

Supplementary material

Novel evaluation to measure pneumococcal conjugate vaccine impact in a low-resource setting with minimal baseline data and imminent vaccine introduction, Lao People's Democratic Republic

1. Methods

1.1 Retrospective pneumonia medical record review

Pediatric hospital admission books for all central hospitals and hospital administrative data for all district hospitals in Vientiane Capital were reviewed to ascertain the number of all-cause hospital admissions and hospital admissions for pneumonia, and to calculate the annual incidence of hospitalized pneumonia (the latter in the pre-PCV period), for children aged 2-59 months. During the pre-PCV13 period, there were five central hospitals (Settathirath Hospital, Mahosot Hospital, National Child Hospital, Mother and Child Hospital and Hospital 103), one of which (Mother and Child Hospital) closed at the end of 2011 and one (National Child Hospital) which opened at the beginning of 2012. There were nine district hospitals in operation during the pre-PCV13 period (Pak Ngum Hospital, Santhong Hospital, Naxaithong Hospital, Hadxaifong Hospital, Xaythany Hospital, Sikkotabong Hospital, Sisatanak Hospital, Xaysettha Hospital and Chanthabouly Hospital).

Age, length of stay and diagnosis for pneumonia admissions was recorded from the admission books from the central hospitals. To account for missing data from hospital admission books which were not available for review, various assumptions were made which were based on a number of consistent intra-hospital and inter-hospital patterns in monthly and annual admissions from the available records. For all assumptions, it was assumed that the number of pneumonia and all-cause hospitalizations followed the same pattern within hospitals throughout the three-year period.

In the pre-PCV13 period, the National Child Hospital opened in 2012 and hospital admission books for the National Child Hospital were only available from May to December 2013. We calculated the proportion of all-cause hospitalizations due to pneumonia for January to April and May to December for the Settathirath and Mahosot Hospitals (only two hospitals with complete set of data for 2011-2013) and found that the proportion of all-cause hospitalizations due to pneumonia for both hospitals were consistent between years and between hospitals. We calculated the average of

those hospitalization rates for January to April from the Settathirath and Mahosot Hospitals in 2011, 2012 and 2013, and applied that to the number of hospitalizations at the National Child Hospital in 2013 to estimate the expected number of January to April hospitalizations in this hospital in 2013. There were no hospital admission books for the National Child Hospital for 2012, therefore, it was assumed that the number of hospitalizations were the same in 2012 as for 2013. There were no hospital admission books for the Mother and Child Hospital in 2011. The pediatric ward for this hospital closed at the end of 2011 when it was replaced by the National Child Hospital. It was assumed that the cases that would have attended the Mother and Child Hospital after 2011, now attended National Child Hospital, and the number of hospitalizations for the National Child Hospital in 2013 were assumed to be equivalent to those from the Mother and Child Hospital in 2011. There were no hospital admission books for Hospital 103 for January to May 2012. The same assumptions were made as for the National Child Hospital in 2012. There were no hospital admission books for Hospital 103 in 2011. It was therefore assumed that the number of hospitalizations for Hospital 103 in 2011 were the same as the average 2012 and 2013 Hospital 103 hospitalizations.

To ascertain pneumonia severity and outcomes, available individual medical records were reviewed to record the following: age, sex, residence, demographics, clinical features, length of stay, comorbidities and outcomes (including death in hospital, discharged home to die and persistent signs of severe illness on discharge home). Data were collected from four admitting central Vientiane hospitals for children aged 2-59 months. To ensure clinical data from available medical records were representative of all hospitalizations for pneumonia, common variables (age, length of stay) from hospital admission data were compared between participants with and without medical records using the Mann-Whitney test.

For the nine district hospitals in Vientiane, administrative data were collected to assess the number of all-cause hospitalizations and pneumonia hospitalizations for children aged <5 years old. No individual patient medical records were available for review, but admission data from district hospitals were included in the calculations of the percentage of all admissions that were pneumonia hospitalizations, and the annual incidence calculations. District hospitals have minimal resources, including oxygen, and lack of skilled staff for managing severe pneumonia in children, and the majority of unwell children are advised to attend central hospitals. It was therefore assumed that all admissions to district hospitals were non-severe.

To ascertain whether health seeking behavior and admission practice changed over the pre-PCV13

period, numbers of admissions for other “control” conditions, including bronchiolitis (without a comorbidity of pneumonia), acute diarrheal illness, pharyngitis/tonsillitis, thalassemia, malnutrition, urinary tract infection, febrile seizures and meningitis were collected from central hospital admission books using the same methods of collection and assumptions for missing data as for the pneumonia hospitalizations.

To calculate incidence rates, only patients with a known residential address within the defined catchment area, Vientiane Capital, were included in the numerator for this calculation. However, central hospital admission books did not list the residential address for all patients. Based on the available individual medical record data which have residence recorded, not all patients listed in the hospital admission books resided in the defined population catchment area. To account for this, the percentage of patients hospitalized with pneumonia from within the catchment and outside the catchment were calculated for each central hospital from the available medical record data. The percentage of patients hospitalized with pneumonia from within the catchment and outside the catchment were found to be consistent between years for each hospital, and so the average percentage of patients hospitalized with pneumonia from within the catchment were calculated for each hospital. These percentages were applied to the pneumonia hospitalizations with missing residential address data to estimate the number of pneumonia hospitalizations within the catchment area.

District hospital admission data did not contain residential address data for individual patients, however each district hospital specifically services surrounding villages only. It was therefore assumed that patients admitted to a district hospital were highly likely to reside within that district and hence all admissions to district hospitals within Vientiane Capital were included in incidence calculations for hospitalized pneumonia.

The catchment population was defined as children aged 2-59 months with a known residential address within Vientiane Capital. Based on population and growth data from the Ministry of Health, Lao PDR, the number of children under 5 years of age in the defined catchment was 71,081 for 2011-2013 and 77,537 for 2014-2016. Infants aged 0-1 months were excluded from the population denominator by calculating $2/60^{\text{th}}$ of the Vientiane population aged under 5 years of age, which were then subtracted from the total number of children aged 0-59 months in Vientiane, giving the total number of 68,712 children 2-59 months old for 2011-2013 and 74,952 for 2014-2016.

2. Results

2.1 Pre-PCV13 retrospective pneumonia review

There were hospital admission books available from four of the five central hospitals and 931 individual medical records available for review. Administrative data were available for eight out of nine district hospitals. Four district hospitals (Pak Ngum, Santhong, Naxaithong and Hadxaifong District Hospitals) have been included in the calculations of the percentage of all-cause hospitalizations due to pneumonia, and in the annual incidence calculations of hospitalized pneumonia in Vientiane Capital. Four district hospitals (Sikkotabong, Sisatanak, Xaysettha and Chanthabouly District Hospitals) had no pneumonia hospitalizations recorded for children < 5 years for 2011-2013.

After applying the various assumptions outlined in the methods section, the estimated total number of pneumonia hospitalizations for 2011-2013 for children aged 2-59 months in Vientiane was 3,801, and the estimated number of all-cause hospitalizations was 18,687. The estimated percentage of all-cause hospitalizations due to pneumonia was 20.3% (Table 1). The number of pneumonia hospitalizations at district hospitals was 165, which comprised 4.3% of the total number of pneumonia hospitalizations.

To further determine whether our assumption, that the number of pneumonia hospitalizations were stable throughout the three-year period, was valid, we determined the hospitalization rates for other common conditions, including bronchiolitis (without pneumonia comorbidity), acute diarrheal illness, pharyngitis/tonsillitis, thalassemia, malnutrition, urinary tract infection, febrile seizures and meningitis using admission data from those central hospitals with complete years of data (Settathirath Hospital, Mahosot Hospital and Hospital 103). The percentage of hospitalizations due to these “control” conditions from 2011 to 2013 are shown in Figure S3.

A flowchart to ascertain clinical data on pneumonia from available medical records for each central hospital is shown in Figure S4. Overall 46.6% of all pneumonia hospitalizations to central hospitals in Vientiane Capital had medical records available for review. There was no significant difference in the median age (p-value 0.07) between children whose medical records were available and those who were not. However, median length of stay was longer (p-value <0.001) in those with medical records available (4 days, interquartile range [IQR] 3-5) compared to children without medical records (3 days, IQR 2-5).

All-cause hospitalizations and pneumonia hospitalizations by age and clinical characteristics are shown in Table 2. Almost half (48.5%) of all-cause hospitalizations for infants aged 2-5 months

were due to pneumonia. Severe pneumonia accounted for 57% of children hospitalized with pneumonia. Infants aged 2-5 months had the highest proportion of pneumonia cases that were severe (61.7%). The median age of cases was 15 months (IQR 8-24) and median length of stay 4 days (IQR 3-5). Intensive Care Unit (ICU) admission occurred in 14.6% of children with a median length of ICU stay of 2 days (IQR 1-3). Three patients died during hospitalization. However, 4.8% of cases were discharged against medical advice, and were either still unwell at the time of discharge, or discharged home to die, indicating that the case fatality rate may be as high as 5.2%.