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Identifying UK travellers at increased risk of developing pneumococcal infection: A novel algorithm

Authors

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Running title: Algorithm to determine pneumococcal infection risk by country

Abstract

Background: In 2016, the travel subcommittee of the UK Joint Committee on Vaccination and Immunisation (JCVI) recommended that 13-valent PCV (PCV13) could be offered to travellers aged over 65 years, visiting countries without infant PCV immunisation programmes. This study aimed to identify, collate and review the available evidence to identify specific countries where UK travellers might be at an increased risk of developing pneumococcal infection. The data were then used to develop an algorithm, which could be used to facilitate implementation of the JCVI recommendation.

Methods: We conducted a systematic search of the published data available for pneumococcal disease, PCV vaccine implementation, coverage data and programme duration by country. The primary data sources used were World Health Organization databases and the International Vaccine Access Centre Vaccine Information and Epidemiology Window (VIEW)-hub database. Based on the algorithm, the countries were classified into 'high overall risk', 'intermediate overall risk' and 'low overall risk' from an adult traveller perspective. This could determine whether PCV13 should be recommended for UK adult travellers.

Results: A data search for a total of 228 countries was performed, with risk scores calculated for 188 countries. Overall, 45 countries were classified as 'high overall risk', 86 countries as 'intermediate overall risk', 57 countries as 'low overall risk' and 40 countries as 'unknown'.

Conclusion: To our knowledge this is the first attempt to categorise the risk to UK adult travellers of contracting pneumococcal infection in each country, globally. These findings could be used by national travel advisory bodies and providers of travel vaccines to identify patients at increased risk of pneumococcal infection, who could be offered PCV immunisation.

Introduction

Streptococcus pneumoniae (pneumococcus) is a Gram-positive diplococcus, which is a major cause of morbidity and mortality in children and the elderly worldwide.[1,2] Pneumococci are classified into >96 serotypes, based on their polysaccharide capsule. Diseases caused by pneumococci include serious infections, such as meningitis, bacteraemia and pneumonia.[1,2] Young children (<2 years), older adults (≥65 years) and those with certain underlying comorbidities (e.g. diabetes, heart or respiratory disease) or who are immunocompromised are at increased risk of pneumococcal infection.[1-3]

Two types of pneumococcal vaccine are currently available. These are the plain polysaccharide vaccine (PPSV23)[4] and the pneumococcal conjugate vaccines (PCV10 and PCV13).[5,6] Higher valency conjugate vaccines are also in development. PPSV23 is licensed for all ages over 2 years and contains polysaccharides of serotypes 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19A, 19F, 20, 22F, 23F and 33F.[7] PCV10 is licensed for infants aged between 6 weeks and 5 years and PCV13 is licensed from 6 weeks of age, containing polysaccharides for 10 and 13 serotypes, respectively.[5,6] PCVs offer several advantages over PPSV23: PCVs elicit a T-cell dependent response and can be administered to infants from 6 weeks of age; PCVs induce immunological memory and prevent nasopharyngeal carriage acquisition of vaccine serotypes (VTs) and, therefore, produce herd protection in unvaccinated individuals;[1] and PCVs generate a higher immune response in older adults preventing both bacteraemic and non-bacteraemic pneumonia caused by VTs.[7]

PPSV23 has moderate effectiveness in preventing invasive pneumococcal disease among the elderly, but its effectiveness against invasive pneumococcal disease (IPD) in high-risk adults is lower.[8-10] Effectiveness data for protection against non-invasive pneumococcal disease by PPSV23 has been inconsistent.[11] In addition, the vaccine does not provide protection against nasopharyngeal carriage thereby preventing the development of herd immunity.[8] Furthermore, PPSV23 does not induce immunological memory.[12]

The introduction of PCV infant vaccination programmes has decreased the overall incidence of pneumococcal disease in children through direct protection, and in other age groups through indirect protection.[2,13,14] Despite introduction of these vaccination programmes and global public health efforts, in 2019, the World Health Organization (WHO) estimated that only 48% of infants globally were receiving the full dose of a pneumococcal vaccine, as per individual country recommendations and national immunisation programme.[15] Many older adults from the UK travel abroad, increasing their risk of exposure to potential pathogens, including pneumococcal VTs, which may not be prevalent in the UK.

In the UK, the Joint Committee on Vaccination and Immunisation (JCVI) provides independent advice to the Department of Health on immunisation. In May 2016, the JCVI reviewed whether PCV13 should be offered to travellers aged over 65 years in circumstances where countries did not have an established infant pneumococcal programme.[16] The JCVI travel subcommittee advised that PCV13 could be offered to travellers aged over 65 years who would be staying longer than a month, working with local communities, or in close contact with the local population, in countries without established programmes.[16]

We conducted a systematic search of publicly available data on the levels of pneumococcal infection (invasive and non-invasive), PCV vaccination implementation, duration of the PCV programme, and PCV vaccine coverage in individual countries. In order to help support implementation of the JCVI recommendations, these data were then used to develop an algorithm using a pragmatic approach to identify UK travellers (particularly those aged over

65 years) who may be at increased risk of pneumococcal infection when travelling through, or seeking residence in, specific countries globally. By utilising the latest country-specific data, this algorithm could be used to support national travel advisory bodies and other providers of travel vaccinations, with the option to be regularly updated.

Methods

Data sources

To ensure robust contemporary global data, we explored data sources from recognised established organisations routinely collecting information on pneumococcal disease, such as the WHO, European Centre for Disease Prevention and Control (ECDC) and Centres for Disease Control and Prevention (CDC). All data used for the development of the algorithm can be found in the Supplementary Data Tables provided. The WHO database was searched for individual country data on vaccine coverage and whether an infant PCV immunisation programme was in place.[17] Robust data sources for total cases of pneumococcal disease were identified through the CDC (USA) and ECDC (Europe).[18,19] However, equivalent regional databases for the rest of the Americas, Eastern Mediterranean, South East Asia and Western Pacific were lacking, with no case or incidence data currently published independently by the WHO. The International Vaccine Access Centre (IVAC) Vaccine Information and Epidemiology Window (VIEW)-hub database provided global data for the level of pneumococcal infections by country to address this lack of data.[20] The IVAC VIEW-hub database was searched for data on incidence of pneumococcal infection, duration of vaccine programme and the type of vaccine used in childhood vaccination programmes (PCV13, PCV10 or both).[20] Data collection was initially performed in 2018. These numbers were updated in May 2020 to provide more recent figures for PCV coverage and programme duration, prior to manuscript submission. The WHO and IVAC VIEW-hub lack published data for some specific countries; in these situations an additional search of national public health websites and peer-reviewed literature was carried out.[20-25] This included the *WHO vaccine-preventable diseases: monitoring system 2019 global summary*.[25] Where data could not be found, countries were listed as 'unknown'. All data used for the development of the algorithm can be found in the Supplementary Data Tables provided.

Data collection

Data were collected in a fully-filterable database and organised by the WHO region groupings: AFR – Africa; AMR – Americas; EMR – Eastern Mediterranean; EUR – Europe; SEAR – South East Asia; and WPR – Western Pacific.[26] Data were collected for: 'PCV coverage', defined as the proportion of the infant population vaccinated with PCV; 'PCV programme duration', defined as the completed number of years since the PCV vaccination programme was introduced (completed years up to 1 May 2020); and 'incidence' or case number, defined as the total cases of pneumococcal infections (invasive and non-invasive) per 100,000/year.

Case numbers for pneumococcal disease, stratified by age, country and standardised globally are not available; therefore, a pragmatic and consistent approach was taken using the most recent case data from one main source (IVAC VIEW-hub platform; 2015 figures) and population estimates from a second source (*The World Factbook*, from the US Central Intelligence Agency).[20,27] This ensures that data from different countries are comparable.

Cases per 100,000/year were calculated using the sum of all cases of pneumococcal infection per country in 2015, dividing by the estimated total population of that country and multiplying by 100,000.[20,27] Total cases of pneumococcal infection were calculated across all age groups and included cases of severe pneumonia, pneumonia, pneumococcal meningitis, non-pneumonia non-meningitis (NPNM), and non-severe NPNM.[20] As the data were captured in these categories, cases could not be split into invasive and non-invasive pneumococcal disease. If case numbers were not available for one or more of these categories, the country was given an 'unknown' status for incidence.

Defining country risk

Countries were categorised using a traffic light system as RED (high-risk), AMBER (intermediate-risk) or GREEN (low-risk). For 'level of pneumococcal disease', RED = ≥250 cases/100,000, AMBER = 51–249 cases/100,000 and GREEN = ≤50 cases/100,000. For 'PCV coverage', RED = ≤50%, AMBER = 51–79% and GREEN = ≥80%. For 'PCV programme duration', RED = ≤2 years, AMBER = >2 – <5 years and GREEN = ≥5 years.

Overall risk for each country was categorised using a traffic light system and calculated by combining level of pneumococcal disease, PCV coverage and PCV programme duration data using a scoring system, with each parameter given equal weighting. The algorithm scoring system was defined as follows:

- Cases of pneumococcal infection ≥250/100,000 (RED): 3 points
- Cases of pneumococcal infection 51–249/100,000 (AMBER): 2 points
- Cases of pneumococcal infection ≤50/100,000 (GREEN): 1 point
- PCV coverage ≤50% (RED) or no vaccine programme (BLACK): 3 points
- PCV coverage 51–79% (AMBER): 2 points
- PCV coverage ≥80% (GREEN): 1 point
- PCV programme duration ≤2 years (RED) or no vaccine programme (BLACK): 3 points
- PCV programme duration >2 – <5 years (AMBER): 2 points
- PCV programme duration ≥5 years (GREEN): 1 point

When no pneumococcal conjugate vaccine programme was confirmed in a specific county, 3 points were scored for both PCV programme duration and coverage. To be classed as 'RED' for 'overall risk', countries must score ≥8 points or have ≥2 RED parameters. To be classed as 'AMBER' for 'overall risk', countries must score 4–7 points. To be classed as 'GREEN' for 'overall risk', countries must score 2–3 points. Where countries were missing data for two or more parameters, they were classified as 'unknown'. Where countries were missing data for one parameter, they were classified as follows: 'RED' if both known parameters were RED; 'AMBER' if one or more of the known parameters were AMBER; 'GREEN' if the two known parameters were GREEN. The scoring system was based on a combination of published evidence and expert opinion.[28,29] For example, the *Global Vaccine Action Plan*, published by the WHO in 2013, recommended a coverage target of at least 90% at a national level and at least 80% coverage across every district for all vaccines in national immunisation programmes.[29] The algorithm presented here has been developed with a pragmatic approach, choosing a coverage target of 80% and above to be considered low risk.

Following the May 2020 update for PCV coverage and programme duration, the overall risk scores were also updated. This demonstrates that the spreadsheet and risk categories can be updated relatively easily, making it a viable option for travel immunisers to keep records renewed.

Developing the algorithm

Using the data derived from the search, we developed an algorithm (Figure 1) using a stepwise approach to determine if PCV immunisation should be recommended for travellers. Step 1 determines if the traveller falls into a population at increased risk of contracting pneumococcal infection. The population at increased risk includes clinical risk groups listed in the *Green Book* (Chapter 25: Immunisation Against Infectious Disease), an immunisation guideline developed by Public Health England for healthcare professionals, for whom pneumococcal infection is likely to be more common and/or serious.[30] This includes adults aged over 65 years and those with chronic disease including diabetes and heart disease.[30] Step 2 determines whether the planned destination(s) include any countries where there is an increased risk of contracting IPD. Step 3 considers the specific context of an 'at-risk individual' travelling to a country where the risk of contracting a pneumococcal infection may be elevated.[31] For example, individuals may require PCV13 vaccination if: travelling in a country for an extended period (>3–4 weeks); attending mass gatherings associated with dense crowds including international sporting events; working with local communities;[16] attending Hajj Pilgrimage;[32] or travelling during the 'flu' season (noting that this differs in northern and southern hemispheres). If a PCV10/13 vaccination was administered during the past 12 months then a second PCV13 vaccine would not be required.[6,33] Responses following a second vaccination with PCV13 at 1 year have been demonstrated as non-inferior for a majority of serotypes compared with the initial PCV13 dose.[33]

Results

Burden of pneumococcal disease

Case data were collated for 178 countries (Figure 2). A total of 35 countries had a 'high case load of pneumococcal infection (incidence ≥250/100,000); 77 countries had 'intermediate' case load (incidence 51–249/100,000) and 66 countries were classified as 'low' case load (incidence ≤50/100,000). A total of 50 countries did not have all the individual case numbers required to calculate the total number of cases per 100,000 per year figure and, thus, were classed as 'unknown'. (See Supplementary Data Tables for more details.)

PCV coverage

We identified 144 countries as having an infant PCV immunisation programme at the time of our analysis (Figure 3).[17] Twelve of these countries were classified as having 'low' coverage (PCV coverage ≤50%); 23 countries were classified as 'intermediate' coverage (PCV coverage 51–79%); 109 countries were classified as 'high' coverage (PCV coverage ≥80%). We identified 42 countries who had no coverage data due to no vaccine programme at the time of our analysis and coverage data was unknown for 42 further countries. (See Supplementary Data Tables for more details.)

PCV programme duration

We collected PCV programme duration data for 154 countries, with most of the introduction dates taken from the IVAC VIEW-hub database (last updated 10 July 2018; accessed May 2020).[20] PCV programme introduction was defined as countries that have introduced the vaccine nationally. Of these, 10 had a 'short' duration (≤2 years), 12 countries had an 'intermediate' programme duration (>2 – <5 years) and 132 countries had a 'long' programme duration (≥5 years) (Figure 4). A total of 39 countries had no data to report at the time of our analysis and 35 countries had an unknown programme duration. (See Supplementary Data Tables for more details.)

Overall risk

We classified 45 countries as 'high overall risk' (RED; ≥8 points or have ≥2 RED parameters), 86 countries were classified as 'intermediate overall risk' (AMBER; 4–7 points) and 57 countries as 'low overall risk' (GREEN; 2–3 points) (Figure 5). A further 40 countries were listed as 'unknown' because we were missing data for ≥2 parameters.

It is worth noting that although Austria has had a PCV vaccine programme in place for many years, no coverage data are currently available. Austria was still considered low risk due to the duration and level of disease data. In addition, the vaccination programme start dates for Serbia and Tonga are later than the reported coverage figures and San Marino has coverage data for 2018 but no programme start date has been reported. A lower risk score may have been calculated if start dates were earlier than stated. These anomalies may be due to vaccinations occurring in some areas prior to the official start date and roll-out for the whole country or use in the private sector prior to introduction of the national immunisation programme.

Discussion

The introduction of PCVs has resulted in a substantial decline in pneumococcal infections around the world.[2,13,14,34] However, there are still a large number of cases and deaths worldwide caused by vaccine-preventable serotypes of pneumococcus.[1,34] Our study aimed to generate a list of countries where there is a high risk of contracting pneumococcal infection and to develop an algorithm to identify at-risk patients who may require PCV13 vaccination prior to travelling to these countries. To our knowledge, this is the first attempt to pragmatically define the risk to travellers from the UK of contracting pneumococcal disease when travelling through, or seeking residence in, specific countries globally. Our approach, using a traffic light system, is similar to the guidelines on managing rabies post-exposure published by Public Health England.[35]

By utilising the latest country-specific data, this algorithm could be used by national travel advisory bodies and providers of travel vaccination. Data informing the algorithm should be updated regularly (e.g. every 3–5 years) to reflect the current environment in each country.

As healthcare systems and access to vaccines improve, we would expect more countries to move into the GREEN ‘low risk’ category over time. Childhood PCV vaccination programmes continue to be introduced worldwide, with coverage increasing across both high- and low-income countries.[29] This action is partly driven by WHO recommendations and the *Global Vaccine Action Plan 2011–2020*.[29,36]

Data tables are included in the supplementary material and could be adapted to automatically update risk classification as data sources are updated.

Overall, we identified 36 countries with high level of pneumococcal disease (RED; incidence ≥250 cases/100,000), 13 countries with low PCV coverage (RED; coverage ≤50%), and 10 countries with short programme duration (RED; ≤2 years). Countries with low PCV coverage and short programme duration were evenly spread across WHO regions, however, a large concentration of high incidence countries (n=25) were in the AFR region. Many countries in the AFR region have well-established childhood vaccination programmes (≥5 years) but despite this, all countries in this region had high (RED) or intermediate (AMBER) levels of pneumococcal infections. High overall risk countries were evenly spread across the different regions. In EMR, EUR, SEAR and WPR regions the reason for high overall risk was predominately due to countries having no PCV vaccination programmes in place. We listed 31 countries as 'unknown' in our database and these were predominately small nation countries including various Caribbean islands in AMR region and small islands in WPR region. As predicted, low overall risk countries (GREEN) were more likely to be the most developed or advanced countries (e.g. Australia, USA and many European countries). This could be because these countries have better access to vaccination programmes and, in general, have more advanced healthcare systems that lower the overall risk of infection.[37,38]

Infection levels and case numbers for pneumococcal disease should be interpreted with caution due to the limitations of the dataset. Epidemiological data often differs between countries.[39] In many countries, high-quality mandatory monitoring systems are in place to record cases of pneumococcal disease; however, other countries will have less reliable surveillance systems. There may also be differences in medical practices, laboratory methods, case definitions or disease labelling.[40] This may result in disparities in pneumococcal rates between countries.

A further limitation of this study is the possibility of underestimation of overall risk in certain countries. Data for one parameter was missing for several countries in our dataset and these countries were assigned a risk category based on the two known parameters. However, this approach, although pragmatic, could underestimate the risk evaluation for these countries.

Despite these limitations, this is the first attempt to categorise the risk of contracting pneumococcal infection in each country, globally. These findings provide an evidence base to facilitate implementation of the JCVI recommendation and could be used by national travel advisory bodies and other providers of travel vaccines to identify adults at increased risk of pneumococcal infection whilst travelling. Because this algorithm uses the latest country-specific data, it should be regularly updated, for example, every 3–5 years. In addition, this approach to categorising risk could also be applied to other vaccine-preventable diseases.

Author contributions

GE, JC, HM and MS were involved in the study design, data analysis, data interpretation and drafting of the manuscript. All the authors reviewed and approved the final version of the manuscript.

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Conflicts of interests

GE, JC and HM are employees of Pfizer UK Ltd and hold company shares. MS has received personal fees from GSK, Pfizer, AstraZeneca, MSD and Sanofi Pasteur as a speaker at international meetings and as a member of advisory boards (outside the scope of the submitted work). She has also worked as a contractor for Pfizer.

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Figure legends

Figure 1. PCV travel algorithm.
At-risk population: as defined in Chapter 25 of the *Green Book*. Country of travel: combines country-specific data to categorise potential risk of contracting pneumococcal infection per country. Length of stay +/- other factors: to consider travel for more than 3–4 weeks, gathering in dense crowds, working with local communities, Hajj Pilgrimage, or travelling during 'flu' season.

Figure 2. Level of pneumococcal disease (invasive and non-invasive) – cases per 100,000 population.
High level of disease (≥250 cases/100,000) shown in RED; intermediate level of disease (51–249 cases/100,000) shown in AMBER; low level of disease (≤50 cases/100,000) shown in GREEN; unknown level of disease shown in GREY.

Figure 3. Pneumococcal conjugate vaccines (PCV) immunisation coverage among 1-year-olds (%).

Low coverage (≤50%) shown in RED; intermediate coverage (51–79%) shown in AMBER; high coverage (≥80%) shown in GREEN; countries with no childhood vaccination programmes shown in BLACK; unknown coverage shown in GREY.

Figure 4. Time since PCV childhood vaccination programme was introduced (number of years).

Short programme duration (≤2 years) shown in RED; intermediate programme duration (>2 – <5 years) shown in AMBER; long programme duration (≥5 years) shown in GREEN; countries with no childhood vaccination programmes shown in BLACK; unknown programme duration shown in GREY.

Figure 5. Data synthesis for the PCV travel vaccine algorithm; combining country-specific data to categorise potential risk of contracting pneumococcal infection.

High overall risk (score ≥8 points or two RED parameters) shown in RED; intermediate overall risk (score 4–7 points) shown in AMBER; low overall risk shown in GREEN (score 2–3 points); unknown overall risk shown in GREY. Countries using PCV13 in childhood vaccination programmes visualised with vertical lines; countries using PCV10 in childhood vaccination programmes visualised with horizontal lines; and countries using both PCV13 and PCV10 in childhood vaccination programmes visualised with cross-hatched lines.

Figure 1

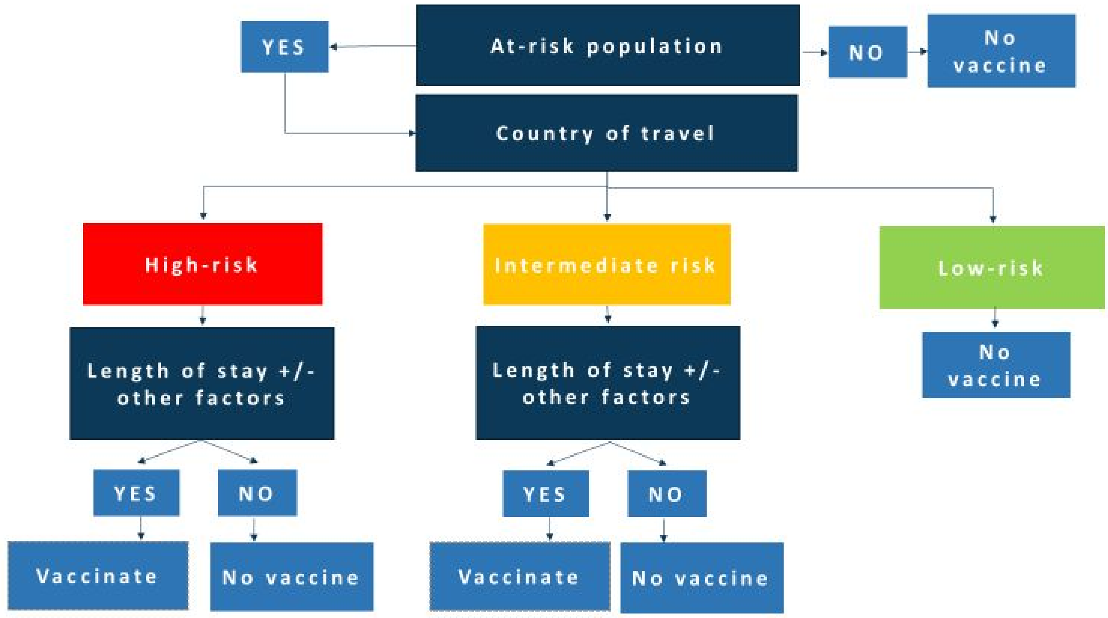

YES
At-risk population
NO
No vaccine
Country of travel
High-risk
Intermediate risk
Low-risk
Length of stay +/- other factors
Length of stay +/- other factors
No vaccine
YES
NO
YES
NO
Vaccinate
No vaccine
Vaccinate
No vaccine

Figure 2

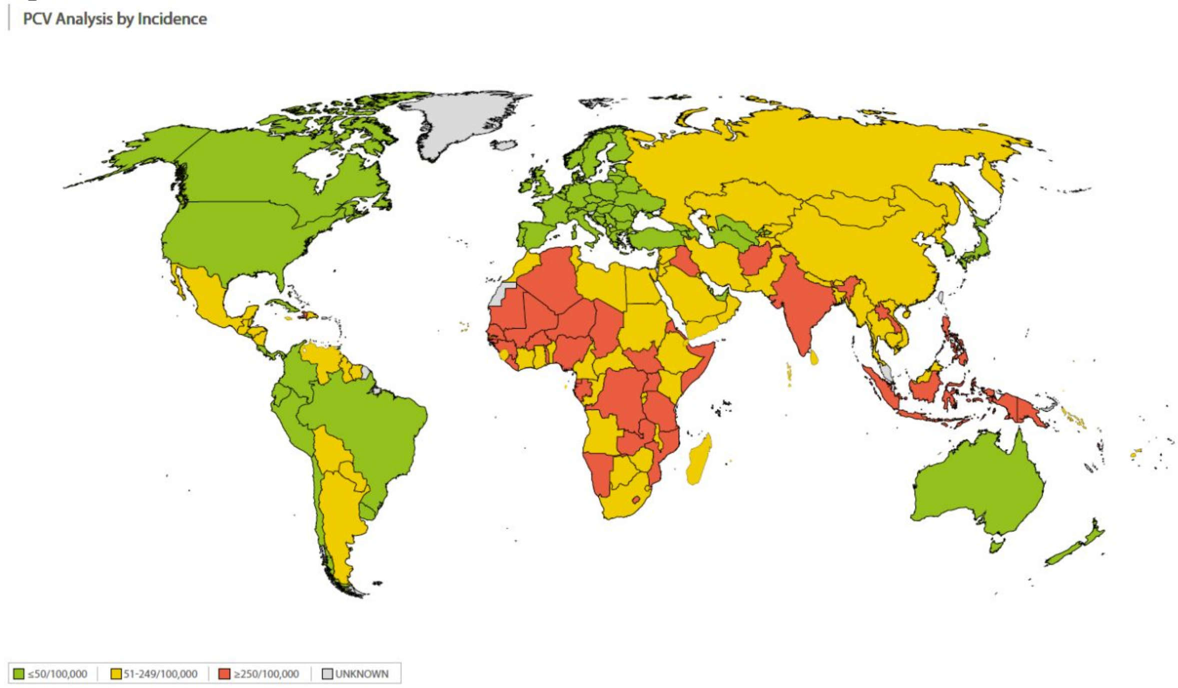

PCV Analysis by Incidence
≤50/100,000
51-249/100,000
≥250/100,000
UNKNOWN

Figure 3

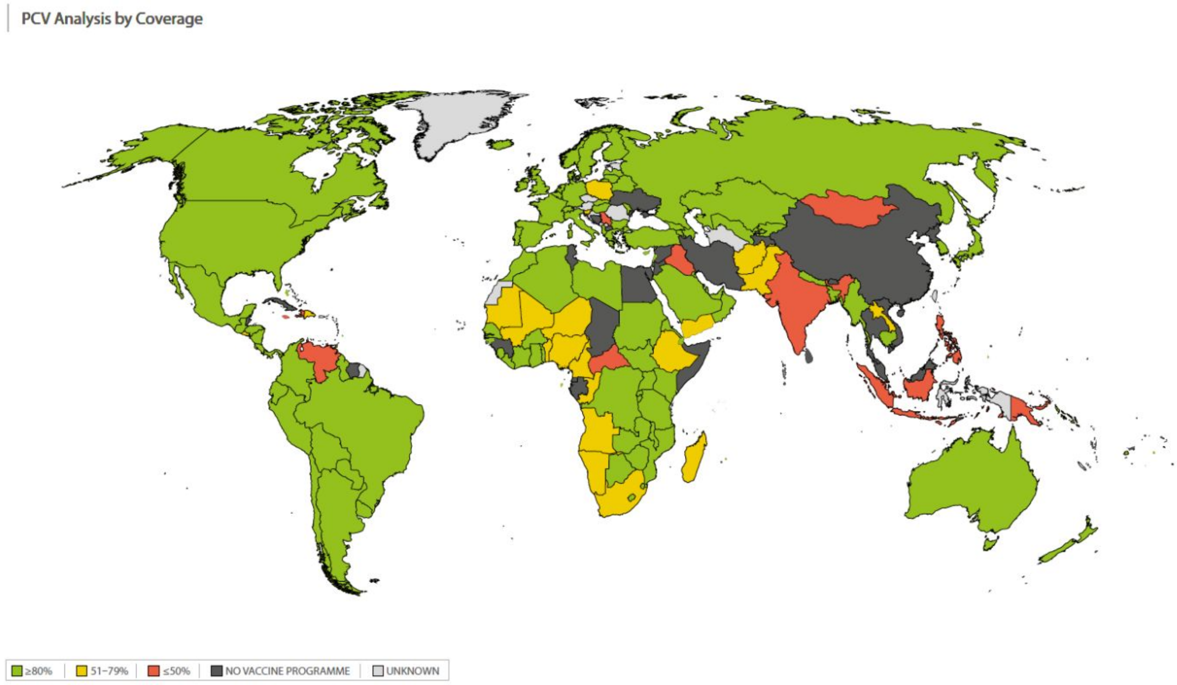

PCV Analysis by Coverage
≥80%
51–79%
≤50%
NO VACCINE PROGRAMME
UNKNOWN

Figure 4

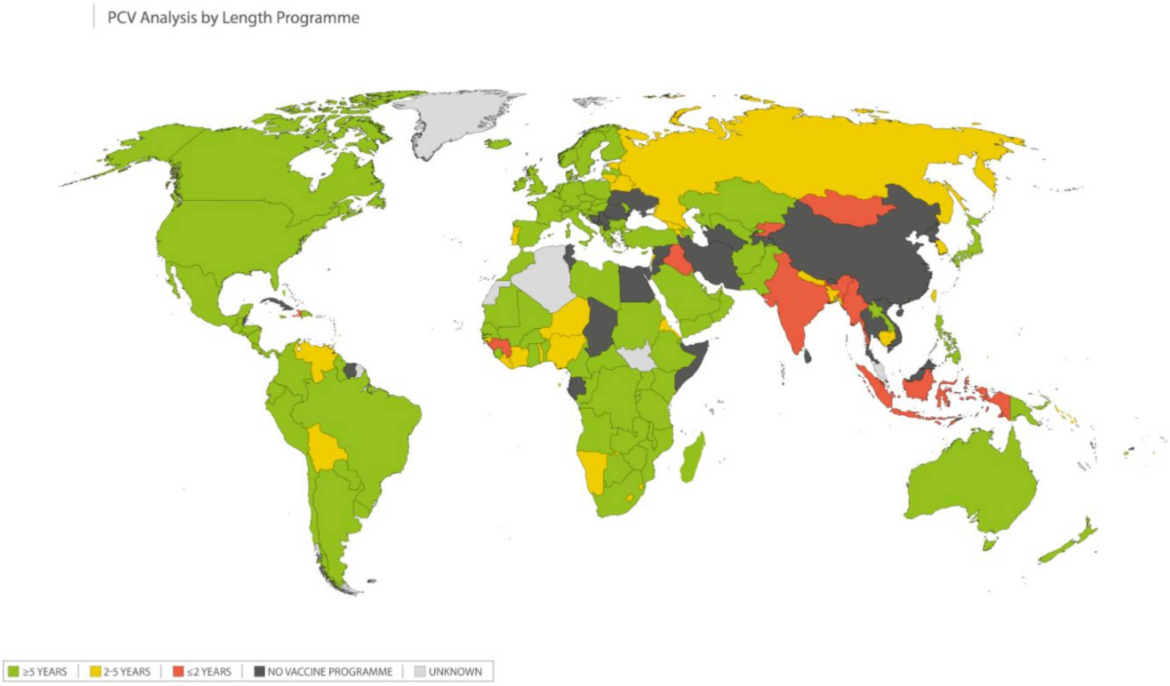
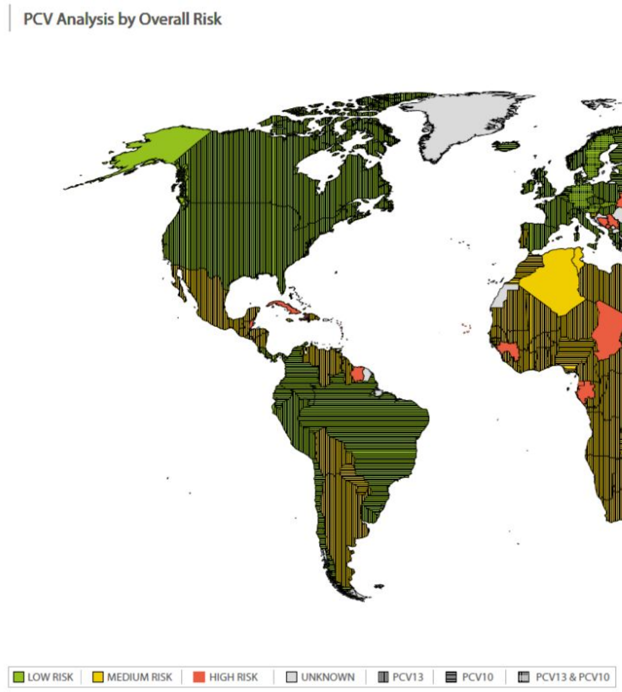
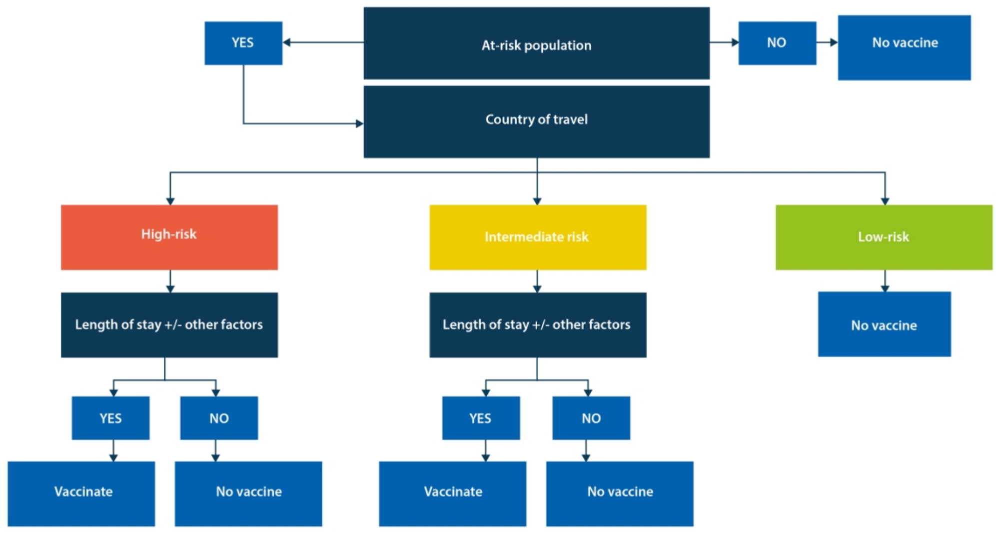

PCV Analysis by Length Programme
≥5 YEARS
2-5 YEARS
≤2 YEARS
NO VACCINE PROGRAMME
UNKNOWN

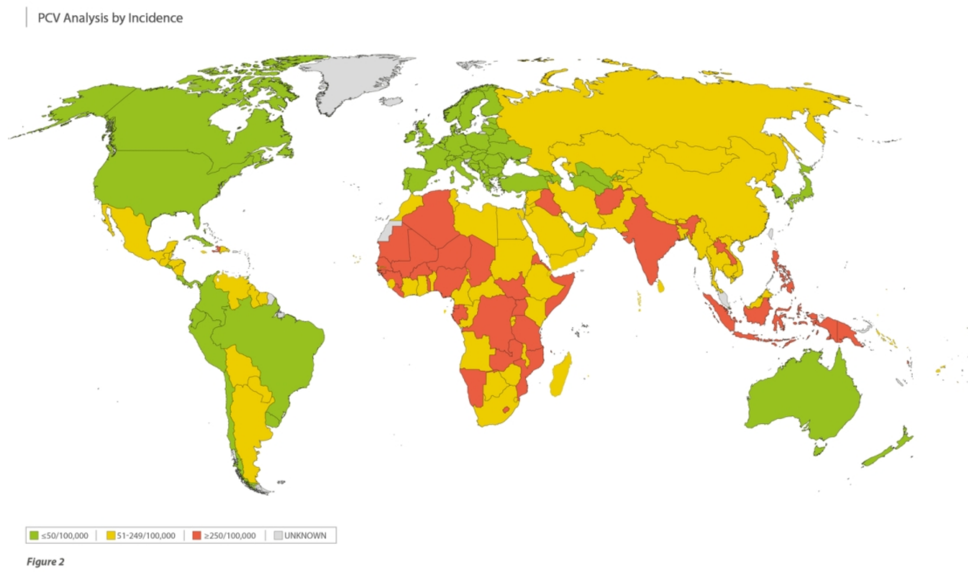
Figure 5


PCV Analysis by Overall Risk
LOW RISK
MEDIUM RISK
HIGH RISK
UNKNOWN
PCV13
PCV10
PCV13 & PCV10



PCV travel algorithm. At-risk population: as defined in Chapter 25 of the Green Book. Country of travel: combines country-specific data to categorise potential risk of contracting pneumococcal infection per country. Length of stay +/- other factors: to consider travel for more than 3–4 weeks, gathering in dense crowds, working with local communities, Hajj Pilgrimage, or travelling during 'flu' season.

180x102mm (300 x 300 DPI)



Level of pneumococcal disease (invasive and non-invasive) – cases per 100,000 population. High level of disease (≥250 cases/100,000) shown in RED; intermediate level of disease (51–249 cases/100,000) shown in AMBER; low level of disease (≤50 cases/100,000) shown in GREEN; unknown level of disease shown in GREY.

129x75mm (300 x 300 DPI)

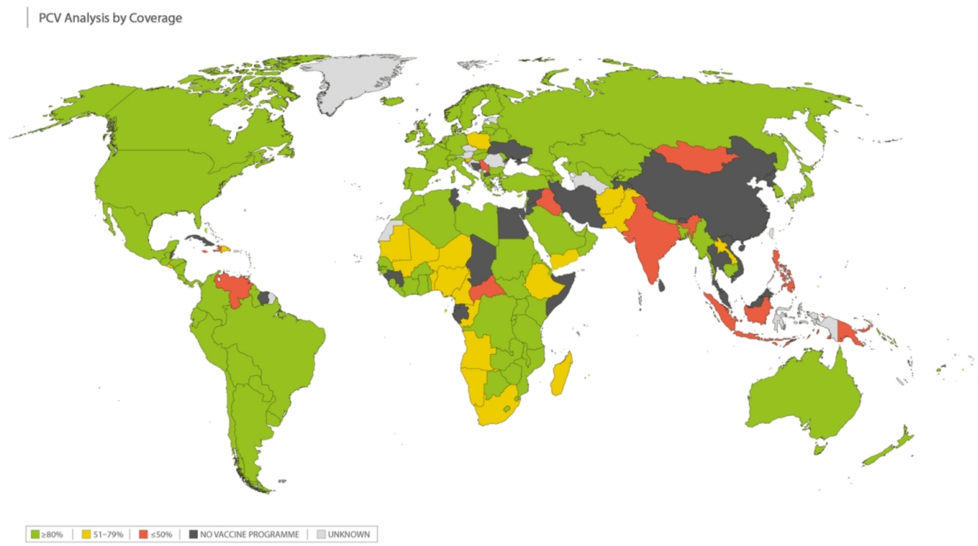
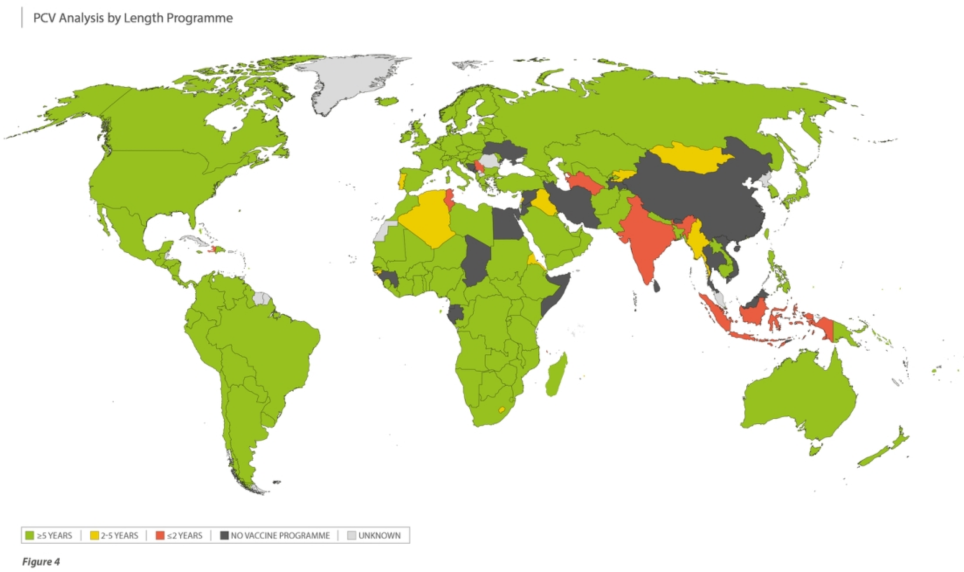


Figure 3

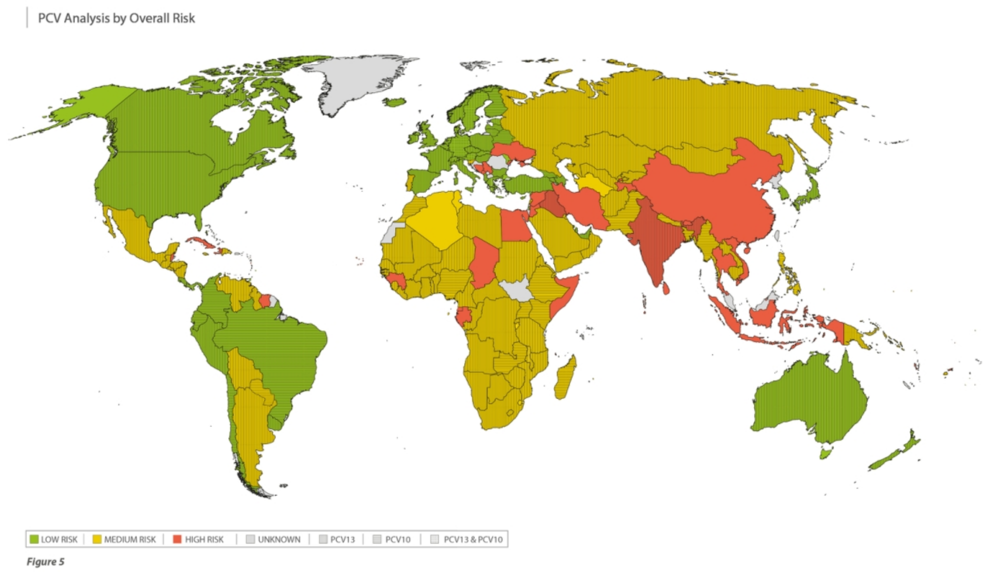
Pneumococcal conjugate vaccines (PCV) immunisation coverage among 1-year-olds (%). Low coverage (≤50%) shown in RED; intermediate coverage (51–79%) shown in AMBER; high coverage (≥80%) shown in GREEN; countries with no childhood vaccination programmes shown in BLACK; unknown coverage shown in GREY.

129x75mm (300 x 300 DPI)



Time since PCV childhood vaccination programme was introduced (number of years). Short programme duration (≤2 years) shown in RED; intermediate programme duration (>2 – <5 years) shown in AMBER; long programme duration (≥5 years) shown in GREEN; countries with no childhood vaccination programmes shown in BLACK; unknown programme duration shown in GREY.

129x75mm (300 x 300 DPI)



Data synthesis for the PCV travel vaccine algorithm; combining country specific data to categorise potential risk of contracting pneumococcal infection. High overall risk (score ≥8 points or two RED parameters) shown in RED; intermediate overall risk (score 4–7 points) shown in AMBER; low overall risk shown in GREEN (score 2–3 points); unknown overall risk shown in GREY. Countries using PCV13 in childhood vaccination programmes visualised with vertical lines; countries using PCV10 in childhood vaccination programmes visualised with horizontal lines; and countries using both PCV13 and PCV10 in childhood vaccination programmes visualised with cross-hatched lines.

129x75mm (300 x 300 DPI)