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Pneumonia prevention: Cost-effectiveness analyses of two vaccines among refugee children aged under two years, *Haemophilus influenzae* type b-containing and pneumococcal conjugate vaccines, during a humanitarian emergency, Yida camp, South Sudan

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Abstract

By September 2013, war between Sudan and South Sudan resulted in >70,000 Sudanese refugees and high pneumonia incidence among the 20,000 refugees in Yida camp, South Sudan. Using Médecins Sans Frontières (MSF)-provided data and modifying our decision-tree models, we estimated if administering *Haemophilus influenzae* type b (Hib)-containing (pentavalent vaccine, also with diphtheria pertussis and tetanus [DPT] and hepatitis B) and pneumococcal conjugate (PCV) vaccines were cost-effective against hospitalized pneumonia. Among children <2 years old, compared with no vaccination, one- and two-doses of combined Hib-containing and PCV would avert an estimated 118 and 125 pneumonia cases, and 8.5 and 9.1 deaths, respectively. The cost per Disability-Adjusted-Life-Year averted for administering combined one- and two-doses was US \$125 and US\$209, respectively. MSF demonstrated that it was possible to administer these vaccines during an emergency and our analysis found it was highly costeffective, even with just one-dose of either vaccine. Despite unknown etiology, there is strong field and now economic rationale for administering Hib and PCV during at least one humanitarian emergency.

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Competing interests

None.

Submission declaration and verification

All authors declare that this work has not been published previously.

Authors' contributions

LMG contributed to the conception, design, acquisition, and analysis of data, and interpretation of data, and writing/revising the manuscript. RH contributed to the analysis and interpretation of the data and revising of the manuscript. STC contributed to the conception, design and analysis of the data, interpretation of data, and revising the manuscript. All authors approved the final manuscript for publication.

Keywords

South Sudan; Humanitarian emergency; *Streptococcus pneumoniae*; PCV; *Haemophilus influenzae* type b; Hib vaccine; Cost-effectiveness; Supplemental immunization activity; Routine immunization

1. Introduction

War has occurred between South Sudan and Sudan for decades and continues today despite the 2011 independence, which was expected to bring stability to the country. On 2 August 2012, an international health non-governmental organization, Médecins Sans Frontières (MSF), announced a health catastrophe for Yida camp, in northern South Sudan because of increasing arrivals of Sudanese refugees from across the border, overstretched camps, and the high numbers of children with malnutrition, who were further weakened by diarrhea, malaria and respiratory infections [1]. Black et al. (2010) found that pneumonia and diarrhea are the leading causes of childhood deaths globally and the major causes of lower respiratory-associated or pneumonia deaths are *Haemophilus influenzae* type b (Hib) and *Streptococcus pneumoniae* [2]. Through the end of 2012 in Yida camp, respiratory infections continued and even increased for acute respiratory infections (ARI) among outpatients. Therefore, MSF prepared in the ensuing months to vaccinate against Hib and *Streptococcus pneumoniae* with all training and logistics completed and the vaccine finally arriving the first of July 2013 to provide three rounds each of Hib and pneumococcal conjugate (PCV) vaccines. From their data reported December 2013, we performed a cost-effectiveness analysis from the perspective of MSF [3].

2. Methods

Using the MSF data (Table 1), we used our previously developed decision-tree models (Fig. 1) for one- and two-dose Hib-containing and PCV vaccinations separately and in combination to estimate the vaccines' impact and cost-effectiveness following the target population in their first 2 years of life [4]. We did not include indirect non-medical costs as the MSF report provided neither indirect costs, e.g., time lost to parents, nor non-medical costs, e.g., transportation.

From the MSF report using estimates provided from the United Nations High Commissioner for Refugees (UNHCR), the mid-2012 total population was 20,000 [3]. Given 585 persons were hospitalized with ARI [3], presumptively mainly pneumonia, the annual incidence was 2925/100,000 total population. This rate would be higher among young children; however, is similar to double the estimated African childhood Hib pneumonia incidence (3448/100,000 children aged <5 years) [5]. Doubling the reported childhood Hib incidence was done because of the high degree of malnutrition and overcrowding, inadequate shelter and blankets during a humanitarian emergency [4]. Comparing the annual African childhood Hib pneumonia rate, pneumococcal pneumonia has double the incidence [6]. Therefore, the childhood pneumococcal pneumonia incidence was assumed to be 5850/100,000 children aged <5 years (Table 1). Invasive disease, such as meningitis or sepsis, was not considered.

Table 1 provides other MSF report data for target population, vaccine coverage/wastage, and vaccination program costs that were used.

We assumed 75% of children would use healthcare services. Vaccine effectiveness data for South Sudan were unavailable. From a Gambian study, Hib vaccine efficacy against radiologically defined pneumonia was 22.4% (95% confidence interval [95%CI] 1.9–38.6) [7]; we assumed one-dose efficacy was 20% [3]. From another Gambian trial, two-dose PCV efficacy against clinical or severe clinical pneumonia was 37% (95% CI 25–48) [8]; one-dose was assumed to be 29% [3].

We used World Health Organization (WHO) estimates for Africa-specific childhood case fatality rates (CFR) for Hib and pneumococcal pneumonia [5,6]. Because Hib and pneumococcal CFRs were similar we used one rate. We estimated the medical visit cost at US\$1.01/day using the average cost for Ethiopia and Kenya— neighboring countries [9] and multiplied it by the average stay of 4 days [10]. Medication costs (\$12.34)/pneumonia case were estimated from previous reports (Table 1) [11].

We compared the costs and benefits of the July-September 2013 MSF conducted Hib-containing and PCV campaigns under base-case scenarios: (1) no vaccination, (2–5) one- and two-dose Hib-containing vaccine or PCV, and (6–7) one-dose or two-doses of combined Hib-containing vaccine and PCV using Microsoft® Excel 2010 (Redmond, WA). We estimated the incremental cost-effectiveness ratio (ICER) as cost per Disability-Adjusted-Life-Year (DALY) averted expressed in 2013 US dollars. DALYs used were WHO life expectancy data weighted by years lost and disability from pneumonia, with the mean duration of four hospital-days and no long-term sequel among survivors [12]. To determine if intervention was cost-effective, we used the WHO threshold for highly cost-effective intervention of less than the country's gross domestic product (GDP)/capita vs. the cost/DALY averted [13]; South Sudan 2013 GDP/capita was US\$1045 [14].

A one-way sensitivity analysis was conducted to evaluate the impact of changing values of several parameters on ICER for two-doses of each vaccine or both vaccines combined (Table 1). These one-way sensitivity analyses were examined using tornado diagrams. A threshold analysis was done to decipher the break-even price of two-doses of Hib-containing and PCV vaccines when all other variables are held at their base-case value. Finally, a probabilistic sensitivity analysis (PSA) was done on those variables that indicated an impact on the cost result after performing the one-way sensitivity analysis. This allowed us to limit the number of variables selected for this analysis. Up to 5000 iterations were performed to obtain the cost distribution results. All future costs and DALY estimates were discounted at an annual rate of 3%.

3. Results

Tables 2 and 3 summarize all findings. For no vaccination, estimated total pneumonia cases and associated deaths were 507 and 37, respectively, with 380 medical visits costing US \$6232.

One-dose and two-dose Hib-containing vaccination prevented an estimated 30 and 33 Hib pneumonia cases, and estimated 2 and 3 deaths, respectively while reducing medical costs by approximately US\$400 for each scenario (Table 2). One- and two-dose PCV would avert an estimated 98 and 105 pneumococcal pneumonia cases, and estimated 7 and 8 deaths averted, respectively. For one- and two-dose PCV, the medical cost averted was about \$1100 and \$1300, respectively. The greatest impact was seen with combined one- and two-doses of Hib-containing and PCV; they averted 118 and 125 pneumonia cases, and 8.5 and 9.1 deaths, respectively with the largest medical cost reductions of approximately US\$1500 for each scenario.

Table 3 shows administering one- and two-doses of Hib-containing vaccines yield ICER/DALY averted of US\$211 and US \$310, while costing US\$945 and US\$1388 per case averted, respectively. One- and two-doses of PCV yield ICER/DALY averted of US \$148 and US\$210, respectively and \$664 and \$942, respectively, for cost per case averted. The combined one- and two-doses of Hib-containing and PCV campaigns would yield ICER/DALY averted of US\$125 and US\$209, respectively and \$559 and \$936, respectively, for cost per case averted. Therefore given the South Sudan 2013 GDP/capita of US\$1045, all six scenarios had a cost/DALY averted ranging from \$125 (one-dose combined vaccines) to \$310 (2 doses of PCV) that are highly cost-effective.

In one-way sensitivity analysis, the base-case estimates for the two-doses of each or combined vaccines were most affected by vaccine efficacy, disease burden of the bacteria prevented, and CFR. The greatest range of costs/DALY averted was seen for two-doses Hib: \$199–\$1025 for lower and upper sensitivity limits for vaccine efficacy of 1.9–38.6% and \$245.27–\$416.80 for lower and upper limit for Hib disease burden of 2194–3656/100,000 children. No other analyses ranged by greater than \$135 for cost/DALY averted (Fig. 2).

Although the cost of the vaccine was known, Fig. 3 presents how cost-effectiveness of each vaccine varies as the unit price of vaccines are varied up to \$100. Using the threshold cost-effectiveness of GDP per capita (\$1045 in US\$ for 2013), Hib-containing vaccine would be considered very cost-effective until a unit price of \$25 and cost-effective up to a unit price of \$80. PCV vaccine would be considered very cost-effective up to a unit price of \$85.

Fig. 4 represents the probabilistic sensitivity analyses for 2- doses of Hib-containing vaccine (Fig. 4A) and PCV (Fig. 4B). For 2-doses of Hib-containing vaccine the maximum DALYs averted was 801 with a mean of 31. For 2-doses of PCV the maximum DALYs averted was 1090 with a mean of 85.

4. Discussion

In humanitarian emergencies, excess communicable disease-associated morbidity and mortality, including pneumonia, are avoidable. Effective vaccines exist but are rarely administered. Using MSF data for Hib-containing and pneumococcal vaccinations, we found administration highly cost-effective even with one-dose of either vaccine for children in their first 2 years of life when examining cost/DALY averted [15]. Hib and pneumococcus are important causes of childhood bacterial meningitis, too; these vaccines can also prevent

meningitis [7,8], likely making them more even cost-effective than this analysis showed. Post-immunization evaluation and continued surveillance for ARI/pneumonia remain critical and will help to determine if these vaccines have been successful in lowering the ARI rates and related causes of morbidity and mortality.

We used conservative rates for Hib and pneumococcal pneumonia (MSF-provided total ARI inpatient figures); our prior study doubled the childhood African incidence because of the level of malnutrition, overcrowding, and inadequate shelter during an emergency. Additionally, MSF cost of vaccines was more than Global Alliance for Vaccines and Immunization (GAVI Alliance)- supplied vaccines increasing the cost-side of model.

Similar to other studies, we found vaccine efficacy, CFR, and disease burden had the greatest influence on the cost-effectiveness [16,17]. Although MSF provided much information, we used sensitivity analyses for many estimates—disease burden; duration, use and outcome of healthcare; and vaccine efficacies—these analyses still showed the costs/DALY averted was less than South Sudan's GDP/capita.

Although, WHO/Strategic Advisory Group of Experts (SAGE) on Immunization framework for decision-making of vaccination in acute humanitarian emergencies has been developed, until recently measles has been the only vaccine administered in humanitarian emergencies [18,19]. The three steps for this framework have been met for Hib and PCV through MSF's experience in Yida camp: the ARI risk is high; the vaccines exist, are safe and amenable to giving in mass campaigns or as part of routine immunization; and they can be administered in a humanitarian setting [19]. GAVI-Alliance needs to consider supporting administration of Hib and PCV for children in emergency settings now that we know it is feasible to provide these life-saving immunizations to these most vulnerable young people. ARI data during humanitarian emergencies are limited; few studies examined morbidity and even fewer the specific pathogens [20]; but in developing countries, Hib and pneumococcus are the most frequent causes of bacterial pneumonia. Therefore, despite a lack of etiology there is strong field and now economic rationale for administering Hib and PCV during at least one humanitarian emergency.

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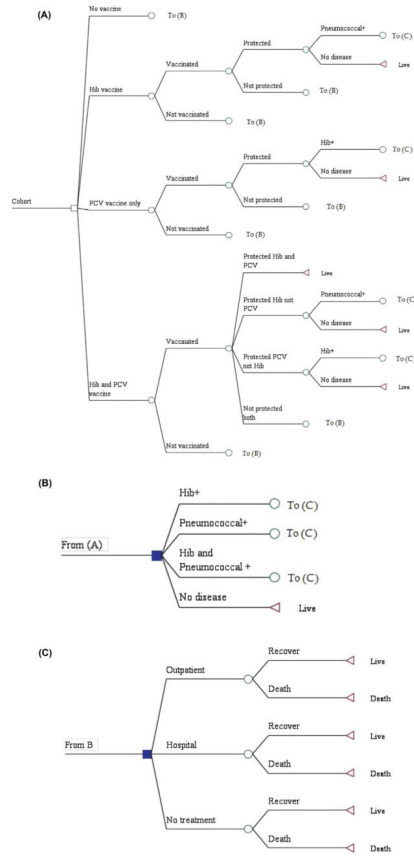


Fig. 1.
Decision tree.

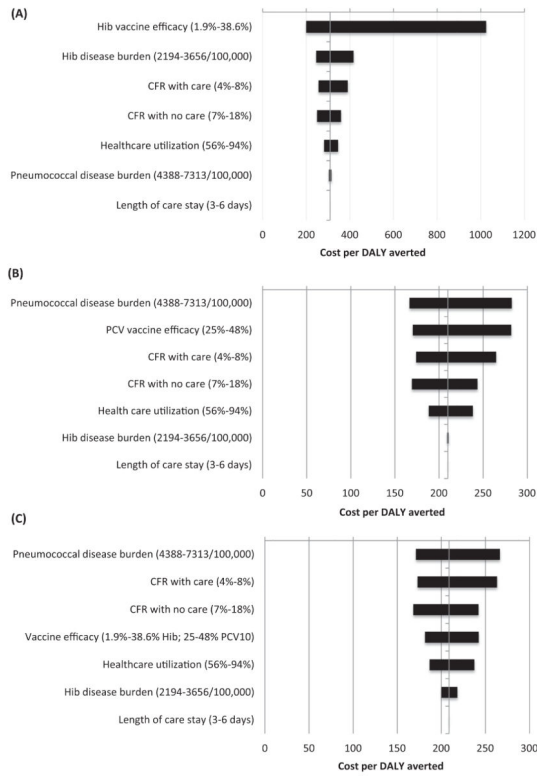


Fig. 2. Tornado diagrams of univariate sensitivity analysis. (A) 2 doses of Hib-containing vaccine, (B) 2 doses of PCV vaccine, and (C) 2 dose Hib/2 dose PCV vaccine.

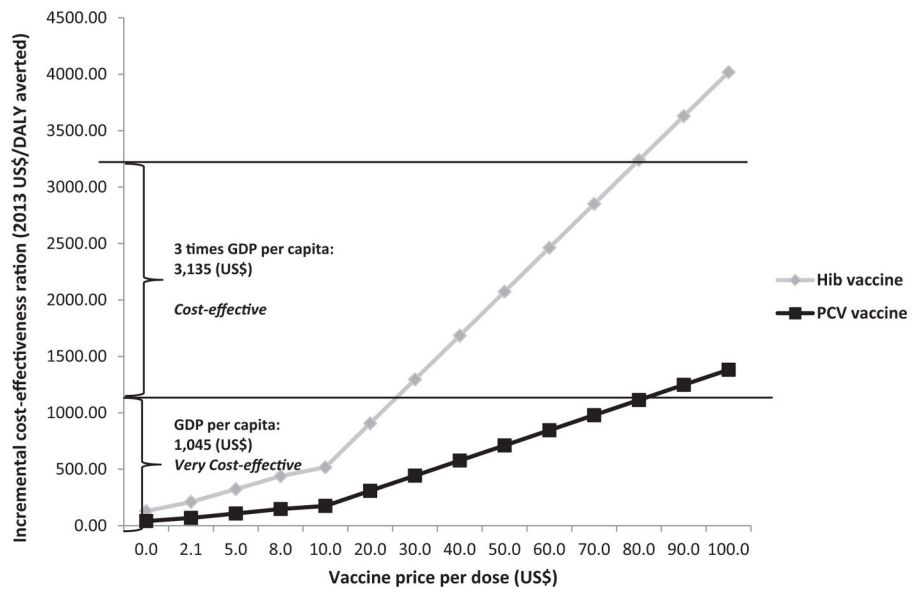


Fig. 3. Cost-effective threshold analysis by vaccine price. Vaccine unit price varied up to \$100 with the threshold cost-effectiveness ratio at the lower horizontal line based on South Sudan's GDP per capita and at the upper horizontal line based on three times that GDP per capita.

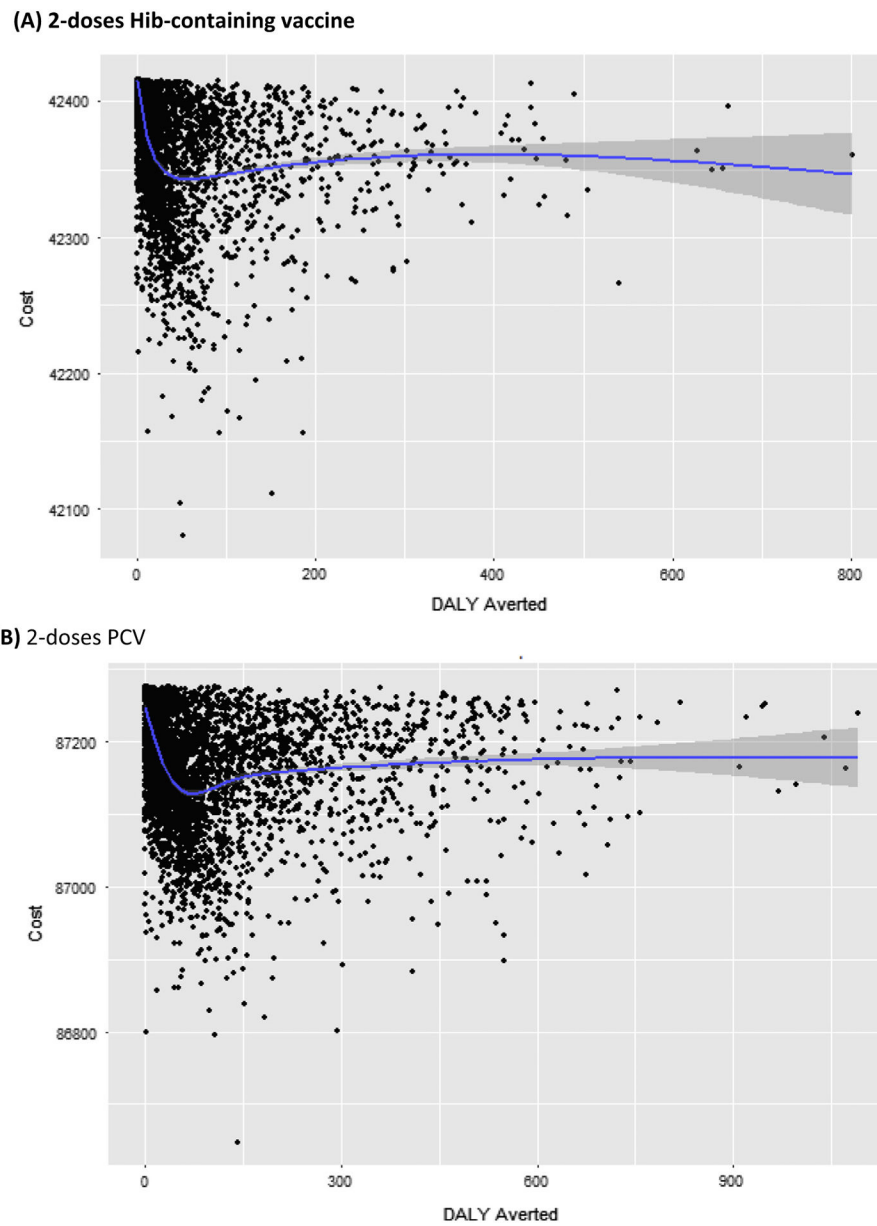


Fig. 4. Probabilistic Sensitivity Analysis. (A) 2-doses Hib-containing vaccine. (B) 2-doses PCV. DALY, disability-adjusted life year lost.

Table 1

2013 supplemental immunization activity of MSF, Yida refugee camp, South Sudan.

Parameter	Base-case estimate	Sensitivity range	References
Target population	5781	NA	[3]
Epidemiologic			
Hib pneumonia rate (per 100,000, annual)	2925	2194–3656 ($\pm 25\%$)	[3,5]
Pneumococcal pneumonia rate (per 100,000, annual)	5850	4388–7313 ($\pm 25\%$)	Doubled Hib [5,6]
Clinical			
Children's healthcare utilization, %	75	94–56 ($\pm 25\%$)	Assumption
Vaccine coverage per survey, %			
1 dose	89.2	NA	[3]
2 doses	66.1	NA	[3]
Hib vaccine efficacy for radiologically defined pneumonia, %			
1 dose	20.0	0.5–25.0 (+25%)	Assumption [4]
2 doses	22.4	1.9–38.6	[7]
PCV vaccine efficacy for clinical or severe clinical pneumonia, %			
1 dose	29.0	0.5–36.25 (+25%)	Assumption [4]
2 doses	37.0	25.0–48.0	[8]
Case Fatality Rate (CFR, aged < 5 years), %			
Care	6	4–8	[5,6]
No care	11	7–18	[5,6]
Length of inpatient stay, days	4	3–6	[10]
Vaccine wastage (%)	1	NA	[3]
Economic, US\$			
Hib vaccine price/dose	2.10	NA	[3]
PCV price/dose	7.97	NA	[3]
Cost/dose delivered, excluding expatriate staff	3.45	NA	[3]
Total care cost/day	1.01	NA	[9]
Medication costs/case of pneumonia	12.34	NA	[11]

Costs were adjusted to 2013 levels.

Table 2

Impact of Hib-containing and PCV vaccination program on total pneumonia events among children aged <2 years, Yida refugee camp, South Sudan, 2013.

Events	Number of events	(Lower Limit [LL]-Upper L [UL])	Averted	(LL-UL)
Without vaccination program				
Cases	507	(423–507)	–	
Deaths	37	(29–46)	–	
Number of DALYs	2274	(1804–2823)	–	
Medical visits	380	(284–477)	–	
Medical costs (US\$)	6232	(5194–7271)	–	
1 dose Hib vaccination program				
Cases	477	(393–562)	30	(1–38)
Deaths	35	(34–37)	2	(0–3)
Number of DALYs	2139	(1697–2655)	135	(3–169)
Medical visits	358	(448–267)	23	(17–28)
Medical costs (US\$)	5861	(4376–7346)	371	(9–463)
Vaccination costs (US\$)	29,192	–	–	
Total costs (US\$)	35,053	(33,568–36,538)	–	
2 dose Hib vaccination program				
Cases	474	(390–559)	33	(25–41)
Deaths	34	(27–42)	3 (2–4)	
Number of DALYs	2127	(1687–2640)	147	(45–229)
Medical visits	356	(266–446)	25	(7–38)
Medical costs (US\$)	5828	(4352–7305)	403	(122–626)
Vaccination costs (US\$)	50,824	–	–	
Total costs (US\$)	56,652	(50,824–58,129)	–	
1 dose PCV vaccination program				
Cases	487	(398–506)	98	(2–109)
Deaths	30	(24–38)	7	(0–8)
Number of DALYs	1882	(1493–2336)	392	(7–490)
Medical visits	315	(235–395)	66	(1–87)
Medical costs (US\$)	5157	(3851–6464)	1075	(19–1347)
Vaccination costs (US\$)	60,067	–	–	
Total costs (US\$)	65,224	(63,917–66,530)	–	
2 dose PCV vaccination program				
Cases	402	(344–460)	105	(78–132)
Deaths	29	(23–36)	8 (6–10)	
Number of DALYs	1802	(1492–2237)	472	(352–586)
Medical visits	301	(235–395)	79	(49–99)
Medical costs (US\$)	4937	(3687–6188)	1294	(965–1622)
Vaccination costs (US\$)	104,579	–	–	
Total costs (US\$)	109,516	(108,801–110,231)	–	

Events	Number of events	(Lower Limit [LL]-Upper L [UL])	Averted	(LL-UL)
1 dose Hib/1 dose PCV vaccination program				
Cases	390	(327–505)	118	(2–147)
Deaths	28	(22–37)	8.5	(0–11)
Number of DALYs	1747	(1386–2264)	528	(10–659)
Medical visits	292	(225–379)	88	(2–111)
Medical costs (US\$)	4787	(3574–6204)	1445	(28–1811)
Vaccination costs (US\$)	71,112	–	–	
Total costs (US\$)	75,899	(74,686–77,316)	–	
2 dose Hib/2 dose PCV vaccination program				
Cases	382	(324–440)	125	(99–151)
Deaths	28	(22–34)	9.1 (7–11)	
Number of DALYs	1713	(1359–2126)	561	(443–697)
Medical visits	287	(214–359)	94	(70–118)
Medical costs (US\$)	4694	(3505–5883)	1538	(1148–1928)
Vaccination costs (US\$)	122,595	–	–	
Total costs (US\$)	127,289	(126,100–128,478)	–	

Table 3

Cost-effectiveness of *Haemophilus influenzae* type b (Hib)-containing and pneumococcal conjugate vaccine (PCV) compared with no vaccination among children aged <2 years, Yida refugee camp, South Sudan, 2013.

(US\$)	1 dose Hib (LL-UL)	2 dose Hib (LL-UL)	1 dose PCV (LL-UL)	2 dose PCV (LL-UL)	1 dose each Hib and PCV (LL-UL)	2 doses each Hib and PCV (LL-UL)
Cost/DALY averted	211 (168–8628)	310 (199–1025)	148 (118–8877)	210 (166–283)	125 (100–6502)	209 (168–266)
Cost/case averted	945 (752–38,685)	1388 (894–4594)	664 (527–39,801)	941 (746,267)	559 (446–29,150)	936 (767–1194)
Cost/death averted	13,038 (10,368–533,590)	19,146 (12,332–63,367)	9161 (7267–548,981)	12,986 (10,292–17,472)	7703 (6157–402,068)	12,909 (10,696–16,475)

LL – lower limit.

UL – upper limit.