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Reactogenicity of Primary Vaccination with Hexavalent Vaccines in Infants: Mathematical Projections in Four Southeast Asian Countries

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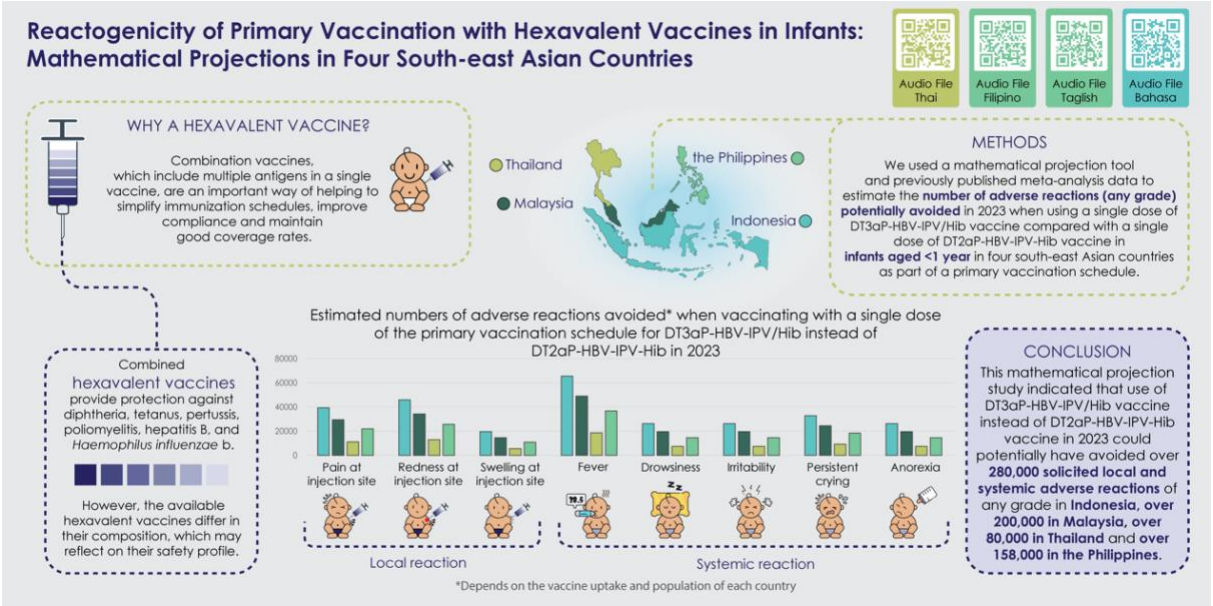
Abstract
Hexavalent vaccines against diphtheria (D), tetanus (T), pertussis (P), hepatitis B (HBV), polio (IPV) and *Haemophilus influenzae b* (Hib) are established in the immunization of infants in many countries. A meta-analysis of results from six head-to-head clinical trials comparing two hexavalent vaccines reported that the rate of three local (redness, pain and swelling at the injection site) and five systemic (fever, drowsiness, persistent crying, irritability and anorexia) adverse reactions was lower for the DT3aP-HBV-IPV/Hib vaccine than for the DT2aP-HBV-IPV-Hib vaccine. The objective of this analysis was to compare the impact of adverse reactions after a single dose of the primary series of DT3aP-HBV-IPV/Hib vaccine versus DT2aP-HBV-IPV-Hib vaccine in the infant populations of four countries in Southeast Asia (Indonesia, Malaysia, the Philippines and Thailand). A previously published mathematical projection tool was combined with published data to estimate the number of adverse reactions potentially avoided in 2023 by using DT3aP-HBV-IPV/Hib vaccine compared with DT2aP-HBV-IPV-Hib vaccine. The results indicated that for every 100 infants vaccinated, using DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib would be expected to avoid adverse reactions, ranging from 3 events of swelling at the injection site to 10 events of fever. In 2023, over 280,000 solicited local and systemic adverse reactions of any grade could have been avoided in Indonesia, over 200,000 in Malaysia, over 80,000 in Thailand and over 158,000 in the Philippines. These results could be useful to healthcare decision-makers considering immunization strategies in Southeast Asia.

Keywords: Hexavalent Vaccine, Adverse Events, Reactogenicity, Indonesia, Malaysia, Philippines, Thailand



1. Introduction

Vaccination against infectious disease is recognized as a highly effective method of reducing mortality and morbidity in children, with an estimated 2.5 million deaths prevented annually in children aged <5 years by use of measles, polio and diphtheria-tetanus-pertussis (DTP) vaccines (Centers for Disease Control Prevention, 2011). The number of recommended routine pediatric vaccinations has increased over time, and recommended vaccination schedules for infants in the United States cover immunization against 14 diseases, including hepatitis B virus (HBV), *Haemophilus influenzae b* (Hib), pneumococcus, rotavirus and rubella (Skibinski et al., 2011). Combination vaccines, which include multiple antigens in a single vaccine, are an important way of helping to simplify immunization schedules, improve compliance and maintain good coverage rates (Koslap-Petraco & Judelsohn, 2008). Hexavalent vaccines, including DTP, Hib, HBV and inactivated poliovirus (IPV), are now established in European vaccination schedules (Obando-Pacheco et al., 2018).

Three hexavalent vaccines are currently available: DT3aP-HBV-IPV/Hib (Infanrix hexa, GSK) (European Medicines Agency, 2021b); DT2aP-HBV-IPV-Hib (Hexaxim [outside Europe] or Hexyon/Hexacima [in Europe], Sanofi Pasteur) (European Medicines Agency, 2021a); and DT5aP-HBV-IPV-Hib (Vaxelis, MCM Vaccine Company) (European Medicines Agency, 2021c). The vaccines have several differences in their composition, including the quantity of diphtheria antigen, the number of pertussis antigens, the HBV and Hib components, and the adjuvant used (Knuf et al., 2021). Vaccine availability varies between countries. In Thailand, Indonesia and the Philippines, the National Immunization Program (NIP) uses a pentavalent vaccine and hexavalent vaccines are available in the private market. In Malaysia, the NIP uses a hexavalent vaccine.

Non-inferiority of the immune responses to the DT2aP-HBV-IPV-Hib and DT5aP-HBV-IPV-Hib vaccines, compared with the DT3aP-HBV-IPV/Hib vaccine, has been demonstrated in randomized clinical trials (RCTs), but the trials did not conduct formal statistical comparisons of safety profiles (Mukherjee et al., 2021). Individual studies indicated a trend towards a higher frequency of local reactions and fever for DT2aP-HBV-IPV-Hib compared with DT3aP-HBV-IPV/Hib, but individual studies may not have sufficient power to determine whether differences are statistically significant. Pooling data from several clinical trials in a meta-analysis can increase the power of the analysis. A systematic literature review and meta-analysis have been conducted to estimate the relative risk of solicited adverse reactions in infants for DT3aP-HBV-IPV/Hib vaccine compared with DT2aP-HBV-IPV-Hib vaccine (Mukherjee et al., 2021). This review extracted data from six head-to-head trials reporting local and systemic reactions after the primary series of DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib vaccines in infants. The analysis did not include DT5aP-HBV-IPV-Hib vaccine, as only two trials of this vaccine were

identified in the literature search (Mukherjee et al., 2021). The results of the meta-analysis indicated that the risk of solicited local and systemic reactions was lower for DT3aP-HBV-IPV/Hib vaccine than DT2aP-HBV-IPV-Hib vaccine. The odds ratios (OR) for redness, pain and swelling at the injection site were 0.72 (95% confidence interval [CI] 0.63, 0.83), 0.74 (95% CI 0.62, 0.89) and 0.86 (95% CI 0.74, 0.99), respectively. Regarding systemic reactions, the OR for fever was 0.67 (95% CI 0.54, 0.83), for persistent crying 0.72 (95% CI 0.61, 0.84), for drowsiness 0.82 (95% CI 0.71, 0.94), for irritability 0.82 (95% CI 0.69, 0.98) and for anorexia 0.83 (95% CI 0.72, 0.95) (Mukherjee et al., 2021).

To explore the impact of such differences in reactogenicity profiles, a decision-support tool was developed to investigate the burden of adverse reactions to DT3aP-HBV-IPV/Hib vaccine compared with DT2aP-HBV-IPV-Hib vaccine if implemented in a NIP (George et al., 2023). A previous publication has estimated the potential impact in six countries (Austria, Czech Republic, France, Jordan, Spain and the Netherlands) (George et al., 2023). The objective of the present study was to compare the impact of adverse reactions after a single dose of the primary series of DT3aP-HBV-IPV/Hib vaccine versus DT2aP-HBV-IPV-Hib vaccine in the infant populations of four countries in Southeast Asia, Indonesia, Malaysia, the Philippines and Thailand.

2. Methods

2.1. Input data

Data on the incidence of solicited adverse reactions after any vaccine dose in the primary series of vaccinations with DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib vaccines were obtained from a previously published systematic review and meta-analysis (Mukherjee et al., 2021). Eight adverse reactions investigated in this meta-analysis showed a statistically significant difference between the DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib vaccines and were included in the present analysis. These included three local reactions (redness, pain and swelling at the injection site) and five systemic reactions (fever, drowsiness, irritability, persistent crying and anorexia). The input data for these eight adverse reactions used in the present analysis are shown in Table 1 (Mukherjee et al., 2021).

Table 1: Input data for the incidence/proportion of solicited adverse reactions. Adapted from Mukherjee et al. (Mukherjee et al., 2021).

Parameter	Value [95% Confidence interval (CI)]
1. Pooled incidence/ proportion of adverse reactions for DT2aP-HBV-IPV-Hib	
Pain at injection site, any grade	0.81 (0.73, 0.87)
Redness at injection site, any grade	0.57 (0.50, 0.64)
Swelling at injection site, any grade	0.40 (0.34, 0.47)
Fever, any grade	0.58 (0.40, 0.74)
Drowsiness, any grade	0.65 (0.54, 0.75)
Irritability, any grade	0.84 (0.75, 0.90)
Persistent crying, any grade	0.78 (0.72, 0.83)
Anorexia, any grade	0.49 (0.41, 0.57)
2. Pooled incidence/ proportion of adverse reactions for DT3aP-HBV-IPV/Hib	
Pain at injection site, any grade	0.75 (0.69, 0.80)
Redness at injection site, any grade	0.50 (0.42, 0.57)
Swelling at injection site, any grade	0.37 (0.30, 0.44)
Fever, any grade	0.48 (0.36, 0.61)
Drowsiness, any grade	0.61 (0.49, 0.72)
Irritability, any grade	0.80 (0.73, 0.86)
Persistent crying, any grade	0.73 (0.64, 0.81)
Anorexia, any grade	0.45 (0.37, 0.54)

Odds ratio (OR; 95% CI) of this adverse reaction occurring after vaccinating with DT3aP-HBV-IPV/Hib versus vaccinating with DT2aP-HBV-IPV-Hib	
Pain at injection site, any grade	0.74 (0.62, 0.89)
Redness at injection site, any grade	0.72 (0.63, 0.83)
Swelling at injection site, any grade	0.86 (0.74, 0.99)
Fever, any grade	0.67 (0.54, 0.83)
Drowsiness, any grade	0.82 (0.71, 0.94)
Irritability, any grade	0.82 (0.69, 0.98)
Persistent crying, any grade	0.72 (0.61, 0.84)
Anorexia, any grade	0.83 (0.72, 0.95)

aP, acellular pertussis; CI, confidence interval; D, diphtheria; HBV, hepatitis B virus; Hib, *Haemophilus influenzae b*; IPV, inactivated poliovirus; OR, odds ratio; T, tetanus

Population projections for the number of infants aged <1 year in 2023 for each of the four countries were obtained from United Nations estimates (United Nations Department of Economic and Social Affairs Population Division, 2022). The estimated eligible populations for 2023 were 4,377,655 for Indonesia, 506,486 for Malaysia, 624,122 for Thailand and 2,451,006 for the Philippines.

Vaccine coverage inputs were 15% in Indonesia (assumption based on current use of hexavalent vaccine in the private sector), 97% in Malaysia (World Health Organization), 30% in Thailand (assumption based on current use of hexavalent vaccine in the private sector), and 15% in the Philippines (based on estimates of immunization through private providers) (Coe et al., 2017).

2.2. Mathematical projection tool

A mathematical projection tool was developed using Microsoft Excel 2016 to compare the safety profiles of the hexavalent vaccines DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib. The tool estimated the number of each type of adverse reaction expected for a single dose of each vaccine administered during the first year of life in each of the four countries, by applying the data on proportion of adverse reactions with each vaccine (Table 1) to the number of infants vaccinated in each country in 2023 (calculated from the population data and vaccine coverage data outlined above).

It was assumed that the adverse reaction data from the published meta-analysis (Mukherjee et al., 2021) could be applied to the populations of Southeast Asia. One of the studies included in the meta-analysis was conducted in Thailand, supporting this assumption. Vaccine doses administered after the age of 1 year, combinations of adverse reactions and catch-up vaccination programs were not considered in the analysis.

2.3. Estimation of absolute risk reduction (ARR)

The mathematical projection tool calculated the absolute risk reduction (ARR) for each adverse reaction type, defined as the difference between estimated risk of the incidence of an adverse reaction due to DT3aP-HBV-IPV/Hib and risk of the incidence of an adverse reaction due to DT2aP-HBV-IPV-Hib, expressed as a percentage. For each adverse reaction, the mean value of ARR was calculated using the equation:

$$Absolute\ risk\ reduction\ for\ an\ adverse\ reaction, A = \bar{x}_{risk\ of\ A_{DT2aP-HBV-IPV-Hib}} - \bar{x}_{risk\ of\ A_{DT3aP-HBV-IPV/Hib}}$$

The 95% confidence interval for the ARR was calculated by the formula:

$$\pm z * \sqrt{\frac{\sigma^2_{risk\ of\ A_{DT2aP-HBV-IPV-Hib}}}{n_{DT2aP-HBV-IPV-Hib}} + \frac{\sigma^2_{risk\ of\ A_{DT3aP-HBV-IPV/Hib}}}{n_{DT3aP-HBV-IPV/Hib}}}$$

$\sigma^2_{risk\ of\ A_{DT2aP-HBV-IPV-Hib}}$ is the square of the variances of the estimated risk of the incidence of the adverse reaction A due to DT2aP-HBV-IPV-Hib;

$\sigma^2_{risk\ of\ A_{DT3aP-HBV-IPV/Hib}}$ is the square of the variances of the estimated risk of the incidence of the adverse reaction A due to DT3aP-HBV-IPV/Hib;

$n_{DT2aP-HBV-IPV-Hib}$ is the sample size considered for DT2aP-HBV-IPV-Hib;
$n_{DT3aP-HBV-IPV/Hib}$ is the sample size considered for DT3aP-HBV-IPV/Hib;
z =1.96, because a 95% CI is considered

Applying the ARR to a population would give the number of adverse reactions averted by vaccinating with DT3aP-HBV-IPV/Hib versus vaccinating with DT2aP-HBV-IPV-Hib.

2.4. Sensitivity analysis

One-way sensitivity analysis was conducted for the adverse reactions averted for each adverse reaction type. The base-case value was the difference in adverse reactions between DT2aP-HBV-IPV-Hib and DT3aP-HBV-IPV/Hib calculated using the ARR. The parameters used in the sensitivity analysis are summarized in Table 2. For the incidence of adverse reactions with each vaccine and for the ARR, a variation of two standard deviations above or below the base case was used. For vaccination coverage, a variation of 5 percentage points above or below the base-case rate was used, although in Malaysia the base-case coverage was 97% and the maximum value in the sensitivity analysis was 100%.

Table 2: Parameters used in one-way sensitivity analysis

Parameters	**Minimum**	**Maximum**
Vaccination coverage [a]	-5%	+5% (maximum 100%)
Indonesia	10%	20%
Malaysia	92%	100%
Thailand	25%	35%
The Philippines	10%	20%
Population for 2023	-10% of population	+10% of population
AR incidence/ proportion of DT2aP-HBV-IPV-Hib	-2 SD of mean	+2 SD of mean
AR incidence/ proportion of DT3aP-HBV-IPV/Hib	-2 SD of mean	+2 SD of mean
Absolute risk reduction	-2 SD of mean	+2 SD of mean

[a] Vaccination coverage was varied by adding or subtracting 5 percentage points from the base case for each country, subject to a maximum of 100%. In Malaysia the base-case coverage was 97% and therefore the maximum value in the sensitivity analysis was 100%.

aP, acellular pertussis; AR, adverse reaction; D, diphtheria; HBV, hepatitis B virus; Hib, *Haemophilus influenzae b*; IPV, inactivated poliovirus; SD, standard deviation; T, tetanus

3. Results

3.1. Estimated absolute risk reduction

The ARR values calculated in this analysis are shown in Figure 1. The number of adverse reactions (of any grade) expected to be avoided for every 100 infants vaccinated by using DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib ranged from 3.0 events of swelling at the injection site to 10.0 events of fever (Figure 1).

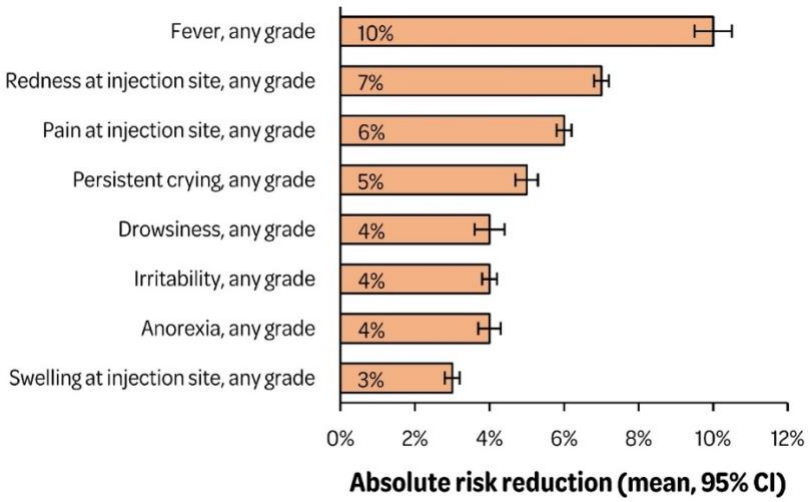


Figure 1: Calculated absolute risk reduction (ARR) for vaccinating with DT3aP-HBV-IPV/Hib versus vaccinating with DT2aP-HBV-IPV-Hib.

aP, acellular pertussis; CI, confidence interval; D, diphtheria; HBV, hepatitis B virus; Hib, *Haemophilus influenzae b*; IPV, inactivated poliovirus; T, tetanus

3.2. Estimated number of adverse reactions

The estimated number of each type of adverse reaction after administration of a single dose of DT2aP-HBV-IPV-Hib or DT3aP-HBV-IPV/Hib in each of the four countries in 2023 is shown in Figure 2.

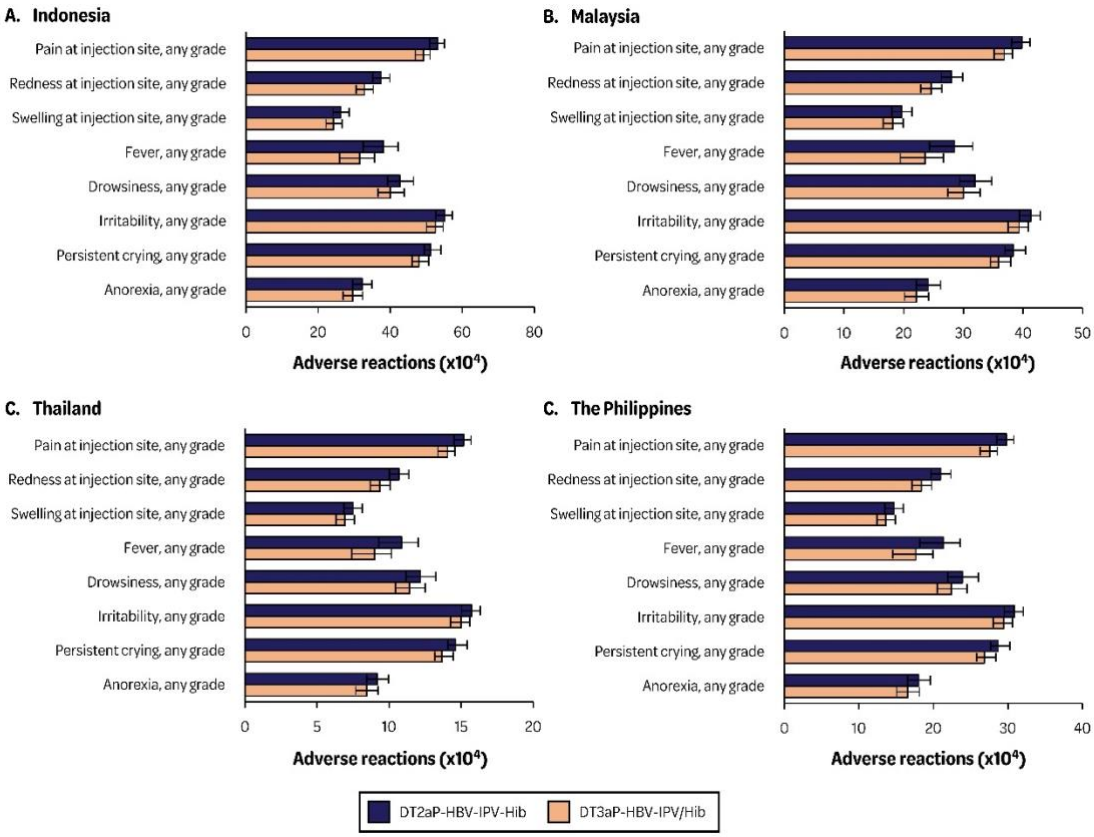


Figure 2: Estimated numbers of adverse reactions when vaccinating with a single dose of the primary vaccination schedule for DT3aP-HBV-IPV/Hib or DT2aP-HBV-IPV-Hib in (a) Indonesia, (b) Malaysia, (c) Thailand, (d) the Philippines

aP, acellular pertussis; D, diphtheria; HBV, hepatitis B virus; Hib, *Haemophilus influenzae b*; IPV, inactivated poliovirus; T, tetanus

The estimated number of each type of adverse reaction avoided over a five-year period (2023–2027) by vaccinating with DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib in each of the four countries is shown in Table 3.

Table 3: Estimated numbers of adverse reactions avoided when vaccinating with a single dose of the primary vaccination schedule for DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib in each of the four countries over five years (2023–2027).

Year	Estimated number of adverse reactions avoided (any grade)								
	Pain at injection site	**Redness at injection site**	**Swelling at injection site**	**Fever**	**Drowsiness**	**Irritability**	**Persistent crying**	**Anorexia**	**Total**
Indonesia									
2023	39,398	45,965	19,699	65,664	26,265	26,265	32,832	26,265	282,353
2024	39,196	45,729	19,598	65,327	26,131	26,131	32,663	26,131	280,906
2025	39,088	45,603	19,544	65,148	26,059	26,059	32,574	26,059	280,134
2026	38,978	45,475	19,489	64,964	25,985	25,985	32,482	25,985	279,343
2027	38,827	45,298	19,413	64,712	25,884	25,884	32,356	25,884	278,258
Total 2023–2027	195,487	228,070	97,743	325,815	130,324	130,324	162,907	130,324	1,400,994
Malaysia									
2023	29,477	34,390	14,738	49,129	19,651	19,651	24,564	19,651	211,251
2024	29,358	34,251	14,679	48,930	19,572	19,572	24,465	19,572	210,399
2025	29,226	34,097	14,613	48,710	19,484	19,484	24,355	19,484	209,453
2026	29,101	33,951	14,550	48,501	19,400	19,400	24,250	19,400	208,553
2027	28,960	33,787	14,480	48,267	19,306	19,306	24,133	19,306	207,545
Total 2023–2027	146,122	170,476	73,060	243,537	97,413	97,413	121,767	97,413	1,047,201
Thailand									
2023	11,234	13,106	5,617	18,723	7,489	7,489	9,361	7,489	80,508
2024	11,087	12,935	5,543	18,479	7,391	7,391	9,239	7,391	79,456
2025	10,987	12,818	5,493	18,312	7,324	7,324	9,156	7,324	78,738
2026	10,936	12,758	5,468	18,226	7,290	7,290	9,113	7,290	78,371
2027	10,878	12,691	5,439	18,130	7,252	7,252	9,065	7,252	77,959
Total 2023–2027	55,122	64,308	27,560	91,870	36,746	36,746	45,934	36,746	395,032
Philippines									
2023	22,059	25,735	11,029	36,765	14,706	14,706	18,382	14,706	158,088
2024	22,123	25,810	11,061	36,871	14,748	14,748	18,435	14,748	158,544
2025	22,184	25,881	11,092	36,973	14,789	14,789	18,486	14,789	158,983
2026	22,236	25,942	11,118	37,060	14,824	14,824	18,530	14,824	159,358
2027	22,292	26,008	11,146	37,154	14,861	14,861	18,577	14,861	159,760
Total 2023–2027	110,894	129,376	55,446	184,823	73,928	73,928	92,410	73,928	794,733

aP, acellular pertussis; D, diphtheria; HBV, hepatitis B virus; Hib, *Haemophilus influenzae b*; IPV, inactivated poliovirus; T, tetanus

The estimated number of each type of adverse reaction avoided in each country in 2023 by vaccinating with DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib is shown in Figure 3.

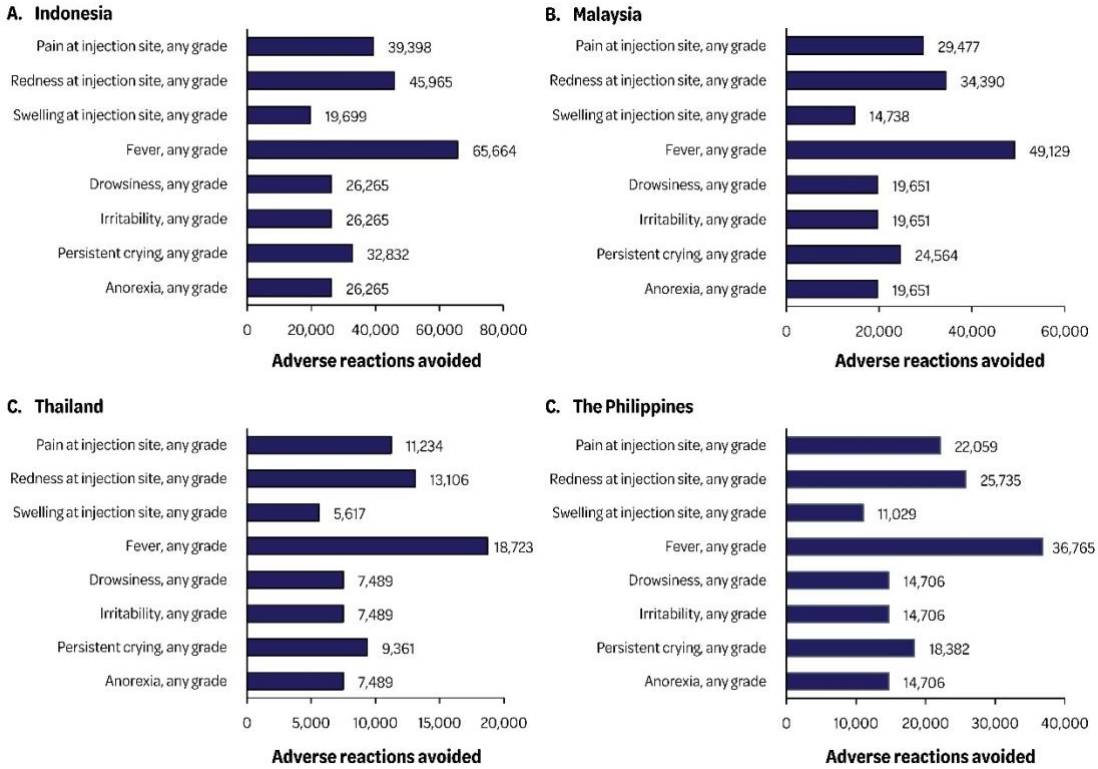


Figure 3: Estimated numbers of adverse reactions avoided when vaccinating with a single dose of the primary vaccination schedule for DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib in 2023 in (a) Indonesia, (b) Malaysia, (c) Thailand, (d) the Philippines.

aP, acellular pertussis; D, diphtheria; HBV, hepatitis B virus; Hib, *Haemophilus influenzae b*; IPV, inactivated poliovirus; T, tetanus

3.3. One-way sensitivity analysis

The results of the one-way sensitivity analysis for the number of the two most frequent adverse reactions (fever, and redness at the injection site) avoided in 2023 by vaccinating with DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib are shown for each of the four countries in Figure 4. The parameters with the most impact on the results were generally the incidence/proportion of adverse reactions with each vaccine, followed by vaccination coverage.

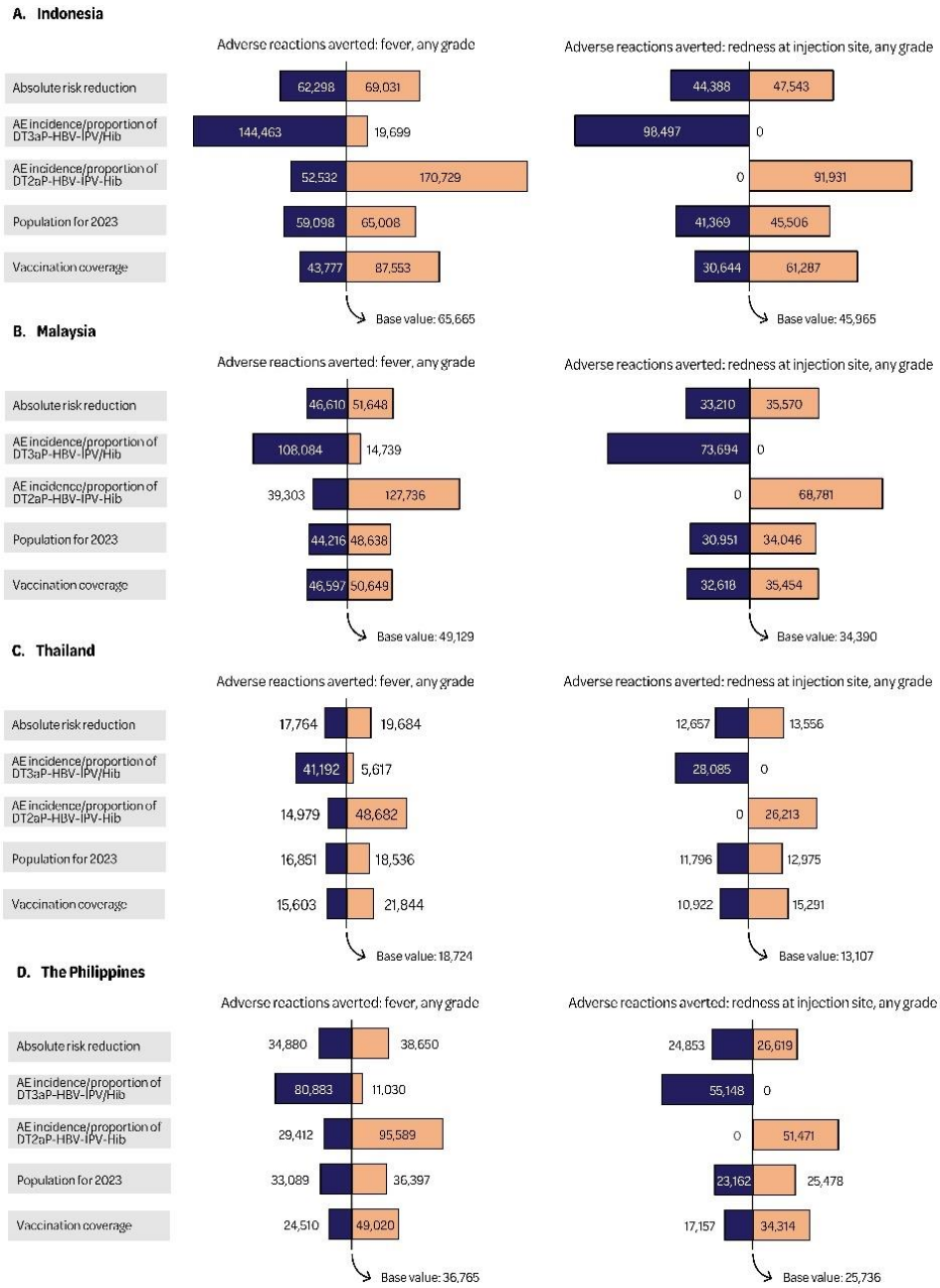


Figure 4: One-way sensitivity analysis on the number of adverse reactions of fever and redness at the injection site avoided when vaccinating with a single dose of the primary vaccination schedule for DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib in 2023 in (a) Indonesia, (b) Malaysia, (c) Thailand, (d) the Philippines.

AE, adverse event; aP, acellular pertussis; D, diphtheria; HBV, hepatitis B virus; Hib, Haemophilus influenzae b; IPV, inactivated poliovirus; T, tetanus

4. Discussion

This analysis used a mathematical projection tool to estimate the number of eight different types of adverse reactions after a single dose of DT3aP-HBV-IPV/Hib or DT2aP-HBV-IPV-Hib in infants aged <1 year in 2023 and beyond in four countries in south-east Asia (Indonesia, Malaysia, Thailand and the Philippines). The results indicated that using DT3aP-HBV-IPV/Hib would reduce projected adverse reactions by 3.0–10.0%, compared with DT2aP-HBV-IPV-Hib, i.e., vaccination with DT3aP-HBV-IPV/Hib instead of DT2aP-HBV-IPV-Hib would be expected to avoid adverse reactions ranging from 3 events of swelling at the injection site to 10 events of fever for every 100 infants vaccinated. The adverse event with the largest differential between the vaccines was fever, followed by redness at the injection site. In 2023, the results indicate that over 65,000 occurrences of fever in Indonesia, over 49,000 in Malaysia, over 18,000 in Thailand and over 36,000 in the Philippines could have been avoided. Taking all eight adverse reactions together, over 280,000 could have been avoided in Indonesia, over 200,000 in Malaysia, over 80,000 in Thailand and over 158,000 in the Philippines.

The study has several strengths. First, it was based on data obtained from a robust systematic literature review and meta-analysis that included RCTs conducted in a broad range of countries (Mukherjee et al., 2021). Second, one of the RCTs included in the meta-analysis was conducted in one of the countries in this analysis (Thailand). Third, the data included adverse reactions of any grade, providing a broad picture of the range of reactions that could affect vaccine recipients and their caregivers.

Nevertheless, this study also has a number of limitations. First, the input data on the incidence/proportion of adverse reactions for each vaccine were derived from a meta-analysis of data from head-to-head RCTs (Mukherjee et al., 2021), as few data from real-world studies are currently available. RCTs are conducted under controlled conditions and may not be representative of the situation encountered in routine clinical practice. However, the acceptable safety profile of DT3aP-HBV-IPV/Hib has been confirmed by analysis of data over ten years of vaccine use in the Australian NIP (Bayliss et al., 2021). Second, vaccine coverage estimates for some of the countries in this study were low, reflecting differences in vaccine availability. For example, some countries have hexavalent vaccines included in the NIP, whereas in others they are available only through the private sector, and some countries include pentavalent vaccines in the NIP with different hexavalent vaccines available through the private sector. Third, the analysis considered only a single dose of vaccine, and so would not capture adverse reactions associated with the other doses in the primary schedule, typically two or three doses, or with any catch-up vaccinations. Therefore, the analysis presented here would be expected to under-estimate the total number of adverse reactions expected from the overall vaccination program. Fourth, the analysis was based on numbers of adverse reactions, and as one infant may experience multiple adverse reactions, the overall number of infants affected by adverse reactions may be lower than the estimated number of adverse reactions. Finally, the third available hexavalent vaccine, DT5aP-HBV-IPV-Hib, was not included in the analysis due to a lack of available data.

Many factors may influence the willingness of parents to have their children vaccinated, including perceptions of individual and community vaccine benefits and perceived vaccine safety (Rosso et al., 2020). Individuals' knowledge, past experiences, perceptions about vaccination, and moral and religious convictions interact with historical, social and political contexts (Aps et al., 2018). In some countries, low rates of vaccination have been associated with outbreaks of vaccine-preventable diseases such as measles and pertussis (Aps et al., 2018). Adverse reactions to vaccine administration may potentially affect parents' willingness to vaccinate their children. A systematic review of factors affecting vaccine uptake in young children found that 'not perceiving vaccines to cause adverse effects' was one of the factors associated with vaccine uptake (Smith et al., 2017). A mother's first vaccination experience with a baby can have an important influence on maternal attitudes to vaccination; for example, feeling that the baby was hurt or experiencing the baby crying after vaccination may lead to concerns about vaccine safety that may in turn contribute to under-vaccination of the child (Betsch et al., 2018). In a study of 506 mothers in Jordan, 39.2% of the mothers agreed that vaccines cause side effects, and 14.6% agreed that they did not offer vaccination to their children because of injection-associated pain (Masadeh et al., 2014). Lower

vaccine coverage could reduce the substantial direct and indirect benefits associated with vaccination (Barnighausen et al., 2011).

Adverse reactions to vaccination can be directly associated with healthcare resource utilization and economic costs, although these may be difficult to estimate. For example, a child experiencing fever after vaccination may need to visit a healthcare professional, and/or one or both of the parents may need to take time away from work to care for the child. A study using data from the United Kingdom (UK), Canada and the Netherlands attempted to estimate the cost of adverse reactions following measles immunization (Carabin et al., 2002). The average cost per vaccinee was estimated at United States dollars (US$)1.55 (95% CI 0.28, 4.35) in the Netherlands, US$2.08 (95% CI 0.48, 5.52) in the UK and US$1.58 (95% CI 0.41, 4.15) in Canada, with fever accounting for 87%, 88% and 84% of the total, respectively (Carabin et al., 2002). A vaccine with a lower frequency of adverse reactions could reduce costs, and potentially help to reduce vaccine hesitancy among parents and support improved vaccine coverage.

5. Conclusion

The results of this analysis using a mathematical modelling approach and published data indicate that primary vaccination of infants with DT3aP-HBV-IPV/Hib would be expected to be associated with fewer adverse reactions than vaccination with DT2aP-HBV-IPV-Hib in four countries in Southeast Asia. These results will be valuable to healthcare decision-makers considering immunization strategies in Southeast Asia.

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