Effect of Pneumococcal Conjugate Vaccine on Pneumonia Incidence Rates among Children 2–59 Months of Age, Mongolia, 2015–2021

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Starting in June 2016, the 13-valent pneumococcal conjugate vaccine (PCV13) was introduced into the routine immunization program of Mongolia by using a 2+1 dosing schedule, phased by district. We used prospective hospital surveillance to evaluate the vaccine's effect on pneumonia incidence rates among children 2–59 months of age over a 6-year period. Of 17,607 children with pneumonia, overall adjusted incidence rate ratios showed decreased primary endpoint pneumonia, very severe pneumonia, and probable pneumococcal pneumonia until June 2021. Results excluding and including the COVID-19 pandemic period were similar. Pneumonia declined in 3 districts that introduced PCV13 with catch-up campaigns but not in the 1 district that did not. After PCV13 introduction, vaccine-type pneumococcal carriage prevalence decreased by 44% and nonvaccine-type carriage increased by 49%. After PCV13 introduction in Mongolia, the incidence of more specific pneumonia endpoints declined in children 2–59 months of age; additional benefits were conferred by catch-up campaigns.

Globally, the most common infectious cause of death among children 1–59 months of age is lower respiratory tract infection (1). Despite vaccine availability, *Streptococcus pneumoniae* causes a substantial proportion of severe pneumonia cases, attributed to 18.3% of severe pneumonia episodes and 32.7% of all pneumonia deaths in children globally (2). Pneumonia disease burden is highest among younger children and in certain regions such as southern Asia and Africa (2).

Mongolia is a lower-middle-income country in central Asia. Half of the Mongolia population of 3.3 million live in the capital city of Ulaanbaatar (3). Similar to other low- and middle-income countries (LMICs), several demographic and socioeconomic factors in Mongolia increase the risk for childhood pneumonia (4). Rapid urbanization with expansion of informal living areas and coal use during winter has resulted in poor air quality in Ulaanbaatar (5). Air pollution exacerbates respiratory diseases such as asthma and increases the risk for pneumonia (6).

In the past 2 decades, pneumococcal conjugate vaccines (PCVs) have had a substantial public health effect globally; effectiveness against hospitalization for invasive pneumococcal disease, clinical pneumonia, and radiologically confirmed pneumonia has been demonstrated (7,8). Modeling has estimated that, in children <5 years of age, introduction of 13-valent PCV (PCV13) resulted in a reduction of 175 million cases of pneumococcal disease and 625,000 associated deaths worldwide over 10 years (9). Among those cases, 14 million illnesses and 374,550 deaths

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resulted from pneumococcal pneumonia (9); however, 6 countries in Asia have yet to introduce PCV into their national immunization programs, and in 2021, >25 million children in those regions still did not have access to the vaccines (10). Data from Asia with regard to pneumonia burden and PCV effect are lacking; only 2 studies have demonstrated the effect of PCV13 (11,12).

Starting in 2016, PCV13 was introduced into the routine infant immunization program of Mongolia, phased by district, in the context of an expanded pneumonia surveillance program to monitor vaccine effect (13). Baseline data estimated that clinical pneumonia incidence among children 2–59 months was 31.8 cases/1,000 population and for severe pneumonia was 19.2 cases/1,000 population (14). To ensure sustainability of the program in Mongolia, PCV13 was introduced in stages because the country was transitioning from Gavi funding (15).

Our study goal was to estimate the effect of PCV13 introduction on clinical and radiologic pneumonia endpoints among hospitalized children 2–59 months of age living in 4 districts of Ulaanbaatar, Mongolia, over a 6-year period. The 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 (HREC 33203). Written informed consent was obtained from all parents/caregivers for enrolled children before any study procedures were conducted.

Methods

Study Setting

Expanded hospital-based pneumonia surveillance was initiated in 4 districts of Ulaanbaatar in April 2015 as previously described (13,14). Mongolia introduced PCV13 into the national immunization program in a 2+1 schedule (2, 4, and 9 months) by district: June 2016 (Songinokhairkhan [SKD] and Sukhbaatar [SBD]), July 2017 (Bayanzurkh [BZD]), and March 2018 (Chingeltei [CHD]). Catch-up campaigns were instituted in the districts in which PCV13 was introduced in 2016 and 2017 (13,14). During 2017–2021, PCV13 coverage among the target age group from all introduced districts was reported to be 95%–98% (16).

Study Population and Design

During April 2015–June 2021, we enrolled children 2–59 months of age who were admitted to 1 of 4 four participating district hospitals (or the tertiary hospital if they resided in one of the relevant districts) and met the specific study case definition for clinical pneumonia. We excluded patients with bronchiolitis and bronchitis. Protocol details have been previously published (13) (Appendix, https://wwwnc.cdc.gov/EID/article/30/3/23-0864-App1.pdf). Bloodsamples, nasopharyngeal swab samples, and chest radiographs were collected for all enrolled patients or for whom consent was provided. To ensure that no eligible patients were missed, dedicated study staff ensured that patients were correctly enrolled by clinical hospital staff.

The primary study outcome was World Health Organization (WHO)–defined primary endpoint pneumonia (PEP) (17). Secondary outcomes were clinical pneumonia (all cases); severe pneumonia (WHO 2005 case definition [18]); very severe pneumonia (severe cases complicated by empyema, intensive care unit admission, persistent severe disease after discharge, hypoxia, or death [14]); hypoxic pneumonia (oxygen saturation <90%); probable pneumococcal pneumonia (PPP) (19) (elevated C-reactive protein with either PEP [19] or high pneumococcal nasopharyngeal carriage); or definite pneumococcal pneumonia (positive blood or pleural fluid culture) and pneumococcal carriage (13).

Sample Collection and Laboratory Procedures

We adhered to WHO recommended methods for nasopharyngeal sample collection, handling, and transport (20). We tested nasopharyngeal swab samples for pneumococci by using *lytA* real-time quantitative PCR and molecular serotyping by DNA microarray (Appendix) (21). We tested 1,000 patients/year for pneumococci, including all patients with PEP (primary objective) and a random sample of remaining patients.

Statistical Analyses

We summarized categorical variables with frequency counts and percentages and demographic variables by district and overall. To determine changes before and after PCV13 introduction, we compared characteristics of children during the 2 periods. We calculated crude annual incidence rates for April–March because surveillance started in April 2015 and pneumonia was highly seasonal and most cases were identified during winter. We obtained annual population estimates for denominators from the Mongolian Ministry of Health. We calculated CIs for incidence estimates by using a Poisson distribution. We based the definitions of pre-PCV13 and post-PCV13 periods on month of vaccine introduction at the district level. We calculated crude incidence rates and incidence rate ratios (IRRs) comparing pre-PCV13 and post-PCV13

periods for all patients and stratified them by district and age group.

We calculated adjusted IRRs (aIRRs) for different pneumonia endpoints comparing pre-PCV13 and post-PCV13 periods by using negative binomial regression with separate models for data until February 2020 (excluding the COVID-19 pandemic period) and June 2021 (end of study). All models included terms for PCV13 introduction, district, age group, and a categorical variable for each calendar month elapsed (to account for secular trends), with log-transformed population denominators included as an offset. To allow for a differential effect between districts, we included an interaction term between PCV13 and district for district-specific effects. The model coefficients were exponentiated to obtain IRRs with 95% CIs. We calculated percent reduction in pneumonia rates as (1 – IRR) × 100%. We conducted 2 sensitivity analyses for IRR calculations. We first introduced a 1-year lag period for effect of PCV introduction and then stratified IRRs by age group (2–23 months and 24–59 months).

We used univariable and multivariable log-binomial regression to estimate crude and adjusted prevalence ratios (aPR) for overall, PCV13-type and non-PCV13–type prevalence of pneumococcal carriage. To adjust prevalence ratios, we used a common set of confounders, selected by using a directed acyclic graph based on current literature (Appendix Figure 1). We calculated prevalence ratios by comparing the post-PCV13 with the pre-PCV13 period for all endpoints. Reductions in PCV13 carriage were calculated as (1 – aPR) × 100%. We used Stata statistical software 17.0 (StataCorp LLC, https://www.stata.com) to analyze data.

Results

During April 1, 2015–June 30, 2021, a total of 55,691 children 2–59 months of age with acute lower respiratory tract infections were admitted to one of the study hospitals; 17,688 (32%) were assessed according to the study case definition, received study consent, and were enrolled (Appendix Figure 2). Among the 17,607 confirmed to meet all study eligibility criteria, 71% were 2–23 months of age, 54% were male and 46% female, and most were admitted during autumn and winter (Appendix Table 1). More than two thirds of households had single children <5 years of age, and 21% of children attended kindergarten. Most participants (15,248 [87%]) had a risk-factor questionnaire completed by a parent or caregiver; 81% (14,184), underwent chest radiography; and 87% (15,411) had nasopharyngeal swab samples collected and processed, of which 6,545 swabs were tested for pneumococci. Of 13,602 children for whom complete data were available to assess PPP, 11% met the case definition. Blood cultures were performed for 15,232 (87%) children, but only 14 (0.1%) were culture-positive for *S. pneumoniae*. For 2 children, *S. pneumoniae* was cultured from pleural fluid; and for 1 child, blood culture was also positive.

The highest numbers of patients were enrolled from the largest districts, SKD and BZD. Differences were observed between the 4 study districts (Appendix Table 1). Most households in CHD (2,984/3,703 [81%]) and SKD (3,259/4,568 [71%]) used coal or wood as the main fuel source, and only half of the households in SBD and BZD used those smoky fuels. The highest proportions of participants living in crowded households were in CHD (32%) and SKD (36%) or living in informal housing were also in those same 2 districts (39% for CHD and 45% for SKD). Overall, 77% of participants had severe pneumonia; proportions were slightly higher in CHD (79%) and SKD (81%). A total of 37% of participants had very severe pneumonia; percentages were highest in BZD (43%) and CHD (46%). Of 13,755 children with interpretable chest radiographs, 1,813 (13%) had PEP (Appendix Table 1).

Pneumonia incidence rates were highly seasonal; case numbers were highest during winter (October–February) (Figure 1; Appendix Figure 3). After PCV13 introduction, peak incidence of all clinical pneumonia decreased, except in CHD, which had no PCV catch-up campaign (Figure 1). Pneumonia incidence decreased from February 2020 through June 2021, when COVID-19 restrictions, including kindergarten/school closures, were in place. No winter peak was observed during the 2020–21 season (Figure 1; Appendix Figure 3). Overall, 32% of admitted patients met the study case definition, which was intended to exclude patients with milder pneumonia (Appendix Figure 4).

The profile of participants differed before and after introduction of PCV13 (Appendix Table 2). Compared with the pre-PCV13 period, percentages were lower for children previously admitted (48% before vs. 42% after; p<0.0001), with hypoxia (22% before vs. 17% after; p<0.0001), or with primary endpoint pneumonia (14% before vs. 13% after; p = 0.007) in the post-PCV13 period. The percentage of children with severe and very severe pneumonia in the post-PCV13 period was also reduced (Appendix Table 2).

By March 2020 (early COVID-19 pandemic restrictions), changes for crude IRRs varied by pneumonia diagnosis and district (Appendix Table 3). For all districts combined, IRR was reduced for all patients

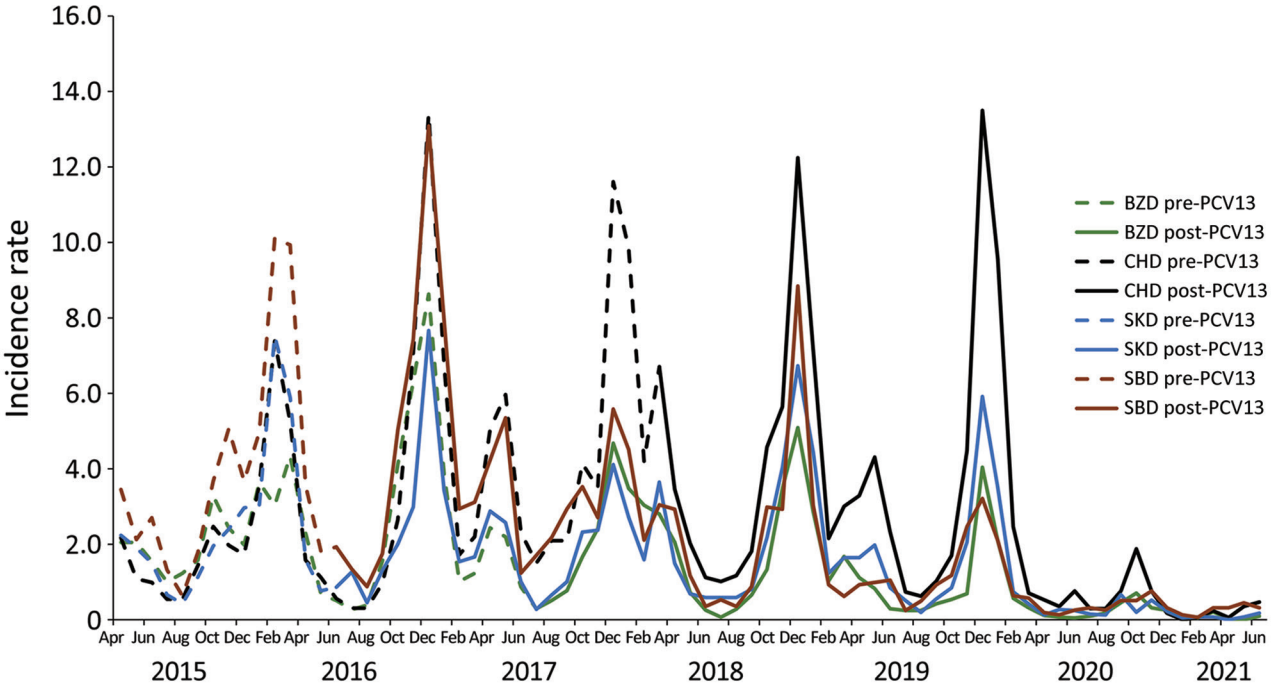

Figure 1. All clinical pneumonia incidence rates (cases/1,000 population) by month and district in children 2–59 months of age, Ulaanbaatar, Mongolia, April 2015–June 2021. BZD, Bayanzurkh District; CHD, Chingeltei District; PCV13, 13-valent pneumococcal conjugate vaccine; SBD, Sukhbaatar District; SKD, Songinokhairkhan District.

with all clinical pneumonia (21%, 95% CI 18%–23%), PEP (20%, 95% CI 12%–27%), severe pneumonia (23%, 95% CI 20%–25%), very severe pneumonia (26%, 95% CI 22%–29%), hypoxic pneumonia (34%, 95% CI 29%–39%), and PPP (38%, 95% CI 31%–44%). Individual districts mainly showed reductions, except for CHD, which showed increases in IRRs in cases of all clinical, severe, and very severe pneumonia. By March 2021, which included a period of COVID-19 restrictions, additional reductions were observed in line with reduced case numbers, and PEP was reduced by 36% (95% CI 29%–42%) (Appendix Table 3). We found some variability by age group; slightly larger reductions were observed for the 24–59-month age group compared with the younger age group (Appendix Table 4). Annual incidence rates were highest in 2016 in SKD, SBD, and BZD, but CHD showed high incidence rates until 2019 (Appendix Table 5).

To account for secular trends and district effect not accounted for in crude IRRs, we calculated aIRRs for different pneumonia endpoints until February 2020 before extensive COVID-19 lockdown measures (Figure 2; Appendix Table 6). Those aIRRs showed a reduction in all clinical pneumonia rates in 3 of the districts (BZD 0.71, 95% CI 0.59–0.85; SKD 0.86, 95% CI 0.70–1.07; SBD 0.64, 95% CI 0.51–0.79) and an increase in 1 district (CHD 1.68, 95% CI 1.41–2.01) where PCV13 was introduced last without a catch-up campaign. The trends observed in the other pneumonia endpoints were similar across districts. For all districts combined by February 2020, aIRRs showed a reduction in PEP (0.72, 95% CI 0.56–0.93), very severe pneumonia (0.77, 95% CI 0.64–0.93), and PPP (0.77, 95% CI 0.61–0.97); however, reductions were not shown for severe pneumonia (0.97, 95% CI 0.82–1.15), hypoxic pneumonia (0.83, 95% CI 0.67–1.04), or all clinical pneumonia (1.01, 95% CI 0.87–1.17) (Figure 2; Appendix Table 6). Reductions were similar until June 2021 (Figure 3, Appendix Table 6).

A total of 6,545 samples were tested for pneumococci. Overall, 3,056 (47%) were positive for pneumococcal carriage and 2,557 (84%) were culturable and had serotyping results, of which 1,058 (41%) had PCV13-type serotypes, 1,267 (50%) had non–PCV13-type serotypes, and 232 (9%) had both types of serotype identified. In all districts combined, overall pneumococcal carriage prevalence (any serotype) did not change between the pre-PCV13 (48%) and post-PCV13 (46%) periods (adjusted prevalence ratio [aPR] 0.98, 95% CI 0.92–1.04) overall or in the individual districts (Table). PCV13-type carriage overall was reduced by 44% (aPR 0.56, 95% CI 0.51–0.62) and in each district ranging from 41% in BZD and SBD to 50% in SKD. Non–PCV13-type carriage increased overall (aPR 1.49, 95% CI 1.32–1.67) and significantly in 2 districts (Table).

Sensitivity Trends

We calculated aIRRs, assuming a delay of 1 year for the effect of PCV13 introduction among all children 2–59 months of age (Appendix Table 7). Results for PEP were similar to those of the main analysis (26% [95% CI 4%–43%] reduction). We observed a greater reduction in clinical pneumonia (24%, 95% CI 9%–36%), severe pneumonia (24%, 95% CI 8%–38%), and very severe pneumonia (30%, 95% CI 14%–44%) compared with the main analyses.

Stratification by age group (2–23 months and 24–59 months) demonstrated a greater reduction in most endpoints among older children. All clinical pneumonia cases were reduced by 12% (95% CI −7% to 27%) (negative numbers indicate an increase), PEP a 38% (95% CI 10%–57%) reduction, severe pneumonia a 13% (95% CI −9% to 30%) reduction, very severe pneumonia a 39% (95% CI 21%–52%) reduction, and hypoxic pneumonia a 31% (95% CI 7%–48%) reduction in all districts combined (Appendix Table 7).

Discussion

In our large-scale surveillance study in Mongolia, a country with a high burden of respiratory disease, we demonstrated the effect of PCV13 introduction on children hospitalized for pneumonia. We found that phased introduction of PCV13 in 4 districts of Ulaanbaatar resulted in reduced disease incidence, with some variability by district, age, and pneumonia endpoint used. Overall, PCV13 led to similar reductions in cases of PEP (28%), very severe pneumonia (23%), and PPP (23%) but no significant reduction of all clinical pneumonia or severe pneumonia. Reductions were observed in 3 districts in which catch-up campaigns were conducted at the time of vaccine introduction. PCV13-type pneumococcal carriage declined overall (44%) and in each individual district. Non–PCV13-type carriage increased overall and significantly in 2 districts. Our surveillance program is one of few programs reporting PCV13 effect on pneumonia for a high-burden LMIC in Asia.

Many countries have used invasive pneumococcal disease (IPD) to determine PCV effect. Because IPD is rare and requires robust laboratory capacity, using IPD is often not possible in LMICs, nor is it an ideal metric in countries such as Mongolia with small populations and few annual IPD cases detected. Pneumonia surveillance can be an indicator of PCV effect. A challenge in studying PCV effect on pneumonia is that young children do not produce sputum, very few cases are bacteremic, and no diagnostic tests are available for nonbacteremic pneumococcal pneumonia in this age group.

In Fiji, a time-series analysis 5 years after PCV10 introduction found a reduction in pediatric hospitalizations for pneumonia, varying by age and pneumonia endpoint (22). Similar to the Fiji study, we found that compared with younger children, the reduction of pneumonia was greater among children 24–59 months of age, although a lower proportion of children in that group were fully vaccinated. It is likely that a higher percentage of cases in the older group were caused by pneumococcus and in the younger (<2 years of age) group by respiratory syncytial virus (23).

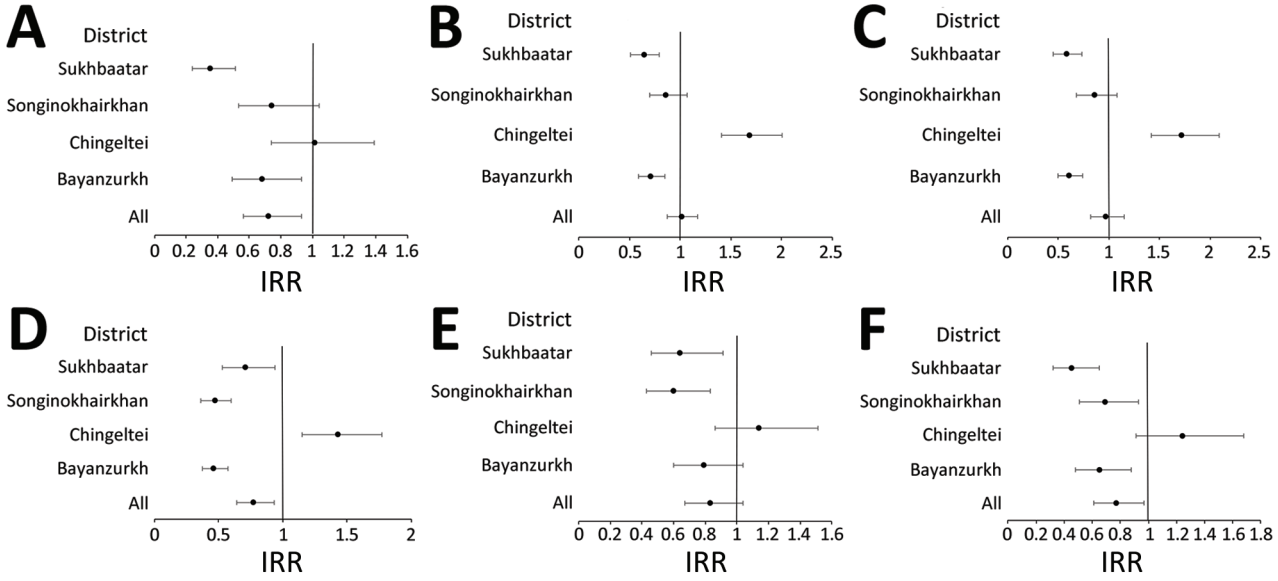

Figure 2. Adjusted IRRs for pneumonia endpoints for pre-vaccine period (April 2015–February 2020, excluding COVID-19 pandemic period) in study of effect of pneumococcal conjugate vaccine on pneumonia incidence rates among children 2–59 months of age, Mongolia, 2015–2021. A) Primary endpoint pneumonia; B) all pneumonia; C) severe pneumonia; D) very severe pneumonia; E) hypoxic pneumonia; F) probable pneumococcal pneumonia. Error bars indicate 95% CIs. IRR, incidence rate ratio.

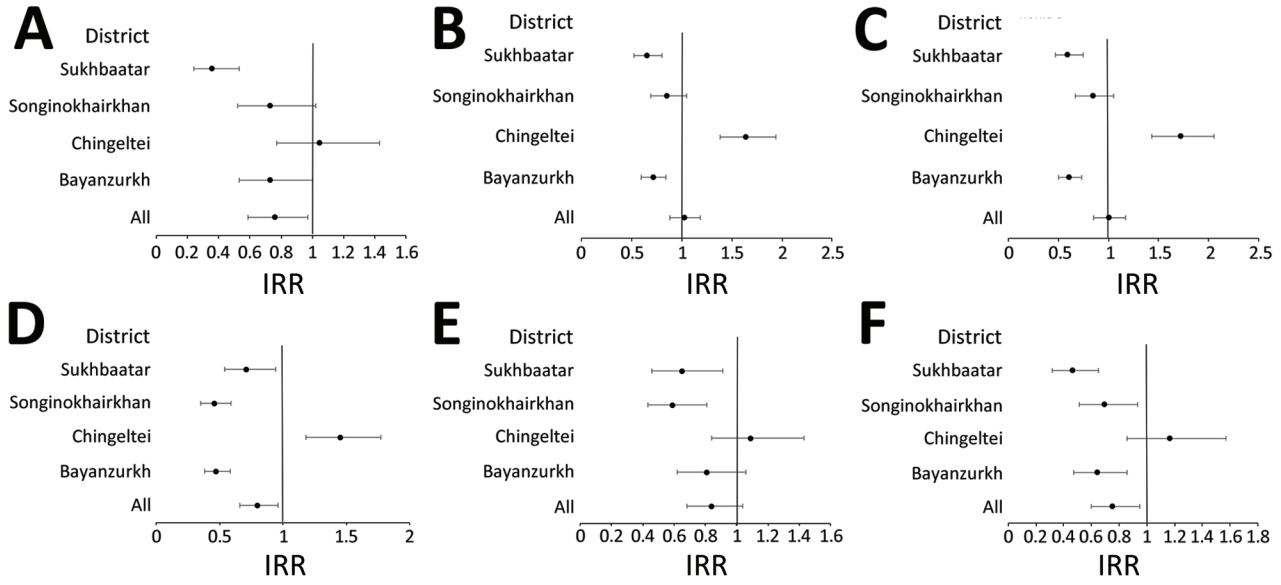

Figure 3. Adjusted IRRs for pneumonia endpoints post-vaccine period (April 2015–June 2021, including COVID-19 pandemic period) in study of effect of pneumococcal conjugate vaccine on pneumonia incidence rates among children 2–59 months of age, Mongolia, 2015–2021. A) Primary endpoint pneumonia; B) all pneumonia; C) severe pneumonia; D) very severe pneumonia; E) hypoxic pneumonia; F) probable pneumococcal pneumonia. Error bars indicate 95% CIs. IRR, incidence rate ratio.

A recent systematic review found a decline in pneumonia hospitalization incidence among children after PCV introduction, although the magnitude of the decline across different endpoints and settings displayed heterogeneity (24). The review demonstrated that PCV effect tended to increase as the pneumonia outcome increased in diagnostic specificity for pneumococcal disease (24). We observed substantial declines in carriage of PCV13 serotypes as well as declines in pneumonia outcomes considered more likely to be caused by pneumococcus, such as PEP and very severe pneumonia.

The decrease in pneumonia cases during 2020 and 2021 probably results from measures put in place to combat the COVID-19 pandemic. Mongolia instituted kindergarten/school closures from the end of January 2020 until September 2021, except for a brief period during late 2020 (25,26). In addition, travel bans, multiple hard lockdowns, and other public health nonpharmaceutical interventions were instituted (25,27), and COVID-19 vaccines were available starting in February 2021 (27). Studies from other countries have shown that restrictions instituted during the COVID-19 pandemic reduced childhood infections (28,29).

The use of catch-up campaigns has been encouraged by WHO as a strategy to increase herd immunity (30). Observational data from LMICs documenting the effect of catch-up campaigns are limited. A transmission dynamic model using data from Kenya indicated that a catch-up campaign among children <5 years of age prevented additional IPD cases and used fewer doses per case averted than routine introduction only (31). In our surveillance program, PCV introduction included a catch-up campaign in 3 of the 4 study districts. Pneumonia incidence was not significantly reduced in the district without catch-up (CHD) but was reduced, especially for more severe pneumonia endpoints, in the other districts. Of note, CHD was the last district to introduce PCV13, and no significant increase in non–PCV13-type carriage was demonstrated. The average annual coverage in eligible age groups in CHD was similar to routine coverage in BZD, where PCV13 was introduced in 2017.

In addition to catch-up campaigns, other explanations for different results between districts are variable smoke exposure, levels of poverty, housing type, crowding, and other factors reflective of known risk factors for pneumonia (4). Movement between districts and migration may also have varied over the study period. A previous publication from Mongolia found evidence of direct and indirect vaccine effects on carriage, which varied by formal and informal living conditions (32). We observed a reduction (46%) in vaccine-type pneumococcal carriage 3–5 years after introduction in 4 districts. We identified residual circulation of vaccine serotypes (17%) despite high PCV coverage, similar to findings in Malawi and South Africa (33,34).

One study strength is establishment of an expanded active pneumonia surveillance program on preexisting WHO invasive bacterial disease surveillance

Table. Carriage prevalence and prevalence ratios for pneumococcal carriage among 6,545 children with pneumonia before and after PCV13 availability, 4 districts, Mongolia, 2015–2021*

Pneumococcal type	Pre-PCV13, no./total	Pre-PCV13 prevalence, % (95% CI)	Post-PCV13 no./total	Post-PCV13 prevalence, % (95% CI)	Unadjusted prevalence ratio (95% CI)	Adjusted prevalence ratio (95% CI)†
Overall pneumococci						
All districts	882/1,837	48.0 (45.7–50.3)	2,174/4,708	46.2 (44.7–47.6)	0.96 (0.91–1.02)	0.98 (0.92–1.04)
Bayanzurkh	263/657	40.0 (36.2–43.9)	363/905	40.1 (36.9–43.4)	1.00 (0.89–1.13)	1.06 (0.93–1.21)
Chingeltei	341/592	57.6 (53.5–61.6)	565/1,194	47.3 (44.4–50.2)	0.82 (0.75–0.90)	0.81 (0.73–0.90)
Songinokhairkhan	184/368	50.0 (44.8–55.2)	953/1,891	50.4 (48.1–52.7)	1.01 (0.90–1.13)	1.00 (0.89–1.12)
Sukhbaatar	94/220	42.7 (36.1–49.5)	293/718	40.8 (37.2–44.5)	0.95 (0.80–1.14)	0.95 (0.79–1.14)
PCV13 serotypes						
All districts	548/1,742	31.4 (29.3–33.7)	742/4,304	17.2 (16.1–18.4)	0.55 (0.50–0.60)	0.56 (0.51–0.62)
Bayanzurkh	161/614	26.2 (22.8–29.9)	119/830	14.3 (12.0–16.9)	0.55 (0.44–0.68)	0.59 (0.47–0.75)
Chingeltei	200/566	35.3 (31.4–39.4)	205/1,077	19.0 (16.7–21.5)	0.54 (0.46–0.64)	0.53 (0.44–0.63)
Songinokhairkhan	127/354	35.9 (30.9–41.1)	306/1,737	17.6 (15.8–19.5)	0.49 (0.41–0.58)	0.50 (0.42–0.61)
Sukhbaatar	60/208	28.8 (22.8–35.5)	112/660	17.0 (14.2–20.0)	0.59 (0.45–0.77)	0.59 (0.44–0.78)
Non-PCV13 serotypes						
All districts	329/1,742	18.9 (17.1–20.8)	1,170/4,304	27.2 (25.8–28.5)	1.44 (1.29–1.60)	1.49 (1.32–1.67)
Bayanzurkh	76/614	12.4 (9.9–15.2)	193/830	23.2 (20.4–26.3)	1.88 (1.47–2.40)	1.95 (1.49–2.55)
Chingeltei	152/566	26.8 (23.2–30.7)	286/1,077	26.5 (23.9–29.3)	0.99 (0.83–1.17)	0.96 (0.79–1.17)
Songinokhairkhan	69/354	19.5 (15.5–24.0)	550/1,737	31.7 (29.5–33.9)	1.62 (1.30–2.03)	1.57 (1.24–1.99)
Sukhbaatar	32/208	15.4 (10.8–21.0)	141/660	21.4 (18.3–24.7)	1.39 (0.98–1.97)	1.26 (0.88–1.81)

*Overall, PCV13 serotypes and non-PCV13 serotypes. PCV13, 13-valent pneumococcal conjugate vaccine.
†Adjusted by using a common set of confounders: age, informal housing, other children <5 y of age in the home, coal used for fuel, household income, crowding, maternal education, season, and antimicrobial drug receipt 48 h before admission.

in 4 districts of Ulaanbaatar. All patients admitted for pneumonia were screened daily by clinical staff, and they were enrolled if they met a prespecified case definition. The case definition selected for more severe cases. To ensure that all eligible patients were identified, dedicated study staff monitored weekly enrollments performed by clinical staff. Any eligible patients that were missed were enrolled retrospectively, ensuring a high inclusion rate. The 6-year study included a considerable number of patients admitted for respiratory conditions. A structured questionnaire was completed for participants, and most underwent chest radiography and specimen collection. The radiographs were reread by 2 experienced independent radiologists using WHO guidelines (17), and sensitive molecular methods were used to measure pneumococcal carriage and determine serotypes (20). In Mongolia, hospitalization is free for all children <5 years of age, which reduces bias associated with access to care. In addition, Mongolia has a structured public healthcare system in which most patients flow from primary care to district hospitals, enabling population-based estimates. The adherence of patients to this referral pathway can sometimes vary, however, by socioeconomic status and setting (35).

The first limitation our study was that although we had only 1 year of pre-PCV13 data in all districts, because of a phased PCV13 introduction, we had 2–3 years of data before vaccine introduction in half of the districts. Second, the study included only 4 Ulaanbaatar districts, so the results may not be generalizable to all children in Mongolia, although the included districts are the largest in Ulaanbaatar and half the country's population live in this city. Third, we did not collect data for a nonrespiratory control condition and could not account for other interventions, such as air pollution measures, which may have affected pneumonia trends. Fourth, the COVID-19 pandemic affected case numbers; however, adjusted IRRs were similar before or including this period. Last, ongoing internal migration of inhabitants and a possible increase in unregistered migrants during a migration ban (2017–2020) (36) may have potentially affected denominators and thus incidence rates. In addition, urban redevelopment of traditional tented housing (ger) districts resulted in the temporary relocation of inhabitants from ger to other subdistricts (37). Redevelopment and relocation were reported in the ger subdistricts of CHD during 2016 and 2017 (37), which may have resulted in lower case numbers reported in these years, because of patients accessing alternative district hospitals, and contributed to an overall rate increase.

In conclusion, PCV13 introduction into the childhood immunization schedule in Mongolia, with catch-up vaccination in 3 districts, resulted in substantially reduced pneumonia incidence. The decreases were more prominent for more severe disease endpoints and in PCV13-type pneumococcal colonization. Other countries that have satisfactory PCV coverage can expect decreased severe pneumonia cases and vaccine-type carriage after vaccine introduction. Countries should consider offering catch-up vaccination when introducing PCV and should monitor changes in

disease burden and pneumococcal serotypes through surveillance. Our study adds to limited data available on PCV effects for Asia and for countries transitioning from Gavi financial support.

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E.K.M., C.v.M., and C.S. are responsible for conception/design of the work; C.v.M., T.M., E.K.M., B.T., D.N., and S.D. for study oversight; M.U., B.S., D.L., P.B., and T.M. for acquisition of data; and C.S. and E.M.D. for oversight of pneumococcal carriage data acquisition. C.v.M, T.M., E.M.D., E.K.M., C.S., J.d.C., and M.d.C supported interpretation of the data; C.v.M., and C.N. devised the analysis plan; C.v.M. analyzed the data and drafted the manuscript. All authors were involved in data interpretation and review of the final manuscript.

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Effect of Pneumococcal Conjugate Vaccine on Pneumonia Incidence Rates among Children 2–59 Months of Age, Mongolia, 2015–2021

Appendix

Supplemental Methods

Study setting

Catch-up campaigns were only instituted during the first two years of PCV13 introduction into Songinokhairkhan, Sukhbaatar and Bayanzurkh. In 2018 vaccine was introduced into Chingeltei (in conjunction with the five remaining districts of Ulaanbaatar) without a catch-up campaign as introduction was self-funded by the government.

Study population and design

Of the nine districts of Ulaanbaatar, four (Songinokhairkhan, Sukhbaatar, Chingeltei and Bayanzurkh) were identified by the Government of Mongolia for initial 13-valent pneumococcal conjugate vaccine (PCV13) introduction as part of the country's phased introduction plan. Pneumonia surveillance was also enhanced (from the routine WHO surveillance) in these four districts to evaluate PCV13 impact. The four districts included the two largest districts in Ulaanbaatar and two central districts, making up ~70% of the city's population (*1*).

Children aged 2–59 months admitted with clinical pneumonia, who met the study case definition, were enrolled from April 2015 to June 2021. The all clinical pneumonia case definition included children with cough or difficulty breathing, and respiratory rate ≥50 bpm (for all age groups), or oxygen saturation <90% or a clinical diagnosis of severe pneumonia. Children admitted at one of the four participating secondary district hospitals, or the tertiary hospital if they resided in one of the relevant districts, were included. One of the included district hospitals

(Bayanzurkh) was privatised (*2*). Other private hospitals were not included in the surveillance programme as nearly all children are treated in the public sector for pneumonia. Hospitalisations for children are fully funded by the government (*2*,*3*).

Two standardised questionnaires collected information on demographic variables, presenting symptoms and signs, previous medication, immunisation history, treatment received, and risk factors. Blood samples, nasopharyngeal swabs and chest x-rays were collected for all enrolled cases who consented. Dedicated study staff monitored patient enrolment by clinical hospital staff to ensure that no eligible patients were missed. Participants who were missed by clinical staff were enrolled retrospectively. If participants were enrolled more than 72 hours after admission nasopharyngeal swabs were not collected (*1*).

Case definitions and study outcomes

The enrolment case definition for clinical pneumonia and the specific pneumonia endpoints (study outcomes) are detailed below:

1) All clinical pneumonia surveillance case definition (*1*)

Cough or difficulty breathing, with one of the following:

• an elevated respiratory rate (≥50 bpm for all ages)

• oxygen saturation <90%

• a clinical diagnosis of severe pneumonia

2) WHO-defined primary endpoint pneumonia (*4*):

• End-point consolidation (dense or fluffy opacity that occupies a portion or whole of a lobe or the entire lung that may or may not contain air bronchograms) OR

• Pleural effusion that is in the lateral pleural space and associated with pulmonary parenchymal infiltrate or if the effusion obliterated enough of the hemithorax to obscure an opacity.

3) Severe pneumonia (IMCI 2005 criteria (*5*))

Cough or difficulty breathing and tachypnoea PLUS

• Lower chest indrawing OR

• General danger sign (inability to breastfeed or drink, persistent vomiting, lethargy or reduced level of consciousness, convulsions or severe malnutrition) OR

• Oxygen saturation < 90% or central cyanosis

4) Very severe pneumonia (*6*):

Severe pneumonia with one or more of the following:

• ICU admission/supplementary oxygen

• hypoxia (Oxygen saturation < 90%)

• death

• persistent signs of severe illness post-discharge

• empyema

5) Probable pneumococcal pneumonia (*1*)

Elevated C-reactive protein with

• primary endpoint pneumonia (*7*) OR

• high pneumococcal nasopharyngeal carriage (either high density carriage $>1 \times 10^6$ $\log_{10}$ genome equivalents/ml or carriage of serotypes 1 or 5)

6) Definite pneumococcal pneumonia (*1*):

Pneumonia with a positive blood or pleural fluid culture.

Sample collection and laboratory procedures

We adhered to the WHO recommended methods for nasopharyngeal sample collection, handling and transport (*8*). A flocked, nylon swab was placed in 1 ml skim milk tryptone glucose glycerol media (STGG) immediately following collection. Swabs were stored in a fridge and transported to the National Center for Communicable Diseases where they were aliquoted and stored at ultra-low temperature within 8 hours of collection. Samples were shipped to the Murdoch Children's Research Institute (Parkville, Australia) on dry ice and stored at ultra-low temperature until testing. Nasopharyngeal swabs were tested for pneumococci using *lytA* real-time quantitative PCR (qPCR) and samples that were *lytA* qPCR positive (Ct value < 35) or equivocal (Ct value 35–40) were cultured on horse blood agar containing 5 µg/ml of gentamicin

(Oxoid) (*9*). DNA was extracted from the harvested α-haemolytic growth (*10*) followed by molecular serotyping by DNA microarray as previously described (*11*; C. von Mollendorf, unpub. data, https://doi.org/10.2139/ssrn.4488943). Microarray was performed using Senti-SPv1.5 microarrays (BUGS Bioscience) and analysed using Senti-NET, a custom web-based software (BUGS Bioscience). A total of 1000 cases per year were tested for pneumococci, including all cases with PEP (as this was the primary objective), and a random sample of remaining severe and non-severe cases.

Statistical analysis

To control for seasonal and long-term patterns we included an indicator variable for each elapsed calendar month (time elapsed) over the study period in the main model. We also explored three other options: fitting a spline function of time, Fourier terms and calendar month with a continuous time variable. The time elapsed variable was selected to control for seasonality as it resulted in improved model fit as measured by the Akaike's Information Criterion (AIC). No indicator variables were used to adjust for the impacts of the COVID-19 pandemic, as schools were closed from February 2020 to the end of the surveillance period with no significant reopening. We controlled for the impact of the COVID-19 pandemic by restricting to the pre-pandemic period (April 2015-Feb 2020) and then comparing results from the restricted model to a model including the total period (April 2015-June 2021). Model fit for all final models were evaluated using the AIC.

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Appendix Table 1. Characteristics of 17,607 children 2–59 mo of age enrolled in pneumonia surveillance project from 4 study districts in Ulaanbaatar, Mongolia, April 2015 –June 2021

Category	Sub-category	Bayanzurkh (N = 4976) n/N (%)	Chingeltei (N = 4170) n/N (%)	Songinokhairkhan (N = 5332) n/N (%)	Sukhbaatar (N = 3129) n/N (%)	Total (N = 17,607) n/N (%)
Demographics						
Age group	2–23 mo	3563 (72)	3015 (72)	3805 (71)	2162 (69)	12545 (71)
	24–59 mo	1413 (28)	1155 (28)	1527 (29)	967 (31)	5062 (29)
Sex	Male	2747 (55)	2293 (55)	2806 (53)	1687 (54)	9533 (54)
Primary caregiver	Parent*	3764/4217 (89)	3421/3715 (92)	4148/4572 (91)	2371/2736 (87)	13704/15240 (90)
	Other relative	406/4217 (10)	277/3715 (7)	390/4572 (8)	184/2736 (7)	125715240 (8)
	Other	47/4217 (1)	17/3715 (1)	34/4572 (1)	181/2736 (7)	279/15240 (2)
Risk factors						
Seasons	Summer	365 (7)	334 (8)	457 (9)	310 (10)	1466 (8)
	Autumn	741 (15)	470 (11)	617 (12)	429 (14)	2257 (13)
	Winter	2739 (55)	2443 (59)	2964 (56)	1621 (52)	9767 (56)
	Spring	1131 (23)	923 (22)	1294 (24)	769 (25)	4117 (23)
Malnutrition†	Yes	249/4835 (5)	182/4137 (4)	341/5258 (6)	108/3069 (3)	880/17299 (5)
Currently breastfed	Yes	2326/4220 (55)	2172/3721 (58)	2672/4572 (58)	1452/2739 (53)	8622/15252 (56)
Caesarean section	Yes	990/4210 (23)	1073/3704 (29)	1011/4560 (22)	657/2736 (24)	3731/15210 (24)
Asthma	Yes	284/4148 (7)	353/3696 (10)	351/4540 (8)	199/2721 (7)	1187/15105 (8)
Children aged <5 y in the household	1 child	2961/4208 (70)	2579/3554 (73)	3060/4553 (67)	1822/2721 (67)	10422/15036 (69)
	≥2 children	1247/4208 (30)	975/3554 (27)	1493/4553 (33)	899/2721 (33)	4614/15036 (31)
Child attends daycare /kindergarten‡	Yes	933/4219 (22)	694/3717 (19)	915/4569 (20)	649/2739 (24)	3191/15244 (21)
Chimney in the home	Yes	2098/4215 (50)	2942/3710 (79)	3199/4569 (70)	1493/2739 (54)	9732/15233 (64)
Smoker in the home	Yes	1984/4216 (47)	1678/3712 (45)	2055/4571 (45)	1154/2738 (42)	6871/15237 (45)
Smokes inside the house	Yes	529/4201 (13)	314/3710 (8)	548/4565 (12)	261/2738 (9)	1,652/15214 (11)
Caregiver smokes	Yes	216/4206 (5)	178/3713 (5)	184/4569 (4)	134/2739 (5)	712/15227 (5)
Previous admission	Yes	1767/4199 (42)	1950/3693 (53)	2001/4548 (44)	1007/2713 (37)	6725/15153 (44)
Socioeconomic factors						
Fuel used in the home	Electricity or Gas	2085/4208 (49)	719/3703 (19)	1309/4568 (29)	1250/2735 (46)	5363/15214 (35)
	Coal or Wood	2123/4208 (51)	2984/3703 (81)	3259/4568 (71)	1485/2735 (54)	9851/15214 (65)
Housing#	Formal	2866/4219 (68)	2277/3716 (61)	2493/4571 (55)	1987/2739 (73)	9623/15245 (63)
	Informal	1353/4219 (32)	1439/3716 (39)	2078/4571 (45)	752/2739 (27)	5622/15245 (37)
Mother's education	Primary/Secondary	1956/4196 (47)	2143/3690 (58)	2647/4555 (58)	978/2734 (36)	7724/15175 (51)
	Tertiary	2240/4196 (53)	1547/3690 (42)	1908/4555 (42)	1756/2734 (64)	7451/15175 (49)
Income level§	Above minimum income	2514/4034 (62)	2284/3278 (70)	2313/4442 (52)	1504/2570 (58)	8615/14324 (60)
	At or below minimum income	1520/4034 (38)	994/3278 (30)	2129/4442 (48)	1066/2570 (42)	5709/14324 (40)
Crowding (people per room)	≤3	3139/4167 (75)	2486/3668 (68)	2890/4506 (64)	2203/2724 (81)	10718/15065 (71)
	>3	1028/4167 (25)	1182/3668 (32)	1616/4506 (36)	521/2724 (19)	4347/15065 (29)
Vaccination status						
PCV13 status¶	Pre-PCV13 period	2494/4722 (53)	2236/3804 (59)	1369/5096 (27)	882/2998 (29)	6981/16620 (42)
	Undervaccinated	1182/4722 (25)	1049/3804 (27)	1583/5096 (31)	1098/2998 (37)	4912/16620 (30)
	Vaccinated	1046/4722 (22)	519/3804 (14)	2144/5096 (42)	1018/2998 (34)	4727/16620 (28)
Severity of disease						
Length of hospital stay	≤7 d	3518/4975 (71)	3039/4169 (73)	4522/5329 (85)	2493 (80)	13572/17602 (77)
	8–14 d	1334/4975 (27)	1069/4169 (26)	691/5329 (13)	599 (19)	3693/17602 (21)

Category	Sub-category	Bayanzurkh (N = 4976) n/N (%)	Chingeltei (N = 4170) n/N (%)	Songinokhairkhan (N = 5332) n/N (%)	Sukhbaatar (N = 3129) n/N (%)	Total (N = 17,607) n/N (%)
	≥15 d	123/4975 (2)	61/4169 (1)	116/5329 (2)	37 (1)	337/17602 (2)
Outcome##	Died	14/4790 (0.3)	7/3923 (0.2)	12/4868 (0.2)	7/3038 (0.2)	40/16619 (0.2)
Hypoxic‖	Yes	1116/4734 (24)	790/4025 (20)	768/5140 (15)	518/2990 (17)	3192/16889 (19)
Primary endpoint pneumonia**	Yes	366/3609 (10)	395/3464 (11)	805/4367 (18)	247/2315 (11)	1813/13755 (13)
Severe pneumonia***	Yes	3718/4942 (75)	3270/4117 (79)	4271/5256 (81)	2208/3091 (71)	13467/17406 (77)
Very severe pneumonia^	Yes	2123/4942 (43)	1913/4117 (46)	1433/5256 (27)	966/3091 (31)	6434/17406 (37)
Probable pneumococcal pneumonia^^	Yes	309/3434 (9)	347/3434 (10)	549/4417 (12)	244/2317 (10)	1449/13602 (11)

*Mostly mothers (97%).
†Weight for age −2 standard deviations.
‡Kindergarten for children 2–5 y of age, daycare for children <2 y.
#Formal housing (houses and apartments) and informal housing (ger dwellings).
§Minimum income was considered 170,000₮ per person/per month.
¶Children were considered PCV13 vaccinated if they have received at least two doses when administered at less than 12 mo of age or at least one dose when administered at greater than or equal to 12 mo of age.
##Number of children who died during hospital stay.
‖Hypoxic defined as an oxygen saturation <90%.
**WHO defined primary endpoint pneumonia.
***Severe pneumonia defined according to WHO integrated management of childhood illness 2005 case definition.
^Very severe pneumonia included severe cases complicated by empyema, intensive care unit admission, persistent severe disease post-discharge, hypoxia or death.
^^Probable pneumococcal pneumonia was defined as elevated C-reactive protein with either PEP or high pneumococcal nasopharyngeal carriage (either high density carriage of any serotype greater than $1 \times \log_{10}$ GE/mL, or any carriage of serotypes 1 or 5).

Appendix Table 2. Characteristics of children 2–59 months of age hospitalised with clinical pneumonia in pre- and post-PCV period, April 2015 to June 2021

Category	Sub-category	Pre-PCV period (N=7304) n (%)	Post-PCV period (N=10303) n (%)	p-value*
Demographics				
Age group	2-23 months	5196 (71)	7349 (71)	0.78
	24-59 months	2108 (29)	2954 (29)	
Sex	Male	3958 (54)	5575 (54)	0.91
District	Bayanzurkh	2654 (36)	2322 (22)	<0.001
	Chingeltei	2309 (32)	1860 (18)	
	Songinokhairkhan	1400 (19)	3932 (38)	
	Sukhbaatar	941 (13)	2189 (21)	
Primary caregiver	Parent	5256/5836 (90)	8448/9404 (90)	<0.001
	Other relative	502/5836 (10)	755/9404 (8)	
	Other	78/5836 (1)	201/9404 (2)	
Risk factors				
Seasons	Summer	608 (8)	858 (8)	<0.001
	Autumn	942 (13)	1316 (13)	
	Winter	3731 (51)	6036 (59)	
	Spring	2024 (28)	2093 (20)	
Malnutrition†	Yes	345/7128 (5)	535/10171 (5)	0.21
Currently breastfed	Yes	3226/5837 (55)	5396/9415 (57)	0.01
Caesarean	Yes	1489/5818 (26)	2242/9392 (24)	0.01
Asthma	Yes	574/5760 (10)	613/9345 (6)	<0.001
Children aged <5 years in the household	1 child	4012/5726 (70)	6410/9310 (69)	0.12
	≥2 children	1714/5726 (30)	2900/9310 (31)	
Child attends daycare /kindergarten‡	Yes	1256/5821 (22)	1935/9398 (21)	0.15
Chimney in the home	Yes	3752/5830 (64)	5980/9403 (64)	0.34
Smoker in the home	Yes	2582/5831 (44)	4289/9406 (46)	0.12
Smokes inside the house	Yes	668/5812 (11)	984/9402 (10)	0.05
Caregiver smokes	Yes	310/5824 (5)	402/9403 (4)	0.003
Previous admission	Yes	2782/5794 (48)	3943/9359 (42)	<0.001
Socioeconomic factors				
Fuel used in the home	Electricity or Gas	1987/5828 (34)	3376/9386 (36)	0.02
	Coal or Wood	3841/5828 (66)	6010/9386 (64)	

Category	Sub-category	Pre-PCV period (N=7304) n (%)	Post-PCV period (N=10303) n (%)	p-value*
Housing	Formal	3657/5837 (63)	5966/9408 (63)	0.34
	Informal	2180/5837 (37)	3442/9408 (37)	
Mother's education	Primary/Secondary	2938/5793 (51)	4786/9382 (51)	0.72
	Tertiary	2855/5793 (49)	4596/9382 (49)	
Income level§	Above minimum income	3449/5422 (64)	5166/8902 (58)	<0.001
	At or below minimum income	1973/5422 (36)	3736/8902 (42)	
Crowding (people per room)	<=3	4096/5732 (71)	6622/9333 (71)	0.52
	>3	1636/5732 (29)	2711/9333 (29)	
Severity of disease				
Length of hospital stay	<=7 days	5518/7299 (76)	8053 (78)	<0.001
	8-14 days	1638/7299 (22)	2055 (20)	
	>=15 days	143/7299 (2)	195 (2)	
Outcome	Died	18/6345 (0.3)	22/10274 (0.2)	0.37
Hypoxic‖	Yes	1460/6737 (22)	1732/10153 (17)	<0.001
Primary endpoint pneumonia**	Yes	739/5213 (14)	1074/8542 (13)	0.007
Severe pneumonia***	Yes	5676/7146 (79)	7791/10260 (76)	<0.001
Very severe pneumonia^	Yes	2751/7146 (38)	3683/10260 (36)	0.009
Probable pneumococcal pneumonia^^	Yes	695/4390 (14)	754/7763 (9)	<0.001

*p-values compared pre- versus post-PCV period using chi-squared test.
†Weight for age -2 standard deviations.
‡Kindergarten for children 2-5 years of age, daycare for children <2 years.
§Minimum income was considered 170,000₹ per person/per month.
‖Hypoxic defined as an oxygen saturation <90%.
**WHO defined primary end point pneumonia.
***Severe pneumonia defined according to WHO integrated management of childhood illness 2005 case definition.
^Very severe pneumonia included severe cases complicated by empyema, intensive care unit admission, persistent severe disease post-discharge. hypoxia or death.
^^Probable pneumococcal pneumonia was defined as elevated C-reactive protein with either PEP or high pneumococcal nasopharyngeal carriage (either high density carriage of any serotype greater than $1 \times \log_{10}$ GE/mL, or any carriage of serotypes 1 or 5).

Appendix Table 3. Crude incidence and incidence rate ratios for hospitalised pneumonia by district and diagnosis in the pre- and post-PCV period, for children 2-59 months, from April 2015 to March 2020 and April 2015 to March 2021

Variable	District	Incidence rate pre-PCV introduction (per 1000 pop)	Incidence rate post-PCV introduction until March 2020 (per 1000 pop)*	Incidence rate ratio (95% confidence interval) comparing pre-PCV to post-PCV until March 2020*	Incidence rate post-PCV introduction until March 2021 (per 1000 pop)†	Incidence rate ratio (95% confidence interval) comparing pre-PCV to post-PCV until March 2021†
All clinical pneumonia	All	33.9 (33.2-34.7)	26.9 (26.4-27.5)	0.79 (0.77-0.82)	21.3 (20.9-21.8)	0.63 (0.61-0.65)
	BZD	28.7 (27.6-29.8)	19.1 (18.4-20.0)	0.67 (0.63-0.71)	14.7 (14.1-15.3)	0.51 (0.48-0.54)
	CHD	41.9 (40.2-43.7)	47.4 (45.2-49.6)	1.13 (1.06-1.20)	34.7 (33.1-36.3)	0.83 (0.78-0.88)
	SKD	29.2 (27.7-30.8)	25.1 (24.3-25.9)	0.86 (0.81-0.91)	20.5 (19.9-21.2)	0.70 (0.66-0.75)
	SBD	48.0 (45.0-51.1)	33.7 (32.3-35.2)	0.70 (0.65-0.76)	27.9 (26.7-29.1)	0.58 (0.54-0.63)
Primary endpoint pneumonia‡	All	3.5 (3.2-3.7)	2.8 (2.6-2.9)	0.80 (0.73-0.88)	2.2 (2.1-2.4)	0.64 (0.58-0.71)
	BZD	2.1 (1.8-2.4)	1.3 (1.1-1.5)	0.63 (0.50-0.78)	1.1 (0.9-1.2)	0.51 (0.41-0.63)
	CHD	4.4 (3.9-5.0)	3.8 (3.2-4.5)	0.86 (0.69-1.05)	2.9 (2.4-3.4)	0.65 (0.53-0.80)
	SKD	4.2 (3.7-4.9)	3.9 (3.6-4.2)	0.91 (0.78-1.08)	3.1 (2.9-3.4)	0.74 (0.63-0.87)
	SBD	5.1 (4.2-6.2)	2.2 (1.9-2.6)	0.43 (0.33-0.56)	1.8 (1.5-2.2)	0.36 (0.28-0.47)
Severe pneumonia§	All	26.4 (25.7-27.1)	20.4 (20.0-20.9)	0.77 (0.75-0.80)	16.1 (15.8-16.5)	0.61 (0.59-0.63)
	BZD	22.4 (21.5-23.4)	13.6 (13.0-14.3)	0.61 (0.57-0.65)	10.4 (9.9-10.9)	0.46 (0.43-0.49)
	CHD	32.2 (30.7-33.7)	38.1 (36.1-40.1)	1.18 (1.10-1.27)	27.9 (26.5-29.3)	0.86 (0.81-0.93)
	SKD	23.2 (21.8-24.6)	20.3 (19.6-21.0)	0.88 (0.82-0.94)	16.5 (15.9-17.1)	0.71 (0.66-0.76)
	SBD	36.5 (33.9-39.3)	22.9 (21.7-24.1)	0.63 (0.57-0.69)	19.0 (18.0-20.0)	0.52 (0.47-0.57)
Very severe pneumonia¶	All	12.8 (12.3-13.3)	9.5 (9.2-9.8)	0.74 (0.71-0.78)	7.6 (7.4-7.9)	0.59 (0.57-0.62)
	BZD	12.5 (11.8-13.2)	7.9 (7.4-8.4)	0.63 (0.58-0.69)	6.1 (5.7-6.5)	0.49 (0.45-0.53)
	CHD	17.4 (16.3-18.6)	23.8 (22.2-25.5)	1.37 (1.25-1.50)	17.6 (16.6-18.8)	1.01 (0.93-1.11)
	SKD	9.0 (8.2-10.0)	6.4 (6.0-6.8)	0.71 (0.63-0.80)	5.2 (4.9-5.5)	0.58 (0.52-0.65)
	SBD	10.5 (9.1-12.0)	11.6 (10.8-12.5)	1.11 (0.95-1.30)	9.7 (9.0-10.4)	0.92 (0.79-1.08)
Hypoxic pneumonia‖	All	6.8 (6.4-7.2)	4.5 (4.3-4.7)	0.66 (0.61-0.71)	3.6 (3.4-3.8)	0.53 (0.49-0.56)
	BZD	5.9 (5.5-6.5)	4.5 (4.2-4.9)	0.76 (0.68-0.86)	3.5 (3.3-3.9)	0.60 (0.53-0.67)
	CHD	8.9 (8.2-9.8)	7.5 (6.7-8.5)	0.84 (0.72-0.98)	5.5 (4.9-6.2)	0.62 (0.53-0.71)
	SKD	5.2 (4.6-5.9)	3.3 (3.0-3.6)	0.63 (0.54-0.73)	2.7 (2.5-2.9)	0.51 (0.44-0.60)
	SBD	8.5 (7.2-9.8)	5.4 (4.8-6.0)	0.63 (0.53-0.77)	4.5 (4.0-5.0)	0.53 (0.44-0.64)
Probable pneumococcal pneumonia**	All	3.2 (3.0-3.5)	2.0 (1.8-2.1)	0.62 (0.56-0.69)	1.5 (1.4-1.7)	0.48 (0.43-0.53)
	BZD	2.1 (1.8-2.4)	1.0 (0.8-1.2)	0.48 (0.38-0.61)	0.7 (0.6-0.9)	0.36 (0.28-0.45)
	CHD	4.3 (3.8-4.9)	2.8 (2.3-3.4)	0.66 (0.52-0.84)	2.0 (1.6-2.4)	0.46 (0.36-0.58)
	SKD	3.5 (3.0-4.0)	2.4 (2.2-2.7)	0.70 (0.58-0.85)	2.0 (1.8-2.2)	0.57 (0.47-0.68)
	SBD	4.9 (4.0-6.0)	2.3 (1.9-2.7)	0.46 (0.35-0.60)	1.8 (1.5-2.2)	0.37 (0.29-0.49)

BZD = Bayanzurkh District, CHD = Chingeltei District, SKD = Songinokhairkhan District, SBD = Sukhbaatar District.
Annual incidence rates calculated from April to March. * Incidence rate and incidence rate ratio up to March 2020, approximately start of COVID pandemic impact on the surveillance programme.
†Incidence rate and incidence rate ratio up to March 2021, near study completion.
‡WHO defined primary end point pneumonia.
§Severe pneumonia defined according to WHO integrated management of childhood illness 2005 case definition.
¶Very severe pneumonia included severe cases complicated by empyema, intensive care unit admission, persistent severe disease post-discharge, hypoxia or death.
‖Hypoxic pneumonia defined as an oxygen saturation <90%.
**Probable pneumococcal pneumonia was defined as elevated C-reactive protein with either PEP or high pneumococcal nasopharyngeal carriage (either high density carriage of any serotype greater than 1 × $\log_{10}$ GE/mL, or any carriage of serotypes 1 or 5).

Appendix Table 4. Crude incidence of hospitalised clinical pneumonia by age group and diagnosis in the pre- and post-PCV period, from April 2015 to March 2020 and April 2015 to March 2021.

Variable	Age group	Incidence rate pre-PCV introduction (per 1000 pop)	Incidence rate post-PCV introduction (per 1000 pop) until March 2020*	Incidence rate ratio (95% confidence interval) comparing pre-PCV to post-PCV until March 2020*	Incidence rate post-PCV introduction (per 1000 pop) until March 2021†	Incidence rate ratio (95% confidence interval) comparing pre-PCV to post-PCV until March 2021†
All clinical pneumonia	2-23 months	63.2 (61.5-64.9)	53.7 (52.5-55.0)	0.85 (0.82-0.88)	42.2 (41.3-43.2)	0.67 (0.64-0.69)
	24-59 months	15.8 (15.2-16.5)	12.1 (11.6-12.5)	0.76 (0.72-0.80)	9.6 (9.2-9.9)	0.60 (0.57-0.64)
	2-59 months	33.9 (33.2-34.7)	26.9 (26.4-27.5)	0.79 (0.77-0.82)	21.3 (20.9-21.8)	0.63 (0.61-0.65)
Primary endpoint pneumonia‡	2-23 months	6.4 (5.8-6.9)	5.7 (5.3-6.1)	0.89 (0.80-1.00)	4.5 (4.2-4.8)	0.71 (0.64-0.80)
	24-59 months	1.6 (1.4-1.8)	1.2 (1.0-1.3)	0.72 (0.60-0.86)	0.9 (0.8-1.0)	0.57 (0.47-0.68)
	2-59 months	3.5 (3.2-3.7)	2.8 (2.6-2.9)	0.80 (0.73-0.88)	2.2 (2.1-2.4)	0.64 (0.58-0.71)
Severe pneumonia§	2-23 months	48.7 (47.2-50.3)	40.4 (39.4-41.5)	0.83 (0.80-0.86)	31.7 (30.9-32.6)	0.65 (0.62-0.68)
	24-59 months	12.5 (11.9-13.1)	9.3 (8.9-9.7)	0.74 (0.70-0.79)	7.4 (7.1-7.7)	0.59 (0.55-0.63)
	2-59 months	26.4 (25.7-27.1)	20.4 (20.0-20.9)	0.77 (0.75-0.80)	16.1 (15.8-16.5)	0.61 (0.59-0.63)
Very severe pneumonia¶	2-23 months	23.0 (22.0-24.1)	19.4 (18.7-20.2)	0.84 (0.79-0.90)	15.4 (14.9-16.0)	0.67 (0.63-0.71)
	24-59 months	6.5 (6.0-6.9)	4.0 (3.7-4.3)	0.62 (0.56-0.68)	3.2 (3.0-3.4)	0.49 (0.45-0.54)
	2-59 months	12.8 (12.3-13.3)	9.5 (9.2-9.8)	0.74 (0.71-0.78)	7.6 (7.4-7.9)	0.59 (0.57-0.62)
Hypoxic pneumonia‖	2-23 months	12.2 (11.5-13.0)	9.1 (8.6-9.6)	0.74 (0.68-0.81)	7.2 (6.8-7.6)	0.59 (0.54-0.64)
	24-59 months	3.4 (3.1-3.7)	1.9 (1.7-2.1)	0.56 (0.49-0.64)	1.5 (1.4-1.7)	0.45 (0.39-0.51)
	2-59 months	6.8 (6.4-7.2)	4.5 (4.3-4.7)	0.66 (0.61-0.71)	3.6 (3.4-3.8)	0.53 (0.49-0.57)
Probable pneumococcal pneumonia**	2-23 months	5.5 (5.0-6.0)	3.5 (3.2-3.8)	0.63 (0.55-0.72)	2.7 (2.4-2.9)	0.49 (0.43-0.56)
	24-59 months	1.8 (1.6-2.0)	1.2 (1.0-1.3)	0.65 (0.55-0.78)	0.9 (0.8-1.0)	0.51 (0.42-0.60)
	2-59 months	3.2 (3.0-3.5)	2.0 (1.8-2.1)	0.62 (0.56-0.69)	3.2 (3.0-3.5)	0.48 (0.43-0.53)

Annual incidence rates calculated from April to March.

*Incidence rate and incidence rate ratio up to March 2020, approximately start of COVID pandemic impact on the surveillance programme.

†Incidence rate and incidence rate ratio up to March 2021, near study completion.

‡WHO defined primary end point pneumonia.

§Severe pneumonia defined according to WHO integrated management of childhood illness 2005 case definition.

¶Very severe pneumonia included severe cases complicated by empyema, intensive care unit admission, persistent severe disease post-discharge, hypoxia or death.

‖Hypoxic pneumonia defined as an oxygen saturation <90%.

**Probable pneumococcal pneumonia was defined as elevated C-reactive protein with either PEP or high pneumococcal nasopharyngeal carriage (either high density carriage of any serotype greater than 1 × $\log_{10}$ GE/mL, or any carriage of serotypes 1 or 5).

Appendix Table 5. Crude incidence rates by year for hospitalised clinical pneumonia by district and diagnosis for children aged 2-59 months, April 2015 to June 2021

		Crude Incidence rates (per 1000 population)					
District	**Year**	**All clinical pneumonia**	**Primary endpoint pneumonia***	**Severe pneumonia‡**	**Very severe pneumonia§**	**Hypoxic pneumonia¶**	**Probable pneumococcal pneumonia‖**
Bayanzurkh District	2015	17.11	1.28	14.48	6.45	3.28	1.16
	2016	35.94	2.42	28.56	17.24	8.08	2.54
	2017	22.97	1.74	14.98	8.41	4.34	1.81
	2018	24.39	1.83	17.83	10.41	5.49	1.40
	2019	14.35	0.78	10.30	6.13	3.76	0.51
	2020	5.36	0.68	3.65	2.65	1.85	0.05
	2021	0.43	0.14	0.26	0.21	0.19	0.07
Chingeltei District	2015	13.12	2.04	8.22	5.16	2.50	1.74
	2016	45.61	4.21	34.30	18.26	9.79	4.58
	2017	51.16	6.01	40.98	20.35	11.51	5.62
	2018	55.21	4.62	45.26	27.55	10.12	4.12
	2019	46.00	3.40	36.62	23.38	6.45	2.58
	2020	19.18	1.70	15.47	11.17	2.97	0.36
	2021	1.26	0.13	1.07	0.95	0.32	0.00
Songinokhairkhan District	2015	15.26	3.07	10.99	4.53	2.56	1.73
	2016	36.57	5.05	30.56	9.96	5.47	4.26
	2017	24.96	3.72	20.48	5.70	3.51	3.12
	2018	26.42	3.59	21.82	7.45	3.84	2.78
	2019	22.57	3.42	17.46	6.21	2.92	1.30
	2020	7.41	1.30	5.42	1.81	0.79	0.56
	2021	0.48	0.03	0.34	0.21	0.16	0.03
Sukhbaatar District	2015	25.06	2.38	18.17	3.62	2.02	1.66
	2016	63.71	5.83	46.52	21.22	14.91	5.83
	2017	44.66	2.78	29.53	9.38	6.78	3.87
	2018	31.48	1.99	20.73	11.54	4.71	2.42
	2019	16.55	1.40	12.73	9.55	1.65	0.64
	2020	6.76	0.46	5.18	3.15	1.12	0.33
	2021	1.72	0.14	1.17	0.48	0.21	0.00

*WHO defined primary end point pneumonia.
‡Severe pneumonia defined according to WHO integrated management of childhood illness 2005 case definition.
§Very severe pneumonia included severe cases complicated by empyema, intensive care unit admission, persistent severe disease post-discharge, hypoxia or death.
¶Hypoxic pneumonia defined as an oxygen saturation <90%.
‖Probable pneumococcal pneumonia included PEP or high pneumococcal nasopharyngeal carriage with a C-reactive protein ≥40 mg/dL.

Appendix Table 6. Adjusted incidence rate ratios (aIRR) with 95% confidence interval (95%CI) for different pneumonia endpoints comparing the pre- and post-vaccine periods (April 2015 – Feb 2020 and April 2015 – June 2021) overall and separately in the four districts using negative binomial models

Variable	aIRR (95% CI) until Feb 2020	aIRR (95% CI) until June 2021
All clinical pneumonia		
All districts*	1.01 (0.87-1.17)	1.02 (0.88-1.18)
Bayanzurkh District‡	0.71 (0.59-0.85)	0.71 (0.59-0.84)
Chingeltei District‡	1.68 (1.41-2.01)	1.64 (1.38-1.94)
Songinokhairkhan District‡	0.86 (0.70-1.07)	0.85 (0.69-1.05)
Sukhbaatar District‡	0.64 (0.51-0.79)	0.65 (0.52-0.80)
Primary endpoint pneumonia§		
All districts*	0.72 (0.56-0.93)	0.76 (0.59-0.97)
Bayanzurkh District‡	0.68 (0.49-0.93)	0.73 (0.53-1.00)
Chingeltei District‡	1.01 (0.74-1.39)	1.05 (0.77-1.43)
Songinokhairkhan District‡	0.74 (0.53-1.04)	0.73 (0.52-1.02)
Sukhbaatar District‡	0.35 (0.24-0.51)	0.36 (0.24-0.53)
Severe pneumonia¶		
All districts*	0.97 (0.82-1.15)	1.00 (0.85-1.17)
Bayanzurkh District‡	0.61 (0.50-0.74)	0.60 (0.50-0.73)
Chingeltei District‡	1.72 (1.42-2.09)	1.72 (1.43-2.06)
Songinokhairkhan District‡	0.86 (0.68-1.08)	0.84 (0.67-1.05)
Sukhbaatar District‡	0.58 (0.45-0.73)	0.59 (0.47-0.75)
Very severe pneumonia		
All districts*	0.77 (0.64-0.93)	0.80 (0.66-0.96)
Bayanzurkh District‡	0.46 (0.37-0.57)	0.47 (0.38-0.58)
Chingeltei District‡	1.43 (1.15-1.77)	1.45 (1.18-1.77)
Songinokhairkhan District‡	0.47 (0.36-0.60)	0.46 (0.35-0.59)
Sukhbaatar District‡	0.71 (0.53-0.94)	0.71 (0.54-0.94)
Hypoxic pneumonia**		

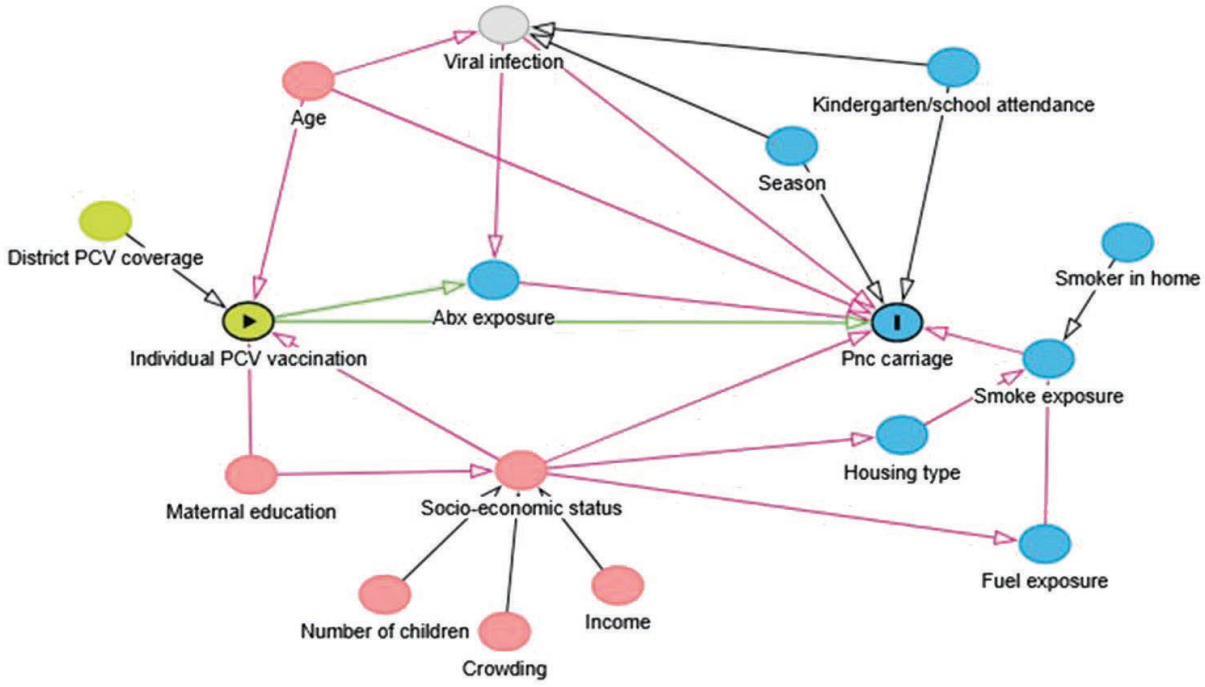
Variable	aIRR (95% CI) until Feb 2020	aIRR (95% CI) until June 2021
All districts*	0.83 (0.67-1.04)	0.84 (0.68-1.04)
Bayanzurkh District‡	0.79 (0.60-1.04)	0.81 (0.62-1.06)
Chingeltei District‡	1.14 (0.86-1.51)	1.09 (0.84-1.43)
Songinokhairkhan District‡	0.60 (0.43-0.83)	0.59 (0.43-0.81)
Sukhbaatar District‡	0.64 (0.46-0.91)	0.65 (0.46-0.91)
Probable pneumococcal pneumonia***		
All districts*	0.77 (0.61-0.97)	0.75 (0.60-0.95)
Bayanzurkh District‡	0.65 (0.48-0.88)	0.64 (0.47-0.86)
Chingeltei District‡	1.24 (0.91-1.68)	1.16 (0.86-1.57)
Songinokhairkhan District‡	0.69 (0.51-0.93)	0.69 (0.51-0.93)
Sukhbaatar District‡	0.45 (0.32-0.65)	0.46 (0.32-0.65)

*Negative binomial model included time elapsed, age group, district and PCV13.
‡Negative binomial model included time elapsed, age group, district and PCV13 with interaction term between district and PCV13 for separate districts.
§WHO defined primary end point pneumonia.
¶Severe pneumonia defined according to WHO integrated management of childhood illness 2005 case definition.
||Very severe pneumonia included severe cases complicated by empyema, intensive care unit admiss.ion, persistent severe disease post-discharge, hypoxia or death.
**Hypoxic pneumonia defined as an oxygen saturation <90%.
***Probable pneumococcal pneumonia included PEP or high pneumococcal nasopharyngeal carriage with a C-reactive protein ≥40 mg/dL.

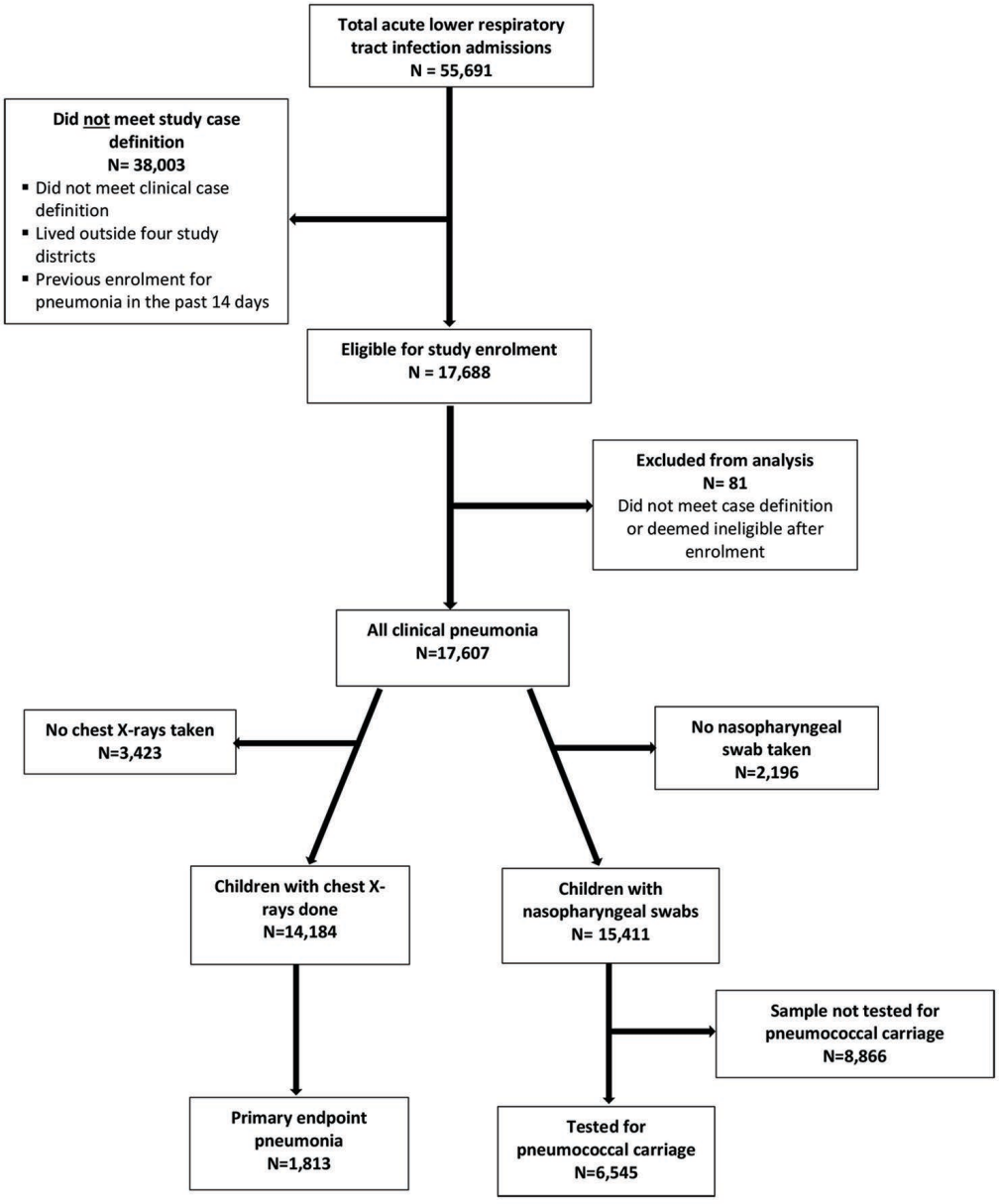
Appendix Table 7. Sensitivity analyses using negative binomial models for different pneumonia endpoints comparing the pre- and post-vaccine periods overall and separately in the four districts (April 2015 – June 2021).

Variable	aIRR (95% confidence interval) with delayed PCV period in children 2-59 months†	aIRR (95% confidence interval) in children 2-23 months‡	aIRR (95% confidence interval) in children 24-59 months‡
All clinical pneumonia			
All districts	0.76 (0.64-0.91)	1.09 (0.91-1.30)	0.88 (0.73-1.07)
Bayanzurkh district	0.61 (0.50-0.74)	0.77 (0.63-0.94)	0.63 (0.50-0.80)
Chingeltei district	1.37 (1.11-1.68)	1.76 (1.45-2.13)	1.38 (1.10-1.74)
Songinokhairkhan district	0.75 (0.62-0.91)	0.82 (0.65-1.04)	0.84 (0.64-1.11)
Sukhbaatar district	0.51 (0.42-0.62)	0.67 (0.53-0.86)	0.58 (0.44-0.78)
Primary endpoint pneumonia§			
All districts	0.74 (0.57-0.96)	0.88 (0.67-1.15)	0.62 (0.43-0.90)
Bayanzurkh district	0.72 (0.51-1.01)	0.88 (0.63-1.21)	0.54 (0.33-0.89)
Chingeltei district	1.04 (0.71-1.51)	1.29 (0.94-1.76)	0.73 (0.45-1.20)
Songinokhairkhan district	0.83 (0.62-1.10)	0.71 (0.51-0.99)	0.86 (0.52-1.43)
Sukhbaatar district	0.43 (0.30-0.62)	0.37 (0.24-0.56)	0.35 (0.20-0.61)
Severe pneumonia¶			
All districts	0.76 (0.62-0.92)	1.05 (0.87-1.28)	0.87 (0.70-1.09)
Bayanzurkh district	0.54 (0.44-0.68)	0.66 (0.54-0.81)	0.55 (0.42-0.72)
Chingeltei district	1.42 (1.14-1.79)	1.81 (1.48-2.21)	1.49 (1.15-1.94)
Songinokhairkhan district	0.73 (0.58-0.90)	0.80 (0.63-1.03)	0.84 (0.61-1.16)
Sukhbaatar district	0.50 (0.40-0.63)	0.61 (0.47-0.79)	0.53 (0.39-0.73)
Very severe pneumonia||			
All districts	0.70 (0.56-0.86)	0.95 (0.77-1.18)	0.61 (0.48-0.79)
Bayanzurkh district	0.46 (0.36-0.59)	0.58 (0.46-0.74)	0.35 (0.26-0.47)
Chingeltei district	1.31 (1.01-1.69)	1.71 (1.36-2.15)	1.08 (0.81-1.43)
Songinokhairkhan district	0.53 (0.41-0.67)	0.51 (0.38-0.68)	0.41 (0.28-0.59)
Sukhbaatar district	0.68 (0.52-0.88)	0.79 (0.58-1.08)	0.62 (0.41-0.93)
Hypoxic pneumonia**			
All districts	0.86 (0.69-1.08)	0.96 (0.75-1.22)	0.69 (0.52-0.93)
Bayanzurkh district	1.09 (0.82-1.43)	0.97 (0.73-1.29)	0.67 (0.46-0.96)
Chingeltei district	1.20 (0.87-1.66)	1.36 (1.02-1.82)	0.81 (0.55-1.19)
Songinokhairkhan district	0.83 (0.63-1.09)	0.61 (0.44-0.86)	0.54 (0.35-0.85)
Sukhbaatar district	0.54 (0.40-0.72)	0.61 (0.43-0.88)	0.69 (0.43-1.12)
Probable pneumococcal pneumonia***			
All districts	0.73 (0.57-0.94)	0.70 (0.53-0.92)	0.80 (0.57-1.13)
Bayanzurkh district	0.60 (0.40-0.88)	0.60 (0.42-0.86)	0.73 (0.46-1.18)
Chingeltei district	1.11 (0.70-1.76)	1.29 (0.90-1.85)	0.92 (0.57-1.50)
Songinokhairkhan district	0.84 (0.63-1.11)	0.57 (0.41-0.81)	0.94 (0.58-1.53)
Sukhbaatar district	0.56 (0.39-0.80)	0.37 (0.24-0.56)	0.57 (0.33-0.97)

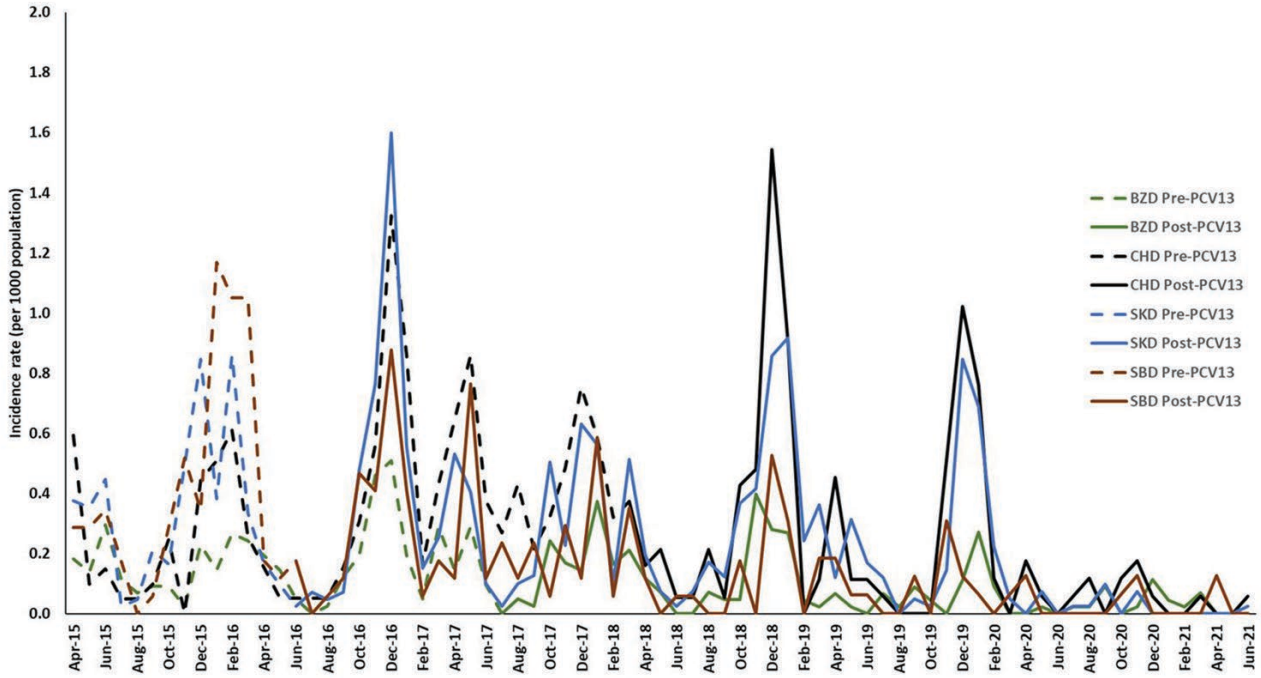
†Negative binomial model included time elapsed, district and PCV13_delay with interaction term between district and PCV13_delay. PCV impact assumed from one-year post-PCV introduction.
‡Negative binomial model included time elapsed, season, district and PCV13 stratified by age group
§WHO defined primary end point pneumonia.
¶Severe pneumonia defined according to WHO integrated management of childhood illness 2005 case definition.
||Very severe pneumonia included severe cases complicated by empyema, intensive care unit admission, persistent severe disease post-discharge, hypoxia or death.
**Hypoxic pneumonia defined as an oxygen saturation <90%.
***Probable pneumococcal pne.umonia included PEP or high pneumococcal nasopharyngeal carriage with a C-reactive protein ≥40 mg/dL.



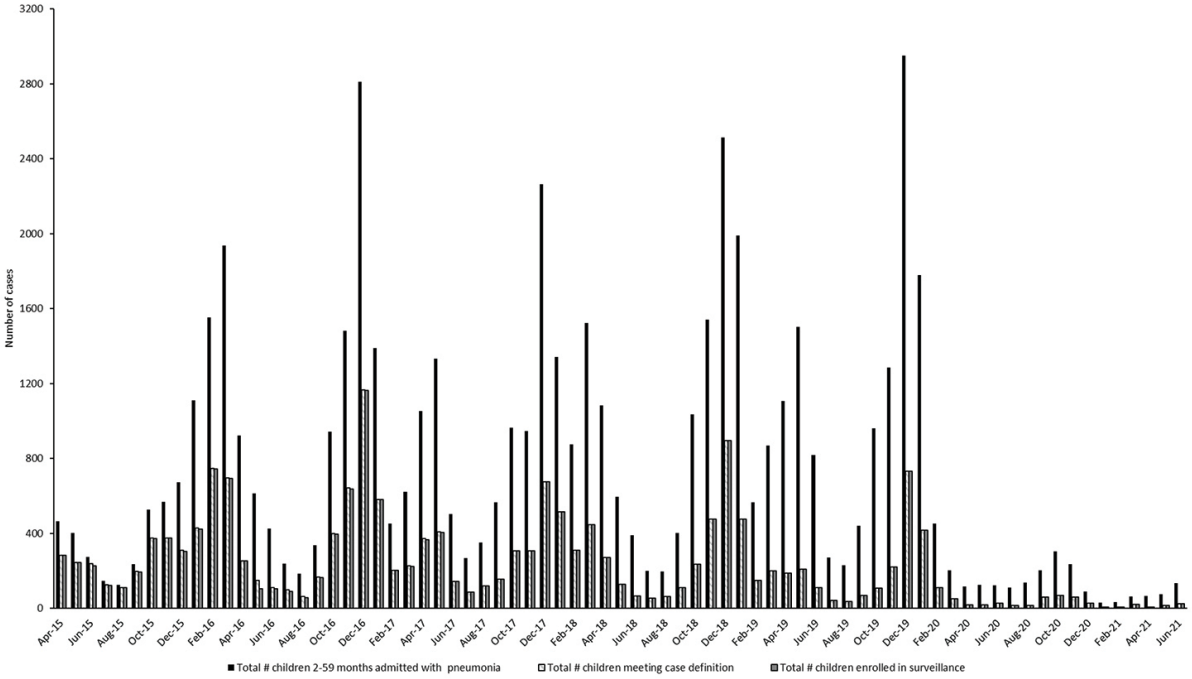
Appendix Figure 1. Directed acyclic graph (DAG) of the association between PCV13 vaccination (exposure) and pneumococcal carriage (outcome) The DAG was used to identify potential confounding variables. The green line highlights the causal relationship under investigation and the pink lines highlight potential biasing pathways. The blue variables are ancestors of the outcome, yellow variables ancestors of the exposure and red variables ancestors of both exposure and outcome. Grey variables represent unobserved variables. Based on this DAG, we identified that adjusting for age group, housing-type, maternal education, household income, household crowding, number of children under five years of age, household fuel type, season and antibiotic exposure may block biasing pathways.



Appendix Figure 2. Flow chart of study participants with pneumonia admissions in four districts of Ulaanbaatar, Mongolia, April 2015–June 2021.



Appendix Figure 3. Primary endpoint pneumonia incidence rates by month and district in children 2-59 months of age, Ulaanbaatar, Mongolia, April 2015 – June 2021.



Appendix Figure 4. Total pneumonia cases admitted, meeting case definition and enrolled in pneumonia surveillance programme for children 2-59 months in all four districts, April 2015 to June 2021.