Changing Incidence of Invasive Pneumococcal Disease in Infants Less Than 90 Days of Age Before and After Introduction of the 13-Valent Pneumococcal Conjugate Vaccine in Blantyre, Malawi

A 14-Year Hospital Based Surveillance Study

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Background: Invasive pneumococcal disease (IPD) in young infants is uncommon but associated with high morbidity and mortality. Accurate data on the burden of IPD in young infants in low-income countries are lacking. We examined the burden of IPD in infants <90 days old in Blantyre, Malawi over a 14-year period and evaluated the indirect impact of the 13-valent pneumococcal conjugate vaccine (PCV13) on vaccine-serotype IPD (VT-IPD) in this population.

Methods: We conducted laboratory-based prospective IPD surveillance in infants <90 days of age admitted to Queen Elizabeth Central Hospital in Blantyre between 2005 and 2018, including 7 years pre-PCV13 and 7 years post-PCV13 introduction. IPD was defined as Streptococcus pneumoniae identified by culture from blood or cerebrospinal fluid. Serotypes were determined by multiplex polymerase chain reaction and latex agglutination testing.

Results: We identified 130 cases of culture-confirmed IPD in infants <90 days old between 2005 and 2018. Total IPD incidence was declining before PCV13 introduction. The mean incidence of IPD was significantly lower in the post-PCV13 era. Serotypes 5 (27.8%) and 1 (15.6%) were most prevalent. Even after PCV13 introduction, VTs remained the primary cause of IPD, with serotype 5 accounting for 17.4% and serotype 1 for 13.0% of cases in young infants.

Conclusion: Vaccine serotypes 1 and 5 were the main cause of IPD in neonates and young infants, both before and after PCV13 introduction. This suggests incomplete indirect protection with persisting VT carriage across the population despite vaccination in this setting. Alternative vaccine schedules and other vaccine introduction approaches need to be considered to protect this vulnerable population.

Key Words: invasive pneumococcal disease, infant, pneumococcal conjugate vaccine

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BACKGROUND

Streptococcus pneumoniae is a major cause of serious bacterial infections, including pneumonia, sepsis and meningitis in young children. Globally, there were an estimated 294,000 pneumococcal deaths in HIV-uninfected children 1–59 months old in 2015, with the majority occurring in sub-Saharan Africa and Asia.1 S. pneumoniae is considered an uncommon but well-recognized cause of invasive bacterial disease in neonates and young infants and has been associated with high morbidity and mortality, with a case fatality rate of up to 14.3%.2 The global burden of neonatal invasive pneumococcal disease (IPD) has been estimated at 36.0 per 100,000 live births in the pre-pneumococcal conjugate vaccine (PCV) period.3 However, accurate data on the burden of IPD in neonates and young infants are lacking, especially in low-income countries.

In Malawi, the under-5 child mortality rate was reduced by two-thirds between 1990 and 2015, with the country, therefore, achieving Millennium Development Goal (MDG) 4. The neonatal mortality declined more slowly (from 50 to 23 deaths per 1000 live births) and remains among the highest in the world.4–5 Severe bacterial infections contribute significantly as a leading cause of death in the neonatal population.6 Work examining the etiology of neonatal sepsis in Blantyre,
Study Setting

In 2005–2018, QECH provided free medical care to the government-funded district and referral hospital with about 25,000 births per year. QECH is a large, teaching hospital in the capital city of Malawi’s southern region, Blantyre, which serves as the reference hospital for the central region of Malawi. QECH provides a large outpatient clinic and an inpatient hospital with about 25,000 pediatric admissions a year. QECH provides free medical care to all residents of Blantyre District, which has a population of 1.8 million people. QECH is located in Blantyre, Malawi, which is a landlocked country in southern sub-Saharan Africa with a population of 19.1 million people. The country is ranked by the World Bank in the lowest income category.13 Located in Blantyre, the capital city of Malawi’s southern region, QECH is a large government-funded district and referral hospital with about 25,000 pediatric admissions a year. QECH provides free medical care to the 1.3 million urban, peri-urban and rural residents of Blantyre District.

Case Ascertainment and Laboratory Confirmation

In accordance with longstanding clinical guidelines, all young infants presenting to QECH with fever (axillary temperature >37.5°C) or clinical suspicion of sepsis or meningitis undergo blood cultures and, where appropriate, lumbar puncture. We have been conducting sentinel surveillance for laboratory-confirmed bloodstream infection and meningitis (including IPD) in all age groups at QECH since 1998, as previously described.14–16 Specimens were processed at the co-located Malawi-Liverpool-Wellcome Clinical Research Programme laboratory, using BD BACTEC (Becton Dickinson, Franklin Lakes, NJ). Those positive by BACTEC were Gram stained. Gram-positive diplococci or Gram-positive cocci in short chains were initially classified as *S. pneumoniae* after testing negative using the catalase test. These isolates were archived on Microbank beads (ProLab Diagnostics) in a +80°C freezer. For subsequent confirmation of *S. pneumoniae* and serotyping, archived isolates were plated on gentamicin-sheep blood agar (SBG; 7% sheep blood, 5 µL gentamicin/mL) and incubated overnight at 37°C in 5% CO2. *S. pneumoniae* growth was confirmed by colony morphology and optochin disc (Oxoid, Basingstoke, UK) susceptibility. The bile solubility test was used on isolates with no or intermediate (zone diameter <14mm) optochin susceptibility. A single colony of confirmed pneumococcus was selected and grown on a new SBG plate as before. Growth from this second plate was used for serotyping by latex agglutination (ImmuLex 7-10-13-valent Pneumotest; Statens Serum Institute, Denmark). The ImmuLex kit allows for differential identification of each PCV13 VT but not for differential identification of non-VT (NVT) serotypes; all pneumococcal isolates that were not VT were therefore reported as NVT. Nucleic acid amplification-based serotyping was performed on samples collected between January 1, 2009 and December 31, 2013, using the ‘Triplex sequential real-time polymerase chain reaction-serotyping Africa’ protocol of the Centers for Disease Control and Prevention.17 Both assays have been shown to be highly accurate and concordant in pneumococcal serotyping.18,19 There was 100% concordance among a random selection (approximately 6%) of serotyped isolates sent for confirmatory serotyping by Quellung reaction at the regional pneumococcal reference laboratory at the National Institute for Communicable Disease in Johannesburg, South Africa. Since 13 August 2011, serotyping has occurred in real time with specimen processing. Isolates collected before 13 August 2011 were retrospectively serotyped. Demographic information (including age and sex) was collected at the time of sampling. Clinical data were not available for prospective collection.

Case Definitions

We analyzed all archived pneumococcal isolates from blood and cerebrospinal fluid (CSF) of infants less than 90 days old admitted to QECH between January 1, 2005 and December 31, 2018. IPD cases were defined as isolation of *S. pneumoniae* from a normally sterile site (ie, blood or CSF). We defined those with a positive CSF culture as “meningitis” and those with a positive blood culture as “bacteremia”. Cases with both a positive CSF and a positive blood culture were classified as “meningitis”. Although it is standard practice to take a CSF sample in all young infants with suspected sepsis, this was not done in all individuals. Cases in infants ≤7 days old were defined as “early-onset” disease and cases in infants 8–89 days old as “late-onset” disease.

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Clinical Syndrome | Total | Pre-PCV13 | Post-PCV13
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Meningitis | 93 (71.5) | 74 (71.2) | 19 (73.1)
Bacteremia | 37 (28.5) | 30 (28.8) | 7 (26.9)
Early onset (0–7 days) | 36 (27.7) | 25 (24.0) | 11 (42.3)
Meningitis | 21 (58.3) | 13 (52.0) | 8 (72.7)
Bacteremia | 15 (41.7) | 12 (48.0) | 3 (27.3)
Late onset (8–89 days) | 94 (72.0) | 79 (76.0) | 15 (57.7)
Meningitis | 72 (76.6) | 61 (77.2) | 11 (73.3)
Bacteremia | 22 (23.4) | 18 (22.8) | 4 (26.7)

Pre-PCV13 period, January 1, 2005–November 11, 2011. Post-PCV13 period January 1, 2012–December 31, 2018. PCV indicates pneumococcal conjugate vaccine.
al36 showed that in Kilifi, Kenya the median time to acquisition was that pneumococcal acquisition occurs very early in life. Tigoi et holds.34,35 Previous studies in low-income settings have described onset disease, which is likely due to acquisition within house-

There is increasing evidence that in the pre-PCV period.29–31 There is increasing evidence that in this setting the current strategy used to implement conjugate vac-
cines does not achieve the optimal reductions in VT pneumococcal carriage as seen in resource-rich countries. Recently, it has been shown that in Malawi, despite high PCV13 uptake, there remains a high persistent residual carriage of all PCV13 serotypes.13 Serotype 1, a common cause of IPD in Africa,32 was responsible for 3% of VT carriage of all ages in that study, consistent with our findings in infants in this population. Furthermore, another study in northern Malawi demonstrated a reduction in VT carriage after PCV13 introduction but found high carriage rates continued to be present among age-ineligible (6-weeks old) infants, with no difference in pneumococcal acquisition between the pre- and post-

PCV indicates pneumococcal conjugate vaccine; SVT, non-vaccine serotype; VT, vaccine serotype.

- Though not all isolates were recoverable, analysis of those that were and were not recoverable showed no statistically significant difference in age, gender or sample type.

This study presents a unique set of data on the burden of IPD in infants less than 90 days old by taking a 3/12 proportion of the children <1-year-old. This method will lead to a small underestimation of the denominator practice will change over time as a consequence of falling IMR. Although the fall in IMR is relatively substantial from about 70 to 40 per 1000 live births, in absolute terms this makes only a small underestimation of IPD due to the challenges with blood volumes for culture in small infants. To our benefit, a large longitudinal study on bloodstream infections in children admitted to QECH has shown that the total pediatric and neo-

The majority (72%) of IPD cases in our study were of late-onset disease, which is likely due to acquisition within house-
holds.43,45 Previous studies in low-income settings have described that pneumococcal acquisition occurs very early in life. Tigo et al showed that in Kilifi, Kenya the median time to acquisition was 38.5 days of life and Heinsbroek et al showed a median time to first acquisition of 59 days of life in northern Malawi.

In our study, 36 (27.7%) of our cases occurred in the first 7 days of life with 17 of these (47.2%) occurring within the first 72 hours after birth. Although horizontal transmission from the mother or other household members remains likely, this suggests potential perinatal transmission at the time of labor. Although S. pneu-

Although this work provides an estimate of vaccine impact, it has several limitations. We were unable to review clinical, follow-up and outcome data for the cases and were not able to collect information on demographics and vaccination status. Our study only represents children who presented to the hospital and not those managed in community health centers or at home, with a resulting risk of underestimation of true numbers. This is likely limited, given the clinical severity of IPD in infants and the fact that QECH is the only hospital in Blan-
tyre District with inpatient pediatric facilities. There remains a further risk of underestimation of IPD due to the challenges with blood volumes for culture in small infants. To our benefit, a large longitudinal study on bloodstream infections in children admitted to QECH has shown that the total pediatric and neo-
aternal admissions have remained broadly constant since 2005.

Furthermore, we estimated the population of infants <90 days old by taking a 3/12 proportion of the children <1-year-old. This method will lead to a small underestimation of the denominator due to the high infant mortality rates (IMR). This underestima-
tion will change over time as a consequence of falling IMR. Although the fall in IMR is relatively substantial from about 70 to 40 per 1000 live births, in absolute terms this makes only marginal differences to the denominator practice and we feel is an acceptable error in the context of these data. Though not all isolates were recoverable, analysis of those that were and were not recoverable showed no statistically significant difference in age, gender or sample type.

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**CONCLUSION**

This study demonstrates that IPD incidence among neonates and young infants has declined over the past decade in Blantyre,
Malawi. However, pneumococcal vaccine serotypes were the main cause of IPD both before and after PCV13 introduction. We believe that there is incomplete indirect protection in this group, of which most are too young to derive direct protection from vaccination. Strategies such as maternal or neonatal immunization or schedule change with a booster dose to achieve greater reductions in the general population carriage need to be considered to protect this vulnerable population. Further studies to evaluate schedule change in this setting are underway.

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