**Impact of the Introduction of Pneumococcal Conjugate Vaccination on Invasive Pneumococcal Disease in The Gambia: Population-Based Surveillance Before and After Vaccine Introduction**

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**Summary**

**Background**  There is little information on the impact of pneumococcal conjugate vaccines (PCV) in low-income countries. We measured their impact on invasive pneumococcal disease (IPD) in The Gambia where the 7-valent vaccine (PCV7) was introduced in August 2009, followed by PCV13 in May 2011.

**Methods** We conducted population-based surveillance for IPD among those aged 2 months and greater using standardised criteria. We compared IPD incidence between baseline and PCV13 periods, adjusting for changes in case ascertainment over time.

**Findings** We investigated 14 650 patients and identified 320 IPD cases. Compared with baseline, IPD incidence decreased by 55% [95% CI 30, 71] in the 2–23 month age group, from 253 to 113 per 100 000. This was due to an 82% [64, 91] reduction of serotypes covered by PCV13. In the 2–4 years age group, IPD incidence decreased 56% [25, 75], from 113 to 49 per 100 000, with a 68% [39, 83] reduction in PCV13 serotypes. The incidence of non-PCV13 serotypes in children aged 2–59 months increased 47% [-21, 275] from 28 to 41 per 100 000, with a broad range of serotypes. The incidence of non-pneumococcal bacteraemia varied little over time.

**Interpretation** The Gambian PCV programme reduced the incidence of IPD in children aged 2–59 months by approximately 55%. Further surveillance is needed to determine the maximum impact in the 2–4 years and older age groups, and to monitor serotype replacement. Low and middle-income countries that introduce PCV13 can expect substantial reductions in IPD.

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**Introduction**

In 2008, there were an estimated 541 000 deaths due to pneumococcal disease globally among under 5 year old children.1 Africa accounted for 57% of these deaths.1Pneumococcal conjugate vaccines (PCV) have been effective in high-income countries, reducing the incidence of invasive pneumococcal disease (IPD) in vaccinated and unvaccinated individuals.2-4 Fifty-three low-income countries have now introduced PCV5 into their routine immunisation programmes and robust evaluation of impact is a priority.

In South Africa, where the population has a high prevalence of HIV infection, the introduction of PCV7 was associated with reduced rates of IPD in young children and adults.6 The Gambia has a high burden of pneumococcal disease and relatively low HIV prevalence.7,8 A Gambian trial of a 9-valent PCV, which ended in 2004, showed 77% efficacy against IPD due to vaccine serotypes, 50% against IPD overall, 37% against radiologic pneumonia, and 16% against overall mortality.9 Based on these results, and WHO recommendations, The Gambia introduced PCV7 nationally in 2009, followed by PCV13 in 2011. We measured the impact of routine infant vaccination with PCV on IPD using standardised population-based surveillance.

**Methods**

Study setting

The study was undertaken in Upper River Region, The Gambia, where the Medical Research Council (UK) has a field station in the town of Basse. Residents of the Basse Heath and Demographic Surveillance System (BHDSS) are served by Basse Health Centre and five smaller health facilities (figure S1).

Surveillance and population

We conducted population-based surveillance for suspected pneumonia, septicaemia, and meningitis between May 12, 2008 and December 31, 2014. The surveillance population included all residents of the BHDSS aged 2 months or greater. The population is enumerated every 4 months with births, deaths, migrations, and vaccinations being recorded. The estimated population in 2014 was 179 108 with 18% aged under 5 years.

Vaccine introduction

The Gambia Government introduced PCV7 into the expanded programme of immunisation (EPI) on August 19, 2009, with a schedule of three doses at ages 2, 3, and 4 months, co-administered with pentavalent vaccine. Children who presented to maternal-child-health clinics aged less than 6 months were eligible to receive three doses, while older children who presented were eligible to receive one dose. PCV13 was introduced in May 2011 without catch-up.

Surveillance procedures

The surveillance methods have been described previously.10 In brief, nurses assessed all individuals who presented as an outpatient or who were admitted to one of the six health facilities in the study area. Enrolment involved standardised screening of patients for referral to a clinician in Basse. Clinicians applied standardised criteria to identify patients with suspected pneumonia, septicaemia or meningitis and requested blood culture, lumbar puncture, and/or chest radiography according to protocol (figure S2 and tables S1, S2, S3). Aspiration of pleural fluid or lung aspiration was performed on patients with a pleural effusion or dense peripheral consolidation radiologically. We defined IPD as a compatible illness with isolation of *Streptococcus pneumoniae* from a normally sterile site. Vaccine failure was defined as IPD following two or more doses of PCV covering the homologous serotype, given more than 14 days before the event.11,12 Weight was recorded using a digital scale (TANITA, Arlington Heights, USA) and height using a ShorrBoard® (Weigh and Measure, Olney, USA). Rapid malaria tests (ICT Diagnostics, Cape Town, South Africa) were conducted on all patients with suspected pneumonia, septicaemia, or meningitis from August to December (the malaria transmission season) and in a 10% random sample from January to July. Samples were not collected between October 5 and November 3, 2010 when the Field Station flooded.

Microbiology

Blood, lung aspirate, cerebrospinal fluid, pleural fluid, and other microbiological samples were processed in Basse using standard methods.13 *S. pneumoniae* was identified by morphology and optochin sensitivity. All pneumococcal isolates were confirmed at the MRC Fajara, WHO Regional Reference Laboratory, and serotyped using a latex agglutination assay employing factor and group-specific antisera (Statens Serum Institut, Copenhagen, Denmark). Serotypes 6A and 6B were differentiated from 6C by a polymerase chain reaction.14 Serotyping of 10% of isolates was repeated at the National Institute for Communicable Diseases in South Africa. The laboratories in Basse and Fajara submitted to external quality assurance throughout the study (UK National External Quality Assessment Service, WHO reference laboratory Denmark, and the Royal Australasian College of Pathologists).

Ethics

The study was approved by the Gambia Government/MRC Joint Institutional Ethics Committee (number 1087) and the ethics committee of the London School of Hygiene and Tropical Medicine. Participants, or their guardians, gave written, informed consent.

Statistical analysis

The primary outcome of the study was the incidence of IPD, in four categories: overall IPD and IPD due to PCV7 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F, and cross-reactive 6A),15 serotypes in PCV13 but not PCV7 (1, 3, 5, 7F, 19A, excluding 6A), and non-vaccine serotypes.

We calculated the incidence of IPD by dividing the number of cases by the mid-point population estimates from the BHDSS and multiplying by 100 000. Age groups were pre-specified as 2–23 months, 2–4 years, 5–14 years, and 15 years and over (adults). In order to calculate the incidence in 2008 we extrapolated cases for the unobserved period January 1 to May 11. We derived the number of unobserved cases in 2008 by multiplying the number of observed cases from May 12 to December 31, 2008 by the average ratio of cases before and after May 12 in each of the years 2009 and 2011–2014. The unobserved cases were grouped using the pre-PCV age and serotype distribution from 2008/09. For the flood period in 2010, we extrapolated cases using the number of observed cases in 2010 multiplied by the average ratio of cases during the same period in each of the years 2009 and 2011–2014. We applied the age and serotype distribution of the observed cases in 2010 to the unobserved cases in 2010.

We corrected for age-specific changes in the number of individuals eligible for investigation per unit population by adjusting the counts of annual IPD by age group, assuming the same serotype distribution as that of the observed cases each year. Annual, age-specific, counts of IPD were adjusted to the mean rate of enrolment of patients eligible for investigation.

We assessed the impact of the PCV programme by calculating the ratio of the incidence of IPD in the last two years of surveillance (2013/2014) compared to the ‘baseline’ first two years (May 12, 2008 to May 11, 2010). We used the Poisson distribution to calculate incidence rate ratios (IRR) and 95% confidence intervals (CI). The widths of the confidence intervals were inflated to allow for over-dispersion found in the 2–23 month and 5–14 year age groups, estimated from a subject-level Poisson regression analysis of 2008/09 pre-PCV IPD data. Statistical significance was set at a p-value less than 0·05. We used STATA (version 12·1) and MATLAB (version R2015a) for analysis.

To investigate potential bias due to temporal changes in health care seeking, patient investigation, or confounding due to secular trends in epidemic serotypes we conducted three *a priori* stratified analyses, excluding: outpatients; cases identified by lung aspiration alone; and cases caused by serotype 1 or 5. To assess the effect of temporal trends in invasive bacterial disease, we evaluated the incidence of non-pneumococcal bacteraemia, as a control condition, extrapolating case counts for missing periods in the same manner as for IPD. We also evaluated temporal changes in the prevalence of contaminated blood cultures, malnutrition, and malaria in patients eligible for investigation.

Role of the funding source

The study was funded by GAVI’s PneumoADIP, the Bill & Melinda Gates Foundation, and MRC (UK). None of the funding sources were involved in data collection, analysis, or interpretation of data. The corresponding author had full access to the data and was responsible for the final decision to submit the manuscript for publication.

**Results**

Vaccine coverage

Coverage of two or more doses of PCV before 12 months of age in children born in the last 6 months of 2013 was 94% (3151/3364). While the first two years of surveillance overlapped with the introduction of PCV7, the coverage of at least two doses of PCV7 in 2–23 month old children reached only approximately 35% by April 2010 (figure 1A) and coverage of one dose in children aged over 6 months was approximately 4%, indicating a limited potential impact of PCV7 in the baseline period. The proportion of 2–23 month old children who had received at least two doses of PCV13 reached a plateau of around 73% in mid-2013 (figure 1B). The proportion of 2–4 year old children who had received at least two doses of PCV13 reached 50% by the end of 2014, and was still increasing.

Screening and investigation

A total of 17 795 patients were screened for referral to a clinician (figure 2). Surveillance performance was consistently high, including the annual proportion of patients referred who were clinically evaluated (98%–99%), the annual proportion who had microbiological investigation when indicated (90%–97%), and the proportion of IPD cases with serotyping results (98·8%, 316/320). The proportion of patients who had a lung aspiration was approximately 1% in the baseline and 2013/14 periods, and 6% in 2010 and 2011 (figure S3).

Cases of invasive pneumococcal disease

We identified 320 cases of IPD (table 1). Pneumonia was suspected in 212 (66%) cases, septicaemia in 70 (22%), and meningitis in 38 (12%). Twenty-eight cases died, with 15% (12/81) mortality in the first year of life. Children aged 2–11 months were more likely to have IPD caused by non-vaccine serotypes than those aged 1–4 years (51/79 [66%] versus 33/161 [20%], p<0·001). There were no significant differences in gender, nutritional status or mortality between vaccine or non-vaccine serotype cases.

Impact of the immunisation programme

Among all ages, 111 cases of IPD were recorded in the baseline two years; 38 (34%) were PCV7 serotype, 55 (50%) were PCV13 only serotype, and 21 (26%) were non-vaccine type (table 2). In the 2013/14 period there were 67 cases; 12 (18%) were PCV7 serotype, 26 (38%) were PCV13 only serotype, and 29 (44%) were non-vaccine type. After adjustment of case counts, there was a 55% [95% CI 30, 71] reduction in the incidence of IPD from baseline to 2013/14 in children aged 2–23 months, from 253 cases per 100 000 to 113 cases per 100 000 (table 2, figure 3). There was a reduction of 56% [25, 75] in those aged 2–4 years, from 113 to 49 cases per 100 000. There was a non-significant reduction in IPD among those aged 5–14 years of 16% [-125, 69]. Incidence among adults fell 59% [-3, 84], from 9 to 4 cases per 100 000.

In the 2–23 month age group, PCV7 type IPD declined by 83% [57, 93], from a baseline of 122 cases to 21 per 100 000 in 2013/14; PCV13 type IPD fell 82% [64, 91], from 195 to 35 per 100 000, and PCV13 only type IPD declined 82% [44, 94], from 78 to 14 per 100 000. Analysis restricted to the 6–23 month age group, with vaccine coverage over 80% (figure S4), is shown in table S4. Lesser reductions occurred in 2–4 year olds; PCV7 type IPD fell by 74% [26, 91] from 44 to 11 per 100 000, PCV13 type IPD fell 68% [39, 83] from 99 to 31 per 100 000, and PCV13 only type IPD fell 62% [15, 83] from 58 to 22 per 100 000 (table 2, figure 3). There was no evidence of a reduction in PCV13 or PCV13 only type IPD in the 5–14 year old age group. There were non-significant reductions in the incidence of PCV13 and PCV13 only type IPD in adults, 50% [-32, 81] and 48% [-39, 80] respectively.

We observed a non-significant, 48% [-30, 213] increase in non-vaccine type IPD in the 2–23 month age group, from 49 to 75 per 100 000, and an increase of 27% [-61­, 313] among 2–4 year olds. Combined, non-vaccine type IPD increased 47% [-21, 175] in those aged 2–59 months.

The estimates of PCV impact were unchanged in stratified analyses excluding outpatients and cases detected only by lung aspiration (tables S5 and S6). When cases due to serotypes 1 or 5 were excluded, vaccine impact against PCV13 serotypes was unchanged (table S7). There was no change in the incidence of the control condition of non-pneumococcal bacteraemia between the baseline and 2013/14 period (table S8, figure S5).

The prevalence of malaria in patients aged 2–59 months and 5 years and greater, and eligible for investigation, fluctuated between 5% and 17%, and 10% and 24% respectively, throughout the study period, with no significant difference in prevalence between baseline and 2013/14 (figure S6 and S7). The prevalence of malnutrition and blood culture contamination throughout the study among children eligible for investigation was stable around 14% (figure S8) and 7% (figure S9) respectively.

Serotype-specific changes

The impact of PCV7 in the 2–59 month age group was evident from 2011 with reduced cases of serotypes 6A and 14 (figure 4A). Cases of serotype 5 were reduced in 2013/14 (figure 4B). Fifteen different serotypes contributed to the increase in non-vaccine type IPD in 2014 (figure 4C). In the 5 years and over age group there was a peak of serotype 5 in 2010 with one case detected in 2013 and in 2014 (figure 4D). The number of serotype 1 episodes in 2014 was similar to that observed in earlier years of surveillance (figure 4D). There were 17 episodes of IPD associated with vaccine failure; two for serotypes 1, 6A, 19A, and 19F; four for 23F, and five for serotype 14. Four children with vaccine failure were severely malnourished (table S9)

**Discussion**

Population-based surveillance over almost 7 years has demonstrated that, in the 2–23 month age group, there was an 82% reduction in IPD due to PCV13 serotypes and a 55% reduction in all IPD following introduction of PCV into the Gambian EPI. In the 2–4 years age group, there was a 68% reduction in IPD due to PCV13 serotypes and a 56% reduction in all IPD.

Our findings are similar to those seen in other settings soon after implementation of PCV. Estimates of PCV7 impact on all IPD less than 2 years of age have varied between 56%in England and Wales16 and 69% in the United States15 and South Africa6 with a somewhat greater impact associated with PCV10/13; 62% in Oxford, England,17 71% in Denmark,18 78% in England and Wales,4 and 80% in Finland.19 Our study may have under-estimated vaccine impact in the 2–23 month age group due to the possible influence of PCV7 in our baseline period and the fact that the proportion of children with at least two doses had not peaked by the beginning of 2013. The 56% reduction in IPD in the 2–4 years age group observed in our study is less than the 75% observed in England and Wales,4,16 although ours is probably an underestimate.

Herd protection in unimmunised children and adults following the introduction of PCV has been documented in many settings.4,6,15,16–18 Consistent with these finding, we observed a trend towards reduced IPD in adults, but our findings should be interpreted with caution given the small numbers of cases. Data from Kilifi, Kenya, indicate likely herd protection effects of PCV10, as carriage of vaccine-type pneumococci in children and older individuals was reduced by two-thirds following an extensive catch-up campaign.20

We observed a 48% [-30, 213] increase in non-PCV13 type IPD in the 2–59 month age group. Following the introduction of PCV7 in developed countries, non-vaccine type IPD increased two to three fold, although largely due to serotypes covered by PCV13.21 Non-vaccine type IPD has increased following the introduction of PCV13 in Denmark,18 and England and Wales,4 but such a change is not yet evident in the United States. 22 It may take several years of surveillance post-PCV13 introduction to see the full effect.21

We observed temporal changes in some serotypes that were likely to be independent of vaccine introduction. Serotype 5 peaked in all age groups in 2010, whereas those under 5 years of age experienced an increase in serotype 12F disease in 2011 (figure 4). Such temporal changes in serotypes, and the limited numbers of cases, necessitate cautious interpretation of serotype-specific results. The impact of PCV13 against serotype 1 that has been observed in other settings4,6,23 was not yet evident in our study. Impact against this important serotype may require further time for the coverage of PCV13 to increase in the 2–4 years age group in which serotype 1 is more prevalent. Continued surveillance is required to confirm vaccine impact against this serotype in our setting.

Our study has several strengths. All screening, clinical investigation criteria, case definitions, and laboratory practices were standardised and consistently applied throughout the study.10 However, there were some limitations. After initial piloting there was only 16 months of surveillance before the introduction of PCV7. However, the proportion of children who had received at least two doses of PCV7 remained low for several months after vaccine introduction, allowing a 2 year baseline period. Before and after studies are prone to bias and confounding due to changes in factors apart from vaccination which influence the detection and risk of pneumococcal disease in the population. Our analysis provided some reassurance in this regard, with adjustment for temporal changes in the rate of patient investigation, demonstration of a stable incidence of the control condition of non-pneumococcal bacteraemia, and no change in estimates in stratified analyses.

The vaccine impact which we observed in The Gambia resulted from a PCV programme using a standard schedule and an introduction with effectively no catch-up campaign, the programmatic circumstances found in most low-income countries. Thus, our findings have important implications for EPI programmes in other low-income countries and provide reassurance for those that have already introduced PCV. Questions to answer going forward which make ongoing surveillance in The Gambia and a limited number of other settings a high priority include measuring the maximum impact in those over the age of 2 years, the extent of herd protection, the magnitude of serotype replacement, and impact on pneumonia. These data will provide crucial information regarding considerations of alternative immunisation schedules and the need and prioritisation of modified conjugate vaccines and vaccines designed to prevent disease due to all pneumococcal serotypes.

**Contributors**

RA, PH, and OL proposed the study idea. GM, IP, DS, SH, MJ, MK, PH, RA, and TC established the surveillance system and GM oversaw it throughout. GM, AA, and DS trained and supervised clinicians and staff on study procedures. IH, UU, DA, MN, OA, JP, YO, BA, BM, AF, BE, RI, BK, PG, EO, OO, EU, EG clinically evaluated and investigated the patients and maintained quality assurance over clinical procedures. IH, MJ, and GM supervised the collection of demographic and vaccination data. HB, UI, AM, and RS supervised the microbiology in Basse. DN, SJ, and MA supervised serotyping in Fajara. SS and YLJ provided central level logistic support and supervision to the EPI and Disease Control department in the Ministry of Health. LC supervised the EPI in URR. TC provided institutional support and central level liaison with the Ministry of Health. SH provided departmental support at MRC Gambia. MK and OL provided administrative support and technical feedback in the initial years of the study. GM, DJ, PH, and BG developed the analysis plan and performed the analysis. MK, SH, and KM reviewed the analysis plan. GM, PH, DJ, KM, and BG interpreted the findings. GM, DJ, and PH drafted the paper. All authors contributed to the writing of the final manuscript.

**Conflicts of interests**

RA is currently employed by GlaxoSmithKline Vaccines and received grant awards from WHO, GAVI Alliance, and the Bill & Melinda Gates Foundation whilst employed at MRC Gambia. MK, SH, and BG received grants from the Bill & Melinda Gates Foundation. MK received grants from the Gavi Alliance, Merck, and Pfizer, and personal fees from Pfizer. The other authors declare that they have no conflicts of interest.

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