentage change of each serotype recovered in 2018–19 compared to 2020–21 (average number of cases each year, pre-pandemic *vs* during the pandemic). Heat maps depicting the number of cases of each serotype recovered per year and by age group are shown for *H influenzae* (C) and *N meningitidis* (D). Number of cases of *H influenzae* by country are shown (E), displaying only those countries where at least 100 cases in total had been reported across all four study years. Circles represent the total number of cases each year, and lines indicate the increasing or decreasing trend year by year, with all serotypes depicted by the dashed line and *H influenzae* serotype b (Hib) depicted by the solid line. ND=not determined.

there were concomitant increases in *S pneumoniae* cases; figure 1). Similar associations were observed for *H influenzae* and *N meningitidis*, but not *S agalactiae* (appendix pp 3–5).

Time-series analyses by northern and southern hemispheres for each of the bacterial species showed an overall reduction in cases of disease caused by *S pneumoniae*, *H influenzae*, and *N meningitidis*, but not *S agalactiae*, during the pandemic (figure 2). Notably, cases due to *S pneumoniae*, *H influenzae*, and *N meningitidis* were increasing by the end of 2021. Google CCMR data were used to assess the point at which there was a step change that precipitated the reduction in cases of disease within each country, which was from March, 2020 (when the pandemic was declared), in both the northern and southern hemispheres (figure 2).

The data were meta-analysed by hemisphere, the results of which showed a significant reduction in the risk of invasive disease caused by *S pneumoniae* (RR 0·47; 95% CI 0·40–0·55), *H influenzae* (0·51; 0·40–0·66), and *N meningitidis* (0·26; 0·21–0·31) but not *S agalactiae* (1·02; 0·75–1·40; figure 3). Sensitivity analyses supported the use of the ARIMA model (appendix p 6), which estimated that 36 289 (95% PI 17 145–55 434) cases were averted in these 30 countries during the first 2 years of the pandemic (table 2).

Data were then stratified by serotype or group and patient age. Among *S pneumoniae* cases, there were significant reductions in the case count of all major serotypes in 2020–21, although cases of disease due to some serotypes were beginning to increase in the latter months of 2021 (figures 2, 4A). Case numbers in 2020–21 were reduced in every age category and there were no major changes in the overall patterns of disease by age or serotype (figure 4B).

Stratification of *H influenzae* cases by serotype and patient age showed a reduction in case counts of all serotypes except for serotype b (Hib), which decreased in 2020 and then increased at the end of 2021 (p<0·0001). However, the total number of Hib cases remained very low: only 276 Hib cases were reported among 24 countries in 2021 (figure 5A). Overall, Hib cases increased among children aged 0–4 years in 2021 (n=146) versus 2020 (n=87; figure 5C). When stratified by country, the increase in Hib infections was primarily observed in five countries in 2021: the Netherlands (n=70), France (n=50), South Africa (n=43), Israel (n=27), and Paraguay (n=10; figure 5E).[6,16] Among cases of *N meningitidis* there was a significant reduction in infections due to all serogroups (but especially capsule groups W, C, and Y), with no obvious changes in the patterns of disease by age group (figure 5B, D).

Discussion

Our statistical models estimated that, on average, more than 36 000 cases of life-threatening invasive bacterial diseases caused by *S pneumoniae*, *H influenzae*, and

National Medicines Institute, Warsaw, Poland (A Kuch PhD, Prof A Skoczyńska PhD); Finnish Institute for Health and Welfare, Helsinki, Finland (L Lindholm MSc, L Siira PhD, M Toropainen PhD, A Vainio PhD); Respiratory and Vaccine Preventable Bacteria Reference Unit, UK Health Security Agency, London, UK (D Litt PhD, C Sheppard PhD); National Belgian Reference Centre for *Haemophilus influenzae*, Laboratoire des Hôpitaux Universitaires de Bruxelles-Universitair Laboratorium van Brussel, Brussels, Belgium (Prof D Martiny PhD); Faculty of Medicine and Pharmacy, University of Mons, Mons, Belgium (Prof D Martiny); Meningococcal National Reference Centre, Sciensano, Belgium (W Mattheus PhD); Population Health Medicine, Public Health and Primary Care, Trinity College Dublin, Dublin, Ireland (Prof N D McCarthy DPhil); Division of Public Health Surveillance and Response, National Institute for Communicable Diseases, Division of the National Health Laboratory Service, Johannesburg, South Africa (S Meiring MBChB); Public Health Agency of Sweden, Solna, Sweden (E Morfeldt PhD); Streptococcal Reference Laboratory, Institute of Environmental Science and Research Limited, Porirua, New Zealand (J Morgan HND); Medicine Department, Universitat Internacional de Catalunya, Barcelona, Spain (Prof C Muñoz-Almagro); University of Otago, Christchurch, New Zealand (Prof D Murdoch MD); Laboratoire National de Sante, Dudelange, Luxembourg (M Perrin MD); Ministère de la Santé - Direction de la santé, Luxembourg (A Mzabi MD); National Reference Laboratory for Haemophilus Infections, Centre for Epidemiology and Microbiology, National Institute of Public Health, Prague, Czech Republic (L Novakova MSc); NSW Pneumococcal Reference Laboratory, Institute of Clinical Pathology and Medical Research - NSW Health Pathology, Sydney, NSW,

Australia (S Oftadeh PhD);
Laboratorio de Referencia e
Investigación en Resistencia a
Antibióticos e Infecciones
Relacionadas con la Asistencia
Sanitaria, Centro Nacional de
Microbiología, Instituto de
Salud Carlos III, Majadahonda,
Madrid, Spain
(M Pérez-Vázquez PhD); CIBER
de Enfermedades Infecciosas,
Instituto de Salud Carlos III,
Madrid, Spain
(M Pérez-Vázquez); National
Belgian Reference Centre for
Haemophilus influenzae,
Laboratoire des Hôpitaux
Universitaires de Bruxelles-
Universitair Laboratorium van
Brussel, Brussels, Belgium
(B Prevost PhD); Public Health
Laboratories–Jerusalem, Public
Health Services, Ministry of
Health, Jerusalem, Israel
(A Rokney PhD, M Ron PhD);
Bacterial Respiratory Infection
Service, Scottish Microbiology
Reference Laboratories,
Glasgow Royal Infirmary,
Glasgow, UK (K J Scott PhD);
NSW Pneumococcal Reference
Laboratory, Institute of Clinical
Pathology and Medical
Research - NSW Health
Pathology, Sydney, NSW,
Australia
(Prof V Sintchenko PhD); Sydney
Institute for Infectious
Diseases, University of Sydney,
NSW, Australia
(Prof V Sintchenko); Bacterial
Respiratory Infection Service,
Scottish Microbiology
Reference Laboratories,
Glasgow Royal Infirmary,
Glasgow, UK
(Prof A J Smith FRCPath); College
of Medical, Veterinary & Life
Sciences, University of
Glasgow, Glasgow, UK
(Prof A J Smith); Centre for
Infectious Disease Control,
National Institute for Public
Health and the Environment,
Bilthoven, Netherlands
(A Steens PhD); National
Meningitis Reference
Laboratory, Department of
Public Health Policy, School of
Public Health, University of
West Attica, Athens, Greece
(Prof G Tzanakaki PhD);
Department of Medical
Microbiology, German National
Reference Centre for
Streptococci, University
Hospital RWTH Aachen,
Aachen, Germany
(M P G van der Linden PhD);
Department of Medical
Microbiology and Infection

N meningitidis were averted in the countries participating in the IRIS Consortium during the first 2 years of the COVID-19 pandemic. The large number of averted cases reduced the morbidity and mortality associated with these infections, which would have eased the burden on some health-care systems during the pandemic. The documented reduction in infections was most plausibly due to the worldwide implementation of COVID-19 containment measures aimed at reducing transmission of SARS-CoV-2, which simultaneously reduced transmission of other microbes that spread via respiratory secretions, including those studied by the IRIS Consortium.

Our findings cannot be explained by under-reporting of data by hospitals and laboratories that were overwhelmed by the pandemic. In most of the 30 countries and territories represented in this analysis, it is a legal requirement to report cases of invasive disease caused by the pathogens covered in this study, and the inclusion of *S agalactiae* as a non-respiratory comparator organism provided reassurance that the surveillance programmes in these laboratories were functioning without major disruptions during the pandemic.

The findings show that although cases of disease remained significantly lower in 2020–21 compared to pre-pandemic levels, rates of disease were increasing in some countries and territories towards the end of 2021.[17,18] It is therefore reasonable to predict that rates of invasive bacterial infections will return to pre-pandemic levels in due course. Furthermore, the 2021 data showed a small overall increase in Hib cases after an initial decrease in 2020. However, other factors could have influenced these dynamics even before the pandemic, such as changes to Hib vaccines or vaccine schedules (or both), or pre-pandemic increases in the incidence of Hib infection.[6,16] Renewed emphasis on the active surveillance of invasive diseases caused by Hib is certainly warranted going forward.

An important concern now, as people have returned to normalised social interactions, is which pathogens will cause disease. The usual patterns of microbial transmission were altered during the pandemic, and if the microbiome within the upper respiratory tract was also disrupted, this could lead to changes in the prevalence of serotypes or groups associated with disease, increased prevalence of circulating non-vaccine types, or emergence of non-traditional disease-associated types.[19,20] If the microbiome was not substantially disrupted, then one might expect a return to disease patterns that are recognisable to those observed before the pandemic. Time will reveal which of these outcomes proves to be true.

There is also growing concern around decreased population immunity or a so-called immunity debt (ie, a higher proportion of susceptible individuals within a population because of reduced exposure to commonly circulating microbes) as a result of pandemic restrictions,

which could lead to future outbreaks of disease.[21,22] Certain populations might be at increased risk of infection, such as children born during the pandemic; teenagers and young adults because of their increased social mixing; and older people because of immunosenescence, high rates of underlying comorbidities, and frailty. The situation is further compounded by disruptions in routine vaccination schedules around the world since health-care systems were reorganised to deal with the threat of the pandemic, but at the expense of providing other essential public health services.[23–26] For example, reinstatement of routine paediatric vaccination programmes is one of the most important post-pandemic challenges that remains to be addressed in many parts of the world.

In addition to reduced exposure to pathogens, the typical patterns of respiratory disease were disrupted during the pandemic, and the prevalence of commonly circulating respiratory viruses such as respiratory syncytial virus and influenza viruses was also reduced during the pandemic due to the implementation of COVID-19 containment measures.[27,28] Two recent studies reported a correlation between the reduced prevalence of respiratory viruses and reductions in diseases due to *S pneumoniae* during the pandemic.[29,30] Further work will be necessary to better understand any causative relationship between respiratory viruses and colonising nasopharyngeal bacteria, mechanisms of co-infections, and to mechanistically understand how one microbe might influence the pathogenicity of another.

Limitations of the time-series analyses in this study included difficulties in fitting ARIMA models to individual countries and territories. Each country has its own pattern of disease and public health restrictions, and some countries reported relatively small case numbers. This necessitated temporal pooling by month and geographical pooling by hemisphere, leading to wider prediction intervals and reduced predictive power of the models. Although we assessed data from 2018 to 2021, when taking account of a yearly trend, the necessary seasonal adjustment in the model leads to a loss of a year's worth of data, which affected our sample size.[12]

Despite these limitations, strengths of these analyses included the large datasets rapidly contributed by investigators, which spanned 4 years and increased the power of these analyses. Additionally, high-quality data at a national level were made available by accredited reference laboratories undergoing routine audit and data validation practices, which minimised information bias. Selection bias is likely to be minimal because the bacteria under investigation cause diseases that necessitate urgent hospital care, and legislation in most of these countries and territories mandates the reporting of invasive diseases due to one or more of these bacteria. We also tested a range of time-series analyses to ensure the robustness of the results and the findings were reproducible.

As our societies emerge from the COVID-19 pandemic, this large prospective study by the IRIS Consortium allows for timely detection of changes in invasive diseases caused by *S pneumoniae*, *H influenzae*, and *N meningitidis*, and provides a means to detect and address substantial changes that will undoubtedly occur. Most importantly, it is essential that any ongoing disruptions to bacterial vaccination programmes are resolved since diseases due to these bacteria are devastating but can be prevented by safe and effective vaccines already used in many countries worldwide.

Prevention, and Netherlands Reference Laboratory for Bacterial Meningitis, Amsterdam University Medical Center, University of Amsterdam, Amsterdam, Netherlands (Prof N M van Sorge PhD); Laboratory of Medical Biology and National Reference Centre for Pneumococci, Intercommunal Hospital of Créteil, Créteil, France (E Varon MD); National Laboratory for Meningitis and Pneumococcal Infections, Center of Bacteriology, Institute Adolfo Lutz, São Paulo, Brazil (R Zanella PhD)

Correspondence to:
Professor Angela Brueggemann, Nuffield Department of Population Health, University of Oxford, Oxford OX3 7LF, UK
angela.brueggemann@ndph.ox.ac.uk

References

1 GBD 2019 Antimicrobial Resistance Collaborators. Global mortality associated with 33 bacterial pathogens in 2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2022; **400:** 2221–48.

2 Mazamay S, Guégan JF, Diallo N, et al. An overview of bacterial meningitis epidemics in Africa from 1928 to 2018 with a focus on epidemics "outside-the-belt". *BMC Infect Dis* 2021; **21:** 1027.

3 Antimicrobial Resistance Collaborators. Global burden of bacterial antimicrobial resistance in 2019: a systematic analysis. *Lancet* 2022; **399:** 629–55.

4 Brueggemann AB, Jansen van Rensburg MJ, Shaw D, et al. Changes in the incidence of invasive disease due to *Streptococcus pneumoniae, Haemophilus influenzae*, and *Neisseria meningitidis* during the COVID-19 pandemic in 26 countries and territories in the Invasive Respiratory Infection Surveillance Initiative: a prospective analysis of surveillance data. *Lancet Digit Health* 2021; **3:** e360–70.

5 Casanova C, Küffer M, Leib SL, Hilty M. Re-emergence of invasive pneumococcal disease (IPD) and increase of serotype 23B after easing of COVID-19 measures, Switzerland, 2021. *Emerg Microbes Infect* 2021; **10:** 2202–04.

6 Deghmane AE, Taha MK. Changes in Invasive *Neisseria meningitidis* and *Haemophilus influenzae* infections in France during the COVID-19 pandemic. *Microorganisms* 2022; **10:** 907.

7 Steens A, Knol MJ, Freudenburg-de Graaf W, de Melker HE, van der Ende A, van Sorge NM. Pathogen- and type-specific changes in invasive bacterial disease epidemiology during the first year of the COVID-19 pandemic in the Netherlands. *Microorganisms* 2022; **10:** 972.

8 Nielsen RT, Dalby T, Emborg HD, et al. COVID-19 preventive measures coincided with a marked decline in other infectious diseases in Denmark, spring 2020. *Epidemiol Infect* 2022; **150:** e138.

9 Ciruela P, Soldevila N, García-Garcia JJ, et al. Effect of COVID-19 pandemic on invasive pneumococcal disease in children, Catalonia, Spain. *Emerg Infect Dis* 2022; **28:** 2321–25.

10 Tavares T, Pinho L, Bonifácio Andrade E. Group B streptococcal neonatal meningitis. *Clin Microbiol Rev* 2022; **35:** e0007921.

11 Hale T, Angrist N, Goldszmidt R, et al. A global panel database of pandemic policies (Oxford COVID-19 Government Response Tracker). *Nat Hum Behav* 2021; **5:** 529–38.

12 Schaffer AL, Dobbins TA, Pearson SA. Interrupted time series analysis using autoregressive integrated moving average (ARIMA) models: a guide for evaluating large-scale health interventions. *BMC Med Res Methodol* 2021; **21:** 58.

13 Hyndman RJ, Athanasopoulos G. Forecasting: principles and practice, 3rd edn. Melbourne, VIC: OTexts, 2021.

14 Penfold RB, Zhang F. Use of interrupted time series analysis in evaluating health care quality improvements. *Acad Pediatr* 2013; **13** (suppl): S38–44.

15 Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw* 2010; **36:** 1–48.

16 Steens A, Stanoeva KR, Knol MJ, Mariman R, de Melker HE, van Sorge NM. Increase in invasive disease caused by *Haemophilus influenzae* b, the Netherlands, 2020 to 2021. *Euro Surveill* 2021; **26:** 2100956.

17 Bertran M, Amin-Chowdhury Z, Sheppard CL, et al. Increased incidence of invasive pneumococcal disease among children after COVID-19 pandemic, England. *Emerg Infect Dis* 2022; **28:** 1669–72.

18 Perniciaro S, van der Linden M, Weinberger DM. Reemergence of invasive pneumococcal disease in Germany during the spring and summer of 2021. *Clin Infect Dis* 2022; **75:** 1149–53.

19 Rocafort M, Henares D, Brotons P, et al. Impact of COVID-19 lockdown on the nasopharyngeal microbiota of children and adults self-confined at home. *Viruses* 2022; **14:** 1521.

20 Willen L, Ekinci E, Cuypers L, Theeten H, Desmet S. Infant pneumococcal carriage in Belgium not affected by COVID-19 containment measures. *Front Cell Infect Microbiol* 2022; **11:** 825427.

21 Cohen R, Ashman M, Taha MK, et al. Pediatric Infectious Disease Group (GPIP) position paper on the immune debt of the COVID-19 pandemic in childhood, how can we fill the immunity gap? *Infect Dis Now* 2021; **51:** 418–23.

22 Messacar K, Baker RE, Park SW, Nguyen-Tran H, Cataldi JR, Grenfell B. Preparing for uncertainty: endemic paediatric viral illnesses after COVID-19 pandemic disruption. *Lancet* 2022; **400:** 1663–65.

23 SeyedAlinaghi S, Karimi A, Mojdeganlou H, et al. Impact of COVID-19 pandemic on routine vaccination coverage of children and adolescents: a systematic review. *Health Sci Rep* 2022; **5:** e00516.

24 McQuaid F, Mulholland R, Sangpang Rai Y, et al. Uptake of infant and preschool immunisations in Scotland and England during the COVID-19 pandemic: an observational study of routinely collected data. *PLoS Med* 2022; **19:** e1003916.

25 Causey K, Fullman N, Sorensen RJD, et al. Estimating global and regional disruptions to routine childhood vaccine coverage during the COVID-19 pandemic in 2020: a modelling study. *Lancet* 2021; **398:** 522–34.

26 WHO. Immunization coverage. July 14, 2022. https://www.who.int/news-room/fact-sheets/detail/immunization-coverage (accessed Dec 1, 2022).

27 Agha R, Avner JR. Delayed seasonal RSV surge observed during the COVID-19 pandemic. *Pediatrics* 2021; **148:** e2021052089.

28 Koutsakos M, Wheatley AK, Laurie K, Kent SJ, Rockman S. Influenza lineage extinction during the COVID-19 pandemic? *Nat Rev Microbiol* 2021; **19:** 741–42.

29 Danino D, Ben-Shimol S, van der Beek BA, et al. Decline in pneumococcal disease in young children during the coronavirus disease 2019 (COVID-19) pandemic in Israel associated with suppression of seasonal respiratory viruses, despite persistent pneumococcal carriage: a prospective cohort study. *Clin Infect Dis* 2022; **75:** e1154–64.

30 Rybak A, Levy C, Angoulvant F, et al. Association of nonpharmaceutical interventions during the COVID-19 pandemic with invasive pneumococcal disease, pneumococcal carriage, and respiratory viral infections among children in France. *JAMA Netw Open* 2022; **5:** e2218959.