Global review of the distribution of pneumococcal disease by age and region

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EXECUTIVE SUMMARY

Background: The pneumococcal conjugate vaccine (PCV) schedule adopted by individual countries varies by the age of first dose, number of doses administered and the dosage intervals. Many countries have adopted a "2+1" schedule or follow the traditional EPI "3+0" schedule. The benefit of one schedule over the other, in terms of vaccine effectiveness, is currently being reviewed. In order to inform decision making on whether one schedule may offer more protection than the other, it is important to firstly understand the distribution of pneumococcal disease.

Aims: To determine whether the distribution of invasive pneumococcal disease (IPD), pneumococcal meningitis, WHO radiographic and hospitalised WHO clinical pneumonia in children aged 0 to 59 months varies significantly between and within regions. In addition, the impact of a different PCV schedules was estimated.

Methods: Sites were identified by a literature review and informal methods. Individuals were contacted and co-operation was requested to supply data on IPD, pneumococcal meningitis, WHO radiographic and hospitalised WHO clinical pneumonia, finely stratified by age. The proportion of cases aged between 6- 11m, and the proportion aged between 12- 23m by region were compared, and national data were compared with regional averages where possible. A model was constructed to estimate the proportional risk by month for the period 0-59m of age for regions and selected countries. Using these curves as the basis, curves were overlaid to describe the impact of PCV.

Results: Of 153 possible respondents identified, contact was made with 98 (64%). Fifty-nine (39%) supplied data. There were 22 and 10 populations for cases and deaths from IPD, and 21 and 12 populations for pneumococcal meningitis, respectively. There were 12 WHO radiographic pneumonia and 12 hospitalised WHO clinical pneumonia populations included. There was considerable variation between and within regions in the way surveillance data was collected. For the modelling, there were data on 16 populations for IPD from AFR, AMR, EUR, SEAR and WPR, with a median (IQR) sample size 795 (461 to 1639). For pneumococcal meningitis, there were data on 15 populations from AFR, AMR and SEAR with a median (IQR) sample size of 282 (180 to 453). For EMR, only data from Yemen for pneumonia was available.

Of all the cases of IPD in children aged 0-59m, about 20% of cases occur in infants aged <6m 50% in infants aged <12m, 75% in children aged <24m, and 90% in children aged <36m. For IPD, the median age ranged from 39.1 to 55 weeks of age in AFR, 38.6 to 52 weeks of age in AMR (excluding USA), and 27.1 to 44.8 weeks of age in SEAR. Australia was the only country represented in WPR with a later median age of 66.3 to 71.9 weeks, similar to the USA.

The peak of pneumococcal meningitis is earlier than IPD. Of all the cases of pneumococcal meningitis in children age 0-59m, about 40% of cases occur in infants aged <6m, 65% in infants aged <12m, 83% in children aged <24m, and 90% in children aged <36m. For pneumococcal meningitis, the median age ranged from 26.5 to 32.1 weeks of age in AFR, 25.8 to 33.7 weeks of age in AMR, and 25.3 to 29.9 weeks of age in SEAR. There were no WPR or EMR countries represented.

Over half of IPD (57%) in infants aged <2m is pneumococcal meningitis. There is uncertainty about the proportion of IPD cases occurring in infants <2m, particularly for low income countries. However, based on the small amount of data supplied, about 6% and 8% of the cases of IPD and pneumococcal meningitis are in children aged <2m, representing a lower rate than the peak which is usually between 2 and 6m. For low income countries, this may be an underestimate of the contribution of young infants. We cannot say for certain, but for the poorest of countries a negative exponential curve might be a more appropriate description of the distribution of pneumococcal disease. Despite some uncertainty about the rates of pneumococcal infection in very young infants, from the data supplied (n=578), between 32-79% of the serotypes occurring in this age group would be covered by PCV10 or PCV13.

For WHO radiographic pneumonia, between 8.7% and 52.4% of cases occur in infants aged <6m. The median age ranged from 39.4 to 45.4 weeks of age in AFR, 58.3 weeks of age in AMR, 24.6 weeks of age in SEAR, and 36.5 to 73.2 weeks of age in WPR. For hospitalised WHO clinical pneumonia, the distribution is similar. Between 18.6% and 54.1% of cases occur in infants aged <6m. The median age ranged from 37.5 to 42.3 weeks of age in AFR, 23.4 to 42.5 weeks of age in SEAR, and 36.1 to 68.0 weeks in WPR. Bangladesh had the lowest median of 52.4 and 54.1 weeks of age for WHO radiographic pneumonia and hospitalised WHO clinical pneumonia, respectively, while Vietnam had the highest median of 73.2 and 68.0 weeks of age for WHO radiographic pneumonia and hospitalised WHO clinical pneumonia, respectively. In general, within each country the median age of WHO radiographic pneumonia and for hospitalised WHO clinical pneumonia were similar. Our data indicates that hospitalised pneumonia mortality is greatest in younger infants.

Conclusions: There is not convincing evidence of major differences between or within regions with respect to the age distribution of cases of IPD, pneumococcal meningitis and pneumonia. To a large extent IPD and pneumococcal meningitis are diseases of infants with 50% and 65% of cases occurring in infants <12m respectively. There is considerable uncertainty about the proportion of IPD cases occurring in infants <2m, particularly for low income countries. In most settings, a considerable proportion of serotypes causing IPD in the <2m age group are currently contained in PCV10 of PCV13. The peak of WHO radiographic and hospitalised WHO clinical pneumonia appears to occur in a slightly older age group. Our data indicates that

pneumonia mortality is greatest in younger infants consistent with community based studies using verbal autopsy methods (1, 2).

Because the peak of pneumococcal disease occurs in early infancy, any delay in the administration of 3 primary doses (3p) of PCV would result in many children being left unprotected in the absence of herd immunity. Moreover, a PCV dose given with measles vaccine at around 9m may too late to offer much protection to the children in the at risk age groups (if 2 primary doses (2p) provide insufficient protection and no herd immunity). Our data supports that in all countries protection against pneumococcal disease should be achieved as early as possible. Many children will be unprotected from pneumococcal disease if the vaccination is given later than recommended, coverage is incomplete, and herd effects are negligible.

In terms of the schedule for existing vaccines, especially in low income countries:

- Regardless of the adopted schedule, improving the timeliness of vaccination and the coverage achieved will provide more children with some direct protection at an earlier age;
- An early first dose (i.e at 6w) will provide more children with direct protection at an age when they need it, compared with a first dose given at a later age;
- The advantages and disadvantages of providing the third dose as part of the primary series or as a booster at 9 or 12m also need to be evaluated in light of the conditions of the vaccination programme. Additional evidence from low middle income countries on herd effects of PCV is required.

1. BACKGROUND

Worldwide, pneumococcal conjugate vaccines (PCV7, PCV10, PCV13) are currently included in 22 national immunisation schedules (2010). The actual PCV schedule adopted by individual countries varies with respect to the total number of doses administered, the interval between doses, and the age administered. Many European and Latin American countries have adopted a "2+1" schedule, with the first 2 doses administered in infancy, approximately 8 weeks apart, with the third dose given late in the first year or early in the second year of life. The effectiveness of this schedule on the reduction of invasive pneumococcal disease (IPD) has been shown in a number of developed countries (3-5).

The current WHO position statement recommends a "3p" schedule in concordance with the EPI schedule, but allows for alternative schedules, as supported by evidence from clinical trials and routine use settings. The WHO position statement recommends the first dose to be given at 6 weeks of age with a minimum of 4 weeks between subsequent doses.

The optimal timing of the administration of the third dose of PCV (either given as a third dose in a primary series at 14 weeks of age, or as a "booster" after 9m) and the impact this may have on vaccine effectiveness in the first 9-12m when infants are most at risk of disease, needs to be addressed. It is therefore important to understand the distribution of pneumococcal disease and estimate whether either schedule is likely to be less effective.

In order for countries to make informed decisions about the introduction of PCV and which immunisation schedule to adopt, we aimed to estimate whether there are obvious differences in the age distribution of pneumococcal disease (IPD, pneumococcal meningitis, WHO radiographic and hospitalised WHO clinical pneumonia) between regions (and countries), which need to be taken into consideration prior to deciding which PCV immunisation schedule to adopt for a national immunisation program.

2. AIMS AND OBJECTIVES

The aims are to:

- Determine whether the distribution of IPD, pneumococcal meningitis, WHO radiographic pneumonia, and hospitalised WHO clinical pneumonia, in children in the first 5 years of life varies significantly between regions;
- Determine whether the epidemiology differs so significantly within each region, that it is necessary to address this at country, or even sub-national level; and
- Construct a database of sources, contacts, and study design details.

The following analyses were undertaken:

- An analysis of age distribution between regions: the proportion of cases and deaths between 6 and 11m, and the proportion between 12 and 23m were compared; and
- An analysis of the same parameters within each main region, comparing national data within each region.

A modeled curve was constructed to describe the proportional risk by month for the period 0-59m for regions and selected countries. Using these curves as the basis, curves were overlaid to describe the impact of PCV and the impact of a dose given at 9m. These models present a graphical illustration of the different PCV schedules under the various assumptions.

3. METHODS

3.1 Invasive pneumococcal disease and pneumococcal meningitis

A case of IPD was defined as: a child with pneumococcus isolated from a normally sterile site, such as blood, cerebrospinal fluid (CSF), or pleural fluid. A case of pneumococcal meningitis was defined as: laboratory-confirmation by culture or identification (i.e. by Gram stain, antigen detection methods) of pneumococcus in the CSF or from the blood (WHO, 2003) and/or pneumococcus detection by PCR in the CSF (pneumoADIP, 2007), in a child with a clinical syndrome consistent with bacterial meningitis.

IPD and pneumococcal meningitis data were collated from the following sources:

1. Published data
    - A comprehensive global IPD burden of disease review was published in 2009 which included data obtained between 1980 and 2005 from 164 sources (6). These were retrieved from the publically available WHO database (http://www.who.int/immunization_monitoring/burden/Pneumo_hib_estimates/en/index2.html); and
    - For data published from January 2006 to June 2011, surveillance sites supported by the pneumoADIP (http://www.preventpneumo.org/results/pneumoadip_activities/surveillance_and_research/upload/RS-Report-Final1207.pdf), or other known research sites were selected, and pre-vaccine introduction data were requested.
2. Unpublished data
    - The most recent 5 years of pre-vaccine introduction surveillance data were sought from the agencies responsible in high income countries (US:CDC, UK: HPA, Canada, Australia etc) and from the WHO supported surveillance sites; and
    - Cases and deaths in the control group from the phase 3 PCV randomised controlled trials from the Gambia, the Philippines, South Africa, and the US Kaiser Permanente studies were requested from study investigators.

3.2 Pneumonia

The following case definitions were used:

- WHO radiographic (“endpoint”) pneumonia (7); and
- WHO-clinical pneumonia (cough or difficulty breathing with tachypnea (>50 bpm in infants 2 months to <1 year; and >40 bpm in children aged one to < five years) or lower chest wall indrawing); and

Only cases that passively presented to a health facility and were hospitalised were included.

Pneumonia data were collated from the following sources:

1. Published data
   - Review of the 278 studies listed in the WHO ARI database (http://www.who.int/child_adolescent_health/data/cherg/en/index.html);
   - Review of the 28 studies included in the previous WHO review of clinical pneumonia (8);
   - For data published between 2006 to June 2011, known surveillance sites supported by the pneumoADIP were selected (http://www.preventpneumo.org/results/pneumoadip_activities/surveillance_and_research/upload/RS-Report-Final1207.pdf); and
   - Relevant studies on WHO radiographic pneumonia were identified through a review of the literature to include manuscripts published from 1996 to June 2011 including EMRO - Virtual Health Sciences Library, AIM, IMSEAR, EMBASE-Medline, LILIACS, ClinicalTrialsCochrane, and WPRIM.

2. Unpublished data
   - Cases and deaths in the control group from the phase 3 PCV randomised controlled trials from the Gambia, the Philippines, South Africa, the US Kaiser Permanente studies were requested from study investigators.

3.3 Database

A database was constructed including information on source, region/country, year, selected details of study design, and age specific data (cases and deaths in 0-2, 2-3, 4-5, 6-11, 12-23, 24-35, 36-47, 48-59 month olds). Sites were requested to supply age data in the finest categories their database would allow.

3.4 Analysis

Data were entered into an excel spreadsheet proforma by each of the informants. The returned spreadsheets were checked for completeness and the informants were asked to clarify any inconsistencies. The cleaned data was exported to Stata version 11 for analysis.

The proportion of IPD, pneumococcal meningitis, and WHO radiographic and hospitalised WHO clinical pneumonia cases and deaths were calculated for children aged 2-59m for various age categories. Cases who were HIV positive were excluded from the analysis. A Chi-square or Fisher's exact test was used to compare proportions. A p-value of ≤0.05 was considered statistically significant.

Where surveillance sites were unsure of the date of birth of a case, the site recorded the child's age to the nearest 6 or 12 months creating 'spikes' of cases at 12, 18, 24 and 30 months. These were most plainly seen in the distributions with age groups of one month.

To help summarise and visualise the observed distributions and smooth out these spikes, theoretical distributions were fitted. Statistics calculated for the theoretical distributions included the mean, standard deviation and selected percentiles. Gamma and lognormal distributions were tried. Results reported are for gamma distributions, since these generally provided the better fits[1]. As well as varying the mean and standard deviation of the theoretical distribution, the fitting process allowed for lateral shifting so as to cater for non-zero incidence at age 0 (left/negative shifting) and variations in the durability of protection by maternal antibodies (right/positive shifting). Goodness of fit was measured by root mean square deviation, with observations weighted by the width of the age group. In each case the parameters giving the minimum weighted root mean square deviation were found numerically from a grid of starting points using Excel Solver.

For some of the countries represented in this survey there were data from the DHS or MICS on the distribution of children's ages at DTP and/or OPV 1, 2 and 3. To aid assessment of the timeliness of vaccination in relation to age at pneumococcal disease we constructed 'age/incidence/dose profiles'. For each week of life, the % of all cases of pneumococcal meningitis at age <36m in that week in the fitted distribution was multiplied by the mean coverage for that week with 1, 2 and 3 doses of OPV and the first dose of MCV. This gives the % of cases at each week of age during the pre-vaccine era that would have been protected by 1, 2 or 3 doses and a booster, assuming that the PCV was added to the EPI programme using the standard schedule, and that the age distribution of cases was unchanged.

To assess the comparability of surveillance data, countries were compared by the following analyses:

- Where IPD and pneumococcal data were collected from the same site, the proportions of IPD that was due to pneumococcal meningitis in the 4-5m, 6-11m, and 2-59m age group were compared;
- The case fatality ratios for IPD and pneumococcal meningitis for 6-11m, 12-23m, and 2-59m; and 4-5m, 6-11m, and 2-59m respectively were compared; and
- Where WHO radiographic pneumonia and hospitalised WHO clinical pneumonia were collected from the same site, the proportions of clinical cases that were radiographic in 6-11m, the 12-23m, and 2-59m were compared.

[1] The gamma distribution is the probability distribution of waiting times until the kth arrival in a Poisson process. It is commonly used to model waiting times. Points on a gamma distributions lie between zero and infinity.

- Neonatal cases presented a special problem. In most settings, hospital series of cases tended to exclude neonates. These may have been managed by different groups. In many developing country settings ascertainment is likely to have been very poor, due to a reluctance to perform lumbar punctures in this age group and inadequate microbiology. In addition, in many settings these cases would never have been brought to a hospital. In sub-Saharan Africa, the Kenya data came from a site with excellent microbiology and a well defined population under surveillance. It is possible that the high rates of neonatal IPD and pneumococcal meningitis in Kenya are indicative of the situation elsewhere in Africa, but there are insufficient data from elsewhere to determine this. To avoid the introduction of bias from this factor, comparisons were made between countries excluding infants aged <2m.

4. RESULTS

4.1 Literature search

The search terms and results of the literature search are summarised in Table 1 (IPD and pneumococcal meningitis) and Table 2 (pneumonia).

4.2 Database of contacts

On the basis of the literature search a database of contacts of 123 and 30 possible informants for IPD/pneumococcal meningitis and pneumonia, respectively, was constructed. The results of attempts to contact the informants are shown in Table 3. The corresponding authors and contacts identified were contacted at least twice to request age-specific data.

4.3 Selection of studies

The database includes the age in months of the cases and deaths for 22 and 10 populations for IPD, and 21 and 12 populations for pneumococcal meningitis, respectively (Tables 4 and 5). There were 12 WHO radiographic pneumonia and 12 hospitalised WHO clinical pneumonia populations included (Tables 6 and 7). For the modelling, there were data on 16 populations for IPD from AFR, AMR, EUR, SEAR and WPR, with a median (IQR) sample size 795 (461 to 1639). For pneumococcal meningitis, there were data on 15 populations from AFR, AMR and SEAR with a median (IQR) sample size of 282 (180 to 453).

4.4 Proportion of IPD and pneumococcal meningitis cases and deaths, and WHO radiographic pneumonia and hospitalised WHO clinical pneumonia cases between 6-11m, and 12-23m, by region

To determine whether it is possible to generalise between the regions with regard to the proportions of cases in different age groups, comparisons were made between the proportions of cases in the 6-11 months and 12-23 months age groups. Tables 8 and 9 show the proportions of IPD and pneumococcal meningitis cases and deaths, WHO radiographic pneumonia and hospitalised WHO clinical pneumonia cases and deaths between 6-11m and 12-23m, by region. Despite statistically significant differences being found between WHO regions for the proportions of cases occurring in the 6-11m age group for IPD, pneumococcal meningitis, WHO radiographic and hospitalised WHO clinical pneumonia the proportions of cases occurring in this age group ranged between 25-31%, 29-38%, 20-31%, and 24-35%, respectively, and therefore we don't believe these differences to be substantial. Significant differences were also found between regions for the 12-23m group. In general, the proportion of IPD cases that were due to pneumococcal meningitis was higher in younger infants than older infants (Table 10). While for all the syndromes, the proportions of cases in these 2 age

groups were significantly different between the regions, the differences were not large, suggesting that the age distributions are similar.

There were no significant differences between regions for IPD or pneumococcal meningitis for the proportion of deaths occurring in each age group (Table 8). For all regions, with the exception of AMR the proportions of deaths from IPD and pneumococcal meningitis were higher in the 6-11m age group compared with the 12-23m age group. However AMR only reported a total of 13 deaths. For all regions, with the exception of WPR, the proportion of deaths from pneumonia were 2-4 fold higher in the 6-11m group compared with the 12-23m group. WPR reported a total of only 2 deaths.

Table 8: Proportion of IPD and pneumococcal meningitis cases and deaths between 6-11m and 12-23m in children aged 2-59m, by region

Region			% of all cases		% of all deaths	
	n of sites	Total cases 2-59m (deaths)	6-11m	12-23m	6-11m	12-23m
IPD			**p=0.006**	**p<0.001**	**p=0.459**	**p=0.46**
Africa	4	2836 (443)	27%	27%	31%	19%
Americas	6	8492 (118)	25%	32%	26%	22%
Europe	2	776	31%	25%	-	-
South-East Asia	4	656 (32)	27%	18%	25%	19%
Western Pacific	4	733 (7)	25%	38%	43%	0%
Pneumococcal meningitis			**p=0.011**	**p<0.001**	**p=0.956**	**p=0.705**
Africa	7	1583 (322)	30%	18%	31%	18%
Americas	9	2818 (121)	29%	19%	30%	19%
Europe	1	351	38%	20%	-	-
South-East Asia	2	346 (25)	32%	10%	32%	12%
Western Pacific	1	107	29%	31%	-	-

Table 9: Proportions of WHO radiographic pneumonia and hospitalised WHO clinical pneumonia cases and deaths between 6-11m and 12-23m in children aged 2-59m, by region

Region			% of all cases		% of all deaths	
	n of sites	Total cases 2-59m (deaths)	6-11m	12-23m	6-11m	12-23m
WHO radiographic pneumonia			**p<0.001**	**p<0.001**	**p=0.779[1]**	**p=0.675[1]**
Africa	3	420 (28)	29%	28%	36%	14%
Americas	1	1708 (6)	20%	31%	33%	0%
South-East Asia	1	918 (34)	31%	15%	24%	6%
Western Pacific	2	201 (4)	23%	42%	25%	0%
Hospitalised WHO clinical pneumonia			**p=0.002**	**p<0.001**	**p=0.608[1]**	**p=0.172[1]**
Africa	4	2916 (90)	26%	31%	33%	12%
Eastern Mediterranean	1	153 (34)	35%	17%	35%	15%
South-East Asia	2	12335 (150)	28%	22%	28%	9%
Western Pacific	2	777 (2)	24%	38%	0%	50%

[1]Fisher's exact test p-value reported due to small numbers

Significant differences within countries in a given region were found in the proportion of IPD cases due to pneumococcal meningitis (range of 15-39% for AFR, and 16-88% for AMR in the 4-5m age group), except for the 4-5m age group for the countries within SEAR (Table 10). There were significant differences in the IPD case fatality ratios between countries in the same region (with a range of 10-26% for AFR, and 0.5-4% for AMR in the 4-5m age group), except for countries within SEAR and WPR (Table 11). There were significant differences in the pneumococcal meningitis case fatality ratios between countries in the same region, except for the 4-5m group in AMR (Table 12). However, there is likely to be a substantial under reporting of deaths from all diseases. There were no significant differences in the proportion of

hospitalised WHO clinical pneumonia cases that were radiographically confirmed between countries in the same region, except for the 6-11m and 2-59m age groups in WPR (Table 13).

There is not convincing evidence of major differences between or within regions with respect to the age distribution of cases of IPD, pneumococcal meningitis and pneumonia. These findings suggest there may be considerable variation between countries in a given region and within regions in the way surveillance data is collected which may be due to a variety of factors including, but not limited to, health seeking behaviour, access to care, and the surveillance methods used.

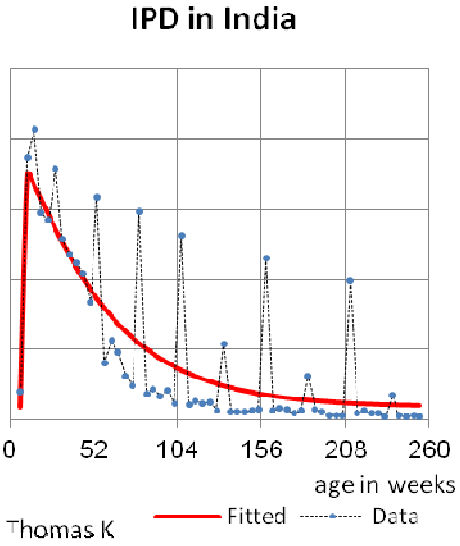
4.5 Proportions of IPD cases occurring between 6-11m due to serotypes 6B and 23F, by region

Table 14 shows the proportion of IPD cases occurring between 6-11m due to serotypes 6B and 23F. There were no statistically significant differences between countries within regions, except for AFR (range 0-15%) and AMR (range 6-21%) for serotype 6B, and EUR for serotype 23F (range 4-13%). A low proportion of 6B and 23F serotypes caused IPD in the 6-11m age group for SEAR (≤2% and ≤3% respectively), and WPR (≤4% and ≤8% respectively), although the sample sizes were small.

4.6 Proportional risk of pneumococcal disease by month of age

In order to assess the distribution of cases in more detail, data were modeled. The plot on the left of Figure 1, shows the percentage of hospital admissions for IPD in children aged <36m, for each month of age from the USA ABC surveillance site in the pre-vaccine era. The plot on the right is the equivalent for India. The peak is in much younger children. However there is a good deal of 'heaping' (rounding up or down of reported values) around ages 3, 6, 12, 18, 24 36 and 48m.

Figure 1: Fit of gamma distribution in two large datasets with monthly intervals (n = 2239 and n = 8243). The vertical axis is the same for both plots.

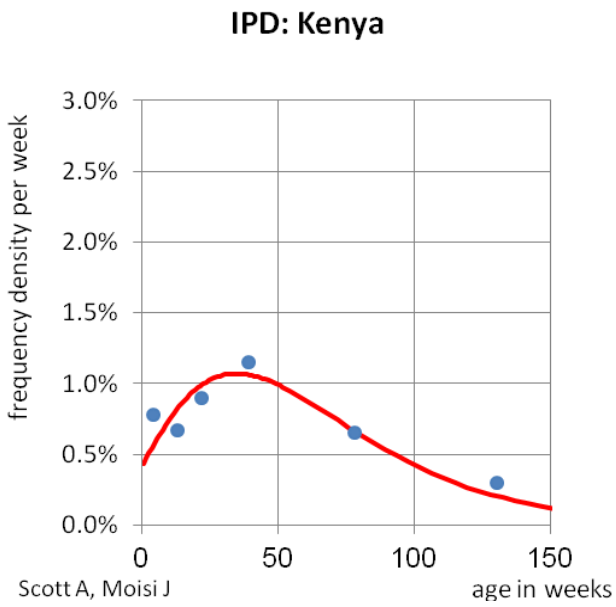


Gamma distributions (from a family of curves which are bell-shaped but skewed to the right) appear to fit both sets of data reasonably well. Distributions from this family were fitted to all datasets including more than 100 cases. Tables 15-17 show summary statistics on ages at IPD, pneumococcal meningitis, WHO radiographic pneumonia, and hospitalised WHO clinical pneumonia events. The peak of pneumococcal meningitis is earlier than that of IPD. Of all the cases of pneumococcal meningitis in children age 0-59m, about 40% of cases occur in infants aged <6m, 65% in infants aged <12m, 83% in children aged <24m, and 90% in children aged <36m. For IPD the figures are 20%, 50%, 75% and 90% respectively.

For IPD, the median age ranged from 39.1 to 55 weeks of age in AFR, 38.6 to 52 weeks of age in AMR (excluding USA), and 27.1 to 44.8 weeks of age in SEAR. Australia was the only country represented in WPR with a median age of 66.3 to 71.9 weeks. For developed countries, the USA and Australia had a similar median age for IPD. However the median age for IPD in the Netherlands was considerably lower at 43 weeks of age. This may be due to a lower threshold for taking blood cultures in febrile infants.

Figure 2 shows these results graphically for Kenya with fitted gamma distributions to the observed 2006-2010 IPD data. Other countries are shown in Figure 3. In general, there is consistency in the shape of the curve with an early peak and a variable shift to the left. This shift to the left is more pronounced in the low income countries, indicating an earlier age for the peak of disease.

Figure 2: Fit of gamma distribution for IPD, Kenya



Based on the small amount of data supplied from the countries listed in Tables 10 and 11, about 6% and 8% of the cases of IPD and pneumococcal meningitis occur in infants aged <2m, respectively. However, it is likely that for all developing countries there is a degree of under-reporting in this age group which may be quite large. In some settings this age group was ignored. In others there are likely to be major problems with care seeking and investigation of cases in this age group.

For pneumococcal meningitis, the median ages ranged from 27 to 32 weeks of age in AFR, 26 to 34 weeks of age in AMR, and 25 to 30 weeks of age in SEAR (Table 16). There were no WPR countries represented. The only developed country represented, The Netherlands, had the highest median age of 38 weeks. Figure 4 shows this graphically, with fitted gamma distributions to the observed data from various countries. Again there is considerable consistency in the shape of the curve with an early peak and a shift to the left of the gamma distributions. The peak of pneumococcal meningitis is earlier than IPD.

Table 15: Age distributions for IPD

						Cumulative % up to				Fitted curve			
		n	*mean*	*25th %ile*	*median*	*2m*	*3m*	*4m*	*6m*	*mean*	*std*	*shift*	*fit WRMSQE*
AFR	Kenya	256	89.5	30.1	51.8	7.0%	9.7%	12.4%	20.3%	76.0	43.8	16.1	0.03%
	Mozambique	624	77.7	31.9	55.0	4.9%	8.0%	11.1%	18.3%	67.2	46.9	-1.8	0.04%
	S Africa	1688	66.7	20.4	39.2	8.2%	13.5%	18.9%	35.3%	42.5	31.7	0.0	0.04%
AMR	Argentina	2089	86.0	24.5	49.8	7.0%	11.6%	16.3%	26.8%	67.6	61.2	0.0	0.03%
	Brazil	1788	73.2	22.7	46.6	7.1%	12.2%	17.2%	29.5%	60.5	49.8	0.0	0.03%
	Chile	1756	75.6	20.8	40.1	11.0%	15.9%	20.9%	30.6%	71.8	31.6	35.0	0.06%
	Colombia	1126	74.7	19.7	38.6	8.8%	14.6%	20.4%	36.1%	42.4	33.1	0.0	0.04%
	Dominican Rep	526	76.7	26.5	51.9	4.9%	9.7%	14.5%	24.5%	63.0	47.5	0.0	0.03%
	USA	2239	80.5	40.2	65.1	1.9%	3.1%	4.3%	9.3%	80.3	35.8	12.3	0.01%
EUR	Netherlands	736	73.8	23.7	43.0	6.1%	10.6%	15.1%	28.4%	50.1	39.2	-4.0	0.06%
SEAR	Bangladesh	304	46.2	15.8	27.1	10.7%	19.1%	27.5%	48.6%	30.9	22.6	0.0	0.03%
	India	292	91.1	24.2	44.8	0.5%	6.5%	12.6%	28.0%	47.6	42.2	-4.0	0.04%
WPR	Australia, NT	168	81.7	41.1	66.3	2.0%	2.6%	3.2%	7.7%	67.8	38.3	-4.0	0.02%
	Australia, NSW	503	90.3	43.2	71.9	2.3%	3.3%	4.2%	7.6%	81.8	46.8	0.8	0.03%

The age distribution is shown by WHO region and country for children aged <3 years. The sample size (n) is shown for each country, with estimated mean and median age in weeks of IPD event. The percentiles show the estimated age in weeks that 10% and 25th of cases of IPD are estimated to occur. The 2m, 3m, 4m, and 6m percentages estimate the percentage of IPD cases that occur by each age.

WMSQE = weighted mean square error

Table 16: Age distributions for pneumococcal meningitis

						Cumulative % up to				Fitted curve			
		n	*mean*	*25th %ile*	*median*	*2m*	*3m*	*4m*	*6m*	*mean*	*std*	*shift*	*fit WRMSQE*
AFR	Burkina Faso	142	66.5	13.8	26.5	8.5%	22.2%	35.8%	49.5%	27.0	18.5	0.0	0.12%
	Kenya	100	64.7	13.8	33.1	21.0%	24.4%	27.7%	41.3%	42.0	41.9	0.0	0.08%
	Niger	509	47.4	14.8	30.3	15.2%	22.0%	28.8%	45.0%	47.4	26.3	20.3	0.01%
	S Africa, routine	484	52.5	17.8	30.1	8.1%	15.7%	23.2%	44.6%	32.9	21.9	0.0	0.04%
	S Africa, enhanced	310	58.6	17.9	27.8	10.6%	16.7%	22.9%	47.8%	40.7	19.6	11.5	0.08%
	Uganda	331	69.6	15.2	32.1	13.7%	21.0%	28.4%	44.2%	42.7	37.7	0.0	0.03%
AMR	Argentina	498	56.8	14.4	29.2	12.0%	21.7%	31.4%	46.8%	30.0	25.0	0.0	0.07%
	Brazil, Hospital Couto Maia	148	58.8	14.2	25.8	**5.6%**	20.5%	35.4%	50.2%	23.0	16.0	0.0	0.15%
	Brazil, São Paulo	1111	63.4	17.8	33.7	9.1%	16.3%	23.5%	41.0%	37.7	28.1	0.0	0.04%
	Chile	376	47.0	12.2	27.3	19.1%	26.5%	34.0%	48.6%	39.9	38.6	0.0	0.01%
	Colombia	540	58.5	16.0	27.6	11.0%	19.0%	27.0%	48.0%	32.7	22.7	0.8	0.04%
	Dominican Rep	210	59.4	17.1	32.7	7.5%	16.1%	24.8%	42.8%	36.0	28.0	0.0	0.06%
EUR	Netherlands	362	62.3	23.2	38.1	**3.7%**	7.9%	12.2%	31.1%	38.0	22.0	0.0	0.04%
SEAR	Bangladesh	242	40.4	15.5	25.3	9.3%	18.9%	28.5%	51.9%	31.9	17.4	5.6	0.02%
	India	124	76.4	19.1	29.9	0.7%	9.8%	18.9%	45.3%	43.8	15.0	20.1	0.06%

The age distribution is shown by WHO region and country for children aged <3 years. The sample size (n) is shown for each country, with estimated mean and median age in weeks of pneumococcal meningitis event. The percentiles show the estimated age in weeks that 10% and 25th of cases of pneumococcal meningitis are estimated to occur. The 2m, 3m, 4m, and 6m percentages estimate the percentage of pneumococcal meningitis cases that occur by each age. Summary data for the fitted gamma distributions are shown.

WMSQE = weighted mean square error

Table 17: Age distributions for WHO radiographic pneumonia and hospitalised WHO clinical pneumonia

						Cumulative % up to				Fitted curve			
		n	mean	25th %ile	median	2m	3m	4m	6m	mean	std	shift	fit WRMSQE
Hospitalised WHO clinical pneumonia													
AFR	CAR	362	52.4	21.0	42.3	4.4%	12.1%	19.7%	31.4%	47.1	45.3	-4.0	0.04%
	Malawi	174	49.6	21.9	39.8	0.6%	8.8%	17.0%	31.5%	39.0	33.8	-4.0	0.03%
	S Africa	683	47.8	16.3	37.5	7.7%	17.2%	26.7%	38.7%	38.5	29.3	0.0	0.08%
SEAR	Bangladesh	5015	36.0	10.6	23.4	21.2%	30.4%	39.7%	54.1%	36.8	36.8	0.0	0.03%
	India	7081	53.6	22.7	42.5	0.6%	8.6%	16.5%	29.9%	60.5	49.8	0.0	0.10%
WPR	Fiji	333	43.6	17.4	36.1	16.2%	20.4%	24.5%	37.4%	77.0	44.9	0.0	0.19%
	Vietnam	449	68.6	35.9	68.0	2.5%	6.7%	10.9%	18.6%	31.9	27.7	0.0	0.23%
WHO radiographic pneumonia													
AFR	CAR	130	50.5	21.2	39.4	3.6%	11.1%	18.5%	32.2%	42.4	33.1	0.0	0.07%
	Malawi	62	57.0	27.8	45.4	0.3%	4.0%	7.7%	22.4%	47.6	42.2	-4.0	0.07%
	South Africa	221	53.2	21.4	44.2	5.4%	11.5%	17.5%	32.9%	54.4	47.5	0.0	0.06%
AMR	Uruguay	1466	64.6	29.3	58.3	4.9%	8.9%	12.9%	21.9%	80.3	35.8	12.3	0.09%
SEAR	Bangladesh	996	36.0	13.3	24.6	12.5%	24.2%	35.8%	52.4%	30.0	22.0	0.0	0.06%
WPR	Fiji	78	44.2	14.1	36.5	22.0%	24.3%	26.7%	39.6%	67.8	38.3	-4.0	0.22%
	Vietnam	126	75.4	45.9	73.2	0.1%	2.0%	3.8%	8.7%	19.7	13.8	0.0	0.39%

The age distribution is shown by WHO region and country for children aged <3 years. The sample size (n) is shown for each country, with estimated mean and median age in weeks of pneumococcal meningitis event. The percentiles show the estimated age in weeks that 10% and 25th of cases of pneumococcal meningitis are estimated to occur. The 2m, 3m, 4m, and 6m percentages estimate the percentage of pneumococcal meningitis cases that occur by each age. Summary data for the fitted gamma distributions are shown.

WMSQE = weighted mean square error

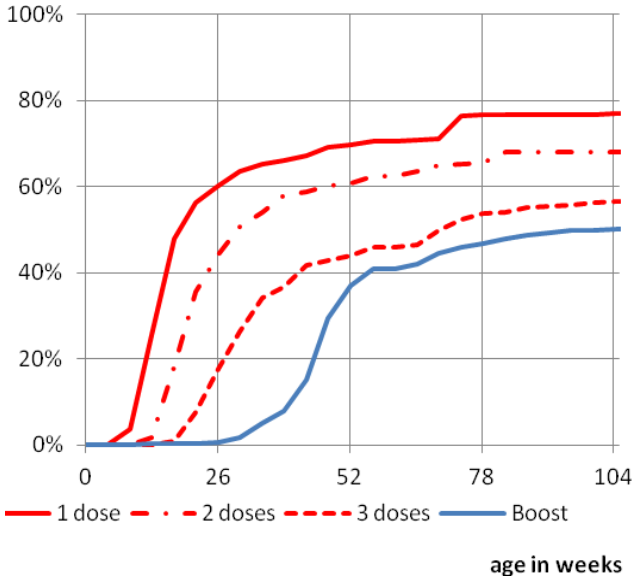
For WHO radiographic pneumonia, between 8.7% and 52.4% of cases occur in infants aged <6m (Table 17). The median ages ranged from 39.4 to 45.4 weeks of age in AFR sites, 58.3 weeks in AMR, 24.6 weeks in SEAR, and 36.5 to 73.2 weeks in WPR sites. For hospitalised WHO clinical pneumonia, between 18.6% and 54.1% of cases occur in infants aged <6m (Table 17). The median age ranged from 37.5 to 42.3 weeks of age in AFR, 23.4 to 42.5 weeks of age in SEAR, and 36.1 to 68.0 weeks in WPR. Bangladesh had the lowest median ages of 52.4 and 54.1 weeks for WHO radiographic pneumonia and for hospitalised WHO clinical pneumonia, respectively, whilst Vietnam had the highest median ages of 73.2 and 68.0 weeks for WHO radiographic pneumonia and for hospitalised WHO clinical pneumonia, respectively. In general, within each country the median ages of WHO radiographic pneumonia and hospitalised WHO clinical pneumonia were similar.

4.6 Model of the impact of pneumococcal conjugate vaccine

To estimate the impact of different PCV schedules on the number of children protected from pneumococcal disease, the models of the age distribution of disease (using pneumococcal meningitis as an example) were combined with the EPI actual vaccination coverage by age from various countries. Figure 5 shows the percentage of children vaccinated by weeks of age up to 2 years given by data from the Multiple Indicator Cluster Survey for Niger for 2004-6 (OPV1, OPV2, OPV3 and measles containing vaccine here referred to as boost), and the pneumococcal meningitis age distribution curve.

Figure 6 combines data from both graphs in Figure 5. This gives the percentage of cases at each week of age during the pre-vaccine era that would have been protected by 1, 2 or 3 doses, assuming that PCV was added to the EPI programme using the standard schedule, and that the age distribution of cases was unchanged. The outer envelope of the curve is the same as Figure 4 up to 104 weeks, showing the frequency distribution of pneumococcal meningitis episodes with no vaccination programme. The dark outer area under the curve labelled ‘0 doses’ shows the cases that would have had no protection against their pneumococcal meningitis event if a PCV had been administered at the same time as OPV. Paler areas represent the cases that would have had 1 or 2 PCV doses. In blue we present the area under the curve that will receive direct protection from a booster dose given at 9m. Thus while Figure 5 shows the vaccine coverage of *children*, Figure 6 shows the coverage of *cases to be prevented.*

Figure 5: OPV and MCV coverage based on the MICS 2004-6, Niger



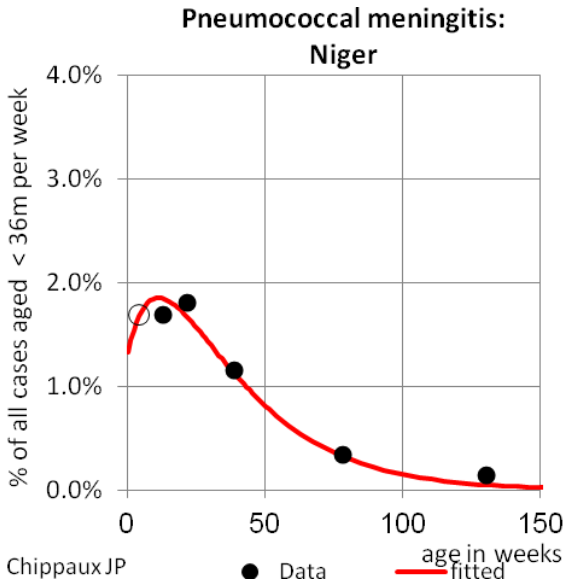


Figure 6: Pneumococcal meningitis and estimated number of PCV doses given by week of age: Niamey, Niger

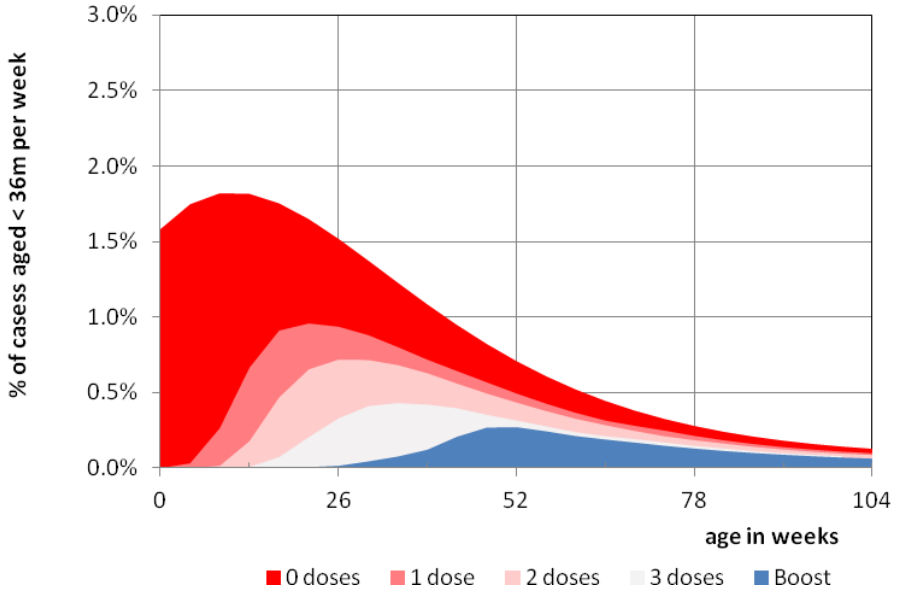
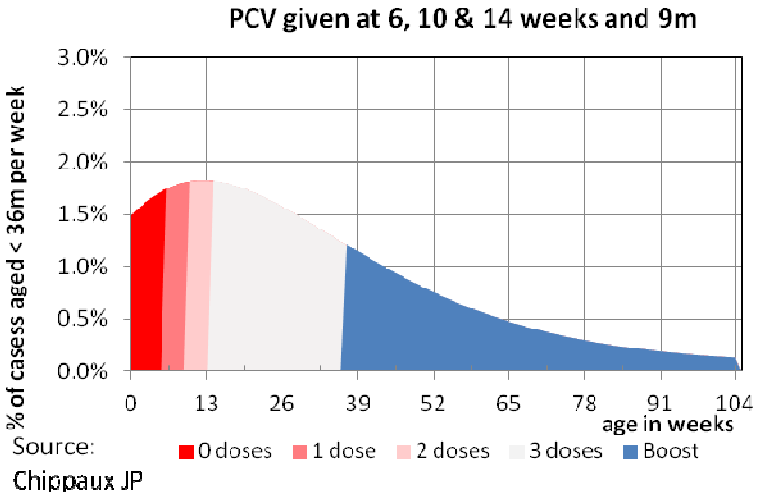
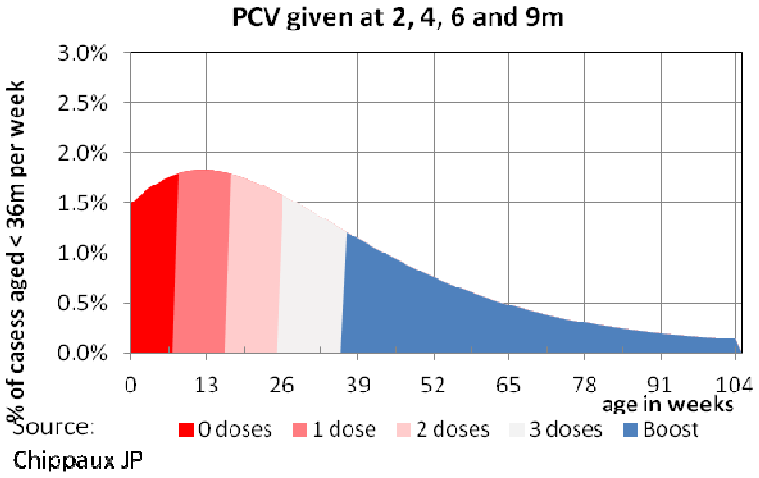


Figure 7 compares what would happen if all infants (100% coverage) were given PCV on time and according to the EPI schedule (6, 10, and 14 weeks of age), or given PCV on time according to a 2, 4, and 6m schedule. In comparison to Figure 6, if children were vaccinated on time with either schedule, there would be less unprotected children. The 'real' curves (Figure 6) involve <100% coverage and are not given on time so the red and pink areas are larger. However, more cases would be left unprotected if given a 2, 4, 6m schedule compared with a 6, 10, 14 week schedule (Figure 7). The bright red area on the left is smaller for the 6 week first dose than the 8 week first dose (as it ends 2 weeks earlier). The biggest difference seen is between a third dose at 10 weeks and a 3rd dose at 6m. The booster is shown as being at 9m for both schedules, and the value of the booster for both schedules is similar (Figure 7).

Figure 7: Pneumococcal meningitis and comparison of estimated number of doses of PCV using 2 schedules: Niamey, Niger





With this combination of age distributions (of cases and of child coverage), a large number of children would have no direct protection at all from the PCV programme, based on current EPI practice in Niger, and a substantial number would have only partial protection, particularly for a 3-dose vaccine. Moreover a PCV dose ("boost"), given with measles vaccine at around 9m may be too late to offer much direct protection from pneumococcal meningitis to the children in the at risk age groups, even in Colombia where the third dose is given at 6m (Figure 8) under an assumption of no herd immunity and negligible impact on carriage in the second year of life. Further examples are shown in Figure 8.

DISCUSSION

To a large extent, IPD and pneumococcal meningitis are diseases of infants. The peak of pneumococcal meningitis occurs earlier than IPD. The proportion of cases that occur in infants <12m is greater for pneumococcal meningitis than IPD. Of all the cases of pneumococcal meningitis in children age 0-59m, about 40% of cases occur in infants aged <6m, and 65% in infants aged <12m. For IPD the figures are 20% and 50% respectively.

A high proportion of IPD in children aged <2m is due to pneumococcal meningitis. There is uncertainty about the proportion of IPD cases occurring in infants <2m, particularly for low income countries. However, based on the small amount of data supplied, about 6% and 8% of the cases of IPD and pneumococcal meningitis are in children aged <2m. However, for the poorest of countries this may be an underestimate. There seem to be 3 possibilities for the age distribution of young infant IPD:

- Gamma shaped: steadily rising and falling in a bell shape skewed to the right. This is the most common pattern already described;
- Negative exponential: highest in the young infant period and then declining more or less gradually. This is seen in some low income contexts and may be more common than it seems, but disguised because of under-ascertainment of neonatal cases, especially in countries with a high proportion of home births. According to the figures from Kenya, using data collected from a hospital within a demographic health surveillance site over the past 12 years, infants <2m account for ~25% of IPD in children <59m. However the number of neonatal IPD cases has been noted to be steadily declining (A Scott, pers. comm.). Examples of this are shown in Figure 9.
- Composite: the 'usual' gamma shape but with a neonatal spike added. England and Wales shows the clearest example of this (data not shown) but there is insufficient data collected in fine enough age categories to display this sufficiently.

Despite the uncertainty about the rates of pneumococcal infection in very young infants, from the data supplied (n=578), between 32-79% of the serotypes occurring in this age group would be covered by PCV10 or PCV13 (Table 18).

The distribution of pneumonia cases tends to peak slightly later than IPD and pneumococcal meningitis. Although our data would vastly underestimate all pneumonia deaths, as many children die at home prior to seeking health care, we have found that for most regions, pneumonia deaths occur more frequently in infants than older children. Community based verbal autopsy studies have found a 2-10 fold increased mortality rate from pneumonia in infants <12m compared with children >12m (1, 2). So despite pneumonia being more frequent in slightly older infants and young children, the greatest mortality is in younger

infants. This is consistent with data from the pre-antibiotic era in Western countries which consistently show that pneumonia case fatality rates are highly age dependent, with infants under 6 months of age showing the highest rates.

There are not enough data to be really clear about inter-regional variation, but it does seem that the proportions of younger children are lower in high income countries. There was considerable variation between and within regions in the way surveillance data was collected which may be due to a variety of factors including, but not limited to, health seeking behaviour, access to care, and surveillance methods used.

Many children will be not benefit from direct protection from pneumococcal disease if the administration of the third dose is delayed and the protection achieved with 2p schedules is inferior to that achieved with 3p schedule. However, any direct benefit of one schedule over another at an individual level may be balanced by the benefits of herd immunity at a population level, particularly if the introduction of the vaccine is coupled with a catch up campaign in young children. There are currently no data on the effectiveness of PCV in a developing country setting, nor is it known whether the herd immunity effects or replacement disease seen post PCV introduction in developed countries, will be similar in a developing country setting.

In terms of the schedule for existing vaccines, especially in low income countries:

- Regardless of the adopted schedule, improving the timeliness of vaccination and the coverage will provide more children with some direct protection at an earlier age;
- An early first dose (e.g. at 6w or earlier) will provide more children with direct protection before the peak age of pneumococcal disease; and
- Delaying the administration of the third dose of PCV might leave a substantial proportion of infants without direct protection against some serotypes if the immunological differences between 3p and 2p have clinical significance, and in the absence of herd immunity.

In terms of research and development the following are recommended:

- Systematic surveillance for very young infant IPD and meningitis in low income settings;
- Evaluation of the indirect effects of PCV schedules in low income settings;
- Further research on how to protect very young infants, including research on the effectiveness of schedules starting at 1m of age; and
- Evaluation of the age distribution of pneumonia deaths using verbal autopsy methods.

TABLES

Table 1: IPD and pneumococcal meningitis literature search[1]

	Search	Results
Published data		
WHO pneumococcal disease burden database		164
pneumoADIP supported sites		32
Unpublished data		
Surveillance data from high income countries	USA:CDC, UK:HPA, Australia, Canada, Denmark, New Zealand, and the Netherlands	7
WHO surveillance sites	netSPEAR, Eastern Mediterranean Region Bacterial Meningitis and Pneumonia Surveillance Network, SIREVA II/II+ (12 individual countries included), ICDDRB, IBIS/SAPNA, IEIP, IVI Vietnam, and Mongolia	19
Phase 3 PCV trials	The Gambia, the Philippines, South Africa, the US Kaiser Permanente studies	4

[1]Studies were included if:

a) The case definition for each disease entity fitted the criteria as described;
b) The duration of the study was >12 months;
c) The study was thought to be generalizable to the whole country in which it was undertaken;
d) <25% of the catchment population received PCV before or during the study;
e) There were a minimum of 30 cases in under-five year olds;
f) For population estimates, the denominator was well described; and
g) An email address of one of the authors could be identified.

123 sources of data fitted the inclusion/exclusion criteria.

Table 2: Pneumonia literature search[1]

	Search	Results
Published data		
WHO ARI database [2]		278
Rudan et al (9) [2]		28
pneumoADIP supported sites		4
AIM database[3]	children or child or infant or infants or babies or baby or boys or boy or girls or girl [Key Word] and pneumonia or pneumococcal or pneumoniae or pneumococcus or respiratory tract [Key Word]	15
IMSEAR database [3]	(1996 OR 1997 OR 1998 OR 1999 OR 2000 OR 2001 OR 2002 OR 2003 oR 2004 OR 2005 OR 2006 OR 2007 OR 2008 OR 2009 OR 2010 OR 2011) (children OR child OR infant OR infants OR babies OR baby OR boys OR boy OR girls OR girl) pneumonia OR pneumococcus OR OR pneumoniae OR pneumococcal	417
EMRO - Virtual Health Sciences Library (VHSL) database [3]	pneumonia or pneumococcal or pneumoniae or pneumococcus or respiratory tract [KeyWords] and children or child or infant or infants or babies or baby or boys or boy or girls or girl [KeyWords]	287
EMBASE-Medline/ LILIACS databases [3]	'pneumococcal infection'/exp OR 'pneumococcal infections' OR 'pneumococci infection' OR pneumococcosis OR 'pneumococcus infection' OR 'Streptococcus pneumoniae infection' OR 'pneumococcal infection' OR 'pneumococci infections' OR pneumococcosis OR 'pneumococcus infections' OR 'Streptococcus pneumoniae infections' OR peripneumonia OR pleurisy OR pneumonia OR pleuritis OR pleuropneumonia OR pleuropneumonitis OR 'pneumonic lung' OR 'pulmonal inflammation' OR ' pulmonary inflammation' OR 'pulmonic inflammation' 'child'/exp OR 'child':ti,ab OR 'children'/exp OR 'children':ti,ab OR newborn*:ti,ab OR 'newborn'/exp OR 'newborn':ti,ab OR 'new born':ti,ab OR 'childhood disease'/exp OR 'childhood disease':ti,ab OR 'baby'/exp OR 'baby':ti,ab OR babies OR 'infant'/exp OR 'infant':ti,ab OR infant*:ti,ab OR childhood*:ti,ab OR toddler*:ti,ab OR kid:ti,ab OR kids:ti,ab OR pediatr*:ti,ab OR paediatr*:ti,ab OR 'child death'/exp OR 'child death':ti,ab OR 'child health'/exp OR 'child health':ti,ab OR 'child	1936

	Search	Results
	care'/exp OR 'child care':ti,ab OR 'childhood mortality'/exp OR 'childhood mortality':ti,ab OR 'child hospitalization'/exp OR 'child hospitalization':ti,ab OR 'pediatric hospital'/exp OR 'pediatric hospital':ti,ab OR child*:ti,ab epidemiology'/exp OR incidence:ab,ti OR prevelance:ab,ti OR mortality:ab,ti OR surveillance:ab,ti Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brazil or Bulgaria or 'Burkina Faso' or 'Burkina Fasso' or 'Upper Volta' or Burundi or Urundi or Cambodia or 'Khmer Republic' or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or 'Cape Verde' or 'Central African Republic' or Chad or Chile or China or Colombia or Comoros or 'Comoro Islands' or Comores or Mayotte or Congo or Zaire or 'Costa Rica' or 'Cote d Ivoire' or 'Ivory Coast' or Croatia or Cuba or Cyprus or Czechoslovakia or 'Czech Republic' or Slovakia or 'Slovak Republic' or Djibouti or 'French Somaliland' or Dominica or 'Dominican Republic' or 'East Timor' or 'East Timur' or 'Timor Leste' or Ecuador or Egypt or 'United Arab Republic' or 'El Salvador' or Eritrea or Estonia or Ethiopia or Fiji or Gabon or 'Gabonese Republic' or Gambia or Gaza or 'Georgia Republic' or 'Georgian Republic' or Ghana or 'Gold Coast' or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or Kyrgyz or Kirghiz or Kirgizstan or 'Lao PDR' or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or 'Marshall Islands' or Mauritania or Mauritius or 'Agalega Islands' or Mexico or Micronesia or 'Middle East' or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or 'Netherlands Antilles' or 'New	

	Search	Results
	Caledonia' or Nicaragua or Niger or Nigeria or 'Mariana Islands' or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or 'Puerto Rico' or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or 'Saint Kitts' or 'St Kitts' or Nevis or 'Saint Lucia' or 'St Lucia' or 'Saint Vincent' or 'St Vincent' or Grenadines or Samoa or 'Samoan Islands' or 'Navigator Island' or 'Navigator Islands' or 'Sao Tome' or 'Saudi Arabia' or Senegal or Serbia or Montenegro or Seychelles or 'Sierra Leone' or Slovenia or 'Sri Lanka' or Ceylon or 'Solomon Islands' or Somalia or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or Togolese or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or 'Soviet Union' or 'Union of Soviet Socialist Republics' or Uzbekistan or Uzbek or Vanuatu or 'New Hebrides' or Venezuela or Vietnam or 'Viet Nam' or 'West Bank' or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia OR ((developing or 'less developed' or 'under developed' or underdeveloped or 'middle income' or 'low income' or 'lower income' or underserved or 'under served' or deprived or poor*) and (countr* or nation* or population* or world)):ti,ab OR ((transitional OR developing or 'less developed' or 'lesser developed' or 'under developed' OR underdeveloped or middle income or 'lower income' or 'lower income') AND (economy or economies)):ti,ab OR (low* NEAR/5 (gdp OR gnp OR 'gross domestic' OR 'gross national')):ab,ti OR (low NEAR/3 middle):ab,ti OR (lmic OR lmics OR 'third world' OR 'lami countries' OR 'lami country'):ti,ab OR ' transitional country':ti,ab OR 'transitional countries':ti,ab Step 5 'case report'/exp (Step 1 AND Step 2 AND Step 3 AND Step 4) NOT Step 5 Limit to humans and 1996-2011	
WPRIM database[3]	MeSH:child or Keywords:children OR child OR infant OR infants OR babies OR baby OR boys OR boy OR girls OR girl) and (MeSH:pneumonia or MeSH: pneumonococcal infections or Keywords:pneumonia OR pneumococcal	132
ClinicalTrialsCochrane/ database [3]	pneumonia OR pneumococcus OR OR pneumoniae OR pneumococcal	305

	Search	Results
	(children OR child OR infant OR infants OR babies OR baby OR boys OR boy OR girls OR girl) Morality or surveillance or incidence or prevalence (Step 1 and Step 2 and Step 3) limited to 1996-2011	
Unpublished data		
Phase 3 PCV trials	The Gambia, the Philippines, South Africa, the US Kaiser Permanente studies	4

[1]Studies were included if:

a) The case definition for each disease entity fitted the criteria as described;
b) The cases presented passively to a health facility and were admitted to hospital;
c) The duration of the study was >12 months;
d) The study was thought to be generalisable to the whole country in which it was undertaken;
e) <25% of the catchment population received PCV before or during the study;
f) There were a minimum of 30 cases in under-five year olds;
g) For population estimates, the denominator was well described; and
h) An email address of one of the authors could be identified.

[2]Studies were included if published from 1990 onwards. Case definitions and place of diagnosis were screened by FR. Cases not fitting the case definition or identified by passive surveillance (home) were excluded, along with those studies published prior to 1990. The full text of 39 screened in articles were reviewed by FR and excluded if they did not meet the inclusion/exclusion criteria listed above. 9 sources of data fitted the inclusion/exclusion criteria.

[3]After removing duplicates there were 2561 citations for review. The titles and abstracts were initially screened by FR, and 86 articles were screened in and the full text was independently reviewed by FR and BT. 21 sources of data fitted the inclusion/exclusion criteria.

Table 3: Results of attempts to contact informants

	IPD and Pneumococcal meningitis		Pneumonia	
Outcome	**n of respondents**	**%**	**n of respondents**	**%**
Contact details incomplete/incorrect	13	11%	0	0%
Contact details correct, no response	33	27%	9	30%
Contact made, unable to help	11	9%	3	10%
Contact made, redirected	6	5%	4	13%
Agreed to participate but no data sent	14	11%	1	3%
Data supplied[1]	46	37%	13	44%
	123	**100%**	**30**	**100%**

[1]There were 14 sites/studies which reported the same data and same contact.

Table 4: Information about included IPD studies

Region	Country	Site	Source	Ref	Year started	Duration in months	n of cases[1] deaths[2]	Age distribution of cases and deaths						
								2-3m	4-5m	6-11m	12-23m	24-35m	36-47m	48-59m
AFR	Gambia	Basse, hospital surveillance	Mackenzie G		2008	15.8	42[1]	2%	5%	24%	33%	14%	10%	12%
	Kenya	Kilifi, hospital surveillance	Scott A Moisi J		1998	156	626[1]	6%	7%	24%	29%	14%	11%	9%
							141[2]	8%	11%	27%	20%	15%	11%	8%
	Mozambique	Manhica District Hospital	Sigauque B		2001	120	598[1]	6%	7%	28%	34%	14%	6%	5%
							59[2]	10%	3%	29%	31%	21%	3%	3%
	South Africa	National enhanced surveillance	Von Gottberg A		2005	48	1570[1]	11%	16%	28%	23%	11%	7%	4%
							243[2]	17%	23%	33%	14%	7%	4%	2%
AMR	Argentina	Multicentre laboratory and hospital surveillance	Regueira M		2000	156	1528[1]	5%	7%	21%	28%	19%	11%	9%
	Brazil	Multicentre laboratory and hospital surveillance	Brandileone C		2000	72	1680[1]	10%	11%	25%	26%	17%	7%	4%
	Canada	Quebec	Deceuninck G		2004	12	232[1]	4%	4%	23%	39%	18%	6%	6%
	Chile	Hospital de ninos Roberto del Rio	Lagos R		1994	186	1898[1]	8%	7%	28%	31%	12%	8%	6%
							105[2]	18%	17%	28%	20%	9%	7%	1%
	Colombia	Bogota, hospital surveillance	Agudelo C	(10)	1994	132	1046[1]	12%	13%	26%	20%	12%	10%	7%
	Dominican Republic	Robert Reid Cabral Children's Hospital	Sánchez J		2000	132	505[1]	10%	9%	24%	31%	14%	7%	5%
	USA	ABCs	Moore M		1998	24	2202[1]	2%	5%	27%	44%	13%	6%	3%
							13[2]	8%	8%	16%	38%	15%	15%	0%

Region	Country	Site	Source	Ref	Year started	Duration in months	n of cases[1] deaths[2]	Age distribution of cases and deaths						
								2-3m	4-5m	6-11m	12-23m	24-35m	36-47m	48-59m
EUR	The Netherlands	Reference laboratory	van der Ende A		2001	60	699[1]	9%	12%	30%	25%	10%	8%	6%
	Spain	Gipuzkoa, hospital surveillance	Iglesias S	(11)	1981	240	77[1]	5%	1%	42%	30%	14%	5%	3%
	UK[3]	Hospital episode statistics	McIntosh	(12)	1999	12			**3-5m**	**6-11m**	**12-23m**	**24-35m**	**36-47m**	**48-59m**
							3247[1]	NA	9%	19%	28%	18%	12%	14%
SEAR	Bangladesh	Dhaka Shishu Hospital	Saha S		2004	37	275[1]	19%	21%	32%	15%	6%	3%	2%
							29[2]	41%	14%	28%	17%	0%	0%	0%
		IBIS and SAPNA, hospital surveillance	Thomas K	(13)	1993	48	302[1]	10%	12%	24%	19%	13%	12%	10%
	Nepal	Patan Hospital	Murdoch D	(14)	2005	57	50[1]	10%	18%	22%	14%	8%	12%	16%
	Thailand	IEIP, rural hospital surveillance	Baggett H		2005	58	37[1]	0%	11%	30%	38%	19%	0%	2%
							3[2]	0%	67%	0%	33%	0%	0%	0%
WPR	Australia	Metropolitan NSW laboratory surveillance	McIntyre P		1994	72	493[1]	2%	3%	24%	38%	21%	8%	4%
	Australia	Northern Territory laboratory surveillance	Krause V		1994	60	165[1]	1%	4%	28%	42%	16%	5%	4%
							3[2]	0%	67%	33%	0%	0%	0%	0%
	Australia	Tasmania, laboratory surveillance	Christie D	(15)	1994	84	49[1]	0%	2%	28%	41%	21%	6%	2%
							1[2]	0%	0%	100%	0%	0%	0%	0%
	Fiji	Central division, laboratory surveillance	Russell F	(16)	2004	40	28[1]	14%	25%	25%	11%	17%	4%	4%
							3[2]	0%	33%	33%	33%	0%	0%	0%
						TOTAL	17349[1] 661[2]							

[3]Included in the modelling but excluded from other analyses due to different age cohorts reported

Table 5: Information about included pneumococcal meningitis studies

Region	Country	Site	Source	Ref	Year started	Duration in months	n of cases[1] deaths[2]	Age distribution of cases and deaths						
								2-3m	4-5m	6-11m	12-23m	24-35m	36-47m	48-59m
AFR	Burkina Faso	Population and hospital surveillance	Gessner B	(17)	2002	58	133[1]	27%	11%	24%	14%	8%	6%	10%
							67[2]	34%	7%	24%	16%	5%	5%	9%
	Kenya	Kilifi, hospital surveillance	Scott A Moisi J		1998	156	154[1]	12%	10%	29%	24%	8%	10%	7%
							47[2]	13%	11%	32%	19%	6%	11%	8%
	Mozambique	Manhica Distric Hospital	Sigauque B		2005	72	37[1]	11%	16%	27%	24%	8%	8%	6%
							9[2]	22%	22%	34%	11%	11%	0%	0%
	Niger	Niamey, laboratory surveillance	Campagne G	(18)	1981	120	437[1]	16%	18%	34%	20%	8%	2%	2%
	South Africa	National enhanced surveillance	Von Gottberg A		2005	48	450[1]	17%	21%	34%	13%	8%	4%	3%
							124[2]	17%	23%	39%	10%	6%	4%	1%
	Togo	Hospital surveillance	Gessner B	(17)	2003	74	78[1]	11%	8%	32%	22%	9%	10%	8%
							21[2]	5%	9%	29%	24%	19%	14%	0%
	Uganda	Kampala district, hospita surveillance	Kisakye A	(19)	2001	60	294[1]	15%	15%	23%	21%	9%	7%	10%
							54[2]	14%	4%	22%	35%	13%	6%	6%
AMR	Argentina	Multicentre laboratory and hospital surveillance	Regueira M		2000	156	447[1]	22%	15%	27%	18%	9%	5%	4%
	Brazil	Hospital de Clinicas	Mantese O	(20)	1999	132	31[1]	29%	16%	23%	26%	0%	3%	3%
							10[2]	20%	10%	30%	40%	0%	0%	0%
	Brazil	Multicentre laboratory and hospital surveillance	Brandileone C		2000	72	1026[1]	15%	16%	29%	19%	9%	5%	7%
	Brazil	Hospital Couto	Menezes A		2000	96	142[1]	30%	13%	21%	19%	6%	4%	7%

Region	Country	Site	Source	Ref	Year started	Duration in months	n of cases[1] deaths[2]	Age distribution of cases and deaths						
								2-3m	4-5m	6-11m	12-23m	24-35m	36-47m	48-59m
		Maia					57[2]	33%	11%	28%	12%	7%	4%	5%
	Chile	Hospital de ninos Roberto del Rio	Lagos R		1994	186	310[1]	19%	16%	32%	22%	5%	2%	4%
							44[2]	11%	20%	32%	23%	7%	5%	2%
	Colombia	Bogota, hospita surveillance	Agudelo C		1994	132	490[1]	17%	20%	30%	12%	8%	7%	6%
	Dominican Republic	Robert Reid Cabral Children's Hospital	Sánchez J		2000	132	197[1]	18%	17%	27%	19%	9%	6%	4%
	USA	ABCs	Moore M		1998	24	99[1]	13%	16%	32%	26%	6%	4%	3%
							4[2]	0%	25%	0%	25%	0%	50%	0%
	USA	Memphis, laboratory surveillance	Buckingham S	(21)	1991	108	76[1]	15%	9%	33%	32%	7%	3%	1%
							6[2]	0%	33%	50%	17%	0%	0%	0%
EUR	The Netherlands	Reference laboratory	van der Ende A		2001	60	351[1]	9%	17%	38%	20%	6%	6%	4%
	UK[3]	Hospital Episode Statistics	McIntosh E	(12)	1999	12	281[1]		**3-5m**	**6-11m**	**12-23m**	**24-35m**	**36-47m**	**48-59m**
								NA	22%	38%	19%	12%	4%	5%
SEAR	Bangladesh	Dhaka Shishu Hospital	Saha S		2004	37	222[1]	22%	23%	35%	10%	5%	2%	1%
							25[2]	40%	16%	32%	12%	0%	0%	0%
		IBIS and SAPNA	Thomas K	(13)	1993	48	124[1]	16%	21%	25%	10%	10%	7%	11%
WPR	Australia	Metropolitan NSW, laboratory surveillance	McIntyre P		1994	72	107[1]	5%	16%	29%	31%	9%	6%	4%
						TOTAL	5486[1] 468[2]							

[3]Included in the modelling but excluded from other analyses due to different age cohorts reported

Table 6: Information about included WHO radiographic[1] and clinical pneumonia[2] hospital based surveillance studies

Region	Country	Site	Source	Ref	Year started	Duration in months	n of cases (deaths)	Age distribution of cases (and deaths)						
								2-3m	4-5m	6-11m	12-23m	24-35m	36-47m	48-59m
AFR	Central African Republic	Bangui Hospital	Pepin J	(22)	1996	12	138 (15)[1]	15% (30%)	11% (7%)	33% (47%)	20% (7%)	11% (7%)	7% (7%)	3% (0%)
							333 (47)[2]	13% (36%)	11% (4%)	27% (40%)	29% (11%)	10% (4%)	6% (2%)	3% (2%)
	Gambia	Basse, hospital surveillance	Mackenzie G		2008	15.8	1711 (16)[2]	9% (25%)	10% (12%)	24% (19%)	34% (25%)	13% (13%)	7% (6%)	3% (0%)
	Malawi	Queen Elizabeth Central Hospital	Graham S	(23)	2005	17	69 (6)[1]	7% (50%)	13% (0%)	33% (33%)	25% (17%)	12% (0%)	7% (0%)	3% (0%)
							184 (15)[2]	17% (40%)	13% (20%)	33% (33%)	23% (7%)	8% (0%)	5% (0%)	1% (0%)
	Mozambique[3]	Manhica District Hospital	Sigauque B	(24)	2005	12		**2-3m**	**4-5m**	**6-11m**	**12-23m**			
							59 (6)[1]	10% (10%)	10% (10%)	31% (0%)	49% (80%)	NA	NA	NA
							139 (10)[2]	12% (10%)	10% (20%)	27% (70%)	51% (0%)	NA	NA	NA
AMR	Uruguay	Multicentre, Hospital surveillance	Hortal M	(25)	2001	36	1708 (6)[1]	7% (33%)	7% (0%)	21% (33%)	31% (0%)	16% (17%)	10% (0%)	8% (17%)
EMR	Yemen	Al-Sabeen Hospital for Women and Children	Banajeh S	(26)	1995	12	153 (34)[2]	25% (29%)	15% (12%)	35% (35%)	17% (15%)	6% (6%)	2% (3%)	0% (0%)
SEAR	Bangladesh	Multicentre, hospital surveillance	Naheed A	(27)	2004	36	918 (34)[1]	27% (50%)	17% (14%)	31% (24%)	15% (6%)	6% (0%)	3% (3%)	1% (3%)
							4155 (150)[2]	24% (39%)	17% (15%)	29% (28%)	19% (9%)	7% (5%)	3% (2%)	1% (2%)
		IBIS and SAPNA, hospital surveillance	Thomas K	(13)	1993	48	8180[1]	15%	11%	28%	22%	10%	8%	6%

Region	Country	Site	Source	Ref	Year started	Duration in months	n of cases (deaths)	Age distribution of cases (and deaths)						
								2-3m	4-5m	6-11m	12-23m	24-35m	36-47m	48-59m
	Indonesia[3]	Lombok, hospita surveillance	Gessner B		1999	48		**2-3m**	**4-5m**	**6-11m**	**12-23m**			
							5042 (476)[2]	23% (52%)	19% (23%)	36% (18%)	22% (17%)	NA	NA	NA
WPR	Fiji	Central division	Russell F	(28)	2001	24	81 (6)[1]	6% (25%)	16% (50%)	31% (25%)	36% (0%)	6% (0%)	3% (0%)	2% (0%)
							352 (10)[2]	10% (13%)	14% (37%)	36% (25%)	27% (25%)	6% (0%)	5% (0%)	2% (0%)
	Vietnam	Nha Trang, hospital surveillance	Yoshida L		2007	49	137[1]	4%	4%	20%	45%	19%	4%	4%
							478 (2)[2]	9% (0%)	7% (0%)	16% (0%)	45% (50%)	15% (50%)	5% (0%)	3% (0%)
	Vietnam[3]	Nha Trang, hospital surveillance	Dang D	(29)	2005	16		**1-3m**	**4-6m**	**7-11m**	**12-23m**	**24-35m**	**36-47m**	**48-59m**
							638[1]	16%	12%	18%	36%	14%	3%	7%
							729[2]	17%	12%	17%	36%	13%	4%	1%
						TOTAL	13639 (73)[1] 13276 (760)[2]							

[3]Included in the modelling but excluded from other analyses due to different age cohorts reported

Table 7: Information about included WHO radiographic[1] and clinical pneumonia[2] clinical trial studies[3]

Region	Country	Site	Source	Ref	Year started	Duration in months	n of cases	Cases per 1000 child years follow up						
AFR	South Africa	Soweto	Klugman K Madhi S	(30)	1998	46		**2-3m**	**4-5m**	**6-11m**	**12-23m**	**24-35m**	**36-47m**	**48-59m**
							223[1]	103	117	64	43	13	1	0
							686[2]	500	269	208	109	35	4	0
SEAR	Indonesia	Lombok	Gessner B	(31)	1999	48		**2-3m**	**4-5m**	**6-11m**	**12-23m**			
							691[1]	11	17	13	4	NA	NA	NA
WPR	The Philippines	Bohol	Lucero M	(32)	2000	53	141[1]	17	21	18	9	NA	NA	NA
							1080[2]	174	218	124	61	NA	NA	NA

[3]Included in the modelling but excluded from other analyses due to the differences in study design and reporting of results

Table 10: Comparisons[1] of the proportions of IPD cases that are pneumococcal meningitis in children aged 2-59m, by country and age

Region	Country	4-5m	6-11m	2-59m
AFR		**p<0.001**	**p<0.001**	**p<0.001**
	Kenya	36%	30%	25%
	Mozambique	15%	6%	6%
	South Africa: enhanced surveillance	39%	35%	29%
	South Africa: laboratory and hospital surveillance	18%	11%	10%
AMR		**p<0.001**	**p<0.001**	**p<0.001**
	Argentina	38%	27%	23%
	Brazil	88%	71%	61%
	Chile	36%	18%	16%
	Dominican Republic	73%	44%	39%
	USA	16%	5%	5%
EUR	The Netherlands	73%	63%	50%
SEAR		**p=0.083**	**p<0.001**	**p<0.001**
	Bangladesh	90%	87%	81%
	IBIS and SAPNA	76%	45%	42%

[1] P-values indicate the differences in proportions of cases occurring in the age bracket shown using Chi-square test

Table 11: Comparisons[1] of the IPD case fatality ratio in children aged 2-59m, by country and age

Region	Country	6-11m	12-23m	2-59m
AFR		**p=0.001**	**p=0.038**	**p<0.001**
	Kenya	26%	16%	23%
	Mozambique	10%	9%	10%
	South Africa: enhanced surveillance	19%	10%	15%
AMR		**p<0.001[2]**	**P<0.001**	**p<0.001**
	Chile	5%	4%	6%
	USA	0.3%	0.5%	0.6%
SEAR		**p>0.999[2]**	**p>0.999[2]**	**p=0.780[2]**
	Bangladesh	9%	12%	11%
	Thailand	0%	7%	8%
WPR		**p=0.216[2]**		**p=0.059[2]**
	Australia, Northern Territory	2%	0	2%
	Australia, Tasmania	8%	0	2%
	Fiji	14%	0	11%

[1]P-values indicate the differences in proportions of cases occurring in the age bracket shown using Chi-square or Fisher's exact test

[2]Fisher's exact p-value reported due to small numbers

Table 12: Comparisons[1] of the pneumococcal meningitis case fatality ratio in children aged 2-59m, by country and age

Region	Country	4-5m	6-11m	2-59m
AFR		**p=0.005[2]**	**p=0.029[2]**	**p<0.001**
	Burkina Faso	33%	61%	50%
	Kenya	31%	24%	31%
	Mozambique	33%	11%	24%
	South Africa: enhanced surveillance	31%	20%	28%
	Togo	33%	29%	27%
	Uganda	5%	31%	18%
AMR		**p<0.284[2]**	**p=0.006[2]**	**p<0.001[2]**
	Brazil, Hospital de Clinicas	20%	50%	32%
	Brazil, Hospital Couto Maia	33%	26%	40%
	Chile	18%	15%	14%
	USA, Memphis	29%	4%	8%
	USA, ABCs	6%	4%	4%
SEAR	Bangladesh	8%	13%	11%

[1]P-values indicate the differences in proportions of cases occurring in the age bracket shown using Chi-square or Fisher's exact test

[2]Fisher's exact p-value reported due to small numbers

Table 13: Comparisons[1] of the proportion of WHO clinical pneumonia cases that have WHO radiographic pneumonia in children aged 2-59m, by country and age

Region	Country	6-11m	12-23m	2-59m
AFR		**p=0.168**	**p=0.150**	**p=0.375**
	Central African Republic	42%	28%	37%
	Malawi	38%	40%	38%
	South Africa	31%	39%	33%
SEAR	Bangladesh	23%	18%	22%
WPR		**p=0.008**	**p=0.911**	**p=0.025**
	Fiji	19%	28%	21%
	Vietnam	36%	29%	29%

[1]P-values indicate the differences in proportions of cases occurring in the age bracket shown using Chi-square test

Table 14: Comparison of the proportion of IPD due to serotypes 6B and 23F in children aged 2-11m

Region	Country	Total n serotyped	% 6B 2-11m	% 23F 2-11m
AFR			**p=0.001[1]**	**p=0.865[1]**
	Gambia	12	0%	8%
	Kenya	232	9%	11%
	Mozambique	158	4%	8%
	South Africa: enhanced surveillance	701	15%	11%
AMR			**p=0.001**	**P=0.435[1]**
	Argentina	790	6%	5%
	Brazil	768	13%	5%
	Canada	48	21%	4%
	Chile	649	10%	5%
	Dominican Republic	207	13%	6%
	USA	643	11%	7%
EUR			**p=0.527**	**p=0.037**
	Spain	38	16%	13%
	The Netherlands	355	15%	4%
SEAR			**p=0.707[1]**	**p=0.631[1]**
	Bangladesh	153	2%	3%
	Nepal	19	0%	0%
WPR			**p=0.576[1]**	**p=0.337[1]**
	Australia	52	4%	8%
	Fiji	17	0%	0%

[1]Fisher's exact p-value reported due to small numbers

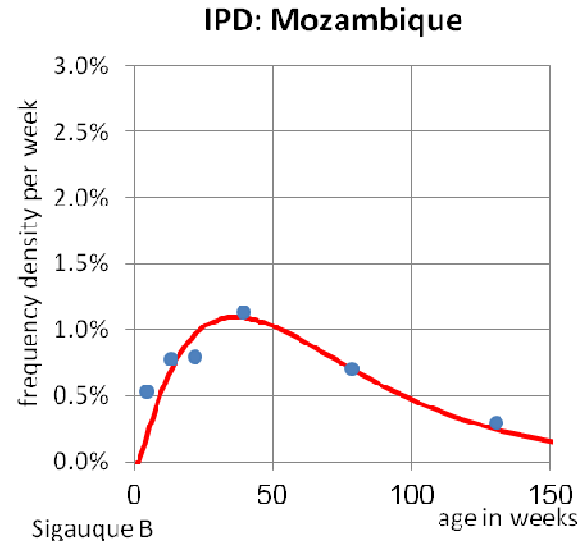
Table 18: Coverage of IPD by PCV10 and PCV13 in infants aged 0-1 month old[1]

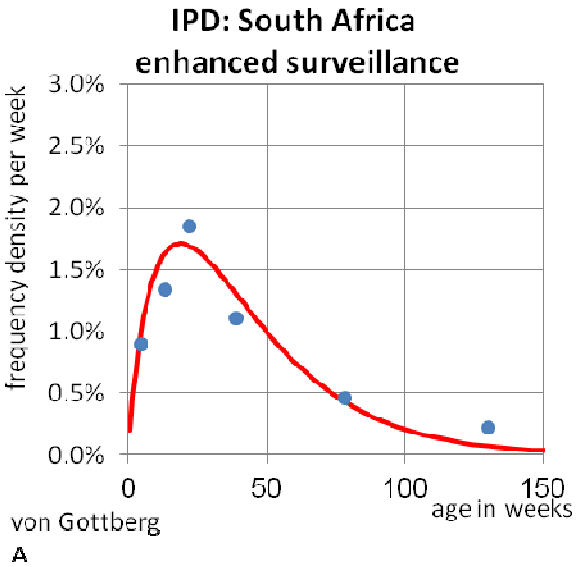
Region	Country	n	PCV10	PCV13
AFR	Kenya	68	69%	78%
	South Africa	157	43%	49%
AMR	Argentina	114	62%	74%
	Brazil	23	61%	70%
	Chile	113	59%	69%
	USA, ABC	38	68%	79%
EUR	The Netherlands	37	49%	57%
SEAR	Bangladesh	28	32%	39%

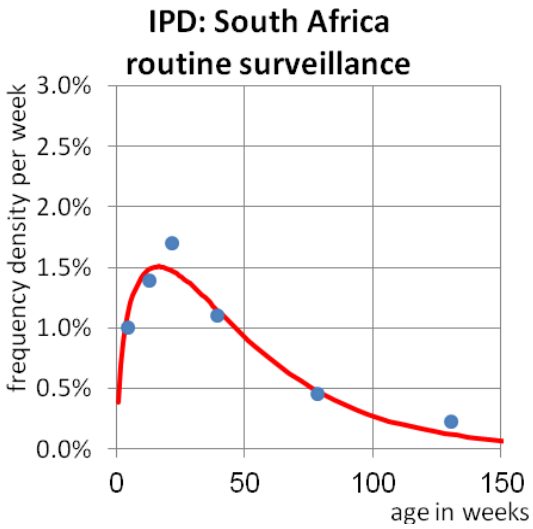
[1]Only countries reporting >20 cases in this age group were included

FIGURES

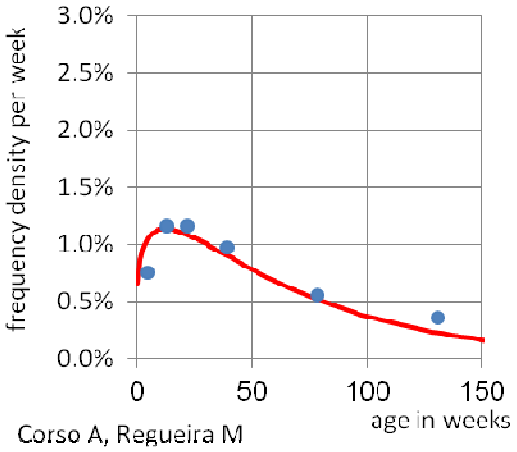
Figure 3: Age distributions for IPD in children aged 0-36m, by country





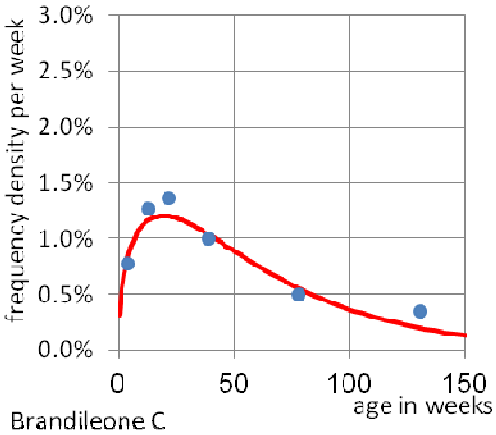


IPD: Argentina



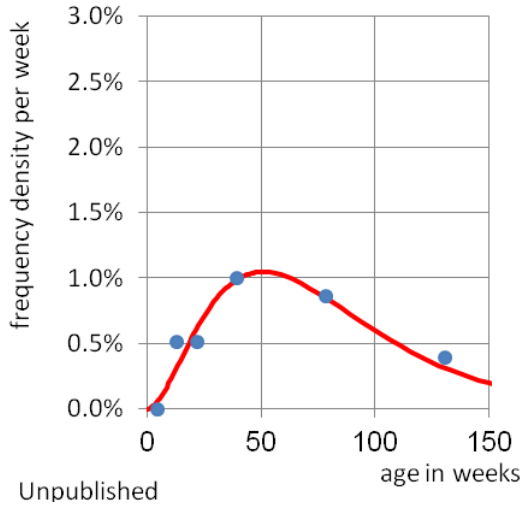
Corso A, Regueira M

IPD: Brazil



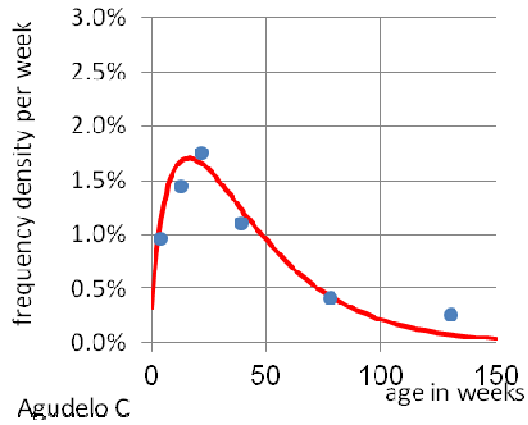
Brandileone C

IPD: Canada



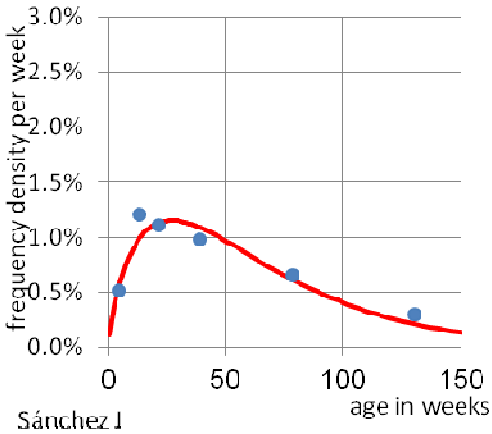
Unpublished

IPD: Colombia

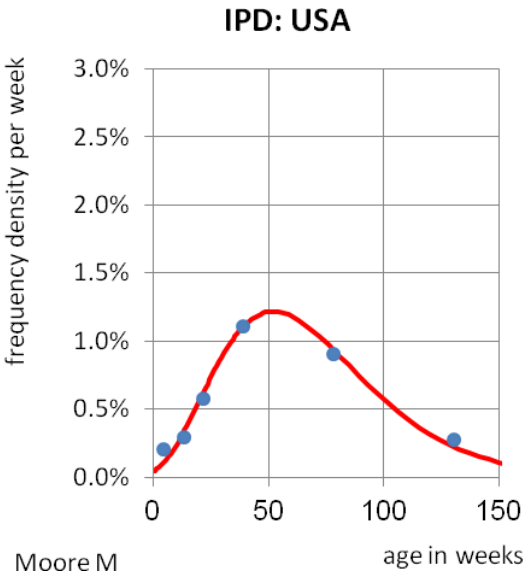


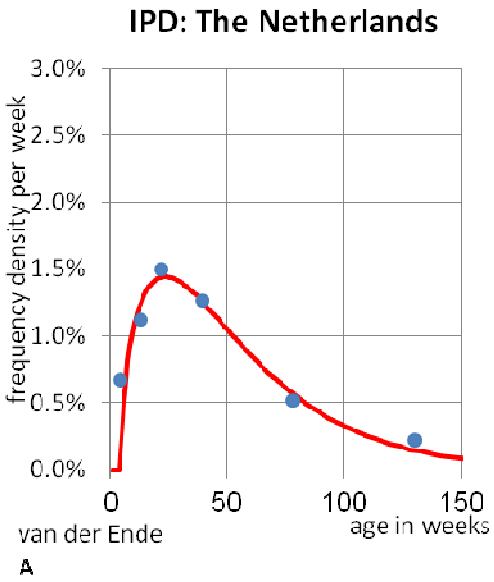
Agudelo C

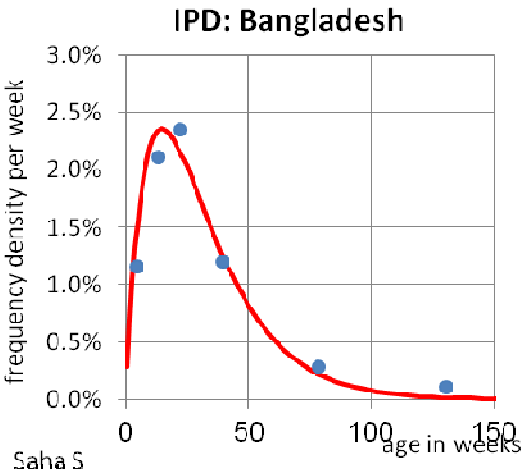
IPD: Dominican Republic

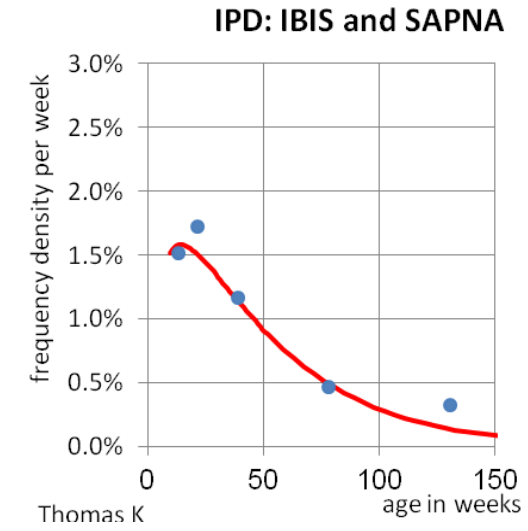


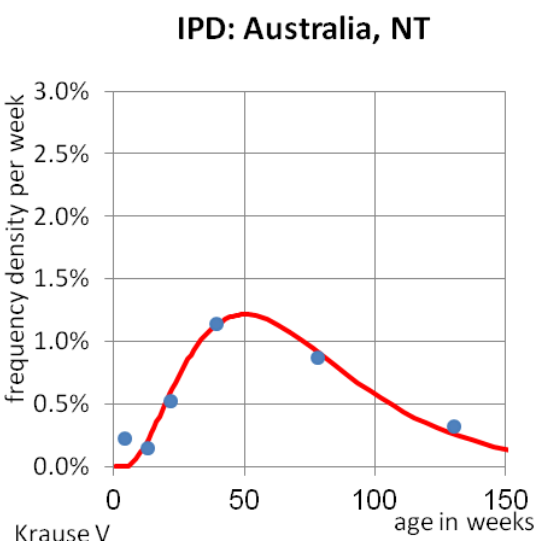
Sánchez J


IPD: USA
frequency density per week
3.0%
2.5%
2.0%
1.5%
1.0%
0.5%
0.0%
0
50
100
150
age in weeks
Moore M


IPD: The Netherlands
frequency density per week
3.0%
2.5%
2.0%
1.5%
1.0%
0.5%
0.0%
0
50
100
150
age in weeks
van der Ende
A


IPD: Bangladesh
frequency density per week
3.0%
2.5%
2.0%
1.5%
1.0%
0.5%
0.0%
0
50
100
150
age in weeks
Saha S


IPD: IBIS and SAPNA
frequency density per week
3.0%
2.5%
2.0%
1.5%
1.0%
0.5%
0.0%
0
50
100
150
age in weeks
Thomas K


IPD: Australia, NT
frequency density per week
3.0%
2.5%
2.0%
1.5%
1.0%
0.5%
0.0%
0
50
100
150
age in weeks
Krause V

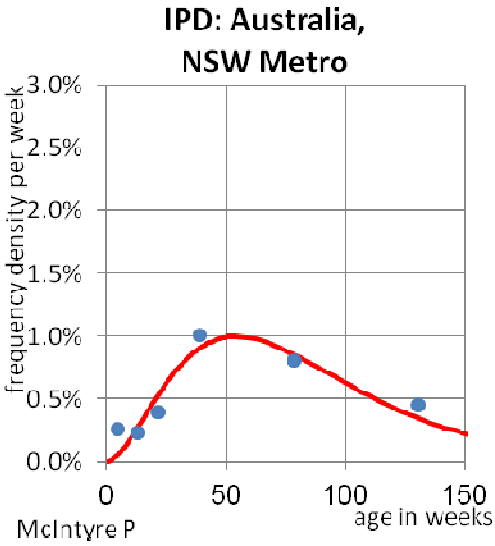
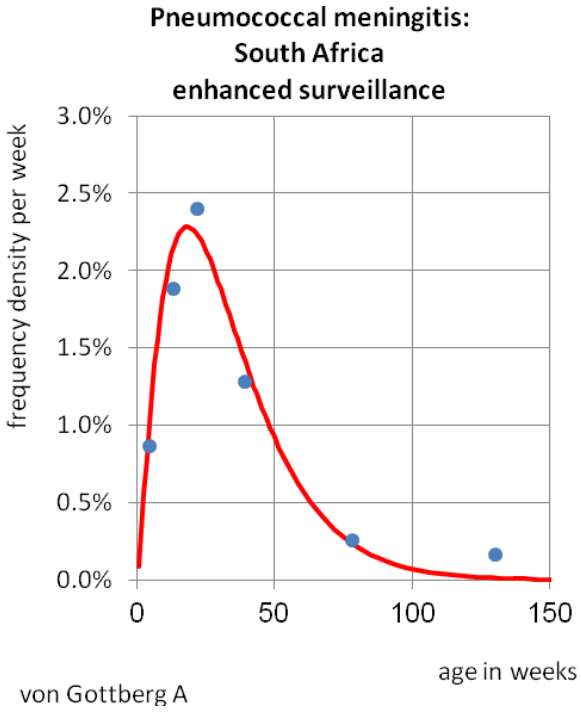
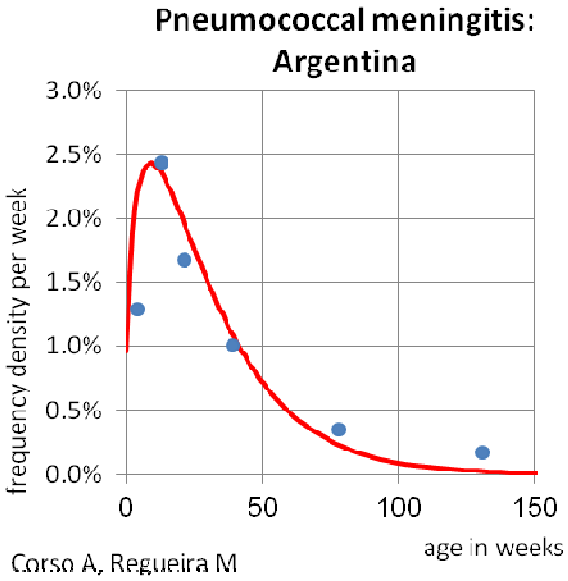

IPD: Australia, NSW Metro
frequency density per week
3.0%
2.5%
2.0%
1.5%
1.0%
0.5%
0.0%
0
50
100
150
age in weeks
McIntyre P

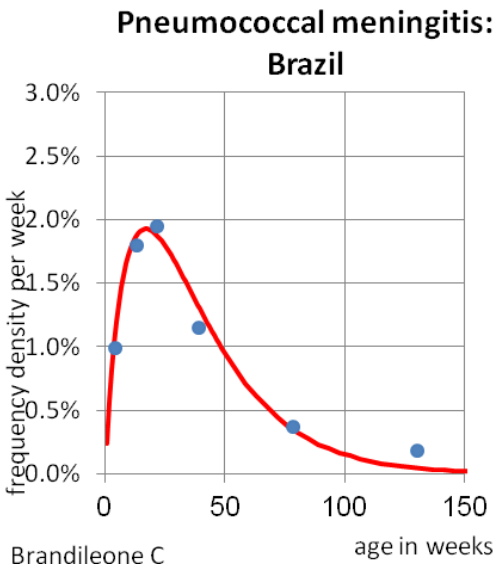
Figure 4: Age distributions for pneumococcal meningitis in children aged 0-36m, by country



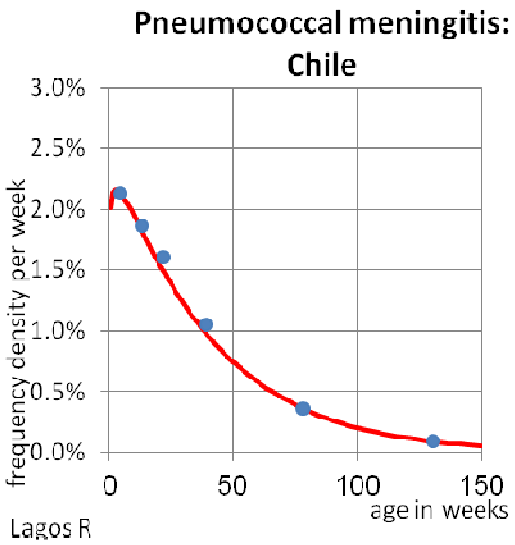
von Gottberg A



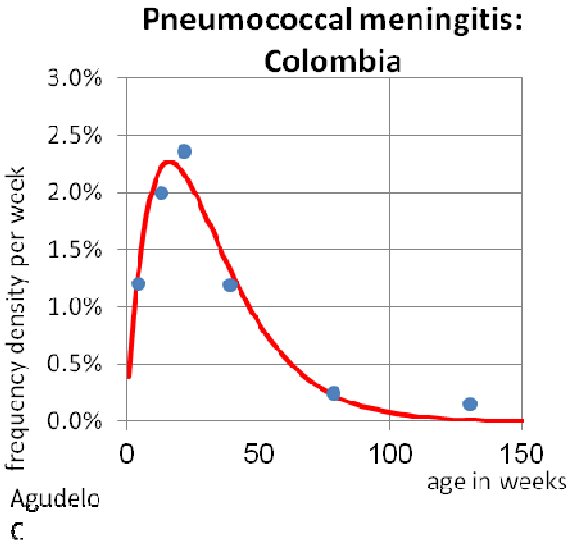
Corso A, Regueira M



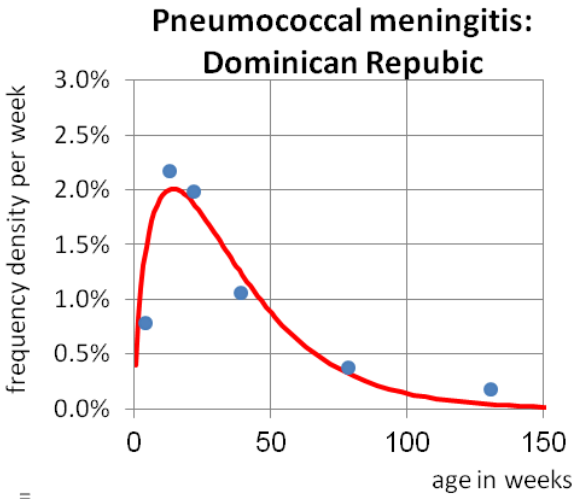
Brandileone C

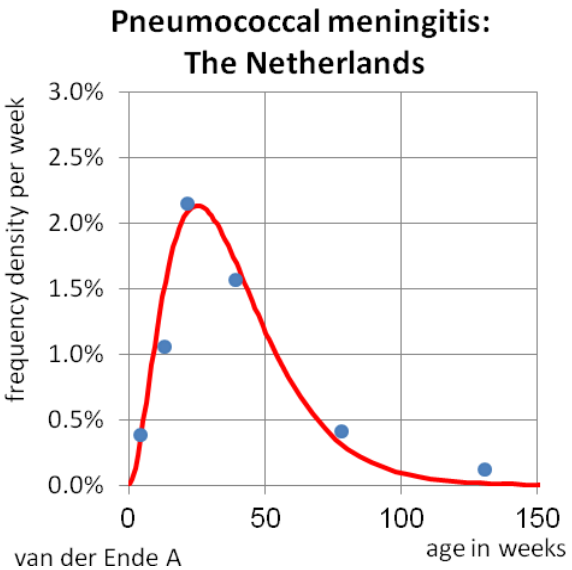


Lagos R

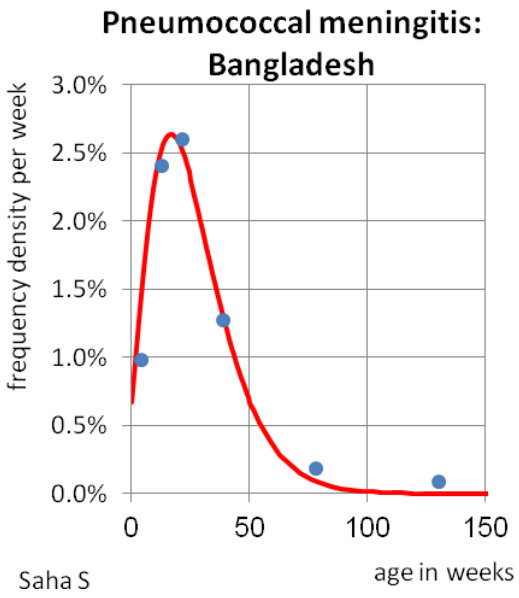


Agudelo C





van der Ende A


Pneumococcal meningitis: Bangladesh
frequency density per week
3.0%
2.5%
2.0%
1.5%
1.0%
0.5%
0.0%
0
50
100
150
age in weeks
Saha S

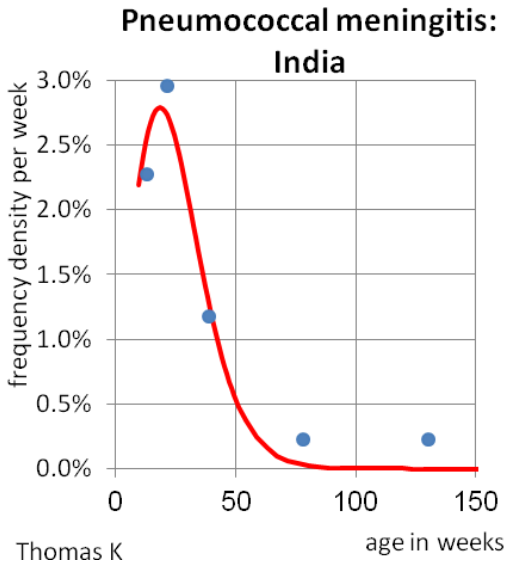
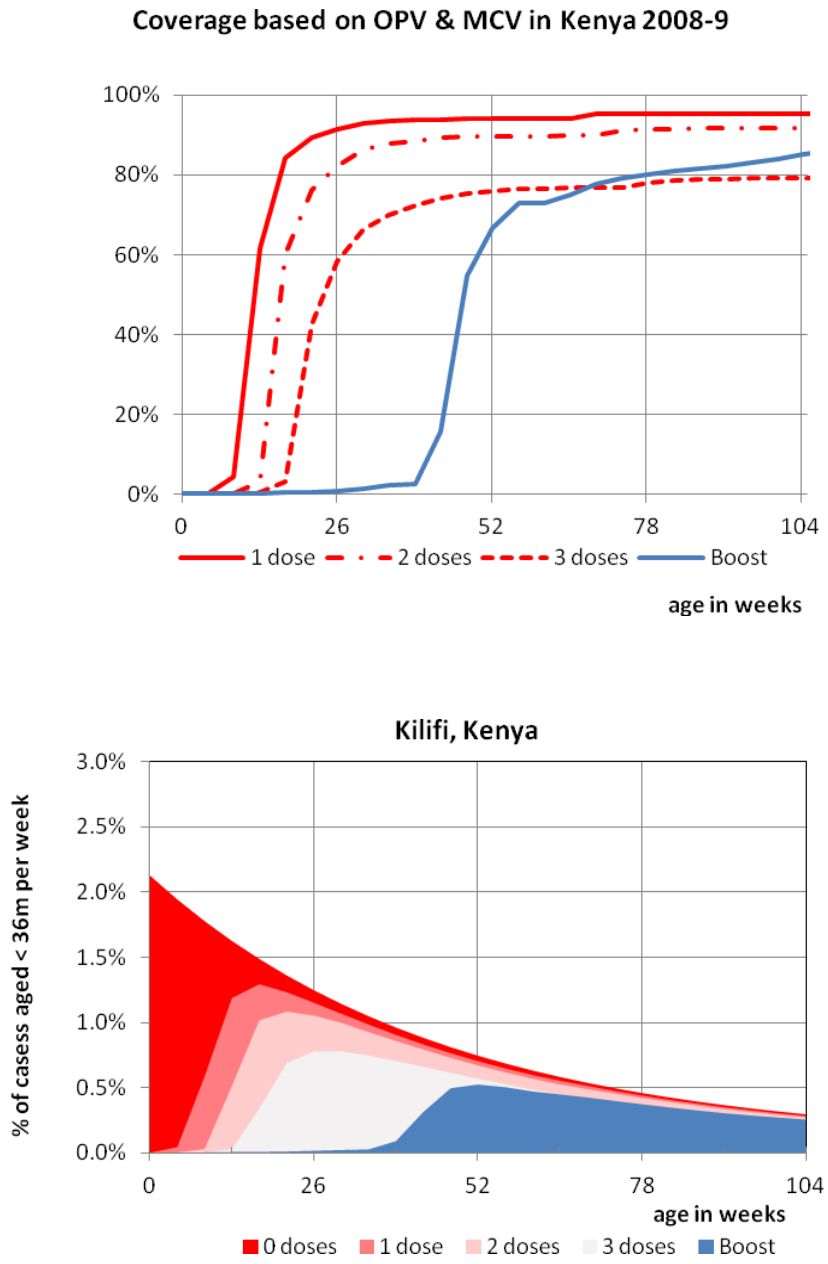
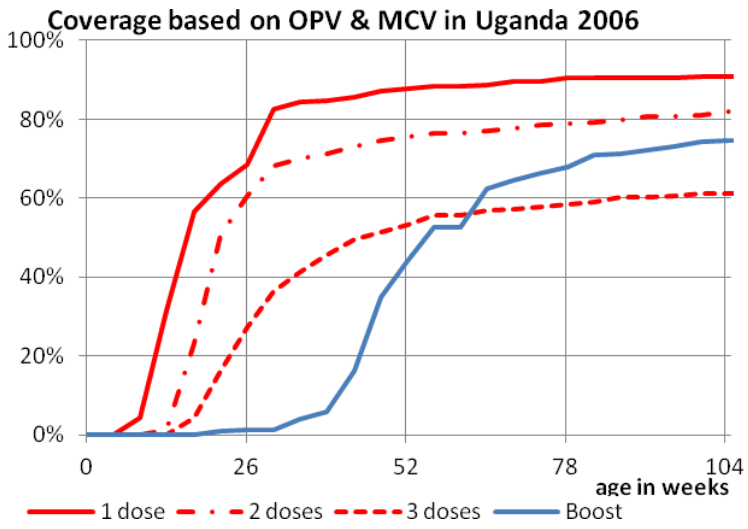
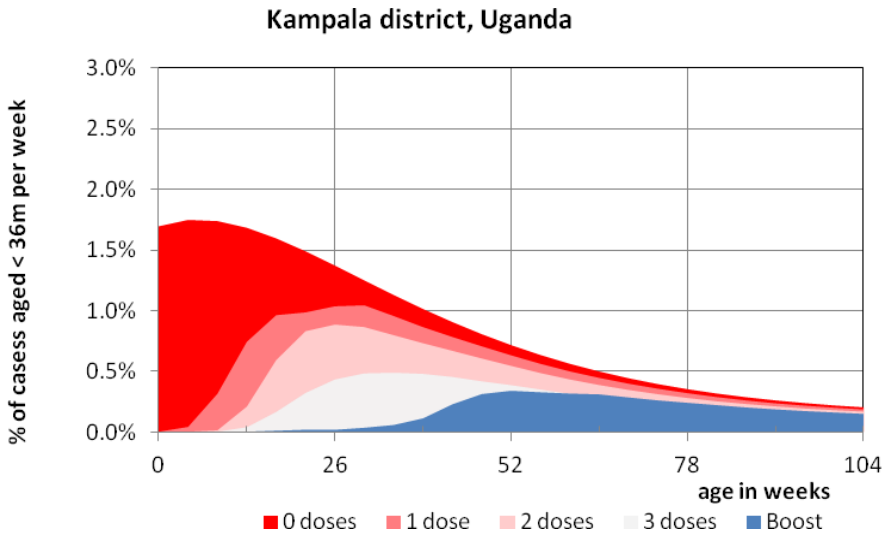
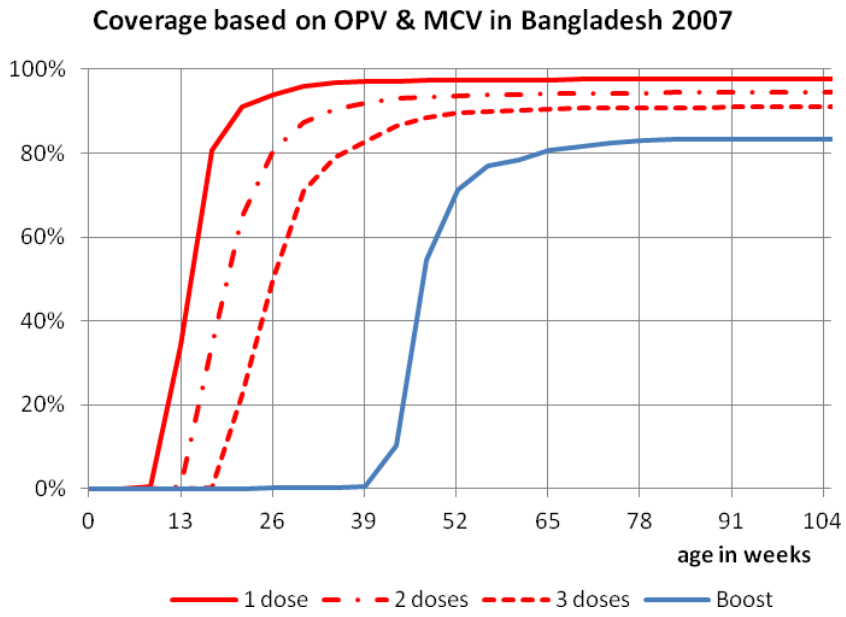

Pneumococcal meningitis: India
frequency density per week
3.0%
2.5%
2.0%
1.5%
1.0%
0.5%
0.0%
0
50
100
150
age in weeks
Thomas K

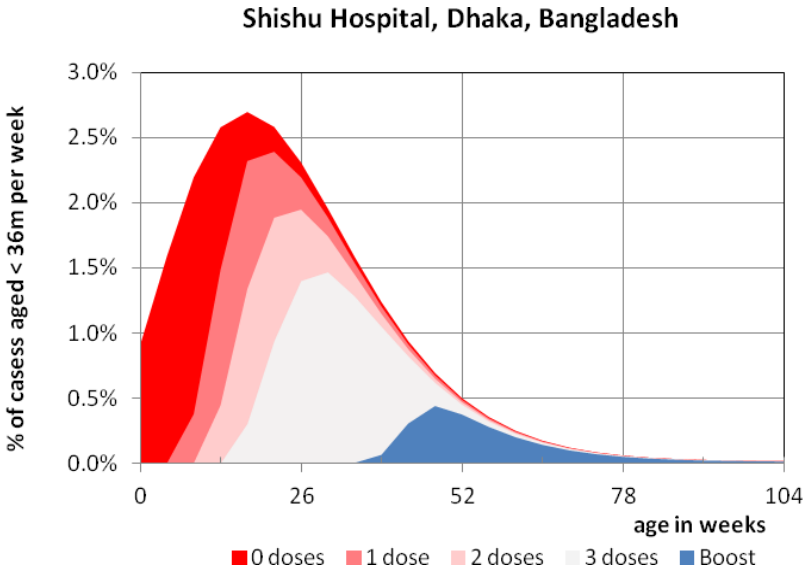
Figure 8: Pneumococcal meningitis and number of PCV doses and MCV given by week of age, by country

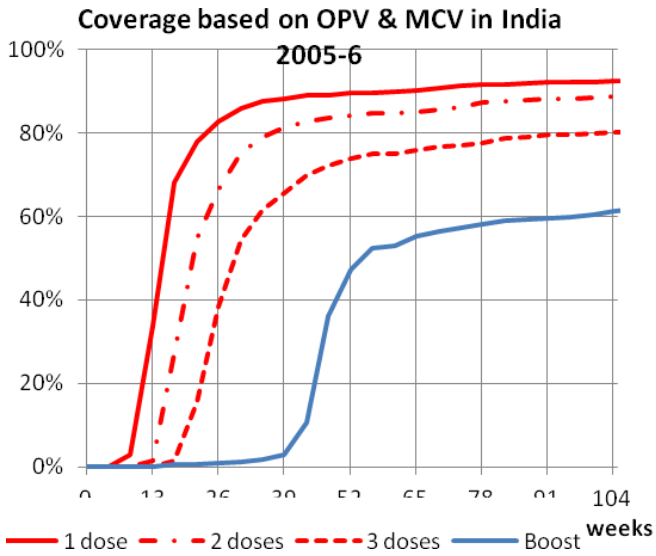


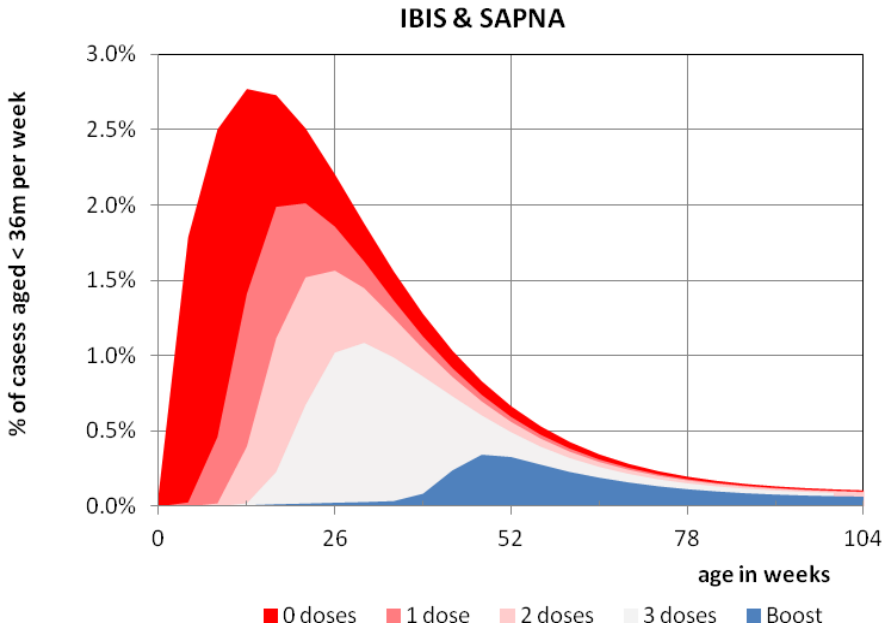

Coverage based on OPV & MCV in Uganda 2006
100%
80%
60%
40%
20%
0%
0
26
52
78
104
age in weeks
1 dose
2 doses
3 doses
Boost

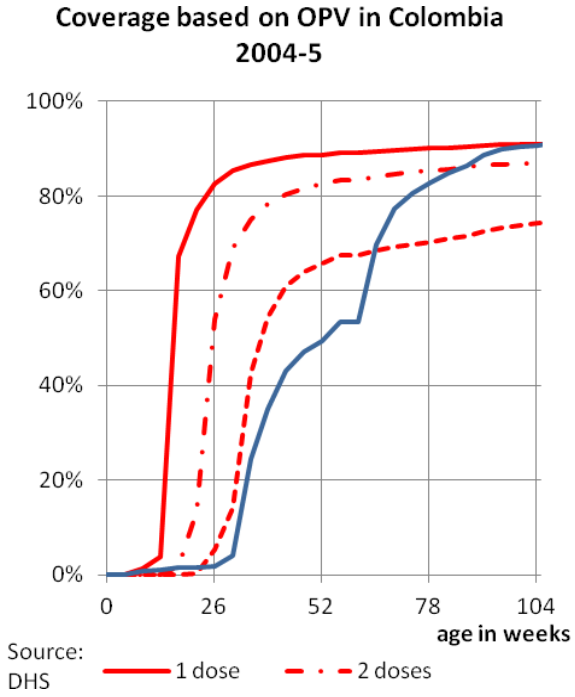

Kampala district, Uganda
% of casess aged < 36m per week
3.0%
2.5%
2.0%
1.5%
1.0%
0.5%
0.0%
0
26
52
78
104
age in weeks
0 doses
1 dose
2 doses
3 doses
Boost

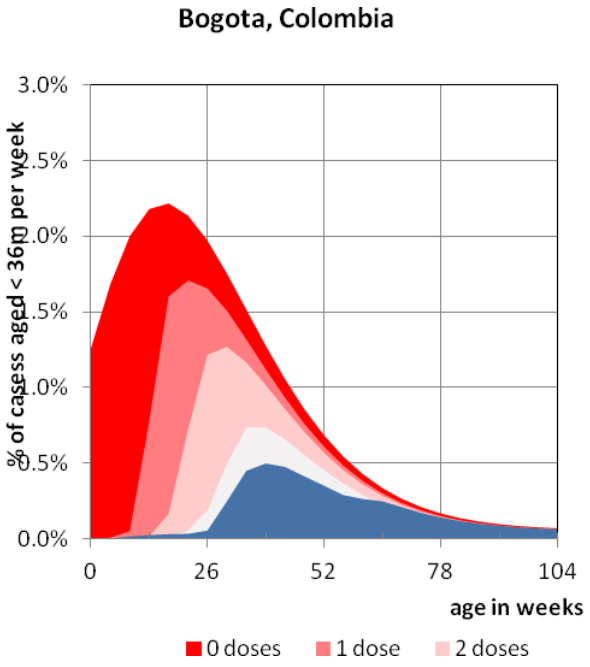

Coverage based on OPV & MCV in Bangladesh 2007
100%
80%
60%
40%
20%
0%
0
13
26
39
52
65
78
91
104
age in weeks
1 dose
2 doses
3 doses
Boost

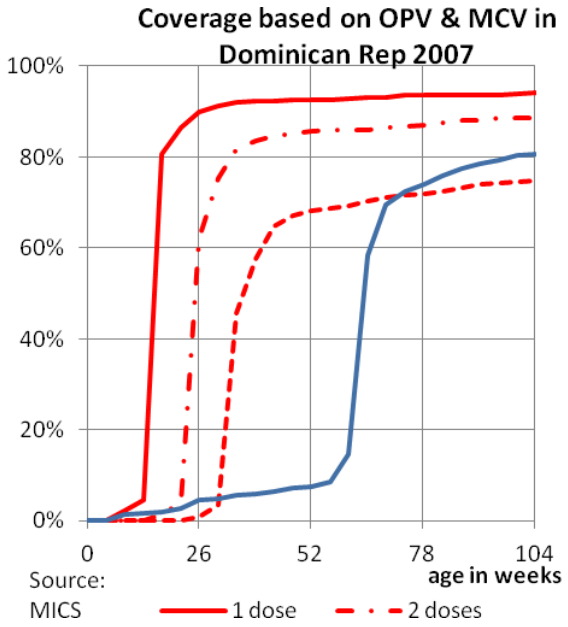

Shishu Hospital, Dhaka, Bangladesh
% of casess aged < 36m per week
3.0%
2.5%
2.0%
1.5%
1.0%
0.5%
0.0%
0
26
52
78
104
age in weeks
0 doses
1 dose
2 doses
3 doses
Boost


Coverage based on OPV & MCV in India
2005-6
100%
80%
60%
40%
20%
0%
104
weeks
1 dose
2 doses
3 doses
Boost


IBIS & SAPNA
% of casess aged < 36m per week
3.0%
2.5%
2.0%
1.5%
1.0%
0.5%
0.0%
0
26
52
78
104
age in weeks
0 doses
1 dose
2 doses
3 doses
Boost


Coverage based on OPV in Colombia
2004-5
100%
80%
60%
40%
20%
0%
0
26
52
78
104
age in weeks
Source:
DHS
1 dose
2 doses


Bogota, Colombia
3.0%
2.5%
2.0%
1.5%
1.0%
0.5%
0.0%
% of cases aged < 36m per week
0
26
52
78
104
age in weeks
0 doses
1 dose
2 doses


Coverage based on OPV & MCV in Dominican Rep 2007
100%
80%
60%
40%
20%
0%
0
26
52
78
104
age in weeks
Source:
MICS
1 dose
2 doses

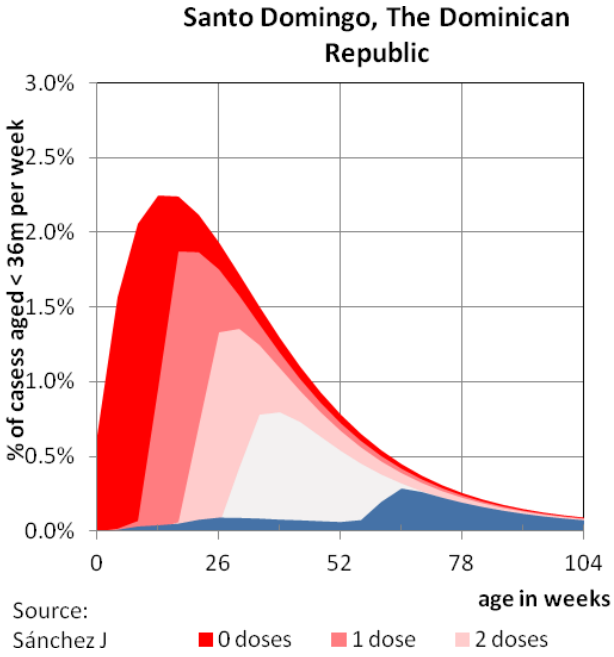
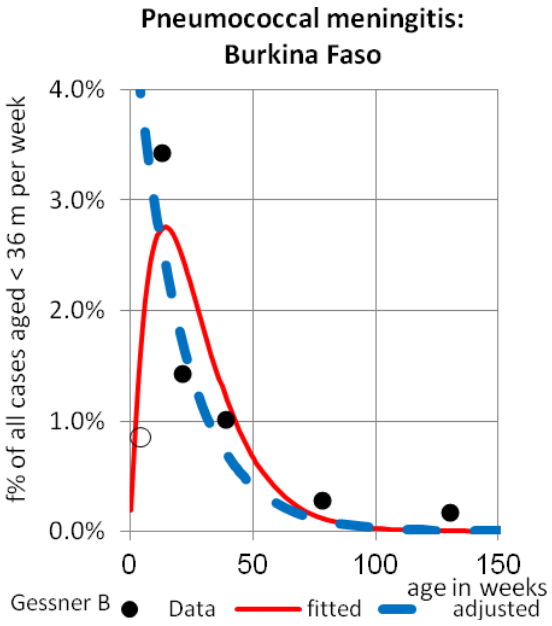
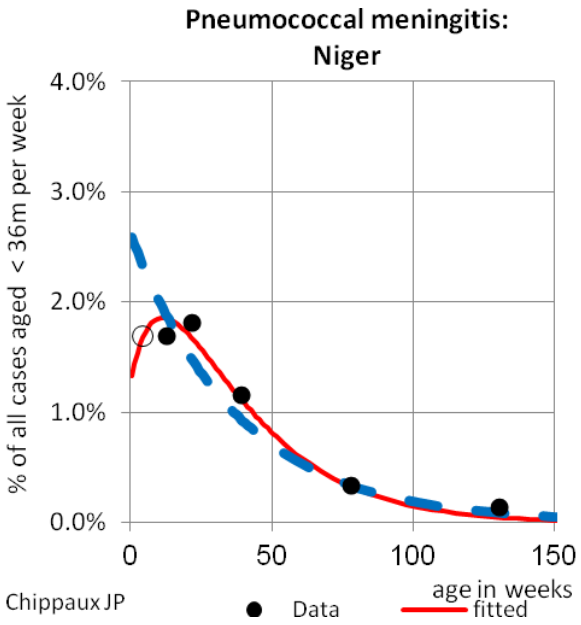
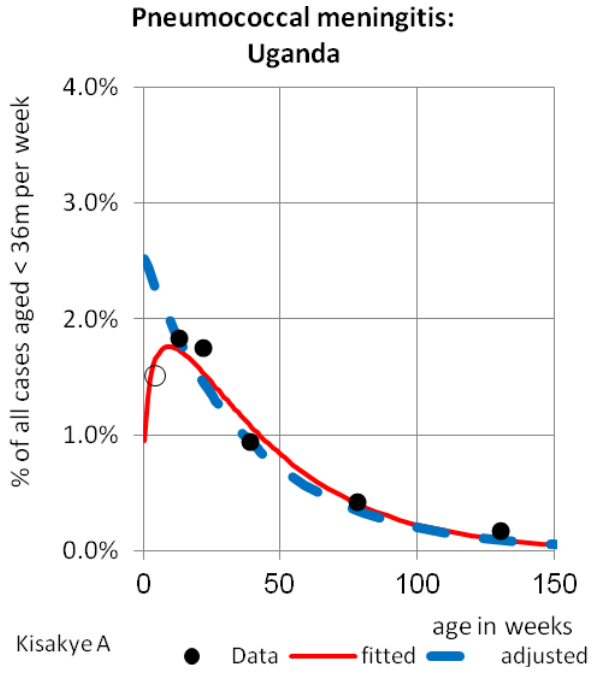

Santo Domingo, The Dominican Republic
3.0%
2.5%
2.0%
1.5%
1.0%
0.5%
0.0%
% of casess aged < 36m per week
0
26
52
78
104
age in weeks
Source:
Sánchez J
0 doses
1 dose
2 doses

Figure 9: Fit of gamma distribution reflecting the uncertainty of pneumococcal meningitis rates in infants <2m: Burkina Faso, Niger, and Uganda







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1. Baggett, H and Rhodes, J. International Emerging Infections Program, Thailand Ministry of Public Health - U.S. Centers for Disease Control and Prevention Collaboration, Nonthaburi, Thailand.
2. Gessner, B. Agence de Medecine Preventive, Paris, France.
3. Deceuninck, G. Equipe de recherche en vaccination. Quebec, Canada.
4. Lagos, R. Centro para Vacunas en Desarrollo-Chile (CVD-Chile), Hospital de Niños Roberto del Río, Santiago, Chile.
5. Mackenzie, G. Medical Research Council Unit, Basse, The Gambia.
6. Moisi, J. Agence de Medecine Preventive, Paris, France.
7. Regueira, M, Corso, A. Servicio Bacteriología Clínica Departamento Bacteriología INEI ANLIS "Dr. Carlos G. Malbrán" Buenos Aires, Argentina.
8. Saha, S. Dept. of Microbiology, Bangladesh Institute of Child Health, Dhaka Shishu Hospital, Dhaka, Bangkadesh.
9. Sánchez, J. Departamento de Enfermedades Infecciosas, Hospital Infantil Dr. Robert Reid Cabral, Santo Domingo, Dominican Republic.
10. Scott, A. KEMRI-Wellcome Trust Research Programme, Kilifi, Kenya.
11. Sigaúque, B. Manhiça Health Research Center, Manhiça, Maputo, Mozambique.
12. van der Ende, A. Academic Medical Center, Department of Medical Microbiology, Reference Laboratory for Bacterial Meningitis, Amsterdam, the Netherlands.
13. Von Gottberg, A. Respiratory and Meningeal Pathogens Research Unit (RMPRU), Johannesburg, South Africa.
14. Yoshida, LM and Suzuki, M. Institute of Tropical Medicine, Nagasaki University, Japan.

APPENDIX 1: References related to included studies

IPD/Meningitis

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APPENDIX 2: Studies not included

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