BMJ Global Health

Infant mortality rates and pneumococcal vaccines: a time-series trend analysis in 194 countries, 1950–2020

Carlos A Sanchez ,[1] Oriana Rivera-Lozada,[2] Michelle Lozada-Urbano,[2] Pablo Best[3]

To cite: Sanchez CA, Rivera-Lozada O, Lozada-Urbano M, *et al*. Infant mortality rates and pneumococcal vaccines: a time-series trend analysis in 194 countries, 1950–2020. *BMJ Glob Health* 2023;**8**:e012752. doi:10.1136/bmjgh-2023-012752

Handling editor Seye Abimbola

Received 3 May 2023
Accepted 1 July 2023

Check for updates

© Author(s) (or their employer(s)) 2023. Re-use permitted under CC BY-NC. No commercial re-use. See rights and permissions. Published by BMJ.

[1]Universidad Peruana de Ciencias Aplicadas, Lima, Peru
[2]Universidad Norbert Wiener, Lima, Peru
[3]Universidad Peruana Cayetano Heredia, Lima, Peru

Correspondence to
Dr Carlos A Sanchez;
csanchez.peru@gmail.com

ABSTRACT

Pneumonia due to *Streptococcus pneumoniae* (pneumococcus) is a major cause of mortality in infants (children under 1 year of age), and pneumococcal conjugate vaccines (PCVs), delivered during the first year of life, are available since the year 2000. Given those two premises, the conclusion follows logically that favourable impact reported for PCVs in preventing pneumococcal disease should be reflected in the infant mortality rates (IMRs) from all causes. Using publicly available datasets, country-level IMR estimates from UNICEF and PCV introduction status from WHO, country-specific time series analysed the temporal relationship between annual IMRs and the introduction of PCVs, providing a unique context into the long-term secular trends of IMRs in countries that included and countries that did not include PCVs in their national immunisation programmes. PCV status was available for 194 countries during the period 1950–2020: 150 (77.3%) of these countries achieved nationwide PCV coverage at some point after the year 2000, 13 (6.7%) achieved only partial or temporary PCV coverage, and 31 (15.9%) never introduced PCVs to their population. One hundred and thirty-nine (92.7%) of countries that reported a decreasing (negative) trend in IMR, also reported a strong correlation with decreasing maternal mortality rates (MMRs), suggesting an improvement in overall child/mother healthcare. Conversely, all but one of the countries that never introduced PCVs in their national immunisation programme also reported a decreasing trend in IMR that strongly correlates with MMRs. IMRs have been decreasing for decades all over the world, but this latest decrease may not be related to PCVs.

SUMMARY BOX

⇒ Pneumococcus is often reported as the most important cause of mortality in young children, but lack of laboratory confirmation is increasing globally, and literature documenting aetiology in fatal infant cases is scarce, yet pneumococcal conjugate vaccines (PCVs) continue to broaden serotype coverage and increase cost.

⇒ PCVs that are developed to stimulate an immune response against very specific pneumococcal serotypes in high-income countries are expected to provide protection against all pneumococcal diseases worldwide, but serotype prevalence varies geographically and among age groups.

⇒ It is possible that the beneficial impact in infant mortality reported by PCVs is just the latest phase in a global trend of improvement in access to healthcare, nutrition, hygiene and education, compared with past decades.

⇒ Without knowing the true burden of disease from pneumococcus in infant mortality, it is difficult to distinguish the true impact of PCVs in this target population.

⇒ This information will help to encourage future efforts towards pneumococcal serotype surveillance systems in middle-income to low-income countries.

INTRODUCTION

Worldwide, vaccines are an important public health prevention tool and pneumonia is considered an important cause of morbidity/mortality and healthcare services utilisation. Pneumonia caused by *Streptococcus pneumoniae* (pneumococcus) is as a major cause of mortality during the first year of life, especially in young children living in low-income and middle-income countries.[1] Pneumonia (usually non-invasive) is the most common pneumococcal disease, but pneumococcus also causes invasive pneumococcal disease (IPD, that is, bacteraemia, meningitis) which are less frequent but more deadly. Since 2000, pneumococcal conjugate vaccines (PCVs), promoted by the WHO, are incorporated into national child immunisation programmes around the world.[1] Before PCVs were available, the highest baseline rate of overall IPDs was observed among children aged 1 year or less.[2] Since pneumonia and IPDs are important causes of mortality in children under 1 year of age, trends in infant mortality rates (IMRs, frequency of deaths in children under 1 year of age for every 1000 live births) could be expected to react to the introduction of PCVs into a country's national immunisation programme. This article aims to provide a

BMJ Glob Health: first published as 10.1136/bmjgh-2023-012752 on 7 August 2023. Downloaded from http://gh.bmj.com/ on October 18, 2023 by guest. Protected by copyright.

unique perspective and context for the analysis of secular trends in IMRs, as they relate to PCVs.

DATA SOURCES AND ANALYSIS

Health indicators are estimates designed to summarise information about priority topics related to population health or health system performance, and provide comparable and actionable information across different geographical, organisational or administrative boundaries and/or can track progress over time.[3] IMRs provide key information about maternal and infant health, serve as a sensitive indicator of living conditions, as well as the coverage and quality of healthcare,[4] and is considered an important marker of the overall health in a country.[5] Annual IMR median data were collected for 196 countries from the Data and Analytics Section; Division of Data, Analytics, Planning and Monitoring of the UNICEF for the period 1950–2020.[6] For each country, the IMR estimate was paired by year with WHO data that summarises country PCV status in the national immunisation programme: 0 for no PCV, 1 for PCV,[7] which defines the before and after periods for each country.

Descriptive and regression analyses were performed. Following a previous review,[8] 78 countries with at least 8 years (time points) after the introduction of PCVs (on or before 2014) were selected and the annual rates were plotted for trend analysis. Average annual mortality rates for before and after periods were compared. Statistical models for trends were estimated in selected countries (the USA, Canada and Australia). A main issue with observations taken over time (ie, time series) is that they are usually correlated,[8] meaning values from a certain time period are not completely independent from the previous value. To account for this autocorrelation, we performed autoregressive integrated moving average (ARIMA) models to fit the data from selected countries to make projections and test the PCV status variable. Interrupted time series analysis (where the periods before and after a point of intervention are compared with assess the intervention's effects) cannot account for: (1) other events concurrent with the policy/programme of interest, (2) changes in instrumentation or case definition or (3) changes in the composition of the intervention group.[8]

A maternal death is defined as 'the death of a woman while pregnant or within 42 days of termination of pregnancy, irrespective of the duration and the site of the pregnancy, from any cause related to or aggravated by the pregnancy or its management, but not from accidental or incidental causes'.[9] Maternal mortality rates (MMRs, the frequency of maternal deaths per 100 000 live births) are also considered an informative health indicator. Annual country-level MMR data from UNICEF was collected for 185 countries during the period 2000–2017,[10] and compared with IMR trends using the Spearman rank correlation test, which is a non-parametric test (does not assume a normal distribution) used to measure the degree of association between two variables. Correlation implies association, not causation.

All statistical analyses were conducted using the SPSS Statistical Software V.23.

FINDINGS OF THE ANALYSIS OF THE DATASETS

Table 1 summarises available data from the WHO website regarding PCV status by country (N=196). A single specific year for PCV introduction into the national immunisation programme was available for 109 (55.6%) countries, 41 (20.9%) countries delayed the introduction across a period of time (range: 1–13 years), 13 (6.6%) countries achieved only temporary (discontinued after 3 years) or limited PCV coverage, and 31 (15.8%) countries never adopted PCVs. No PCV status data were available for the State of Palestine or the territory of Puerto Rico.

Figure 1 shows the adoption of PCVs over time since the year 2000. The first countries to include PCVs in their national immunisation programmes were the USA and Canada, later, over half (54.1%) the countries incorporated PCVs in their programmes between 2011 and 2015. The IMR trends for 78 (71.6%) countries that introduced PCV programmes at a specific year between 2000 and 2014 (with enough time points) are plotted in figure 2, and IMR trends for 31 countries that never adopted PCVs are plotted in figure 3. The UNICEF data show that IMRs are decreasing in most countries, even in countries that never included PCVs in their immunisation programme. The IMR trend for most countries shows an initial rapid decrease in the first five decades, followed by a much slower decline in the recent two decades, when PCVs became available.

ARIMA models forecasting estimates beginning on the year of PCV introduction for three countries with the longest number of years implementing PCVs are also presented in figure 2. The observed rates are slightly lower than those projected for the USA (ARIMA 0,3,2) and Canada (ARIMA 0,3,1), and slightly higher for Australia (ARIMA 2,3,1). However, the introduction of the 'dummy' variable for PCV status did not change the models in any way and the parameter estimate remained not significant, suggesting the IMR trend is not related to the change between before and after PCV periods.

Data for both IMR (period 1950–2020) and MMR (period 2000–2017) were available for 184 (93.8%) countries. A positive (direct) correlation between IMR and MMR was estimated for 170 countries (r Spearman range: 0.035–0.999), with a strong positive correlation (r Spearman>0.700) in 153 (90%) countries. This is consistent with international reports of MMR falling globally by nearly 44% between 1990 and 2015.[11] Negative (inverse) correlations between IMR and MMR were reported for 13 countries (r Spearman range: −0.947 to −0.039), with a strong negative correlation (r Spearman<−0.800) in 5 countries plotted in figure 4: a decreasing IMR with an increasing MMR (the USA, Kuwait and Dominican Republic); or an increasing IMR with a decreasing MMR

BMJ Glob Health: first published as 10.1136/bmjgh-2023-012752 on 7 August 2023. Downloaded from http://gh.bmj.com/ on October 18, 2023 by guest. Protected by copyright.

Table 1 PCV status in the national immunisation programme, by type of status, 2000–2021 (N=196)

PCV introduction 2012–2021		PCV introduction 2000–2011		only high-risk groups	Never introduced PCV
Afghanistan	Mauritania	Albania	Singapore	Antigua and Barbuda	Belize
Algeria	Mauritius	Andorra	Slovakia	Belarus	Cabo Verde
Angola	Mozambique	Australia	Türkiye	Bosnia and Herzegovina	Chad
Armenia	Myanmar	Barbados	United Arab Emirates	Brunei Darussalam	China
Azerbaijan	Namibia	Belgium	UK	Islamic Republic of Iran	Comoros
Bangladesh	Nauru	Benin	USA	Jamaica	Cook Islands
Bhutan	Nepal	Bulgaria	Uruguay	Saint Lucia	Cuba
Bolivia	Niger	Burundi	Yemen		Czechia
Botswana	North Macedonia	Cameroon	**Partial PCV introduction**		DPR of Korea
Burkina Faso	Papua New Guinea	Canada	Argentina	Kazakhstan	Dominica
Cambodia	Paraguay	Central African Republic	Austria	Kuwait	Egypt
Congo	Poland	Denmark	Bahamas	Latvia	Equatorial Guinea
Côte d'Ivoire	Portugal	Ethiopia	Bahrain	Mexico	Estonia
Croatia	Republic of Korea	Gambia	Brazil	Micronesia	Gabon
Djibouti	Romania	Germany	Chile	Monaco	Grenada
Eritrea	Russian Federation	Greece	Colombia	Mongolia	Guinea
Eswatini	Samoa	Honduras	Costa Rica	Nigeria	Jordan
Fiji	San Marino	Hungary	Cyprus	Pakistan	Maldives
Georgia	Sao Tome and Principe	Japan	DR of the Congo	Panama	Montenegro
Ghana	Senegal	Kenya	Dominican Republic	Peru	Saint Kitts and Nevis
Guatemala	Seychelles	Luxembourg	Ecuador	Qatar	Somalia
Guinea-Bissau	Solomon Islands	Malawi	El Salvador	Saudi Arabia	South Sudan
Haiti	Sudan	Mali	Finland	Serbia	Sri Lanka
Kiribati	Togo	Marshall Islands	France	Slovenia	St Vincent and the Grenadines
Kyrgyzstan	Tonga	Morocco	Guyana	South Africa	Suriname
Lao People's DR	Tunisia	Netherlands	Iceland	Spain	Syrian Arab Republic
Lebanon	Turkmenistan	New Zealand	Ireland	Sweden	Tajikistan
Lesotho	Tuvalu	Nicaragua	Israel	Switzerland	Thailand
Liberia	Tanzania	Niue	Italy	Trinidad and Tobago	Timor-Leste
Libya	Uzbekistan	Norway	**Only regional PCV**	Uganda	Ukraine
Lithuania	Vanuatu	Oman	India	**Only IMR data**	Viet Nam
Madagascar	Zambia	Palau	Indonesia	State of Palestine	**Temporary PCV programme**
Malaysia	Zimbabwe	Rwanda	Philippines	**Only MMR data**	Iraq
Malta		Sierra Leone	Republic of Moldova	Puerto Rico	Venezuela

DPR, Democratic People's Republic; DR, Democratic Republic; IMR, infant mortality rate; MMR, maternal mortality rate; PCV, pneumococcal conjugate vaccine; UR, United Republic.

BMJ Glob Health: first published as 10.1136/bmjgh-2023-012752 on 7 August 2023. Downloaded from http://gh.bmj.com/ on October 18, 2023 by guest. Protected by copyright.

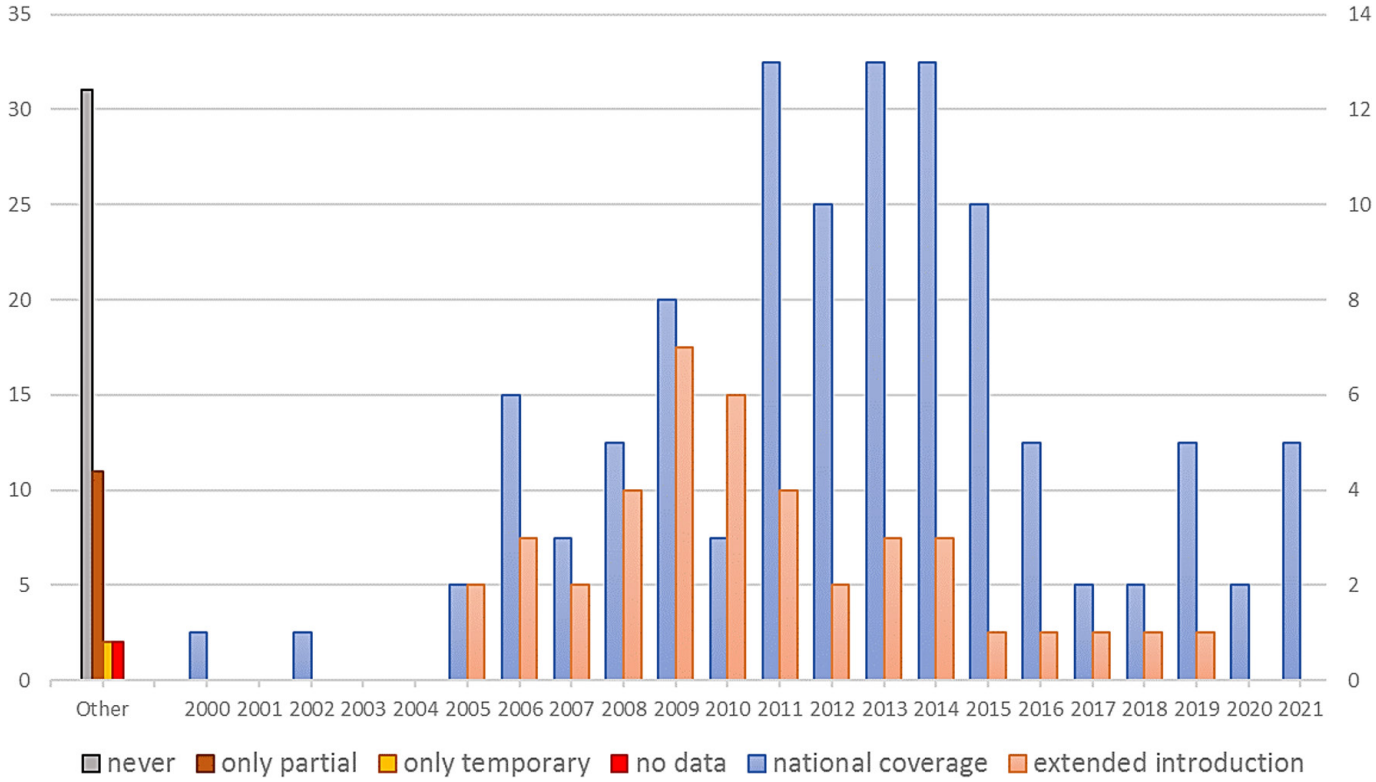

Figure 1 PCV status in the national immunisation programme over time, by status, 2000–2021 (n=196). PCV, pneumococcal conjugate vaccine.

(Fiji and Grenada), and no correlation estimate was available for Greece due to minimal variation in MMRs. The increasing trend in MMR for the USA has been reported as recently as 2021,[12] and for Canada and Jamaica, between 1990 and 2015.[11] It is important to note that this is a trend analysis, not point estimation. For example, the MMRs of the USA, Australia and Canada in 2015 were well below most countries, but the MMR for the USA was twice that of Australia and Canada, while Greece and Kuwait were considered among the safest places to give birth in the world.[11]

INTERPRETATIONS OF THE FINDINGS

The combined decline in IMR and MMR during the past decades, together with the negligible statistical impact of PCV introduction, suggests that an improvement in overall health conditions for young children and women in childbearing age can explain the decrease in mother/child mortality. A study in Italy analysed the decline in infant mortality considering several indicators for maternal age, education and social class, as well as low birth weight and preterm conditions, and concluded that the observed declines were probably due to a general improvement in economic and cultural conditions.[13] A study in Brazil concluded that mortality rates from lower respiratory infections decreased in young children regardless of PCV implementation and the most significant reductions preceded PCV introduction,[14] which is consistent with our findings. This global decline can be largely attributed to a general improvement in living conditions in most countries, and thus the true disease burden of pneumococcus in infant mortality remains to be properly estimated.

Factors to consider before the conclusion

History

Analysing a brief period of time without acknowledging the overall trend can be misleading. The latter part of the 20th century has seen the advent of antibiotics which have been crucial for controlling infectious diseases. Studies comparing a couple of years before and after PCV introduction fail to consider the long-term decreasing trend in IMRs during the past decades and may just be focusing on the latest phase in a global tendency. A study in Brazil going back three decades before PCV introduction reported only a modest (compared with the prevaccine period) reduction in pneumonia mortality in young children.[15] More recently, in the USA (where PCVs were introduced in 2000), between 1999 and 2020, the frequency of infant deaths decreased 30% and infant crude death rate decreased 24%, but the ranking of leading causes of infant death has remained remarkably stable and does not include pneumonia: birth defects or congenital malformations, disorders related to short gestation or preterm birth and low birth weight, and sudden infant death syndrome accounted for 44.8% of infant deaths in 1999, and 43.8% in 2000.[16 17] Bacterial sepsis of newborn was the only infectious disease among the '10

BMJ Glob Health: first published as 10.1136/bmjgh-2023-012752 on 7 August 2023. Downloaded from http://gh.bmj.com/ on October 18, 2023 by guest. Protected by copyright.

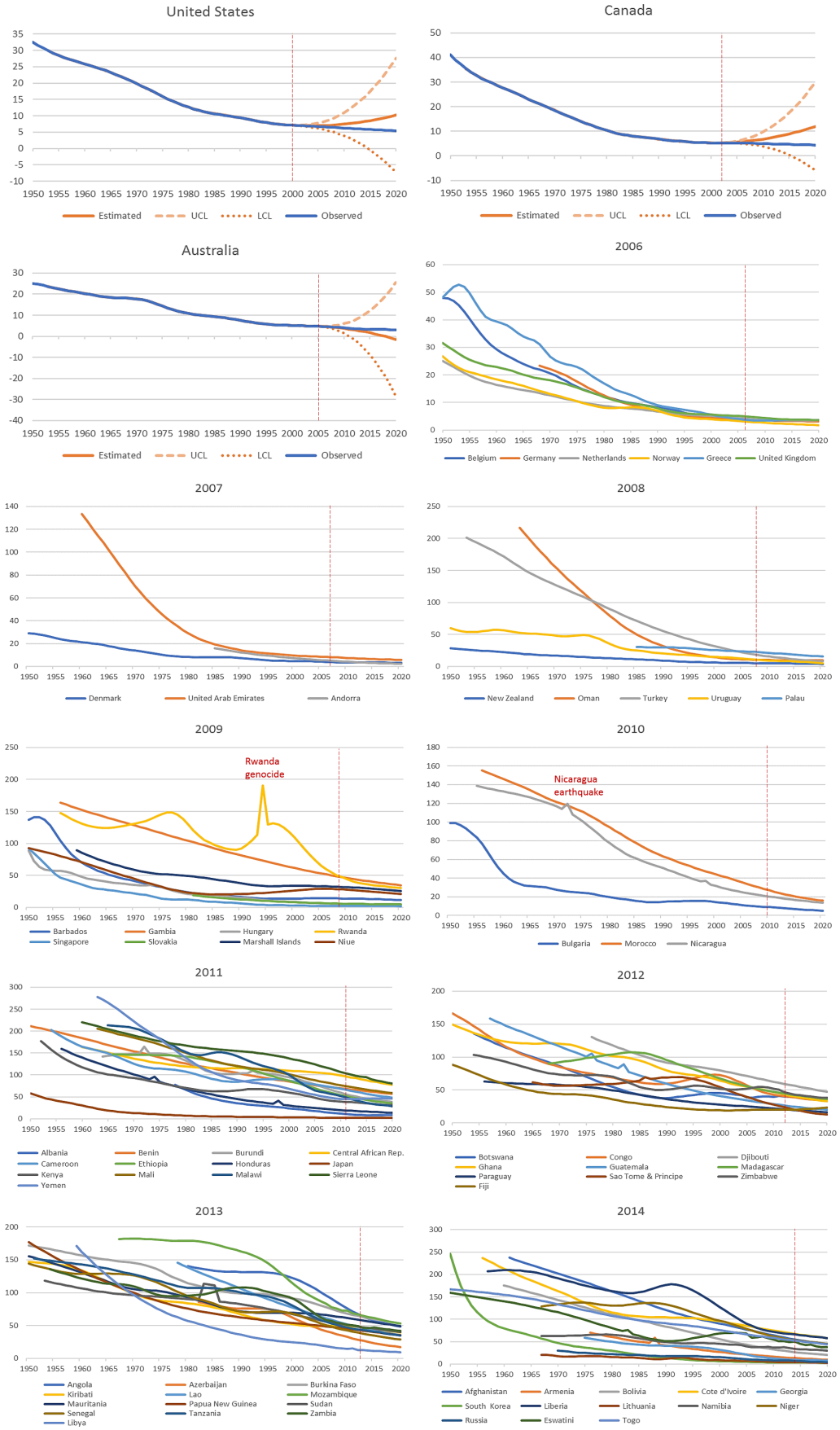

Figure 2 Countries where PCV is administered throughout the entire country and introduced a specific year in the national immunisation programme between 2000 and 2014, by year of introduction (n=78). PCV, pneumococcal conjugate vaccine; UCL, upper confidence level; LCL, lower confidence level.

BMJ Glob Health: first published as 10.1136/bmjgh-2023-012752 on 7 August 2023. Downloaded from http://gh.bmj.com/ on October 18, 2023 by guest. Protected by copyright.

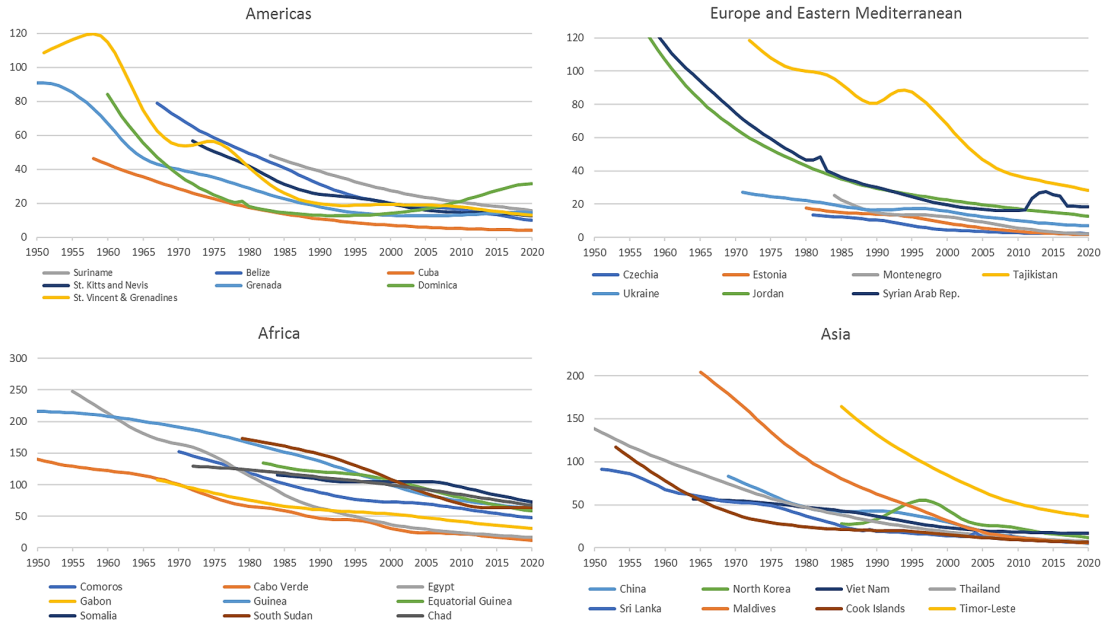

Figure 3 Countries where PCVs were never introduced in the national immunisation programme, by world region (n=31). PCVs, pneumococcal conjugate vaccines.

most common causes of infant death' list representing only 2.5% of infant deaths in 1999 and 2.8% in 2020.[16] Pneumococcus is not commonly associated with infant sepsis.

Age of death

Infant deaths were traditionally divided into neonatal and postneonatal categories according to the age at death, roughly translated to the newborn dying during the first month or the first year of life, respectively. It was believed that neonatal deaths were caused by mostly biologic conditions (endogenous causes) and postneonatal deaths resulted from other conditions such as injuries and socioenvironmental causes (exogenous causes).[18] This is no longer considered to be a precise categorisation, but differences between the cause of death during each period do exist.

Since 1945, several countries have shown an initial rapid rate of decline in postneonatal mortality (infant dying within 28–364 days), followed by a period of much slower decline,[19] this is consistent with our findings. The main factor for this decline is believed to be the gradual prevention of deaths due to infections (particularly gastrointestinal and respiratory), progressively contributing to a smaller proportion of infant mortality.[19] Once a country approaches a situation in which the main causes of death in the first year of life are primarily health problems that cannot be prevented or treated (ie, genetic or congenital), then the decrease in infant mortality slows down.[4] This is consistent with most trends in figures 2 and 3, with or without PCV. Consequently, between 1995 and 2019 in the USA, postneonatal deaths represented only a third of infant mortality,[17] and it is only when we disaggregate the top 10 causes of postneonatal deaths that we find pneumonia, but only accounting for 0.8% of all infant deaths.[16]

Lack of laboratory confirmation

Without laboratory confirmation, a pneumonia death is reported as 'pneumonia due to unspecified organism', which includes other bacteria, viruses or even fungi. A global decline in the quality of microbiology analysis has been proposed in recent years, with fewer studies reportedly identifying any likely pathogen in 50%–70% of pneumonia cases.[20] In the USA, between 1995 and 2019, 2828 infant deaths due to pneumonia caused by unspecified organism were reported, compared with only 45 deaths properly reported as pneumonia due to *S. pneumoniae*.[16] In low-income and middle-income countries, where pneumonia is a major health problem, the isolation of pneumococcus occurs only in a minority of pneumococcal pneumonia cases.[21] Before the advent of PCVs, prospective studies of community-acquired pneumonia among young children reported between 17% and 28% of cases were diagnosed as pneumococcal.[22 23] It was believed at the time that these and other studies probably underestimated the actual proportion of pneumococcal pneumonia cases due to a low sensitivity in routine diagnostic testing.[24] In fact, in the abovementioned studies, 53% and 20% of patients with bacterial pneumonia had a concurrent viral infection, and no aetiology was diagnosed in 52% and 34% of pneumonia cases, respectively.[22 23] Pneumococcus has been historically proclaimed as the most important global cause of pneumonia, but the frequency of pneumococcus as a cause of pneumonia has declined from 95% in the era before antibiotics, to 10%–15% of inpatient pneumonia cases in the USA.[25] Among older adults, pneumococcal

BMJ Glob Health: first published as 10.1136/bmjgh-2023-012752 on 7 August 2023. Downloaded from http://gh.bmj.com/ on October 18, 2023 by guest. Protected by copyright.

Figure 4 Selected countries with negative IMR-MMR Spearman correlation, and Greece, 2000–2017. IMR, infant mortality rate; MMR, maternal mortality rate.

BMJ Glob Health: first published as 10.1136/bmjgh-2023-012752 on 7 August 2023. Downloaded from http://gh.bmj.com/ on October 18, 2023 by guest. Protected by copyright.

prevalence as a cause of community-acquired pneumonia varies across European countries,[26] and could be less important in some parts of Asia,[27] where other pathogens like *Klebsiella pneumoniae* and *Burkholderia pseudomallei* may be predominant.[28] Infant pneumonia may also be evolving.

Vaccine efficacy

The success of PCVs refers to very specific types of pneumococcal disease. Most studies agree that PCVs are very effective in preventing IPD caused by PCV serotypes, and less effective in preventing IPD caused by any serotype: 41.3%,[29] 37.9%[30] and 64.7%[31] more effective. The introduction of PCV7 in 2000 led to substantial reductions in the incidence of IPD among young children, but the per cent reduction was always higher among IPD cases caused by serotypes contained in PCV7 than in IPD cases caused by any serotype.[31] That a vaccine prevents the disease it was designed to prevent is expected, but how important is that disease in the context of the burden on a population is the question that needs to be answered. The role of PCVs on the (more frequent) non-invasive pneumonia is less straight forward, with PCV efficacy in preventing radiograph-confirmed pneumonia being lower than that for IPDs, and much lower for clinically diagnosed pneumonia.[29 30] By 2004, pneumococcal pneumonia rates declined by 65% (95% CI 47% to 77%) for children younger than 2 years in the USA, but all-cause pneumonia hospital admission rates declined by only 39% (95% CI 22% to 52%).[32] The prevention of pneumonia has always been less striking than that for IPDs, but regardless of the low efficacy it was believed to have the potential for tremendous impact given the high burden of pneumonia in infants,[29] but this is not as obvious as it seems. Given new PCVs have recently been approved in the USA for the prevention of IPDs in infants and children,[33] the extrapolation to preventing pneumonia should be fully tested before reaching international immunisation programmes.

Serotypes

By stimulating the immune system, vaccines can improve the response to avoid severe disease and/or death from infection, but only for the specific pathogen they have been created against. Since PCVs protect against colonisation with specific vaccine-type serotypes, knowledge of the distribution of pneumococcal serotypes causing disease is fundamental to evaluate the potential impact of a pneumococcal vaccine[24] because different pneumococcal serotypes vary in their ability to cause disease.[34] Approximately 90 pneumococcal serotypes have been described,[9] and the original PCV7 included the seven most common serotypes isolated from the blood or cerebrospinal fluid of children aged <6 years in the USA and accounted for 80% of IPDs before the introduction of PCVs.[24] Since then, more serotypes have been added to the original seven, increasing the serotype coverage but also the price per vaccine. The new PCV includes 20 serotypes.[33] However, the distribution of pneumococcus serotypes can vary within a region and other parts of the world, and so will the coverage by PCVs.[35] An inequitable global distribution of PCVs may have contributed to the emergence/replacement of serotypes in different countries. Serotype replacement prevents the disease from disappearing completely as new serotypes become predominant. For example, although IPD cases caused by PCV7 serotypes in children declined through 2005 in the USA, overall IPD rates levelled off and plateaued beginning in 2002.[2] Currently, the new PCV announcement proclaims that, in the USA, there remains a considerable burden of disease attributed to serotypes not included in currently approved PCVs.[33]

Morbidity versus mortality risk factors

Intuitively, one might expect that for a vaccine programme to be considered a successful intervention, it must prevent both disease and death, but different factors may be involved for different outcomes, and since efficacy is defined by the outcome measured, the process of estimating cases/events averted is different from those estimating deaths averted. A review of six randomised controlled trials found high-quality evidence on PCV efficacy against developing an IPD, but none of the trials studying all-cause infant mortality were powered enough to investigate the mortality outcome.[30] The recent COVID-19 pandemic highlighted the fact that risk factors for morbidity (ie, age, sex, ethnicity and comorbidities) can be very different from those for mortality (ie, access to an intensive care unit).[36] While infection and progression of pneumonia depend largely on the individual and the environment, access to healthcare can be the most important factor for succumbing to pneumonia, making differences in government investment in healthcare systems (which varies significantly between countries) more relevant. For example, mortality rates of pneumococcal infections in developing countries are considered to be significantly higher than those in the USA and Europe.[35] This makes it (theoretically) possible that a vaccine that is measurably capable of decreasing the number of cases and/or hospitalisations in one country, may still not be able to prevent death in susceptible high-risk populations in another country, making less useful the extrapolation of successful interventions between countries. Caution is needed when extrapolating results from studies in high-income countries due to differences in disease severity and comorbidities. Potential confounders include access to healthcare, living conditions, household size and composition, among others.[37] Also, estimates from observational studies can be confounded by unrelated changes in healthcare utilisation, changes in the underlying health of the population or changes in reporting.[38]

Limitations

Our study has some potential limitations.

BMJ Glob Health: first published as 10.1136/bmjgh-2023-012752 on 7 August 2023. Downloaded from http://gh.bmj.com/ on October 18, 2023 by guest. Protected by copyright.

Data quality

Analysing administrative databases collected for other purposes implies having no control over the quality of the data collection process, nor its manipulation or registration. The representativeness of IMR in middle-income to low-income countries has been questioned for decades.[4] A general deficiency in the detail of mortality from specific causes, especially when the information concerns young children in low-income and middle-income countries, may not be able to distinguish between other causes of acute respiratory disease (ie, influenza, bronchitis, bronchiolitis).[39] Currently, accurate measurement of health indicators remains an immense challenge, but methods have been refined to optimise the use of country-level data and the estimation of uncertainty around the estimates, to generate increasingly accurate and internationally comparable estimates.[11] Accurate international comparisons of IMR data is sometimes controversial because different countries may report IMR differently (ie, lower limits for birth registration or reporting at early gestational ages),[40] inclusion[41] or exclusion[42] criteria. For this reason, this study analyses trends, not point estimates, so countries are compared into themselves and not between each other. Vital statistics mortality data are a fundamental source of demographic, geographical and cause-of-death information, and is also one of the few sources of comparable health-related data for different geographical areas over an extended time period.[43] In the future, strengthening civil registration and vital statistics will support measurement efforts and help track progress of public health interventions.

Study design

Randomised placebo-controlled trials are considered the optimum approach for evaluation of the efficacy of a new intervention, as they are best able to minimise selection and information bias and control confounding.[44] However, the exclusive selection of participants does not represent the general population, and vaccine efficacy does not always predict vaccine effectiveness (ie, the protection attributable to a vaccine administered non-randomly under field conditions).[36] For guiding public health policy, approximating the field effectiveness of an intervention under routine programme conditions may be a more relevant than measuring the efficacy delivered under the optimum conditions of a clinical trial.[44] Also, any vaccine that contributes to disease control by acting against infection, disease or transmission can be considered to be efficient, but protection against severe disease and death (arguably the biggest burden of disease and the most important efficacy endpoint) is difficult to assess in phase III clinical trials due to the unfeasibly large numbers of participants required.[36] Alternative research approaches to the randomised clinical trial are needed after a new vaccine is introduced, so it becomes critical to monitor trends in disease rates.[38] Different study designs have been used to estimate the efficacy of PCV programmes in young children, including controlled clinical trials,[29] randomised clinical trials,[30] before-and-after rate comparison,[2 31] pivotal efficacy studies,[35] simulation models[38 45] and hypothetical cohorts.[46] We make no attempt here to estimate efficacy.

RECOMMENDATIONS

Because serotype prevalence may differ by age group and country, a nationwide serosurveillance system is vital to establishing appropriate vaccination strategies for each country.[47] Provided sufficient cases are detected at baseline, sentinel surveillance can accurately measure the effect of PCVs on the number of children hospitalised with IPD, and serotyping increases accuracy.[31] A continued surveillance is crucial to provide information on locally emerging pneumococcal serotypes and the optimal composition of future conjugate vaccines.[2] Laboratory confirmation is needed to justify broader serotype compilations since vaccine cost-effectiveness diminishes in proportion to the increase in price per dose.[35] The WHO recommends that surveillance should be conducted in selected countries and defined populations with different epidemiological profiles worldwide and should begin at least 2 years prior to PCV introduction and continue for at least 5 years postintroduction.[48] We agree.

CONCLUSION

The lack of a major change in IMR trends after PCV introduction suggests some plausible explanations: pneumococcus may no longer be as important for infant mortality as anticipated, or pneumococcus is important but non-vaccine serotypes may be more actively involved, or PCVs are effective in preventing disease but not mortality. Without laboratory confirmation, it is hard to estimate the true burden of disease from pneumococcus in infants, and thus, the impact of PCVs for any specific outcome remains unclear for many countries.

Contributors CAS made substantial contributions to conception and design and interpretation of data; drafted the article; and had final approval of the version to be published. OR and ML revised data critically for important intellectual content; and had final approval of the version to be published. PB made substantial contributions to conception and design; revised data critically for important intellectual content and had final approval of the version to be published.

Funding The study is a secondary analysis of publicly available data, supported primarily by the Universidad Norbert Wiener's internal research funding 2022.

Disclaimer The authors alone are responsible for the views expressed, which may not necessarily reflect the opinion or policy of their institutions.

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the analysis are available online on their respective websites.

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

BMJ Glob Health: first published as 10.1136/bmjgh-2023-012752 on 7 August 2023. Downloaded from http://gh.bmj.com/ on October 18, 2023 by guest. Protected by copyright.

ORCID iD
Carlos A Sanchez http://orcid.org/0000-0002-2895-547X

REFERENCES

1 Pneumococcal conjugate vaccine for childhood immunization. WHO - position paper - 2007, vol. 82, 12. Weekly Epidemiological Record (WER); 2007. 93–104.
2 Centers for Disease Control and Prevention (CDC). Invasive pneumococcal disease in children 5 years after conjugate vaccine introduction-eight states, 1998--2005. *MMWR* 2008;57:144–8.
3 Institute for Health Information (CITI). What is an indicator? 2023. Available: https://www.cihi.ca/en/access-data-and-reports/health-system-performance-measurement/what-is-an-indicator
4 Langer A, Bobadilla JL, Schlaepfer-Pedrazzini L. Limitations of infant mortality as a health indicator. *Salud Publica Mex* 1990;32:467–73.
5 Centers for Disease Control and Prevention. Infant mortality. 2023. Available: https://www.cdc.gov/reproductivehealth/maternalinfanthealth/infantmortality.htm#print
6 Inter-agency Group for Child Mortality Estimation (UN IGME). Child mortality estimates: country-specific infant mortality rate. 2021. Available: http://data.unicef.org
7 World Health Organization (WHO). Introduction of PCV (Pneumococcal conjugate vaccine). 2023. Available: https://immunizationdata.who.int/pages/vaccine-intro-by-antigen/pneumo_conj.html?ISO_3_CODE=&YEAR=
8 Penfold RB, Zhang F. Use of interrupted time series analysis in evaluating health care quality improvements. *Acad Pediatr* 2013;13:S38–44.
9 World Health Organization (WHO). *International statistical classification of diseases and related health problems, 10th revision (ICD–10)*. Geneva, Switzerland, 2008.
10 Nations International Children's Emergency Fund (UNICEF). MMR-maternal-deaths-and-Ltr_Mmeig-Trends_2000-2017_Revised-2021. 2021. Available: https://data.unicef.org/wp-content/uploads/2019/09/MMR-maternal-deaths-and-LTR_MMEIG-trends_2000-2017_Revised-2021.xlsx [Accessed 23 Mar 2023].
11 World Health Organization (WHO). Trends in maternal mortality: 1990 to 2015, United Nations population division; report no.: WHO/RHR/15.23. Geneva World Health Organization; 2015.
12 Hoyert DL. *Maternal Mortality Rates in the United States, 2021*. *NCHS Health E-Stats*. Centers for Disease Control and Prevention (CDC),National Center for Health Statistics, 2023.
13 Parazzini F, Imazio C, Pampallona S, *et al*. Trends in perinatal, neonatal and postneonatal mortality in Italy, 1955-84. *Soz Praventivmed* 1987;32:286–90.
14 Camargos P, Nascimento-Carvalho CM, Teixeira R, *et al*. Lower respiratory infections mortality among Brazilians under-five before and after national pneumococcal conjugate vaccine implementation. *Vaccine* 2020;38:2559–65.
15 Schuck-Paim C, Taylor RJ, Alonso WJ, *et al*. Effect of pneumococcal conjugate vaccine introduction on childhood pneumonia mortality in Brazil: a retrospective observational study. *Lancet Glob Health* 2019;7:e249–56.
16 Centers for Disease Control and Prevention (CDC). National vital statistics system, mortality 1999-2020 on CDC WONDER online database. 2021. Available: http://wonder.cdc.gov/ucd-icd10.html [Accessed 23 Mar 2023].
17 Ely DM, Driscoll AK. Infant mortality in the United States, 2019: Data from the period linked birth/infant death file. National vital vital statistics reports. Report no.: volume 70, number 14. Centers for Disease Control and Prevention (CDC), U.S. Department of Health and Human Services; 2021.
18 Kirby RS. Neonatal and postneonatal mortality: useful constructs or outdated concepts. *J Perinatol* 1993;13:433–41.
19 Pharoah PO, Morris JN. Postneonatal mortality. *Epidemiol Rev* 1979;1:170–83.
20 Bartlett JG. Decline in microbial studies for patients with pulmonary infections. *Clin Infect Dis* 2004;39:170–2.
21 Rodgers GL, Klugman KP. Surveillance of the impact of pneumococcal conjugate vaccines in developing countries. *Hum Vaccines Immunother* 2016;12:417–20.
22 Turner RB, Lande AE, Chase P, *et al*. Pneumonia in pediatric outpatients: cause and clinical manifestations. *J Pediatr* 1987;111:194–200.
23 Heiskanen-kosma T, Korppi M, Jokinen C, *et al*. Etiology of childhood pneumonia: serologic results of a prospective, population-based study. *Pediatr Infect Dis J* 1998;17:986–91.
24 Centers for Disease Control and Prevention (CDC). Preventing pneumococcal disease among infants and young children. recommendations of the advisory committee on immunization practices (ACIP). *MMWR Recomm Rep* 2000;49:1–35.
25 Musher DM, Thorner AR. Community-acquired pneumonia. *N Engl J Med* 2014;371:1619–28.
26 Rozenbaum MH, Pechlivanoglou P, Werf TS, *et al*. The role of streptococcus pneumoniae in community-acquired pneumonia among adults in Europe: a meta-analysis. *Eur J Clin Microbiol Infect Dis* 2013;32:305–16.
27 Peto L, Nadjm B, Horby P, *et al*. The bacterial aetiology of adult community-acquired pneumonia in Asia: a systematic review. *Trans R Soc Trop Med Hyg* 2014;108:326–37.
28 Song J-H, Thamlikitkul V, Hsueh P-R. Clinical and economic burden of community-acquired pneumonia amongst adults in the Asia-Pacific region. *Int J Antimicrob Agents* 2011;38:108–17.
29 Pavia M, Bianco A, Nobile CGA, *et al*. Efficacy of pneumococcal vaccination in children younger than 24 months: a meta-analysis. *Pediatrics* 2009;123:e1103–10.
30 Lucero MG, Dulalia VE, Nillos LT, *et al*. Pneumococcal conjugate vaccines for preventing vaccine-type invasive pneumococcal disease and X-ray defined pneumonia in children less than two years of age. *Cochrane Database Syst Rev* 2009;2009:CD004977.
31 Hampton LM, Zell ER, Schrag S, *et al*. Sentinel versus population-based surveillance of pneumococcal conjugate vaccine effectiveness. *Bull World Health Organ* 2012;90:568–77.
32 Grijalva CG, Nuorti JP, Arbogast PG, *et al*. Decline in pneumonia admissions after routine childhood Immunisation with pneumococcal conjugate vaccine in the USA: a time series analysis. *Lancet* 2007;369:1179–86.
33 Pfizer. U.S. FDA APPROVES PREVNAR 20®, Pfizer's 20-Valent Pneumococcal conjugate vaccine for infants and children. 2023. Available: https://www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-prevnar-20r-pfizers-20-valent-pneumococcal [Accessed 21 Jun 2023].
34 Brueggemann AB, Griffiths DT, Meats E, *et al*. Clonal relationships between invasive and carriage sstreptococcus pneumoniae and serotype- and clone-specific differences in invasive disease potential. *J Infect Dis* 2003;187:1424–32.
35 Giglio N, Micone P, Gentile A. The pharmacoeconomics of pneumococcal conjugate vaccines in Latin America. *Vaccine* 2011;29 Suppl 3:C35–42.
36 Hodgson SH, Mansatta K, Mallett G, *et al*. What defines an efficacious COVID-19 vaccine? A review of the challenges assessing the clinical efficacy of vaccines against SARS-Cov-2. *Lancet Infectious Diseases* 2021;21:e26–35.
37 Albrich WC, Madhi SA, Lafond KE, *et al*. Herd immunity after pneumococcal conjugate vaccination. *Lancet* 2007;370:218–9.
38 Bruhn CAW, Hetterich S, Schuck-Paim C, *et al*. Estimating the population-level impact of vaccines using synthetic controls. *Proc Natl Acad Sci U S A* 2017;114:1524–9.
39 Acute respiratory infections in the Americas. Epidemiological Bulletin. Pan American Health Organization (PAHO);
40 MacDorman MF, Matthews TJ, Mohangoo AD, *et al*. International comparisons of infant mortality and related factors: United States and Europe, 2010. *Natl Vital Stat Rep* 2014;63:1–6.
41 Organisation for Economic Co-operation and Development (OECD). OECD STAT extracts: health status. 2023. Available: https://stats.oecd.org/Index.aspx?DatasetCode=HEALTH_STAT [Accessed 02 Feb 2023].
42 Liang F-W, Lu T-H, Wu M-H, *et al*. International ranking of infant mortality rates: Taiwan compared with European countries. *Pediatr Neonatol* 2016;57:326–32.
43 Department Health and Human Services (HHS). National vital statistics system - mortality (NVSS-M). 2023. Available: https://health.gov/healthypeople/objectives-and-data/data-sources-and-methods/data-sources/national-vital-statistics-system-mortality-nvss-m [Accessed 02 Feb 2023].
44 Levine OS, Cutts FT. Pneumococcal vaccination and public health. *Lancet* 2007;369:1144–5.
45 Shioda K, Schuck-Paim C, Taylor RJ, *et al*. Challenges in estimating the impact of vaccination with sparse data. *Epidemiology* 2019;30:61–8.
46 Clark A, Jauregui B, Griffiths U, *et al*. TRIVAC decision-support model for evaluating the cost-effectiveness of haemophilus influenzae type B, pneumococcal and rotavirus vaccination. *Vaccine* 2013:C19–29.
47 Song JY, Nahm MH, Moseley MA. Clinical implications of pneumococcal serotypes: invasive disease potential, clinical presentations, and antibiotic resistance. *J Korean Med Sci* 2013;28:4–15.
48 WHO position Paper-2012. Pneumococcal vaccines. *Wkly Epidemiol Rec* 2012;87:129–44.

BMJ Glob Health: first published as 10.1136/bmjgh-2023-012752 on 7 August 2023. Downloaded from http://gh.bmj.com/ on October 18, 2023 by guest. Protected by copyright.