Comparative Economic Evaluation of *Haemophilus influenzae* Type b Vaccination in Belarus and Uzbekistan

Ulla K. Griffiths1, Andrew Clark1, Veronika Shimanovich2, Irina Glinskaya3, Dilorom Tursunova4, Lucia Kim4, Liudmila Mosina5, Rana Hajjeh6, Karen Edmond1

1 Hib Initiative, London School of Hygiene and Tropical Medicine, London, United Kingdom, 2 Republican Centre for Hygiene, Epidemiology and Public Health, Minsk, Belarus, 3 Minsk City Centre for Hygiene and Epidemiology, Minsk, Belarus, 4 Ministry of Health, Tashkent, Uzbekistan, 5 WHO Regional Office for Europe, Copenhagen, Denmark, 6 Center for Disease Control, Atlanta, Georgia, United States of America

Abstract

**Background:** Hib vaccine has gradually been introduced into more and more countries during the past two decades, partly due to GAVI Alliance support to low-income countries. However, since Hib disease burden is difficult to establish in settings with limited diagnostic capacities and since the vaccine continues to be relatively expensive, some Governments remain doubtful about its value leading to concerns about financial sustainability. Similarly, several middle-income countries have not introduced the vaccine. The aim of this study is to estimate and compare the cost-effectiveness of Hib vaccination in a country relying on self-financing (Belarus) and a country eligible for GAVI Alliance support (Uzbekistan).

**Methods and Findings:** A decision analytic model was used to estimate morbidity and mortality from Hib meningitis, Hib pneumonia and other types of Hib disease with and without the vaccine. Treatment costs were attached to each disease event. Data on disease incidence, case fatality ratios and costs were primarily determined from national sources. For the Belarus 2009 birth cohort, Hib vaccine is estimated to prevent 467 invasive disease cases, 4 cases of meningitis sequelae, and 3 deaths, while in Uzbekistan 3,069 invasive cases, 34 sequelae cases and 341 deaths are prevented. Estimated costs per discounted DALY averted are US$ 9,323 in Belarus and US$ 267 in Uzbekistan.

**Conclusion:** The primary reason why the cost-effectiveness values are more favourable in Uzbekistan than in Belarus is that relatively more deaths are averted in Uzbekistan due to higher baseline mortality burden. Two other explanations are that the vaccine price is lower in Uzbekistan and that Uzbekistan uses a three dose schedule compared to four doses in Belarus. However, when seen in the context of the relative ability to pay for public health, the vaccine can be considered cost-effective in both countries.

**Methods**

**Hib disease definitions**

Hib disease was categorised as pneumonia, meningitis, and “non-pneumonia-non-meningitis” (NPNM), replicating groupings...
used by the Global Burden of Hib and Pneumococcal disease project [6,7]. Pneumonia was defined as any case of pneumonia reported by the Ministry of Health surveillance database in Uzbekistan and Belarus, regardless of radiological confirmation. Meningitis was defined as any case of inpatient hospital meningitis. NPNM included other specific diseases in children that can be caused by the Hib bacterium, such as cellulitis, osteo myelitis, septic arthritis and epiglottitis.

Decision analytic model structure
A static, compartmental cohort model was used to estimate Hib disease events for children of the 2009 birth cohorts in the two countries. The model is illustrated in Figure 1. Projected numbers of person-years lived between 1 and 55 months were multiplied by disease incidence rates to estimate Hib cases in each cohort. An all-cause pneumonia incidence rate was used to calculate total pneumonia cases and it was assumed that a proportion of these were caused by Hib. Hib meningitis and Hib NPNM cases were calculated directly from aetiology specific incidence rates. A proportion of cases were assumed to seek health care and each of these incurred an average treatment cost. Hib deaths were estimated from case fatality ratios (CFRs) and a risk of permanent disability was applied to all survivors of Hib meningitis and classified according to type.

The impact of Hib vaccine was estimated as the difference between scenarios with and without the vaccine. In the vaccine scenario, numbers of cases were reduced by dose-specific vaccination coverage and dose-specific vaccine efficacy. Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in expected costs between the two scenarios with the difference in expected health effects, expressed as cases, deaths and lost Disability Adjusted Life Years (DALYs). The analysis was undertaken from a societal perspective; including costs incurred by the Governments, the GAVI Alliance and households. While the Government health sector is dominant in both countries with very limited private health services available, it is common practice in Uzbekistan that patients pay a proportion of drug costs when accessing public services and these were included in the analysis. Transport and time costs were excluded as we did not conduct patient interviews as part of the study.

Future costs and effects were discounted by 3% per year [8]. Treatment costs were estimated in 2009 US$ using exchange rates of 2,793 Belarusian rubles and 1,464 Uzbek som to one US$. The model was developed in Microsoft Excel. Model input parameter values are summarised in Table 1 and justifications for these given below.

Health care utilization
As seen in Figure 1, CFRs are assumed to vary with health care utilisation, implying that the risk of death is higher if no formal health care services are accessed. Similarly, when incidence rate calculations are based on data from hospital surveillance only, it is necessary to adjust these as cases would inevitably be missed in settings with limited access to care. In Uzbekistan, a 2006 Multiple Indicator Cluster Survey reported that of children aged 0–59 months with pneumonia symptoms during the two weeks preceding the survey, only 68% were taken to an appropriate provider [9]. We used this figure to adjust CFRs and hospital disease incidence rates for all types if Hib disease.

Balabanova et al. illustrated that Belarus has the highest health service utilization out of eight former Soviet Union countries[10], and the country also has the largest number of doctors and nurses per 1,000 population within central- and Eastern Europe [11]. In particular, children’s health is monitored closely with general check-ups by all main specialists annually up till 18 years of age [11]. Therefore, we did not adjust hospital incidence rates and CFRs for limited access to care in Belarus.

Hib disease incidence parameters

**Hib meningitis.** Meningitis is the most studied type of Hib disease for three key reasons: it is the most severe form of Hib disease, it has a relatively straightforward clinical diagnosis, and it is the type of Hib disease that can be most easily diagnosed in a laboratory (from cerebrospinal fluid (CSF) of patients with clinical symptoms). Hence, when assessing Hib disease burden, meningitis is often the preferred starting point.

In Belarus, population-based childhood bacterial meningitis surveillance was in place at Minsk City Children’s Infectious Disease Hospital (MCCIDH) during 2002–2007 [12,13]. During the six-year period, 175 purulent meningitis cases were detected in children < 5 years and a bacterial pathogen was identified for 87 of these, giving an average bacterial meningitis incidence rate of 31 per 100,000 children < 5 years (Table 2). 30 of the cases were confirmed as Hib, generating an incidence of 5 per 100,000 children, with annual rates between 1 and 10. However, since 88 of the purulent cases had no confirmed pathogen, this is likely to be an underestimate of the true number. According to WHO guidelines [14] and following methods used in other bacterial meningitis aetiology studies [15], culture negative cases should be allocated to bacterial pathogens according to their proportion of confirmed cases. Hence, we apportioned 34% of the non-confirmed cases to Hib and estimated an adjusted Hib meningitis incidence rate of 10.8 per 100,000 children < 5 years, with a range between 7.4 and 15.1.

Since no population based meningitis surveillance studies have been conducted in Uzbekistan, we used routine surveillance data for our estimates. 234 hospitals reported 5,245 clinical meningitis cases in children < 5 years in 2007, giving an incidence of 166 per 100,000 children. We adjusted this estimate upwards by 32% to account for limited access to care, arriving at 219 per 100,000 children. The proportion of meningitis caused by Hib was approximated from a study conducted by the Uzbek Ministry of Health and the US Naval Medical Research Unit no. 3 in Egypt[16]. 165 CSF samples from children with clinical meningitis admitted to hospitals in Tashkent and Samarkand during 2002–2004 were tested using Polymerase Chain Reaction and 61 were found to be purulent with nine of them confirmed as Hib[16]. The adjusted number is thus 14 cases, equivalent to 8.5% of all the cases tested. We therefore estimated a Hib meningitis incidence of 18.7 per 100,000 children < 5 years (8.5% of 219).

For comparison, the Hib Global Burden of Disease (GBD) project estimated a Hib meningitis incidence rate of 16 per 100,000 children < 5 years for the WHO European region [6]. We used this estimate for both countries in the sensitivity analyses.

**Hib pneumonia.** All-cause pneumonia incidences were determined from routine surveillance systems in both countries. In Belarus, 10,402 pneumonia cases in children less than five years were reported during 2008, giving an annual incidence of 2,302 per 100,000 children, based on an under-five population of 451,960 [17]. 84% of cases were reported from hospitals and the remaining from outpatient clinics. In Uzbekistan, 20,014 pneumonia cases in children less than five years (under-five population is 3,162,151) [17]. 230,201 acute respiratory infections (ARI) cases were reported the same year, 15% of which were hospitalised. When hospitalised ARI cases are included, the incidence rate increases to 1,724 per 100,000. After adjusting for limited access to care, the incidence is 2,277 per 100,000 children < 5 years.
(a) Clinical pneumonia incidence in children < 5 yrs
(b) Percent of clinical pneumonia caused by Hib
(c) Hib NPNM incidence in children < 5 years
(d) Hib meningitis incidence in children < 5 years
(e) Pneumonia CFR without access to care
(f) Pneumonia CFR with access to care
(g) Hib NPNM CFR without access to care
(h) Hib NPNM CFR with access to care
(i) Hib meningitis CFR without access to care
(j) Hib meningitis CFR with access to care
(k) Proportion of Hib pneumonia cases seeking care
(l) Proportion of Hib NPNM cases seeking care
(m) Proportion of Hib meningitis cases seeking care
(n) Proportion of Hib meningitis survivors with disability
(o) Proportion with cognitive difficulties only
(p) Proportion with seizure disorders only
(q) Proportion with hearing loss only
(r) Proportion with motor deficit only
(s) Proportion with visual disturbance only
(t) Proportion with behavioural problems only
(u) Proportion with clinical impairments only
(v) Proportion with multiple disabilities
Since the signs and symptoms of Hib pneumonia cannot be differentiated from those of pneumonia caused by other microorganisms, the incidence of Hib pneumonia can best be approximated from Hib vaccine trials[18]. Meta-analysis of Hib vaccine trials in the Gambia and Indonesia showed that Hib causes approximately 3% (95% CI 3%–14%) of clinical pneumonia [6,7]. This corresponds to Hib pneumonia incidences of 115 and 114 per 100,000 children < 5 years in Belarus and Uzbekistan, respectively. These rates are approximately half of the numbers reported by the GBD project, which estimated an average Hib pneumonia incidence in the WHO European region of 283 per 100,000 children, 5 years in the absence of Hib vaccine (range 259–463) [6]. This estimate is used in sensitivity analyses.

**Hib NPNM.** There are no data on Hib NPNM diseases in Belarus and Uzbekistan. Studies from Bulgaria and Czech Republic assessing all types of Hib diseases reported an average of 0.57 NPNM cases for each meningitis case [19,20]. The most important type was epiglottitis, accounting for 78% of cases. We thus assumed a Hib NPNM incidence of 6.15 and 10.65 per 100,000 children < 5 years in Belarus and Uzbekistan, respectively (Table 1). The GBD project estimated a Hib NPNM incidence rate of 5.0 per 100,000 children, 5 years for the WHO European region [6].

**Case fatality ratios**

In the Minsk city meningitis surveillance project, one of the 30 children with confirmed Hib meningitis died, giving a case fatality ratio of 3.2%. This is comparable to CFRs reported in Western European countries, such as 5% in the United Kingdom [21] and 4% in France [22]. Only six and five pneumonia deaths in children < 5 years were reported in Belarus during 2007 and 2008, respectively. This is equivalent to around 2% of all deaths in children and a CFR of 0.3% for all-cause pneumonia.

In Uzbekistan, 22 children < 5 years were reported to have died from meningitis in 2007, giving a CFR of 0.42%. For Hib meningitis, this figure is however unrealistically low. We used data from an Indian study reporting a hospital CFR of 15% [23] and assumed a CFR of 100% for the 32% of children that do not reach formal health care [24]. The overall CFR was thus 42%. According to Uzbek hospital surveillance data, a total of 214 pneumonia deaths occurred in 2007, generating all-cause hospital pneumonia CFR of 1.07%. We assumed 10% CFR for those without access to care, giving a weighted mean of 4%. NPNM CFRs were assumed similar to those of meningitis for the 78% epiglottitis proportion and zero for the other NPNM diseases (Table 1).

**Meningitis sequelae**

In Belarus, all children that have suffered from meningitis are followed up every three months during the first year after

---

**Table 1. Parameter values used in the base-case analysis.**

| Parameter name                                      | Belarus | Uzbekistan | Sources       |
|-----------------------------------------------------|---------|------------|---------------|
| 2009 live births                                    | 96,337  | 558,459    | Belarus/Uzbek MOH |
| 2009 life expectancy at birth (years)               | 69      | 68         | [17]          |
| 2009 vaccine coverage of third DTP dose             | 96%     | 98%        | [30]          |
| Incidence per 100,000 children < 5 yrs:             |         |            |               |
| All-cause clinical pneumonia                        | 2,302   | 2,277      | Belarus/Uzbek MOH |
| Hib NPNM                                            | 6.15    | 10.65      | [19,20]       |
| Hib meningitis                                      | 10.1    | 18.7       | [12,13]/[16]  |
| Proportion of clinical pneumonia due to Hib         | 5%      | 5%         | [7]           |
| Proportion of meningitis cases with disability      | 12%     | 14.5%      | Minsk City surveillance/[2] |
| Case fatality ratios:                               |         |            |               |
| Hib pneumonia w/o access to care                    | NA      | 10%        | NA/Assumption |
| Hib pneumonia with access to care                   | 0.3%    | 1.07%      | MOHs routine surveillance |
| Hib NPNM w/o access to care                         | NA      | 78%        | NA/Assumption |
| Hib NPNM with access to care                        | 2.5%    | 12%        | Assumptions   |
| Hib meningitis w/o access to care                   | NA      | 100%       | NA/Assumption |
| Hib meningitis with access to care                  | 3.2%    | 15%        | [13]/[23]     |
| Treatment utilization                               |         |            |               |
| Percent of pneumonia cases seeking care             | 100%    | 68%        | [10]/[9]      |
| Percent of NPNM cases seeking care                  | 100%    | 68%        | [10]/[9]      |
| Percent of meningitis cases seeking care            | 100%    | 68%        | [10]/[9]      |

---

[10.1371/journal.pone.0021472.t001](https://doi.org/10.1371/journal.pone.0021472.t001)
discharge and annually for the next two years. Data from MCCIDH revealed that 12% of children with confirmed Hib meningitis suffered from disability at six months follow-up; 75% of these had reduced hearing. Due to lack of data in Uzbekistan we used a global meta-analysis estimate of 14.5% of all Hib meningitis survivors suffering from sequelae [2].

Disability adjusted life years

The standard DALY formula and disability weights of 0.28 and 0.616 for pneumonia and meningitis, respectively, were used [25]. As there are no disability weights available for any of the NPNM diseases, the meningitis weight was used as an approximation, as epiglottitis has comparable severity to meningitis. The duration of episode was assumed similar to the average length of stay in hospital for all acute illnesses and life-long for meningitis sequelae.

Proportions of the eight different types of sequelae were as follows [2], with the respective disability weights in parentheses [25]:
- Cognitive difficulties 7.6% (0.0777), seizure disorders 10.4% (0.0987), hearing loss 22.2% (0.2331), motor deficit 15.3% (0.3884), visual disturbance 3.5% (0.6), behavioural problems 14.6% (0.0777), motor deficit 15.3% (0.4687), and multiple disabilities 18.1%. A weighted disability weight of 0.8571 was calculated for multiple impairments.

Treatment costs

Data on drug usage and average length of stay in hospital were collected from a review of patient records at selected health facilities in both countries. Costs of drugs were collected from hospital pharmacies and the costs per hospital bed-day were provided by hospital administrators. In Belarus, meningitis treatment costs were collected at MCCIDH and pneumonia costs from Minsk Regional Hospital and Stolbtsy District Hospital. In Uzbekistan, treatment costs were collected at MCCIDH and pneumonia costs from a review of patient records at selected health facilities in both countries. Costs of drugs were collected from a review of patient records at selected health facilities in both countries [26].

In Belarus, the average length of stay in hospital was 21 days per meningitis episode and between 12 and 14 days for pneumonia. In this country it is required that children who have suffered from meningitis be re-hospitalised for follow-up one month and again six months after the initial discharge. Out of 18 meningitis cases at MCCIDH, two were re-admitted three times, seven two times and nine one time as part of their follow-up. We thus assumed that all children with meningitis were re-hospitalised 1.6 times with an average length of stay of 9 days. We further assumed three outpatient visits per pneumonia and NPNM episodes and seven visits per meningitis episode [11]. In Uzbekistan, the average length of stay in hospital was 11 days for meningitis and there is no policy for re-admission. The average length of stay for pneumonia was nine days and we assumed two outpatient visits for each Hib disease hospital admission. Costs of outpatient visits were based on WHO estimates; US$ 9.21 per visit in Belarus and US$ 1.53 per visit in Uzbekistan [27].

Hib vaccine assumptions

In Belarus, a ministerial order dictates a four-dose Hib vaccine schedule, following a WHO recommendation of a booster dose in countries where Hib disease frequently occurs in children above 18 months of age [28]. In Minsk City, the schedule is 3, 4, 5 and 18 months, and the combined diphtheria-tetanus-pertussis (DTP)-Hib vaccine is procured from Sanofi Pasteur at US$ 4.95 per dose. We assumed a similar price for the national analysis. In Uzbekistan, three doses of combined DTP-hepatitis B-Hib vaccine are given at 2, 3 and 4 months. In 2010 Unicef procured the vaccine for the GAVI Alliance at a price per dose of US$ 3.00 [29]. Since both countries use a single dose vial, vaccine wastage is only estimated as 5%.

We interviewed vaccine programme staff to assess any logistical costs related to introducing the vaccine. It was revealed that even though vaccine volume had increased, existing cold chain capacities were sufficient in both countries with no additional investments required. In Uzbekistan, a GAVI introduction grant of US$ 100,000 was used for staff training and this cost was included in the analysis.

Vaccination coverage data reported by WHO and Unicef were used [30]. Hib vaccine efficacy was assumed as 86% after three doses [31], 81% after two doses [32] and 51% after one dose [32].

Sensitivity analysis

To illustrate the impact of changes in incidence estimates and CFRs, the primary sensitivity analysis was a scenario using the
WHO European region GBD numbers for both countries; thus assuming that the epidemiological parameters are similar in the two settings. Univariate sensitivity analyses were also done by assuming 100% access to care in Uzbekistan, a Hib vaccine price of US$ 2 per dose and no discounting of future values. Furthermore, since the decision-analytic model is static, indirect effects from lower risk of exposure in unvaccinated children, commonly referred to as “herd immunity”, are not directly incorporated[33]. To evaluate the potential importance of herd effects, we multiplied the direct vaccine impact by 20% in a scenario analysis [34].

Results

Disease impacts

For Belarus, it was estimated that the vaccine prevents 493 Hib disease cases and three deaths each year, while in Uzbekistan 3,072 cases and 341 deaths are averted annually. Four and 34 cases of meningitis sequelae are also prevented each year in Belarus and Uzbekistan, respectively. The results in discounted form are shown in Table 3. Deaths averted represent approximately 0.3% and 1.1% of total 2009 under-five mortality in Belarus and Uzbekistan, respectively.

Treatment costs averted

In Belarus, the average costs per bed-day excluding patient-specific costs, such as drugs and meals, were US$ 40 at MCCIDH and US$ 23 at Stolbtsy District Hospital. When multiplying by average length of stay and including patient-specific items, average meningitis treatment costs amounted to US$ 1,311 per acute episode and average pneumonia costs to US$ 413, US$ 448 and US$ 542 for district, regional and MCCIDH levels, respectively.

Incremental vaccine delivery costs

Without Hib vaccine, costs of vaccines and syringes per fully vaccinated child amounted to approximately US$ 23 in Belarus and US$ 8 in Uzbekistan (Table 4). Introduction of Hib vaccine increases annual costs by 84% in Belarus and 101% in Uzbekistan, leading to costs per fully vaccinated child of US$ 43 and US$ 16, respectively.

Cost-effectiveness

Costs per discounted DALY averted amount to US$ 9,323 in Belarus and US$ 267 in Uzbekistan (Table 5). Since life years gained represent as much as 66% and 97% of incremental DALYs in Belarus and Uzbekistan, respectively, discounting makes a considerable difference to the ICER. Without discounting, the results are US$ 3,573 in Belarus and US$ 77 in Uzbekistan. When using the Uzbekistan GAVI co-financing amount of US$ 0.30 per dose instead of the vaccine price, Hib vaccine is cost saving for the

Table 3. Estimated Hib disease and treatment costs in Belarus and Uzbekistan with and without Hib vaccine for the 2009 birth cohorts.

|                | Belarus                  | Uzbekistan             |
|----------------|--------------------------|-------------------------|
|                | No vaccine | Vaccine | Prevented | No vaccine | Vaccine | Prevented |
| Cases:         |            |         |           |            |         |           |
| Hib pneumonia  | 504        | 95      | 409       | 2,994      | 608     | 2,387     |
| Hib meningitis | 44         | 8       | 36        | 492        | 100     | 392       |
| Hib NPNM       | 27         | 5       | 22        | 280        | 57      | 223       |
| Meningitis sequelae | 5   | 1       | 4        | 41         | 8       | 33        |
| Deaths:        |            |         |           |            |         |           |
| Hib pneumonia  | 1          | 0       | 1         | 120        | 24      | 95        |
| Hib meningitis | 1          | 0       | 1         | 207        | 42      | 165       |
| Hib NPNM       | 1          | 0       | 1         | 92         | 19      | 74        |
| DALYs          | 187        | 35      | 152       | 14,382     | 2,909   | 11,473    |
| No. of outpatient visits | 1,903     | 357     | 1,546     | 5,122      | 1,040   | 4,082     |
| No. of hospital admissions | 647       | 121     | 525       | 2,561      | 520     | 2,041     |
| Outpatient visit costs (US$): |            |         |           |            |         |           |
| Hib pneumonia  | 14,082     | 2,644   | 11,438    | 6,231      | 1,265   | 4,966     |
| Hib meningitis | 2,883      | 541     | 2,342     | 1,023      | 208     | 816       |
| Hib NPNM       | 752        | 141     | 611       | 583        | 118     | 465       |
| Inpatient admission costs (US$): |            |         |           |            |         |           |
| Hib pneumonia  | 223,195    | 41,907  | 181,288   | 397,055    | 80,598  | 316,457   |
| Hib meningitis | 86,705     | 16,280  | 70,425    | 110,921    | 22,516  | 88,405    |
| Hib NPNM       | 20,220     | 3,796   | 16,423    | 63,172     | 12,823  | 50,348    |
| Meningitis sequelae costs (US$) | 75,261 | 14,048  | 61,213    | 905,085    | 182,861 | 722,224   |

doi:10.1371/journal.pone.0021472.t003
Government. Each year, the Uzbek Government saves approximately US$ 6.18 million; 5 million for vaccines and syringes donated by GAVI and 1.18 million in treatment costs averted.

Sensitivity analysis
When using the GBD EURO parameter values for incidence and CFRs the vaccine becomes considerably more cost-effective in Belarus while there are only marginal differences in the Uzbekistan results (Table 5). Since the CFR for meningitis in the GBD EURO estimates is 27%, while we assumed 3.2% in the base case for Belarus, considerably more deaths are averted in the GBD scenario, increasing the cost-effectiveness of the vaccine. Increased access to care in Uzbekistan makes the vaccine less cost-effective as fewer deaths would be averted (Figure 2). In contrast, a reduction in the vaccine price to US$ 2.00 per dose would improve the cost-effectiveness markedly in both countries.

Discussion
Our analysis demonstrated that the ICER is considerably less in Uzbekistan than in Belarus. The most important reason for this difference is that the baseline Hib mortality burden, expressed as case fatality rates, is higher in Uzbekistan than in Belarus, leading to more deaths averted per child vaccinated. Table 6 provides a comparison of key indicators on the two countries. It is seen that the less than five mortality rate is 17 times higher in Uzbekistan than in Belarus and that the proportion due to pneumonia is approximately 21% in Uzbekistan while only 4% in Belarus. Hence, Hib vaccine will prevent proportionally more deaths in Uzbekistan than in Belarus and since mortality is the most important driver of DALYs, the ICER becomes more favourable in Uzbekistan.

Other, albeit less important, explanations for the ICER difference are that the vaccine price is higher in Belarus than in

### Table 4. Vaccine and syringe costs with and without Hib vaccine (2010 US$).

| Antigen     | Belarus | Uzbekistan | Belarus | Uzbekistan |
|-------------|---------|------------|---------|------------|
|             | Doses in schedule Vaccine costs Injection supplies Total | Doses in schedule Vaccine costs Injection supplies Total |
| BCG         | 1       | 14,231     | 9,572   | 23,802     | 1         | 49,928     | 56,931     | 106,859 |
| Hepatitis B | 3       | 184,284    | 26,049  | 210,333    | 4         | 694,253    | 189,769    | 884,023 |
| DTP         | 4       | 63,945     | 34,732  | 98,677     | 4         | 588,462    | 189,769    | 778,232 |
| MMR         | 1       | 245,634    | 12,060  | 257,694    | 1         | 1,121,184  | 54,523     | 1,175,707 |
| OPV         | 2       | 72,178     | -       | 72,178     | 5         | 1,264,578  | -          | 1,264,578 |
| IPV         | 3       | 1,402,315  | 26,049  | 1,428,364  | 0         | -          | -          | -        |
| **Total without Hib vaccine** | 1,982,586 | 108,462 | 2,091,049 | 3,718,406 | 490,993 | 4,209,399 |
| Costs per child w/o Hib vaccine | 21.85 | 1.20 | 23.04 | 7.05 | 0.93 | 7.98 |
| Hib combination vaccine* | 4 | 1,814,760 | 48,239 | 1,862,999 | 3 | 5,345,975 | 142,327 | 5,488,302 |
| **Total with Hib vaccine**** | 3,733,401 | 121,969 | 3,855,371 | 8,102,345 | 348,666 | 8,451,011 |
| Costs per child with Hib vaccine | 41.14 | 1.34 | 42.48 | 15.36 | 0.66 | 16.02 |
| **Incremental costs** | 1,750,815 | 13,507 | 1,764,322 | 4,383,938 | -142,327 | 4,241,611 |

*Global Burden of Disease birth dose and booster dose of DTP at 18 months are included here.
**Hepatitis B vaccine birth dose and booster dose of DTP at 18 months are included here.

### Table 5. Incremental cost-effectiveness of Hib vaccine for the 2009 birth cohort in Belarus and Uzbekistan: Base case analysis and alternative scenario using GBD EURO estimates (discounted values).

|                                     | Belarus | Uzbekistan | Belarus | Uzbekistan |
|-------------------------------------|---------|------------|---------|------------|
| Annual incremental vaccine costs    | 1,764,322 | 4,241,611 | 1,764,322 | 4,241,611 |
| Treatment costs averted             | 343,740  | 1,183,681  | 676,114  | 1,676,923  |
| Annual net costs                    | 1,420,582 | 3,057,930 | 1,088,208 | 2,564,688  |
| Hib disease cases averted           | 467      | 3,002      | 1,081    | 6,373      |
| Hib deaths averted                  | 3        | 334        | 66       | 388        |
| Hib meningitis sequelae cases averted | 4    | 33         | 3        | 36         |
| DALYs averted                       | 152      | 11,473     | 2,316    | 13,313     |
| Incremental costs per death averted | 485,567  | 9,162      | 16,514   | 6,606      |
| Incremental costs per DALY averted  | 9,323    | 267        | 470      | 193        |

*Global Burden of Disease incidence and case fatality rates for the WHO European region [6].

[doi:10.1371/journal.pone.0021472.e004]
[doi:10.1371/journal.pone.0021472.e005]
Uzbekistan and that Belarus uses a four-dose schedule while only three doses are used in Uzbekistan. Incremental vaccine costs per child are consequently US$ 21.17 in Belarus and only US$ 7.0 in Uzbekistan. A booster dose is recommended in countries where Hib disease is a substantial problem in children above 12 months [35]. In the Minsk city meningitis surveillance it was found that as many as 80% of Hib cases were above 12 months; confirming the need for a booster dose. While there is no age-specific data on Hib disease available from Uzbekistan, the requirement for a booster dose might be less in this country. In a review of Hib disease age distributions, Bennett et al. found that while 60% of cases were above 12 months in the WHO European, the average was only 20% in the WHO South East Asian region [36]. It is thus possible that a similar impact is achieved in Uzbekistan with three doses as with four doses in Belarus, but this hypothesis can only be confirmed by undertaking intensive Hib disease surveillance.

When deciding whether Hib vaccine is a good use of scarce resources, the ICER values need to be viewed in relation to ability and willingness to pay for health care. The 2009 Gross Domestic Products (GDP) per capita was US$ 5,560 in Belarus and US$ 1,100 in Uzbekistan [37]. Hence, in relative terms, the Belarus Government is able to pay considerably more per DALY averted than the Uzbekistan Government. According to WHO recommendations, interventions that cost less than GDP per capita should be considered highly cost-effective and those that cost between one and three times GDP per capita cost-effective [38]. Hence, with these thresholds Hib vaccine can be considered highly cost-effective in Uzbekistan and cost-effective in Belarus. While economic evaluations of other interventions are limited in the two countries, a study on rotavirus vaccine in Uzbekistan was published in 2007 [39]. At a rotavirus vaccine price of US$ 5 per course, it was estimated that the costs per discounted DALY averted amount to between US$ 75 and US$ 242; values comparable with our findings for Hib vaccine.

Our results are in a similar range with other economic evaluations of Hib vaccine. In a systematic review it was found that, in 2008 values, the costs per discounted DALY averted amounted to US$ 42 in Kenya, US$ 69 in Indonesia and US$ 10,842 in Moscow [40]. The favourable cost-effectiveness ratios in Kenya and Indonesia can be attributed to higher infant mortality and Hib disease incidence rates in these parts of the world than seen in Eastern Europe and Central Asia [6]. Economic evaluations of Hib vaccine in high-income countries include studies from France [41], Sweden [42,43] and the USA [44]. In the French study, the costs per discounted Quality Adjusted Life Year gained amounted to US$ 8,054, which is comparable to our result from Belarus. In the Swedish and the US studies a cost-benefit approach involving attaching a monetary value to life years lost to death and disability were used and it was concluded that the vaccine is cost saving in both countries.

The main limitation of our study is relatively large uncertainty in the disease-specific parameter values, in particular for pneumonia. This is a limitation faced by all researchers working within the field of invasive bacterial diseases in countries with

---

**Table 6. Comparison of key indicators and study results between the two countries.**

| Indicator | Belarus | Uzbekistan | Source |
|-----------|---------|------------|--------|
| 2009 GDP per capita | US$ 5,560 | US$ 1,100 | [37] |
| Hospital beds per 1,000 population | 11 | 5 | [45] |
| 2008 mortality rate per 100,000 children < 5 years | 1,245 | 21,200 | [46] |
| Percent of deaths due to pneumonia in children < 5 years | 4% | 21% | [46] |
| Percent of deaths in children < 5 years prevented from Hib vaccine | 0.28% | 1.1% | Present analysis |
| Incremental costs of Hib vaccine introduction per fully vaccinated child | US$ 19.44 | US$ 8.04 | Present analysis |
| Incremental costs per discounted DALY averted | US$ 9,323 | US$ 267 | Present analysis |

---

Figure 2. Scenario analysis. Impact on discounted costs per DALY averted from univariate changes in parameter values. doi:10.1371/journal.pone.0021472.g002
laboratory resource constraints. In many settings, the true incidence of Hib disease remains largely unknown because the signs and symptoms are difficult to differentiate from those caused by other microorganisms, such as *Streptococcus pneumoniae*, viruses and parasites. Indeed, the true contribution from a particular bacterium can only be determined from high-quality laboratories, but these are still lacking in many places. Moreover, even in settings with adequate laboratory services, widespread use of antibiotics before hospitalization is an important constraint to detection as this hinders growth of the bacteria. Finally, in many low-income countries, children with the highest disease burden have poor access to care and many die before they reach hospital.

We adjusted for this factor in Uzbekistan, but since the exact value of this proportion is very difficult to determine, this parameter is one of the most uncertain in our analysis.

An additional limitation is the use of a static model that does not reflect the change in the force of infection over time. However, data needed for a dynamic model, such as age-specific carriage rates and population mixing are not readily available from the two countries. We incorporated possible herd immunity effects in a crude manner in the scenario analysis, but this prediction can only be considered a best guess. However, it could be argued that from a policy perspective there is limited additional benefit of a dynamic analysis when a static model, which takes a conservative approach, already demonstrates cost-effectiveness.

To increase the strength of our analysis, we prioritised data from national surveillance systems, even if more reliable values might be available from large-scale epidemiological studies in other countries. Our analysis is thus an example of how to undertake an economic evaluation with data gathered from routine data sources while using results from other countries only as a quality marker. Undertaking the analysis for two countries simultaneously brings several advantages as useful comparisons can be made on both parameter values and the overall results. When assessing the marked differences in terms of costs per discounted DALY averted between the two countries, valuable insights into the most important drivers of the results were made. Moreover, a key limitation frequently stated regarding economic evaluation studies is that they cannot easily be compared because of differences in methodologies. We facilitated such a comparison by using the same decision-analytic model for the two countries.

While data on Hib disease burden from Eastern Europe and Central Asia remain scarce, we have illustrated that the vaccine can be considered cost-effective despite conservative assumptions about incidence and mortality. However, international cost-effectiveness thresholds say nothing about affordability, and with increases in vaccine costs of 84% and 101%, respectively, both Governments should consider carefully the long-term financial sustainability. The GAVI Alliance is currently increasing its support to pneumococcal and rotavirus vaccine introductions and it is likely that its support to Hib vaccine will stop when the current five year commitments come to an end. In countries with relatively high under-five mortality, such as Uzbekistan, Hib vaccine is a highly cost-effective intervention and it is therefore vital that the future financial sustainability of the vaccine is secured.

**Author Contributions**

Conceived and designed the experiments: UKG AC LM RH KE. Performed the experiments: UKG AC VS IG DT LK LM RH KE. Analyzed the data: UKG AC KE. Contributed reagents/materials/analysis tools: UKG AC VS IG DT LK LM RH KE. Wrote the paper: UKG AC RH KE.

**References**

1. Makela PH, Takala AK, Peltola H, Eskola J (1992) Epidemiology of invasive Haemophilus influenzae type b disease. J Infect Dis 165(Suppl 1): S2; 6.
2. Edmond K, Clark A, Korczak V, Sanderson C, Griffis U, et al. (2010) Global and regional risks of disabling sequelae from bacterial meningitis. Lancet Infectious Diseases 10: 317–329.
3. Peltola H, Salo E, Saxen H (2005) Incidence of Haemophilus influenzae type b meningitis during 18 years of vaccine use: observational study using routine hospital data. BMJ (Clinical research ed) 330: 18–19.
4. CDC (2002) Progress toward elimination of Haemophilus influenzae type b invasive disease among infants and children—United States, 1998-2000. MMWR Morb Mortal Wkly (2002) Rep 51: 234–237.
5. Ojo LR, O'Loughlin RE, Cohen AL, Loo JD, Edmond KM, et al. (2010) Global use of Haemophilus influenzae type b conjugate vaccine. Vaccine 28: 7117–7122.
6. Watt JP, Wolfson LJ, O'Brien KL, Henke E, Deloria-Knoll M, et al. (2009) Burden of disease caused by Haemophilus influenzae type b in children younger than 5 years: global estimates. Lancet 374: 903–911.
7. Wolfson L, O'Brien KL, Watt JP, Henke E, Deloria-Knoll MD, et al. (2009) Methods to estimate the global burden of disease due to Haemophilus influenzae type b and Streptococcus pneumoniae in children less than 5 years of age. Lancet Web annex. pp 893–902.
8. WHO (2008) WHO guide for standardization of economic evaluations of immunization programmes; Immunization, Vaccines and Biologicals Department, Geneva, WHO/IVB/08.14.
9. UNICEF and UNFPA (2006) Uzbekistan. Multiple Indicator Cluster Survey, http://www.childinfo.org/files/MICS3_Uzbekistan_FinalReport_2006_En.pdf.
10. Balabanova D, McKee M, Pomerleau J, Rose R, Haerpfer C (2004) Health service utilization in the former soviet union: evidence from eight countries. Health Serv Res 39: 1927–1956.
11. Richardson E, Boerma W, Malikova I, Rusovich V, Fonseko A (2008) Belarus: Health system review. European Observatory on Health Systems and Policies.
12. Glinskaya INGF, Chistenko GN, Fisenko EG, Levshina NN, Ushakovskiy IG, et al. (2008) Features of Hib infection endemic process in Minsk City before immunization. 2nd Russian Conference on Actual Problems of Meningoococcal Infection and Pneumonic Meningitis. October 20-21; Moscow.
13. Mager INFE, Germanovich FA, Voleosar LA, Simanovich TN (2005) Outcomes of Hib-meningitis incidence study and outlooks for immunoprophylaxis. Epidemiology and Infectious Diseases Magazine 3.
14. WHO (2003) Estimating the local burden of Haemophilus influenzae type b (Hib) disease preventable by vaccination. A rapid assessment tool. Geneva, WHO/ V&B/01.27.
15. Mendaikhian J, Watt JP, Mansoor O, Suvdaa N, Edmond K, et al. (2009) Childhood bacterial meningitis in Ulaanbaatar, Mongolia, 2002-2004. Clin Infect Dis 48(Suppl 2): S141–146.
16. Kasimova R (2007) Comparative Study of PCR and Bacteriological Method in the Diagnostics of Meningitis. Journal Doctor 2.
17. United Nations Population Secretariat (2000) World Population Prospects: The 2000 Revision Population database.
18. Chberman T (2003) Describing the epidemiology and aetiology of bacterial pneumonia in children: an unresolved problem. J Health Popul Nutr 23: 1–5.
19. Kojuhova M, Gatcheva N, Setchnova L, Robertson SE, Wenger JD (2002) Epidemiology of meningitis due to Haemophilus influenzae type b in children in Bulgaria: a prospective, population-based surveillance study. Bull World Health Organ 80: 690–695.
20. Lebedova V, Krivova P (2003) The 2001 serological survey in the Czech Republic–Hib invasive disease Haemophilus influenzae b. Cent Eur J Public Health 11(Suppl): S25–30.
21. Booy R, Hodgson SA, Slack MP, Anderson EC, Mayon-White RT, et al. (1993) Invasive Haemophilus influenzae type b disease in the Oxford region (1985-91). Arch Dis Child 69: 225–228.
22. Reintert P, Liscarskiowski A, Dabernet H, Guoyt C, Boucher J, et al. (1993) Epidemiology of Haemophilus influenzae type b disease in France. Vaccine 11(Suppl 1): S38–42.
23. Thomas K, Lalitha MK, Steinhoff (2002) Are Haemophilus influenzae infections a significant problem in India? A prospective study and review. Clin Infect Dis 34: 949–957.
24. Akamu AO, Eghlight M, Scott JA, Griffis U, Keffer (2007) Economic evaluation of delivering Haemophilus influenzae type b vaccine in routine immunization services in Kenya. Bull World Health Organ 85: 511–518.
25. Murray CJL, Lopez AD (1996) The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries, and risk factors in 1990 and projected to 2020. Boston: Harvard School of Public Health.
26. Platmon AE, Griffis U, Voegkova MV, Platmonova OV, Shakhkina IL, et al. (2004) Economic evaluation of Haemophilus influenzae type b vaccination in Moscow, Russian Federation. Vaccine 24: 2367–2376.
27. WHO (2010) CHOosing Interventions that are Cost Effective (WHO-CHOICE) http://www.who.int/choice/country/en/.
28. WHO (2006) WHO position paper on Haemophilus influenzae type b conjugate vaccines. (Replaces WHO position paper on Hib vaccines previously published in the Weekly Epidemiological Record. Wkly Epidemiol Rec 81: 445–452.

29. UNICEF (2010) Product menu for vaccines supplied by Unicef for the GAVI Alliance. http://www.unicef.org/supply/files/Product_Menu_Nov_2010__Published.pdf.

30. WHO (2010) WHO Vaccine Preventable Diseases Monitoring System. 2010 Global Summary. Geneva: WHO. http://www.who.int/immunization_monitoring/en/globalsummary/countryprofileresults.cfm.

31. Obonyo CO, Lau J (2006) Efficacy of Haemophilus influenzae type b vaccination of children: a meta-analysis. Eur J Clin Microbiol Infect Dis 25: 90–97.

32. Mulholland K, Hilton S, Adegbola R, Usen S, Oparzaugo A, et al. (1997) Randomised trial of Haemophilus influenzae type-b tetanus protein conjugate vaccine [corrected] for prevention of pneumonia and meningitis in Gambian infants. Lancet 349: 1191–1197.

33. Kim SY, Goldie SJ (2008) Cost-effectiveness analyses of vaccination programmes: a focused review of modelling approaches. Pharmacoeconomics 26: 191–213.

34. Theodoratou E, Johnson S, Jhass A, Madhi SA, Clark A, et al. (2010) The effect of Haemophilus influenzae type b and pneumococcal conjugate vaccines on childhood pneumonia incidence, severe morbidity and mortality. Int J Epidemiol 39(Suppl 1): i172–185.

35. WHO (2000) Introduction of Haemophilus influenzae type b vaccine into immunization programmes. Management guidelines, including information for health workers and parents. Geneva, WHO/V&B/00.05.

36. Bennett JV, Platonov AE, Slack MPE, Mala P, Burton AH, et al. (2002) Haemophilus influenzae type b (Hib) meningitis in the pre-vaccine era: a global review of incidence, age distributions, and case-fatality rates. Geneva: WHO, WHO/V&B/02.18.

37. World Bank (2011) GDP per capita (current US$). http://data.worldbank.org/indicator/NY.GDP.PCAP.CD Accessed 21st February 2011.

38. WHO (2011) Cost-effectiveness thresholds. http://www.who.int/choice/costs/CER_thresholds/en/index.html.

39. Isakbaeva ET, Musabaev E, Antul L, Rinegans R, Juraev R, et al. (2007) Rotavirus disease in Uzbekistan: cost-effectiveness of a new vaccine. Vaccine 25: 373–380.

40. Grifflins UK, Miners A (2009) Economic evaluations of Haemophilus influenzae type b vaccine: systematic review of the literature. Expert Rev Pharmacoecon Outcomes Res 9: 333–346.

41. Lavravtsova A, Boucher J, Detournay B, Reinert P (1996) Cost-effectiveness evaluation of vaccination against Haemophilus influenzae invasive diseases in France. Vaccine 14: 495–500.

42. Garpenholt O, Silferdal SA, Levin LA (1998) Economic evaluation of general childhood vaccination against Haemophilus influenzae type b in Sweden. Scand J Infect Dis 30: 5–10.

43. Trollfors B (1994) Cost-benefit analysis of general vaccination against Haemophilus influenzae type b in Sweden. Scand J Infect Dis 26: 611–614.

44. Zhou F, Bisgard KM, Yusuf HR, Deuson RR, Bath SK, et al. (2002) Impact of universal Haemophilus influenzae type b vaccination starting at 2 months of age in the United States: an economic analysis. Pediatrics 110: 653–661.

45. World Bank (2011) World Development Indicators. World Bank.

46. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, et al. (2010) Global, regional, and national causes of child mortality in 2008: a systematic analysis. Lancet 375: 1969–1987.