Effect of pneumococcal conjugate vaccination on pneumococcal carriage in hospitalised children aged 2–59 months in Mongolia: an active pneumonia surveillance programme

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Summary

Background Data on changes in pneumococcal serotypes in hospitalised children following the introduction of the pneumococcal conjugate vaccine (PCV) in low-income and middle-income countries are scarce. In 2016, Mongolia introduced the 13-valent PCV (PCV13) into the national immunisation programme. We aimed to describe the trend and impact of PCV13 introduction on pneumococcal carriage in hospitalised children aged 2–59 months with pneumonia in Mongolia over a 6-year period.

Methods In this active surveillance programme, children aged 2–59 months with pneumonia who met the study case definition (cough or difficulty breathing with either respiratory rate ≥50 beats per min, oxygen saturation <90%, or clinical diagnosis of severe pneumonia) were enrolled between April 1, 2015, and June 30, 2021, from four districts in Ulaanbaatar. We tested nasopharyngeal samples collected at enrolment for pneumococci using *lytA* real-time quantitative PCR and conducted molecular serotyping and detection of antimicrobial resistance (AMR) genes with DNA microarray. We used log-binomial regression to estimate prevalence ratios (PRs) of pneumococcal carriage, comparing prevalence in the periods before and after the introduction of PCV13 and between vaccinated and unvaccinated children for three outcomes: overall, PCV13 vaccine-type, and non-PCV13 vaccine-type carriage. PRs were adjusted with covariates that were identified by use of a directed acyclic graph, informed by relevant literature.

Findings A total of 17 688 children were enrolled, of whom 17 607 (99·5%) met the study case criteria. 6545 (42·5%) of 15 411 collected nasopharyngeal swabs were tested for pneumococci. In all age groups, a similar prevalence of pneumococcal carriage was shown between the pre-PCV13 period and post-PCV13 period (882 [48·0%] of 1837 *vs* 2174 [46·2%] of 4708; adjusted PR 0·98 [95% CI 0·92–1·04]; p=0·60). Overall, vaccine-type carriage reduced by 43·6% after the introduction of PCV13 (adjusted PR 0·56 [95% CI 0·51–0·62]; p<0·0001). Younger children (aged 2–23 months) showed a 47·7% reduction in vaccine-type carriage (95% CI 41·2–53·5; adjusted PR 0·52 [95% CI 0·46–0·59]; p<0·0001), whereas children aged 24–59 months had a 29·3% reduction (12·6–42·8; 0·71 [0·57–0·87]; p=0·0014). Prevalence of 6A, 6B, 14, 19F, and 23F decreased following the introduction of PCV13; however, 19F and 6A remained common (5·8% and 2·9%). Non-vaccine-type carriage increased (adjusted PR 1·49 [95% CI 1·32–1·67]), with 15A, NT2, and 15B/C being the most prevalent serotypes. Overall, 1761 (89·3%) of 1978 analysed samples contained at least one AMR gene. The percentage of samples with any AMR gene decreased with vaccine introduction (92·3% in the pre-PCV13 period *vs* 85·3% in the post-PCV13 period; adjusted odds ratio 0·49 [95% CI 0·34–0·70]), with similar decreases for samples with at least three AMR genes (46·8% *vs* 27·6%; 0·44 [0·36–0·55]).

Interpretation 6 years after the introduction of PCV13 in Mongolia, the prevalence of vaccine-type carriage and AMR genes showed a reduction among young hospitalised children with pneumonia. Reductions in vaccine-type carriage are likely to result in reductions in pneumococcal pneumonia.

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Introduction

Lower respiratory tract infections are a common cause of mortality in children younger than 5 years, with countries in sub-Saharan Africa and southeast Asia accounting for more than three-quarters of global deaths from pneumonia in this age group.[1] *Streptococcus pneumoniae* (pneumococcus) is the most common bacterial cause of pneumonia in children.[2] By September, 2023, pneumococcal conjugate vaccines

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Research in context

Evidence before this study

The introduction of the pneumococcal conjugate vaccine (PCV) has reduced pneumococcal disease and vaccine-type carriage among young children; however, the impact of PCVs on pneumococcal carriage in children with pneumonia is not well studied. We searched PubMed for original research articles published in English between Jan 1, 2000, and March 31, 2023, exploring the effect of PCV on pneumococcal carriage in low-income and lower-middle-income countries (LMICs) using the following terms in combination: "pneumococcal conjugate vaccine", "pneumococcal vaccine", "carriage", "coloni#ation", "pneumonia" and "impact". We included studies of childhood pneumonia that included children younger than 5 years and reported on nasopharyngeal carriage as an outcome. We excluded carriage studies in healthy children and studies that did not include carriage results before and after the introduction of PCV. We identified studies from only three LMICs that included hospitalised children with pneumonia or acute respiratory infections, which described changes in the prevalence of pneumococcal carriage following PCV introduction. Among 1485 hospitalised children with acute respiratory infections in Laos, the prevalence of pneumococcal carriage was 36%. 6 years after the introduction of 13-valent PCV (PCV13), PCV13 carriage reduced from 24% to 0% and non-vaccine type carriage increased from 20% to 32%. In Papua New Guinea, vaccination had no effect on overall carriage and PCV13 carriage persisted. In Nepal, 10-valent PCV (PCV10) serotype pneumococcal carriage decreased from 14·1% (before the introduction of PCV10) to 6·5% (4 years after the introduction) in children with clinical pneumonia.

Added value of this study

In this active pneumonia surveillance programme, we report data of pneumococcal carriage from hospitalised children with pneumonia in Mongolia to show the impact of PCV introduction (two doses of PCV13 at age 2 months and 4 months, with a booster dose at age 9 months). Pneumococcal carriage in children with pneumonia is likely to better reflect the serotypes causing disease than are carriage surveys conducted in healthy children. To our knowledge, this study is the largest carriage surveillance programme in children with pneumonia from an LMIC.
We identified that, even in a setting with a high prevalence of risk factors for respiratory disease, PCV introduction resulted in a 44% reduction in vaccine-type carriage, with a greater reduction in children aged 2–23 months. We expect that this reduction in vaccine-type carriage will translate into reductions in pneumococcal disease. Additionally, samples containing any or multiple resistance genes decreased following PCV13 introduction. Increases in non-vaccine serotypes and residual circulation of some vaccine-type serotypes warrant ongoing surveillance. These data are important for countries planning to introduce PCVs and for those with ongoing PCV programmes, to assist in decision making regarding which schedule to use and the number of PCV doses to fund.

Implications of all the available evidence

Our findings address an important data gap for evidence on the impact of PCVs on carriage in children with pneumonia in LMICs. Vaccine impact studies conducted in high-income countries are not always relevant and translatable to LMICs. There are key differences in pneumococcal epidemiology, including transmission and burden, between LMICs and high-income countries. Prevalent antibiotic use in the Asia–Pacific region has resulted in high antibiotic resistance. Furthermore, there are marked geographical differences in serotype distribution and replacement disease. Our data could help to guide similar LMICs regarding policy decisions associated with introducing PCVs, PCV maintenance, choice of PCV valency, and vaccine schedules, and could potentially inform the future development of pneumococcal vaccines.

(PCVs) had been introduced in 165 countries globally; however, 20% of the world's children remain unvaccinated.[3] Robust long-term programmes to measure vaccine impact in low-income and lower-middle-income countries (LMICs) are rare.[3] Pneumococcal data from high-income countries are not always applicable to LMICs due to differences in epidemiology and transmission dynamics.[4]

WHO recommends surveillance of invasive pneumococcal disease to establish vaccine impact;[5] however, this is often not feasible in LMICs. Pneumococcal pneumonia is challenging to diagnose in young children due to difficulties in obtaining sputum and invasive specimens, as well as a scarcity of diagnostic tests in this age group.[6] Nasopharyngeal samples are easier to obtain and provide insight into pneumococcal carriage (ie, presence of the microbe in the upper respiratory tract), which is considered to be a prerequisite for disease.[7] Children younger than 5 years are at higher risk of invasive pneumococcal disease than older children (aged 5–18 years) and are an important reservoir for pneumococcal transmission in the community.[8] As such, carriage studies are important tools to monitor pneumococcal serotype changes in children following the introduction of PCVs in LMICs.[9]

Since the introduction of PCVs, vaccine-type carriage among young children has decreased in settings where PCV is used.[9] There are scarce data from LMICs on the impact of PCVs on pneumococcal carriage in children younger than 5 years with pneumonia.[10–12] Most pneumococcal carriage studies assessing the impact of PCV introduction have been conducted in healthy children, whereas carriage studies in children with pneumonia do not usually describe vaccine impact.[9]

Pneumococcus is an important cause of antimicrobial-resistant infections. PCVs can reduce antimicrobial resistance (AMR) associated with pneumococcal disease due to reductions in vaccine-type serotypes, which commonly contain AMR determinants.[13] High pneumococcal density in the nasopharynx is associated with respiratory disease;

however, PCV impact on pneumococcal carriage density is currently unclear.[14]

Mongolia, an LMIC in central Asia, introduced the 13-valent PCV (PCV13) in June, 2016,[15] due to the high burden of respiratory disease in hospitalised children.[16] Previously, we showed that the introduction of PCV13 significantly reduced vaccine-type pneumococcal carriage in healthy young children in this setting.[17] In the present study, we aimed to describe the trend and impact of PCV13 introduction on pneumococcal carriage in hospitalised children aged 2–59 months with pneumonia in Mongolia over a 6-year period. We investigated changes in serotype prevalence and distribution, as well as pneumococcal carriage density and AMR genes.

Methods

Study design

We conducted an active pneumonia surveillance programme in Ulaanbaatar, the capital city of Mongolia. In April, 2015, expanded hospital-based surveillance of pneumonia was initiated in four districts across Ulaanbaatar (Bayanzurkh, Chingeltei, Songinokhairkhan, and Sukhbaatar).[15,16] The Mongolian Government recommends two doses of PCV13 at age 2 months and 4 months, with a booster dose at age 9 months (ie, 2 + 1 schedule). PCV13 was introduced into the national immunisation programme through a step-wedged design by district, starting with two districts in June, 2016 (Songinokhairkhan and Sukhbaatar); followed by one district in July, 2017 (Bayanzurkh); and the remaining districts of Ulaanbaatar in March, 2018 (including the fourth study district, Chingeltei). No catch-up campaign was included as part of the introduction in 2018.[15,16]

Study enrolment took place from April 1, 2015, to June 30, 2021. This study was approved by the Medical Ethics Review Committee at the Mongolian Ministry of Health and the Royal Children's Hospital Human Research Ethics Committee (33203). Written informed consent was obtained by study staff from all parents or caregivers for enrolled children before any study procedures were conducted.

Participants

Children with pneumonia who met the study case definition (aged 2–59 months with cough or difficulty breathing and either a respiratory rate ≥50 beats per min, oxygen saturation <90%, or clinical diagnosis of severe pneumonia) and were admitted to one of the four participating district hospitals (or the tertiary hospital for relevant district residents) were eligible for inclusion, as previously described.[15]

Primary endpoint pneumonia (PEP) was defined with WHO's chest x-ray criteria;[18] severe pneumonia was defined with the case definition provided by WHO's 2005 handbook on the integrated management of childhood illness;[19] and very severe pneumonia included severe cases complicated by empyema, admission to intensive care, persistent severe disease following hospital discharge, hypoxia, or death.[16] We defined probable pneumococcal pneumonia as an elevated concentration of C-reactive protein with either PEP or high nasopharyngeal carriage of pneumococcus (either high density carriage $>1\times10^6$ $\log_{10}$ genome equivalents per mL, or carriage of serotypes 1 or 5).[15]

Procedures

Hospital staff completed two standardised questionnaires collecting information on participant demographics and medical history, including risk factors for pneumococcal carriage. Staff also collected blood samples, nasopharyngeal swabs, and chest x-rays at the enrolment visit only, following the provision of parental consent.

We used WHO's recommended methods for the collection, handling, and transport of nasopharyngeal samples.[20] Approximately 1000 cases per calendar year were tested for pneumococci, which included all PEP cases and a random sample of the remaining cases. However, fewer samples were available during 2020 and 2021 following a drop in pneumonia cases due to the introduction of non-pharmaceutical interventions and temporary halts in sample collection throughout the period of hard lockdowns in Ulaanbaatar during the COVID-19 pandemic (Dec 6, 2020–Feb 28, 2021, and April 10–May 8, 2021). To compensate for the few samples collected in 2020–21, additional enrolment samples from 2019 were randomly selected for testing to ensure that approximately 3000 samples were tested for these 3 years.

Laboratory methods have previously been described in detail,[11] and are outlined in the appendix (p 2). In brief, DNA was extracted from aliquoted samples and real-time quantitative PCR targeting the *lytA* gene was performed. Carriage density (genome equivalents per mL) was calculated by reference to a standard curve prepared from reference isolate genomic DNA.[11] Molecular serotyping by DNA microarray was conducted as previously described.[11,17] Samples that were positive for *lytA* on quantitative PCR (cycle threshold value <35) and unable to be serotyped (low DNA yield or non-culturable) were considered to be positive for pneumococcus, serotype unknown.[17] PCV13 (or vaccine-type) serotypes were defined as 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, and 23F. Serotypes 15B and 15C were reported as 15B/C and 11F-like serotypes as 11A.[21,22] All other serotypes, including non-encapsulated pneumococci,[21] were considered to be non-PCV13 (ie, non-vaccine serotypes). A swab containing both a vaccine-type serotype and a non-vaccine serotype was considered positive for both. The presence of ten AMR genes was assessed by DNA microarray.[23]

See Online for appendix

Statistical analysis

The primary outcome was the impact of PCV13 on pneumococcal carriage in hospitalised children with pneumonia in Mongolia. Secondary outcomes included vaccine effectiveness, changes in the prevalence and distribution of serotypes, pneumococcal carriage density, and AMR genes.

We summarised categorical variables with frequency counts and percentages. Demographic variables were summarised by PCV13 introduction period and overall. We compared participants chosen for testing with those not tested to establish whether samples differed between these two groups and to check for potential bias. To evaluate risk factors for carriage, we compared participants who had pneumococcal carriage with those who did not. We used a χ^2 test to compare categorical data and a Mann–Whitney test to compare continuous data.

Vaccine impact was assessed by comparing overall, vaccine-type, and non-vaccine-type prevalence of pneumococcal carriage in the periods before and after the introduction of PCV13 (ie, the pre-PCV13 period and the post-PCV13 period), which were defined based on the month of vaccine introduction in the relevant district. Vaccine effectiveness was established by comparing carriage prevalence between vaccinated children (ie, received ≥2 doses at age <12 months of age or ≥1 dose administered at age ≥12 months) and under-vaccinated children (ie, 0–1 dose at age <12 months or no dose at age ≥12 months). For both vaccine impact and vaccine effectiveness, we estimated crude prevalence ratios (PRs) using univariable log-binomial regression and adjusted PRs using multivariable log-binomial regression. A common set of confounders was used to adjust the PRs, with the major difference in the models being the vaccine exposure variable (ie, PCV13 period for vaccine impact and individual vaccination status for vaccine effectiveness). We selected covariates using a directed acyclic graph, informed by relevant literature (appendix p 3), and included introduction period (for individual PCV receipt only), age group (2–23 months or 24–59 months), housing type (formal or informal), maternal education (primary [ages 6–11 years] or secondary [ages 11–18 years], or tertiary [≥18 years]), household income (above or at or below minimum income), household crowding (up to and including or more than three people per room), number of children younger than 5 years (one or at least two), household fuel type (electricity or gas, or coal or wood), season (summer, autumn, winter, or spring) and antibiotic exposure in the 48 h before hospital admission. Reductions in vaccine-type carriage were calculated as (1 − adjusted PR) × 100%. We performed a complete-case analysis including all participants with complete data for all variables in the model.

Carriage prevalence was calculated for individual vaccine-type serotypes and the 19 most common non-vaccine serotypes. Changes were plotted over time and PRs were calculated by comparing the post-PCV13 period with the pre-PCV13 period. Individual serotypes were plotted to 2020 only, given that only 14 samples were found to be positive for pneumococcus in 2021.

Data on the colonisation density of nasopharyngeal pneumococcus were $\log_{10}$ transformed and reported as $\log_{10}$ genome equivalents per mL. Density data were compared between the pre-PCV13 and post-PCV13 periods for all participants and were stratified by different age groups. To establish the effect of PCV13 on colonisation density, we calculated median carriage densities for both vaccinated children and under-vaccinated children. Quantile regression was used to compare the impact of PCV13 on median pneumococcal densities. A reduced common set of confounders was used to adjust the regression coefficient (appendix p 2).

We identified the detection rates of AMR genes for all, vaccine-type, and non-vaccine serotypes. We compared AMR detection rates between the pre-PCV13 and post-PCV13 periods. Only samples that contained a single pneumococcal serotype with no other species identified were included in the AMR analysis. All statistical analyses were performed with Stata (version 17.0).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between April 1, 2015, and June 30, 2021, a total of 17 688 children aged 2–59 months were enrolled, of whom 17 607 (99·5%) met the study case criteria. Pneumonia diagnoses were highly seasonal, with the highest case numbers observed during the colder winter months (ie, November to February) over the 6-year period (appendix p 4). Most participants had a chest x-ray (14 184 [80·6%]), blood culture (15 232 [86·5%]), and a nasopharyngeal swab collected (15 411 [87·5%]). Given that we focused on testing all children who had PEP, children who were tested for pneumococcus were more likely to have more severe disease and risk factors for carriage than were those not tested (appendix p 8). Over the entire study period, 6545 (42·5%) of 15 411 collected nasopharyngeal swabs were tested for pneumococci. Of 5922 swabs collected from the pre-PCV13 period, 1837 (31·0%) swabs were tested; of 9489 swabs collected from the post-PCV13 period, 4708 (49·6%) were tested.

Of the 6545 participants with nasopharyngeal samples that were tested, 4736 (72·4%) were aged 2–23 months, 3567 (54·5%) were boys, 2978 (45·5%) were girls, and 3646 (55·7%) were recruited in the winter (table 1). Among samples tested, participant exposure to smoky fuel (coal or wood) or cigarette smoke in the home was high. Compared with children enrolled during the pre-PCV13 period, a lower proportion of children enrolled in the post-PCV13 period had asthma, previous hospital admission or antibiotic use before admission, or an extended hospital stay (table 1). The proportions of children with PEP, severe pneumonia, very severe pneumonia, and probable pneumococcal pneumonia were lower in the post-PCV13 period than in the pre-PCV13 period. A higher proportion of children were fully vaccinated in the two districts that had introduced PCV first, Songinokhairkhan (1115 [52·9%] of 2107) and Sukhbaatar (375 [41·8%] of 897), compared with the districts Bayanzurkh (441 [30·2%] of 1459) and Chingeltei (410 [26·9%] of 1522). Differences in the carriage of all pneumococcal

types, vaccine-type serotypes, and non-vaccine serotypes were observed between districts.

Over the whole study period, 3056 (46·7%) samples tested positive for pneumococcal carriage. Children who were pneumococci carriers were more likely to have risk factors for carriage (eg, live in crowded or informal households, share a household with more than one child younger than 5 years, or live in a household that uses coal or wood for fuel) and more severe disease (higher prevalence of PEP, severe pneumonia, and probable pneumococcal pneumonia) than children who were not carriers (appendix p 9). The proportion of missing data was less than 10·0% for all variables and 8·5% for PCV13 status specifically.

In all age groups, vaccine impact showed a similar prevalence of pneumococcal carriage between the pre-PCV13 period and post-PCV13 period (882 [48·0%] of 1837 *vs* 2174 [46·2%] of 4708; adjusted PR 0·98 [95% CI 0·92–1·04]; p=0·60; table 2), whereas vaccine-type carriage was reduced by 43·6% in the post-PCV13 period (adjusted PR 0·56 [95% CI 0·51–0·62]; p<0·0001). In the stratified analyses, younger children (aged 2–23 months) were more likely to be fully vaccinated and showed a 47·7% reduction in vaccine-type carriage (95% CI 41·2–53·5; adjusted PR 0·52 [95% CI 0·46–0·59]; p<0·0001), whereas children aged 24–59 months had a 29·3% reduction (95% CI 12·6–42·8; 0·71 [0·57–0·87]; p=0·0014; table 2). Non-vaccine-type carriage increased in all age groups combined (1·49 [1·32–1·67]) and in separate age groups (table 2).

Comparing vaccinated with under-vaccinated children showed a vaccine effectiveness of 26% (95% CI 15–36) for the carriage of vaccine-type serotypes in all children, with higher vaccine effectiveness in older children (39% [17–54]) than in younger children (21% [7–33]; appendix p 10). Annual carriage prevalence for all districts showed a reduction in the carriage of vaccine-type serotypes after 2018 (appendix p 11). Reductions in the carriage of vaccine-type serotypes in individual districts occurred approximately 1 year after the introduction of PCV13, with a net reduction over the study period (appendix pp 11–12).

Of the 3056 samples that tested positive for pneumococcal carriage, 2557 (83·7%) had serotyping results. Ten (0·3%) samples could not be serotyped due to insufficient DNA yield and 489 (16·0%) samples were non-culturable. Among the 2557 positive samples with serotyping results, 2120 (82·9%) contained a single serotype, 397 (15·5%) had two serotypes, 38 (1·5%) had three serotypes, and two (0·1%) had four serotypes. Pneumococcal carriage prevalence and PRs for individual serotypes are provided in the appendix (p 13). Following the introduction of PCV13, non-vaccine serotypes progressively became more common than vaccine-type serotypes (figure 1; appendix p 4). Between the pre-PCV13 and post-PCV13 periods, vaccine-type carriage decreased from 31·5% to 17·2% and non-vaccine-type carriage increased from 18·9% to 27·2% (table 1).

	Total (n=6545)	Pre-PCV13 period (n=1837)	Post-PCV13 period (n=4708)
Demographics			
Age group, months			
2–23	4736/6545 (72·4%)	1307/1837 (71·1%)	3429/4708 (72·8%)
24–59	1809/6545 (27·6%)	530/1837 (28·9%)	1279/4708 (27·2%)
Sex			
Male	3567/6545 (54·5%)	1021/1837 (55·6%)	2546/4708 (54·1%)
Female	2978/6545 (45·5%)	816/1837 (44·4%)	2162/4708 (45·9%)
District			
Bayanzurkh	1562/6545 (23·9%)	657/1837 (35·8%)	905/4708 (19·2%)
Chingeltei	1786/6545 (27·3%)	592/1837 (32·2%)	1194/4708 (25·4%)
Songinokhairkhan	2259/6545 (34·5%)	368/1837 (20·0%)	1891/4708 (40·2%)
Sukhbaatar	938/6545 (14·3%)	220/1837 (12·0%)	718/4708 (15·3%)
Primary caregiver			
Parent*	5842/6466 (90·3%)	1628/1807 (90·1%)	4214/4659 (90·4%)
Other relative	535/6466 (8·3%)	157/1807 (8·7%)	378/4659 (8·1%)
Other	89/6466 (1·4%)	22/1807 (1·2%)	67/4659 (1·4%)
Risk factors			
Season			
Summer	612/6545 (9·4%)	221/1837 (12·0%)	391/4708 (8·3%)
Autumn	807/6545 (12·3%)	219/1837 (11·9%)	588/4708 (12·5%)
Winter	3646/6545 (55·7%)	849/1837 (46·2%)	2797/4708 (59·4%)
Spring	1480/6545 (22·6%)	548/1837 (29·8%)	932/4708 (19·8%)
Malnourished†	372/6445 (5·8%)	110/1791 (6·1%)	262/4654 (5·6%)
Currently breastfed	3703/6474 (57·2%)	973/1808 (53·8%)	2730/4666 (58·5%)
Caesarean section delivery	1572/6456 (24·3%)	431/1803 (23·9%)	1141/4653 (24·5%)
Asthma	492/6421 (7·7%)	186/1788 (10·4%)	306/4633 (6·6%)
Children younger than 5 years in the household			
1	4377/6403 (68·4%)	1215/1776 (68·4%)	3162/4627 (68·3%)
≥2	2026/6403 (31·6%)	561/1776 (31·6%)	1465/4627 (31·7%)
Child attends daycare or kindergarten‡	1251/6455 (19·4%)	362/1801 (20·1%)	889/4654 (19·1%)
Chimney in the home	4170/6461 (64·5%)	1170/1806 (64·8%)	3000/4655 (64·4%)
Adult smoker living in household	2967/6465 (45·9%)	825/1807 (45·7%)	2142/4658 (46·0%)
Adult smoking within the house	702/6458 (10·9%)	226/1802 (12·5%)	476/4656 (10·2%)
Caregiver smokes	302/6464 (4·7%)	113/1807 (6·3%)	189/4657 (4·1%)
Previous hospital admission	2947/6434 (45·8%)	939/1795 (52·3%)	2008/4640 (43·3%)
Antibiotics in 48 h before admission	3253/6479 (50·2%)	983/1821 (54·0%)	2270/4658 (48·7%)
Socioeconomic factors			
Fuel used in the home			
Electricity or gas	2254/6454 (34·9%)	604/1808 (33·4%)	1650/4646 (35·5%)
Coal or wood	4200/6454 (65·1%)	1204/1808 (66·6%)	2996/4646 (64·5%)
Housing			
Formal	4024/6467 (62·2%)	1087/1808 (60·1%)	2937/4659 (63·0%)
Informal	2443/6467 (37·8%)	721/1808 (39·9%)	1722/4659 (37·0%)
Mother's education§			
Primary or secondary	3431/6439 (53·3%)	973/1793 (54·3%)	2458/4646 (52·9%)
Tertiary	3008/6439 (46·7%)	820/1793 (45·7%)	2188/4646 (47·1%)
Income level¶			
Above minimum income	3733/6089 (61·3%)	1043/1685 (61·9%)	2690/4404 (61·1%)
At or below minimum income	2356/6089 (38·7%)	642/1685 (38·1%)	1714/4404 (38·9%)
Crowding, people per room			
≤3	4497/6401 (70·3%)	1226/1770 (69·3%)	3271/4631 (70·6%)
>3	1904/6401 (29·7%)	544/1770 (30·7%)	1360/4631 (29·4%)

(Table 1 continues on next page)

	Total (n=6545)	Pre-PCV13 period (n=1837)	Post-PCV13 period (n=4708)
(Continued from previous page)			
Severity of disease			
Length of hospital stay, days			
≤7	5014/6545 (76·6%)	1324/1837 (72·1%)	3690/4708 (78·4%)
8–14	1402/6545 (21·4%)	469/1837 (25·5%)	933/4708 (19·8%)
≥15	129/6545 (2·0%)	44/1837 (2·4%)	85/4708 (1·8%)
Death	14/6523 (0·2%)	6/1829 (0·3%)	8/4694 (0·2%)
Hypoxia‖	1267/6347 (20·0%)	429/1676 (25·6%)	838/4671 (17·9%)
Primary endpoint pneumonia (defined by WHO)	1739/5996 (29·0%)	709/1627 (43·6%)	1030/4369 (23·6%)
Severe pneumonia**	5203/6512 (79·9%)	1520/1815 (83·7%)	3683/4697 (78·4%)
Very severe pneumonia††	2712/6512 (41·6%)	823/1815 (45·3%)	1889/4697 (40·2%)
Probable pneumococcal pneumonia‡‡	539/6526 (8·3%)	209/1829 (11·4%)	330/4697 (7·0%)
Pneumococcal carriage			
Any	3056/6545 (46·7%)	882/1837 (48·0%)	2174/4708 (46·2%)
PCV13	1290/6046 (21·3%)	548/1742 (31·5%)	742/4304 (17·2%)
Non-PCV13	1499/6046 (24·8%)	329/1742 (18·9%)	1170/4304 (27·2%)

Data are n/N (%). PCV13=13-valent pneumococcal conjugate vaccine. *Mostly mothers (5694 [97·5%] of 5842). †Weight for age –2 SD. ‡Daycare for children aged <2 years; kindergarten for children aged 2–5 years. §Primary or secondary (ages 6–18 years) and tertiary (ages >18 years). ¶Minimum income was considered 170 000₮ per person per month. ‖Defined as an oxygen saturation of less than 90%. **According to the case definition of WHO's 2005 handbook on the integrated management of childhood illness. ††Included severe cases complicated by empyema, admission to intensive care, persistent severe disease following hospital discharge, hypoxia, or death. ‡‡Defined as elevated concentrations of C-reactive protein with either primary endpoint pneumonia or high pneumococcal nasopharyngeal carriage (either high density carriage $>1\times10^6$ $\log_{10}$ genome equivalents per mL, or carriage of serotypes 1 or 5).

Table 1: **Characteristics of children aged 2–59 months tested for pneumococci as part of a pneumonia surveillance programme in the pre-PCV13 and post-PCV13 periods**

The most common individual vaccine-type serotypes were 19F and 6A; the most common non-vaccine serotypes were 15A and non-encapsulated lineage NT2 (appendix pp 5–6). There were dynamic changes in the prevalence of serotypes between 2015 and 2020. In terms of ranking, 19F went from the first to the second most common serotype, whereas 6A went from the second to the ninth most common. NT2 remained common, whereas 15A increased from uncommon to most common from 2018 onwards (appendix p 6). Changes in individual vaccine-type serotypes were similar between younger children (age 2–23 months) and older children (age 24–59 months). In the younger age group, non-vaccine serotypes NT2 (2015–16) and 15A (2018–20) were the most common; in the older age group, 15A replaced NT3b as the most common serotype from 2018 to 2019, then was supplanted by 15B/C in 2020 (figure 2). Overall, there was a statistically significant reduction in the prevalence of several individual vaccine-type serotypes (6A, 6B, 14, 19A, 19F, and 23F) and a significant increase in several individual non-vaccine serotypes (10A, 11A, 13, 15A, and 15B/C) between the pre-PCV13 and post-PCV13 periods (appendix p 13).

In all children who were pneumococci carriers, the median density of all pneumococcal carriage, as well as of vaccine-type and non-vaccine-type carriage, was slightly higher in the post-PCV13 period than in the pre-PCV13 period for all children, younger children, and older children (appendix pp 7, 14). The density of all pneumococcal, vaccine-type, and non-vaccine-type carriage was higher in children vaccinated with PCV13 than in under-vaccinated children (appendix p 15).

AMR genes were frequently detected, with 1761 (89·3%) of 1978 analysed samples containing at least one of the AMR genes assessed. Compared with non-vaccine serotypes, vaccine-type serotypes were more likely to have at least one AMR gene (specifically *tetM*, *mefA*, and *ermB*) and have multiple AMR genes (appendix p 16). The proportion of samples containing *tetM*, *cat*, *mefA*, and *ermB* decreased between the pre-PCV13 and post-PCV13 periods, as did those containing any or multiple resistance genes (table 3). In the post-PCV13 period, we detected 51·0% reduced odds of samples with any antimicrobial resistance genes and 55·6% reduced odds of samples with multiple antimicrobial resistance genes (table 3).

Although 6375 (97·4%) children tested for pneumococcal carriage had blood cultures that were tested, only seven (0·1%) were culture-positive for *S pneumoniae* and four had serotyping results (10F, 14, 9V, and 6A/B/C). One child had the same serotype identified on blood culture and carriage (serotype 14).

Discussion

In a large active surveillance programme examining data on pneumococcal carriage from hospitalised children with pneumonia in Mongolia, we showed a 43·6% reduction in vaccine-type carriage in the post-PCV13 period. This reduction in vaccine-type carriage was even greater among younger children (aged 2–23 months) with the highest carriage rates. This study in children with pneumonia from an LMIC adds to the evidence base of data on carriage in LMICs, where the burden of pneumococcal disease is the highest. We expect that the reduction in vaccine-type carriage will translate into reductions in pneumococcal disease as has been observed in other LMICs with surveillance of invasive pneumococcal disease.[13]

The reduction in vaccine-type carriage observed in the current study is consistent with findings from hospitalised children in Laos.[24] By contrast, no changes in vaccine-type carriage were observed in Papua New Guinea following the introduction of PCV13.[10] Possible explanations for these differences in findings include how vaccination coverage is lower for eligible children in Papua New Guinea than in Mongolia and Laos, as well as the intensity and diversity of carriage in Papua New Guinea, where children acquire pneumococcus early in life, have high density carriage, and carry multiple serotypes.[10] In this study, we observed some variation in the reduction of vaccine-type serotypes by district, probably due to how a catch-up campaign was only implemented in three of the districts at the time of PCV13 introduction and the different lengths of PCV use by district.

Reductions in the carriage of vaccine-type serotypes after the introduction of PCV have been documented from carriage surveys of healthy children in LMICs, including in Mongolia.[17] In healthy children, vaccine-type carriage can persist following the introduction of PCV, even in countries with high vaccination coverage.[25] There is some evidence of

	Pre-PCV13 period	Pre-PCV13 prevalence (95% CI)	Post-PCV13 period	Post-PCV13 prevalence (95% CI)	Unadjusted PR (95% CI)	p value	Adjusted PR (95% CI)*	p value
All pneumococci								
All ages	882/1837 (48·0%)	48·0 (45·7–50·3)	2174/4708 (46·2%)	46·2 (44·7–47·6)	0·96 (0·91–1·02)	0·18	0·98 (0·92–1·04)†	0·60
Age 2–23 months	644/1307 (49·3%)	49·3 (46·5–52·0)	1590/3429 (46·4%)	46·4 (44·7–48·0)	0·94 (0·88–1·01)	0·070	0·97 (0·90–1·04)‡	0·38
Age 24–59 months	238/530 (44·9%)	44·9 (40·6–49·2)	584/1279 (45·7%)	45·7 (42·9–48·4)	1·02 (0·91–1·14)	0·77	1·03 (0·92–1·17)‡	0·57
Vaccine-type serotypes								
All ages	548/1742 (31·5%)	31·4 (29·3–33·7)	742/4304 (17·2%)	17·2 (16·1–18·4)	0·55 (0·50–0·60)	<0·0001	0·56 (0·51–0·62)†	<0·0001
Age 2–23 months	418/1242 (33·7%)	33·6 (31·0–36·3)	538/3139 (17·1%)	17·1 (15·8–18·5)	0·51 (0·46–0·57)	<0·0001	0·52 (0·46–0·59)‡	<0·0001
Age 24–59 months	130/500 (26·0%)	26·0 (22·2–30·1)	204/1165 (17·5%)	17·5 (15·4–19·8)	0·67 (0·55–0·82)	<0·0001	0·71 (0·57–0·87)‡	0·0014
Non-vaccine serotypes								
All ages	329/1742 (18·9%)	18·9 (17·1–20·8)	1170/4304 (27·2%)	27·2 (25·8–28·5)	1·44 (1·29–1·60)	<0·0001	1·49 (1·32–1·67)†	<0·0001
Age 2–23 months	227/1242 (18·3%)	18·3 (16·2–20·5)	863/3139 (27·5%)	27·5 (25·9–29·1)	1·50 (1·32–1·71)	<0·0001	1·58 (1·37–1·82)‡	<0·0001
Age 24–59 months	102/500 (20·4%)	20·4 (16·9–24·2)	307/1165 (26·4%)	26·3 (23·8–29·0)	1·29 (1·06–1·57)	0·011	1·29 (1·04–1·59)‡	0·021

Data are n/N (%), unless otherwise indicated. PCV13=13-valent pneumococcal conjugate vaccine. PR=prevalence ratio. *Used to calculate vaccine impact (1 – adjusted PR) × 100%. †Adjusted using a common set of confounders: age, informal housing, other children younger than 5 years in the home, coal used for fuel, maternal education, crowding, household income, season, and antibiotic exposure before hospital admission. ‡Adjusted using a common set of confounders: informal housing, other children younger than 5 years in the home, coal used for fuel, maternal education, crowding, household income, season, and antibiotic exposure before hospital admission.

Table 2: **Pneumococcal carriage prevalence and PRs for all pneumococci, vaccine-type, and non-vaccine serotypes in hospitalised children with pneumonia in the pre-PCV13 and post-PCV13 periods**

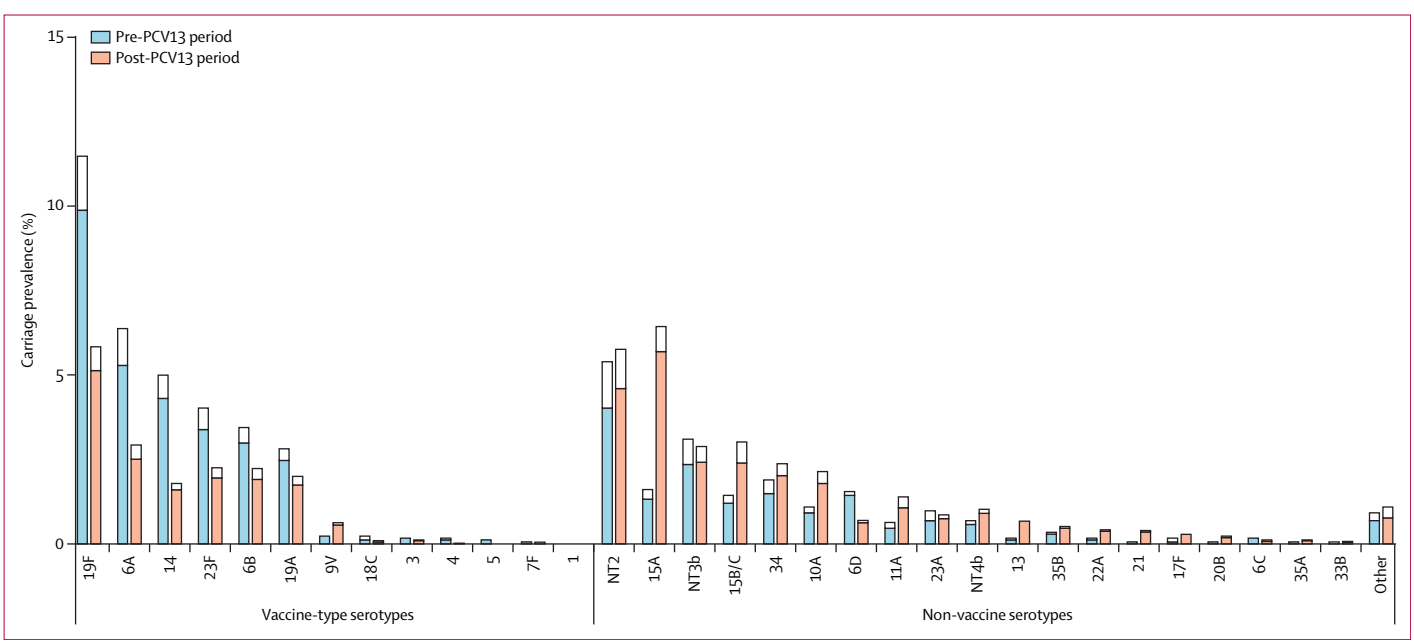

Figure 1: **Carriage prevalence of all vaccine-type serotypes and the most common non-vaccine serotypes in children aged 2–59 months before and after the introduction of PCV13**
Serotypes ordered in decreasing frequency. Solid bars indicate carriage that was detected as a single or major (dominant) serotype; open bars indicate carriage that was detected as a minor (second or third) serotype. NT2, NT3b, and NT4b refer to different lineages of non-encapsulated pneumococci.[21] Other non-vaccine serotypes include all other identified non-vaccine serotypes not listed individually. PCV13=13-valent pneumococcal conjugate vaccine.

vaccine-type persistence in children with respiratory illness,[10] although this has not been observed in all studies.[24] In the present study, although the prevalence of vaccine-type serotypes reduced significantly after the introduction of PCV13, the prevalence of some serotypes, particularly 19F, 6A, and 6B, remained high in the post-PCV13 period. Persistently high residual carriage of vaccine-type serotypes maintains pneumococcal transmission and has the potential to result in ongoing vaccine-type disease. Pneumococcal carriage in children with pneumonia potentially reflects serotypes causing disease; for example, a study from The Gambia found the same pneumococcal serotypes in lung aspirates and nasopharyngeal aspirates from children with severe pneumonia.[26] By contrast, carriage surveys of healthy children are likely to reflect circulating pneumococcal populations. In Mongolia, the most common serotypes were the same between healthy children[17] and children with pneumonia, whereas more differences were seen in serotypes between healthy children and children with pneumonia in Nepal.[12]

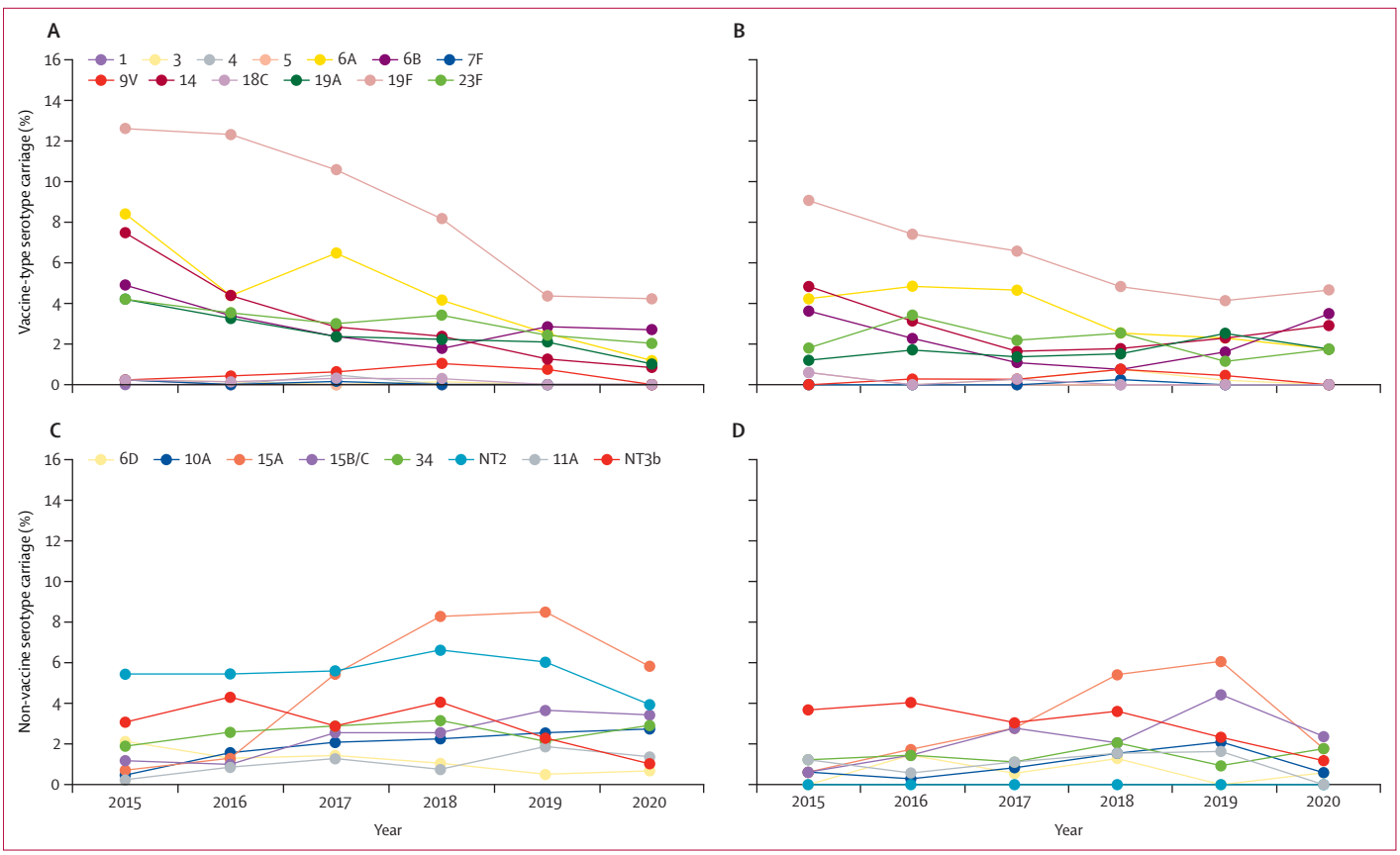

Figure 2: **Nasopharyngeal carriage prevalence of pneumococcal serotypes in children aged 2–59 months**
Vaccine-type serotypes in children aged 2–23 months (A) and in children aged 24–59 months (B). Most common non-vaccine serotypes in children aged 2–23 months (C) and in children aged 24–59 months (D).

	Encoded resistance	Detected in pre-PCV13 period (n=517)	Detected in post-PCV13 period (n=1130)	Adjusted OR* (95% CI)	p value
tetM	Tetracycline	457 (88·4%)	900 (79·6%)	0·51 (0·37–0·69)	<0·0001
tetK	Tetracycline	30 (5·8%)	55 (4·9%)	0·82 (0·52–1·29)	0·39
tetO	Tetracycline	0	2 (0·2%)	1·12 (0·09–not reached)	0·93†
tetL	Tetracycline	2 (0·4%)	4 (0·4%)	0·92 (0·17–5·04)	0·92
cat	Chloramphenicol	112 (21·7%)	151 (13·4%)	0·56 (0·42–0·73)	<0·0001
mefA	Macrolides	228 (44·1%)	360 (31·9%)	0·60 (0·48–0·74)	<0·0001
aphA3	Kanamycin	4 (0·8%)	20 (1·8%)	2·37 (0·80–6·97)	0·12
sat4	Streptothricin	4 (0·8%)	20 (1·8%)	2·37 (0·80–6·97)	0·12
ermB	Erythromycin	381 (73·7%)	703 (62·2%)	0·59 (0·47–0·74)	<0·0001
ermC	Erythromycin	46 (8·9%)	87 (7·7%)	0·87 (0·60–1·27)	0·47
Any antimicrobial resistance gene	NA	477 (92·3%)	964 (85·3%)	0·49 (0·34–0·70)	<0·0001
≥3 antimicrobial resistance genes	NA	242 (46·8%)	312 (27·6%)	0·44 (0·36–0·55)	<0·0001

Data are n (%), unless otherwise indicated. Only samples that contained a single pneumococcal serotype with no other species identified were included in the analysis. NA=not applicable. OR=odds ratio. PCV13=13-valent pneumococcal conjugate vaccine. *ORs compared antimicrobial resistance between the pre-PCV13 and post-PCV13 periods. Logistic regression adjusted for antibiotic exposure in the 48 h before hospital admission and age group. †Exact logistic regression.

Table 3: **Antimicrobial resistance genes detected by microarray in nasopharyngeal samples from hospitalised children (aged 2–59 months) with pneumonia**

We showed that non-vaccine-type carriage significantly increased between the pre-PCV13 and post-PCV13 periods. Although serotype replacement is common, the extent of replacement varies by setting, likely due to a combination of factors.[27] Individual pneumococcal serotypes differ in their potential to cause disease.[28] Most replacement serotypes have low invasive disease potential.[28] In this study, the most common replacement serotypes were 15A, 15B/C, and NT2, which have relatively low invasiveness when comparing serotypes between carriers with invasive pneumococcal

disease and healthy carriers.[28] Carriage of serotype 15A and 23A also increased significantly among healthy children in Mongolia 1 year after the introduction of PCV13.[17] Ongoing surveillance is required to establish whether non-vaccine-type invasiveness remains constant or changes over time in the post-vaccine period.

High pneumococcal density is associated with an increased risk of pneumococcal disease. A study in Viet Nam found higher carriage density among children with acute respiratory infection than among healthy children, and for vaccine-type serotypes than for non-vaccine serotypes.[29] The impact of PCV on pneumococcal density is variable and dependent on several factors, including testing methodology, viral co-infections, age, and previous antibiotic use.[14] Our previous survey on community carriage among healthy children in two districts of Ulaanbaatar showed an increase in both vaccine-type and non-vaccine-type carriage density 1 year after the introduction of PCV13.[17] In the present study, we observed increased carriage density among vaccinated children and in the post-PCV13 period, although absolute differences were small and might not be biologically meaningful.

The detection of AMR genes was high overall. Similar to another study from Laos,[11] more AMR genes were detected in vaccine-type serotypes than in non-vaccine serotypes. Additionally, the proportion of samples with AMR genes decreased following PCV introduction.[11] Historically, inappropriate antibiotic prescribing in hospitalised and non-hospitalised patients in Mongolia has been high, contributing to resistance. Since 2012, progressive policies have been introduced by the Mongolian Government to restrict antibiotic dispensing with a prescription only, but this has been difficult to regulate nationally. Changes in antibiotic practices might have also influenced the AMR reductions observed in this study. It is important that AMR surveillance is ongoing and future studies use methods that can accurately assess pneumococcal AMR.

Our study had several important strengths. We had a systematic, active pneumonia surveillance programme across four districts of Ulaanbaatar over a 6-year period, which is the largest pneumonia surveillance programme with nasopharyngeal carriage samples in an LMIC to date. We performed testing using sensitive molecular methods to identify pneumococcal carriage and serotypes.[20] Testing methods were consistent with pneumonia carriage studies in Laos and Papua New Guinea, allowing direct comparisons between studies.[10,24] Importantly, we were able to establish that, even in a setting with high prevalence of risk factors (including air pollution), PCV13 resulted in a reduction of vaccine-type carriage.

Our study had several limitations. First, not all pneumococcal samples were tested; however, we chose PEP samples that were more likely to be positive for pneumococcus[30] and tested a distribution of samples across the surveillance period. Second, we had a high proportion of non-culturable samples (16·3%), likely due to some children receiving antibiotics before hospital admission. Of note, a hospital-based carriage study from Laos had a similar proportion of non-culturable samples (13·1%).[24] Importantly, the use of a molecular screen allowed us to assess the true prevalence of pneumococcal carriage (inclusive of non-culturable samples), which is likely to have been underestimated in many studies in similar populations with the use of culture-based methods. However, there was some variability in the percentage of pneumococci that could be serotyped over the study period. Third, there was an insufficient number of blood culture samples that were positive for pneumococcus to establish the effect of introducing PCV13 on invasive pneumococcal disease or to explore the correlation between carriage and invasive serotypes. We observed a reduction in the proportion of children who presented with more severe pneumonia and primary endpoint pneumonia in the post-PCV13 period.[31] Fourth, this study only included four districts across Ulaanbaatar, so it might not be generalisable to all children in Mongolia. However, the included districts account for around 70% of the population in Ulaanbaatar and half of the country's population live in this city. Finally, characterisation of AMR was limited to the detection of select resistance genes, and antimicrobial susceptibility testing was not conducted. Half of all children received antibiotics in the 48 h before hospital admission, which might have potentially biased carriage results given that resistant bacteria are more likely to be detected.

We have shown a substantial reduction in vaccine-type carriage following the introduction of PCV13 in hospitalised children in Mongolia. We anticipate a concurrent reduction in pneumococcal disease, particularly given that non-vaccine replacement serotypes were of reduced invasiveness. This study adds to the evidence base of carriage data in children with pneumonia from an LMIC setting with a high disease burden of pneumonia. Ongoing surveillance is important to document serotype trends over time with increasing vaccine coverage. Monitoring serotypes in children with pneumonia will contribute to the evidence base supporting PCV introduction and maintenance in other LMICs and will inform the development of future pneumococcal vaccines.

Contributors

EKM, CvM, and CS conceptualised and designed the study. CvM, TM, BT, DN, and SD were responsible for study oversight. MU, BS, DL, PB, and TM acquired the clinical data. BDO, CLP, AW-H, and MLN acquired the laboratory data. CS, EMD, BDO, and MLN oversaw the acquisition of pneumococcal carriage data. JH interpreted the microarray data. CvM, CS, and CDN devised the statistical analysis plan. TM, BS, DL, MU, PB, and CvM accessed and verified the clinical data. BDO, CLP, MLN, AW-H, JH, CS, and CvM accessed and verified the laboratory data. CvM performed the data analysis and drafted the manuscript. All authors were involved in data interpretation and review of the final manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

CvM, MU, CDN, PB, BS, DL, CS, TM, and EKM are investigators on a Pfizer collaborative research project outside this work. EMD is currently employed by Pfizer. CS, EKM, and CDN are investigators on a Merck Investigator Studies Program grant funded by MSD outside this work. CS has participated in expert panels for MSD and Pfizer. CvM has

participated in expert panels for Pfizer and Merck. JH is the co-founder and shareholder of BUGS Bioscience, a not-for-profit spinout company of St George's, University of London. All other authors declare no competing interests.

Data sharing

De-identified group data can be made available for sharing following application to the corresponding author. This application must include the relevant proposal detailing the intended use of the data and the ethics approval for this proposal, and requires a signed data sharing agreement.

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