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Reduced Costs of Managing Adverse Reactions with DT3aP-HBV-IPV/Hib Versus DT2aP-HBV-IPV-Hib in Vietnam: Results of a Cross-Sectional Survey and Mathematical Projections of Vaccination of Infants

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Abstract

In Vietnam, hexavalent vaccines are routinely given during early childhood. Hexavalent vaccines DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib differ in composition and therefore, reactogenicity, with DT3aP-HBV-IPV/Hib shown to cause fewer adverse reactions (ARs) than DT2aP-HBV-IPV-Hib. Online surveys for physicians and parents/caregivers who manage post-vaccination ARs in children were used to explore AR management in the Vietnamese private healthcare setting. Survey data were used to estimate healthcare resource utilization (HCRU) and its associated costs, and indirect costs to parents/caregivers. A mathematical projection tool used survey results to approximate the difference in costs associated with post-vaccination childhood AR management following primary doses of DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib. Parent/caregiver attitudes towards childhood vaccination in relation to management of ARs in their children were also explored. Around a third of parents/caregivers in Vietnam reported that their child experienced post-vaccination AR(s), the management of which led to significant HCRU and indirect costs to parents/caregivers. A primary dose of DT3aP-HBV-IPV/Hib compared with DT2aP-HBV-IPV-Hib led to 420 985 fewer ARs in Vietnam. Subsequently, HCRU burden and associated direct costs were reduced by ~11% and indirect costs to parents/caregivers were reduced by 14%. Parents/caregivers reported indirect costs of ~3 million VND per parent/caregiver per AR to manage ARs in their children. Additionally, parents/caregivers reported notable emotional concerns over ARs of rashes, diarrhea, and fever. However, despite costs and emotional burdens, most parents/caregivers did not express hesitancy toward future vaccinations. The substantial financial benefits of a vaccine with fewer ARs should be considered from a cost effectiveness perspective by decision-makers when evaluating vaccine alternatives.

Keywords: Acellular Pertussis, Adverse Reactions, Childhood Vaccination, Healthcare Resource Utilization, Hexavalent Vaccine, Vaccine Costs, Vaccine Hesitancy

1. Introduction

In Vietnam, childhood immunization has proven to be cost-effective and highly successful in the prevention of infectious diseases, compared with late-stage interventions (Jit et al., 2015). The World Health Organization's (WHO) Expanded Programme on Immunization (EPI), initiated in 1981, substantially reduced the occurrence of vaccine preventable diseases and their rates of mortality (Nguyen et al., 2015). In 2009, Vietnamese national coverage of vaccines included in the EPI reached an average of 95% in infants under one year of age. However, a Vietnamese cluster survey identified that this coverage varied significantly between vaccines included in the program (diphtheria, tetanus toxoid, hepatitis B, polio, measles, and tuberculosis vaccines), with birth dose hepatitis B coverage as low as 20.6% in 2009 (Nguyen et al., 2015).

Multivalent vaccines may increase vaccination uptake by simplifying vaccination schedules (Özen et al., 2024). Childhood vaccinations against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis, and Hemophilus influenzae type B are often administered together as a hexavalent vaccine worldwide. Currently, there are two hexavalent vaccines containing acellular pertussis licensed for childhood vaccination in the Vietnamese private healthcare setting; DT3aP-HBV-IPV/Hib was licensed in 2006, and DT2aP-HBV-IPV-Hib was licensed in 2018 ("European Medicines Agency 2021a. Hexaxim," ; "European Medicines Agency 2021b. Infanrix Hexa,"). For hexavalent vaccines containing acellular pertussis, the WHO recommends three doses starting at 6 or 8 weeks with 4-week intervals, and a booster dose 6 months after the final dose (*WHO Recommendations for Routine Immunization*, 2024). DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib differ in formulation and antigen constitution, and therefore have different reactogenicity profiles (Knuf et al., 2021).

An open-label study in 2019 evaluating the safety of three early childhood doses of a DT2aP-HBV-IPV-Hib vaccine, found that the hexavalent vaccine was well-tolerated in Vietnamese infants with no safety signals (Vu et al., 2019). The safety profile of a primary early childhood dose of DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib was later compared via a systematic review and meta-analysis of head-to-head randomized controlled trials (RCT) (Mukherjee et al., 2021). The odds ratios of experiencing an adverse reaction (AR) were lower with DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib, varying from 0.67 to 0.96 across the local and systemic ARs analyzed (Mukherjee et al., 2021). In a follow-on analysis, a mathematical projection tool was developed to simulate vaccination of infants with these two hexavalent vaccines in six European countries (George et al., 2023). The absolute risk reduction (ARR) of local or systemic childhood ARs with DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib ranged from 3.0 (95% confidence interval [CI]: 2.8%–3.2%) to 10.0% (95% CI: 9.5%–10.5%) across the ARs analyzed. The study estimated that in 2020, vaccination with DT3aP-HBV-IPV/Hib led to fewer childhood ARs compared with DT2aP-HBV-IPV-Hib, ranging from ~31 000 to >269 000 fewer cases per country (George et al., 2023). Similar results were found when the tool was applied to four countries in Southeast Asia. In 2023, between 80 000 and ~280 000 fewer ARs were estimated with use of one dose of DT3aP-HBV-IPV/Hib over DT2aP-HBV-IPV-Hib across assessed countries (Mohy et al., 2024). These studies highlight the country-level impact of utilizing vaccines with fewer ARs, and the importance of reactogenicity as well as efficacy, when evaluating vaccines.

The management of post-vaccination childhood ARs incurs substantial healthcare resource utilization (HCRU) and associated direct medical costs (Liu et al., 2024). In addition to the burden of post-vaccination ARs on healthcare systems, further hidden costs are also incurred by parents/caregivers when managing post-vaccination ARs experienced by their child. Indeed, a US cross-sectional survey of parents/caregivers of children who received co-administered vaccines, reported an average total of 42 United States Dollars (USD) for medical and treatment costs, and 192 USD for work absenteeism per AR case (Lieu et al., 2000). Despite these costs, childhood vaccines remain a cost-effective intervention. An evaluation of the economic impact of routine childhood immunization over one year (2009) estimated a reduction of ~55.3 billion USD to societal costs, which included administration, parent travel, and absenteeism, compared with no vaccination interventions in the US (Zhou et al., 2014).

Parent/caregiver vaccine hesitancy may be expected to increase if their child experiences a post-vaccination AR (Brown et al., 2010), especially with hexavalent vaccines administered during infancy as these vaccines contain multiple antigens. A recent cross-sectional survey predicted that 8.9% of parents in Vietnam were hesitant towards

childhood vaccination, with hesitancy related to unemployment and exposure to news reporting ARs following vaccinations (Truong et al., 2024). Furthermore, only a third of Vietnamese parents reported vaccinating their child on schedule (Truong et al., 2024). Utilizing vaccines with proven safety profiles is important to improve infant vaccination compliance in Vietnam.

In this study, a survey was completed by physicians who manage post-vaccination ARs in early childhood to assess typical AR management and HCRU in the real-world private healthcare setting in Vietnam. A second survey targeted at parents/caregivers of children who had received an early childhood vaccination was used to estimate the indirect costs incurred by parents/caregivers when managing any ARs their child experienced post-vaccination. With these data, a mathematical projection tool estimated and compared the incidence and associated costs to manage ARs following an early childhood dose of DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib in Vietnam in 2023.

An additional objective was to report the emotional impact of ARs following early childhood vaccination, and the impact of these ARs on parent/caregiver attitudes towards future childhood vaccinations in Vietnam.

2. Methods

2.1. Overall Survey Design

Physicians that manage ARs associated with an early childhood, single-dose vaccination, and parents/caregivers of children who have received a dose of an early childhood vaccination were recruited from existing panels in Vietnam by third-party agencies: Medefield for physicians, and Dynata for parents/caregivers. Eligible participants received the survey link via email. Surveys were completed between 27th July – 31st August 2023, and 5th – 14th July 2023 by physicians and parents/caregivers, respectively.

Physicians based their responses on their caseload of early childhood vaccinations (received at aged 0–14 months) over the past 3 months (recall only). The physician survey aimed to capture physician demographics and the typical management of ARs associated with early childhood vaccination. Responses were used to estimate the HCRU of healthcare professionals (HCPs) visits, treatments prescribed, tests/assessments conducted, and hospitalizations.

Parents/caregivers based their responses on the most recent vaccine administered to their child (aged 0–14 months) within the past 4 months, excluding any received within the 2 weeks prior to survey completion. The parent/caregiver survey aimed to capture child and parent/caregiver demographics, and to estimate the indirect costs incurred in HCP visits, out-of-pocket prescribed treatments, absenteeism and lost earnings, travel and parking expenses, and childcare to manage ARs in their child. Parents/caregivers also completed questions to assess the emotional impact of managing post-vaccination ARs, and their attitudes towards future vaccinations. A seven-point Likert scale was administered for each AR of interest (1: No concern at all – 7: High level of concern), where scores ≥ 5 were considered concerning.

This survey examined 11 specific ARs: injection site pain, injection site redness, injection site swelling, fever, drowsiness, irritability, persistent crying, loss of appetite, vomiting, diarrhea, and rash.

Vaccines in scope of the survey had to be injectable, recommended up to 12 months of age, and administered in Vietnam in the private healthcare setting or as part of the national funded program: hepatitis A, B or AB combined, Bacillus Calmette-Guérin, inactivated polio, combined pentavalent/hexavalent (diphtheria, tetanus, polio, pertussis, Hemophilus influenza type B, and hepatitis B), pneumococcal conjugate, meningitis B or C, varicella, measles, the combined measles, mumps and rubella, meningococcal ACWY conjugate, influenza, and the Japanese encephalitis inactivated vaccine.

2.2. Study Population

To be eligible, the physicians were required to consent; to be fully qualified general practitioners (GPs), primary care physicians (PCPs), or preventative medicine specialists who manage ARs following primary childhood vaccination; to have practiced for at least 3 years, and to manage at least ten cases a month (on average in the past 12 months) of children experiencing post-vaccination ARs.

The parents/caregivers were required to consent, be aged at least 18 years at the time of the child's vaccination and to have been responsible for the wellbeing of the child at the time of vaccination and during the 2 weeks that followed. Parents/caregivers of children who were considered immunocompromised, and therefore may follow different vaccination recommendations and/or whose condition may interfere with the level of reactogenicity, were excluded from the study.

2.3. Estimation of Direct Medical Costs to Manage ARs Associated with Vaccination

Physician data were used to estimate the HCRU for HCP visits, treatments prescribed, tests/assessments conducted, and hospitalizations associated with typical management of each post-vaccination AR. Frequency of each HCRU item was multiplied by published Vietnamese unit cost data for the private healthcare sector to estimate the total cost of each HCRU item. Recent published unitary cost data were collected from literature and official databases by a specialized third-party agency, Weber, and adjusted to account for 2023 inflation levels (**Appendix A1**). Where different published costs were found, the lowest cost was used by default. Costs were calculated in 2023 Vietnamese Dong (VND) and reported as mean cost per case of AR.

2.4. Estimation of Indirect Medical Costs to Manage ARs Associated with Vaccination

Parent/caregiver data were used to estimate the indirect costs incurred from the management of ARs associated with early childhood vaccination. Parents/caregivers were asked to estimate lost employment time, and subsequent losses from household monthly earnings due to absenteeism. Parents/caregivers also estimated the costs of out-of-pocket treatments, childcare, travel, and parking, as well as any other costs for each AR. Costs were calculated in 2023 VND and reported as mean cost per case.

2.5. Costs Comparisons of the Management of ARs with DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib

To compare the cost to manage ARs for each vaccine, the number of individuals vaccinated with at least one dose of DT3aP-HBV-IPV/Hib or DT2aP-HBV-IPV-Hib in the private healthcare setting in Vietnam was estimated, using the 2023 birth cohort and 2022 vaccination coverage (GSK, 2023), (*World Population Prospects 2022: Summary of Results*, 2022).

For each AR, the number of AR cases following a primary dose of DT3aP-HBV-IPV/Hib or DT2aP-HBV-IPV-Hib was calculated by multiplying the total vaccinated population by the proportion of AR cases attributed to one dose of each vaccine (Mukherjee et al., 2021). Subsequent multiplication of the number of AR cases by the proportion of the population that sought medical advice, as reported by the parent/caregiver survey, estimated the number of cases where medical advice was sought for the given AR per vaccine. The number of these cases was then multiplied by the mean HCRU reported for the given AR (HCP visits, treatments prescribed, test/assessments, and hospitalization), as from the physician survey, to estimate the HCRU per vaccine for the given AR. The direct medical costs were then calculated using the published unit cost data from Weber. An example calculation for the direct medical costs of hospitalization to manage fever following a single dose of DT3P-HBV-IPV/Hib is shown in **Equation 1**. The total direct medical costs to manage each post-vaccination AR were calculated by combining the HCP visit, treatments prescribed, tests/assessments conducted, and hospitalization costs. Costs were calculated in 2023 VND and reported as mean cost per case.

$$\begin{aligned}
& 1\,418\,890 \text{ (2023 Vietnamese birth cohort)} \times 69\% \text{ (vaccination coverage in Vietnam)} = \\
& 979\,034 \text{ individuals vaccinated with one dose of DT3P-HBV-IPV/Hib} \\
& 979\,034 \times 48\% \text{ (proportion of DT3P-HBV-IPV/Hib cases leading to fever [Mukherjee et al., 2010])} = 469\,936 \\
& \text{cases of fever after vaccination with one dose of DT3P-HBV-IPV/Hib} \\
& 469\,936 \times 90\% \text{ (proportion of fever cases with sought medical attention [parent/caregiver survey])} = \\
& 422\,943 \text{ cases of sought medical attention for fever} \\
& 422\,943 \times 1.3\% \text{ (hospitalization rate for fever [physician survey])} = \\
& 5\,498 \text{ cases of hospitalization for fever} \\
& 5\,498 \times 3\,850\,000 \text{ VND (unit cost for hospitalization [Weber])} = \\
& 21\,168\,283\,697 \text{ VND calculated in hospitalization costs to manage fever for the Vietnam 2023 birth cohort} \\
& \text{following a single dose of DT3P-HBV-IPV/Hib} \tag{1}
\end{aligned}$$

The same process was used to calculate the indirect costs to parents/caregivers when managing each AR following a childhood dose of DT3aP-HBV-IPV/Hib or DT2aP-HBV-IPV-Hib in Vietnam. Potential reductions in direct and indirect medical costs following one dose of DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib vaccination were calculated by comparing cost estimates for the entire birth cohort from 2023 and per AR. As diarrhea and rash were not analyzed in the RCT review of AR incidence, odds ratios were therefore not calculated (Mukherjee et al., 2021). These two ARs were consequently excluded from the DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib mathematical projection tool. Vomiting was also not included in cost calculations as there were no significant differences in the reported proportions of ARs.

2.6. Statistical Analysis

A descriptive analysis was conducted using the Institute for Business Value (International Business Machines, IBM) Survey Reporter (version 7.5) and Stata (version 17.0). Descriptive statistics were used to summarize the HCRU variables. Specifically for categorical variables: number and frequency, and for numeric/count variables: number, standard deviation, and frequency.

Univariate sensitivity analyses (SA) were performed to assess the costs avoided for all AR types. The AR proportions of DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib were varied based on the 95% CI data from the RCT systematic review and meta-analysis, comparing each vaccine versus the mean of the other vaccine (Mukherjee et al., 2021). A second SA was applied based on an arbitrary variation of 20% applied to the ARRs, as previously described in the mathematical projections of ARs following DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib in six European countries (George et al., 2023).

3. Results

3.1. Demographics

A total of 100 physicians from Vietnam completed the survey and were included in the analysis. Of these, 40 were GPs/PCPs, 59 were pediatric specialists, and one was a preventative medicine specialist. The physicians reported an average caseload of 219 patients per month experiencing ARs associated with early childhood vaccination (primary or booster dose).

A total of 150 parents/caregivers from Vietnam completed the survey and were included in the analysis. On average, the child of the parent/caregiver received their most recent vaccination 3.6 weeks prior to completion of the survey. Most children (43%) were between the ages of 6–9 months at the time of vaccination, 31% were 2–6 months old, 16% of children were <2 months old, and 10% were >9 months old.

3.2. Management of ARs in the Vietnamese Real-World Setting

The majority of parents/caregivers (71%) reported that their child was vaccinated but did not experience an AR. Of those who did experience an AR, 91% of cases caused parents/caregivers to seek medical advice. Fever was

the AR for which medical advice was most often sought, at 90% (n=20 parents/caregivers), followed by the local ARs of injection site pain at 40% (n=20), injection site redness at 33% (n=18), and injection site swelling at 40% (n=15) (**Table 1**).

In terms of HCP visits, pediatricians in Vietnam were most frequently consulted across all ARs examined (50%–71%), except for drowsiness, where 67% of parents/caregivers reported with their child to the emergency room or accident and emergency (A&E) department. For each of the 11 ARs of interest, patient examination was the most common assessment conducted, ranging from 33%–100% of cases, followed by blood tests, and urinalysis (both 0%–33%).

In vaccination cases where parents/caregivers sought medical advice, the physician survey reported that loss of appetite was the AR that most frequently caused hospitalization, with a rate of 1.9% (n=20 physicians). This was followed by a 1.4% (n=14) hospitalization rate for vomiting and 1.3% (n=96) for fever. Injection site pain was the only local AR which resulted in hospitalization, though the rate was low at 0.4% (n=93) (**Table 1**).

Table 1: Type of AR for which Parents/Caregivers Sought Healthcare Advice and Rates of Hospitalization in Vietnam

AR of interest	Percentage of cases where parents/caregivers sought medical advice, % (n) ^a	Percentage of cases where medical advice was sought and which led to hospitalisation, % (n) ^b
Injection site pain	40 (20)	0.4 (93)
Injection site redness	33 (18)	0.0 (71)
Injection site swelling	40 (15)	0.0 (75)
Fever	90 (20)	1.3 (96)
Drowsiness	0 (6)	0.7 (3)
Irritability	14 (7)	0.0 (32)
Persistent crying	14 (14)	0.1 (20)
Loss of appetite	43 (7)	1.9 (20)
Vomiting	0 (0)	1.4 (14)
Diarrhea	0 (1)	0.1 (38)
Rash	100 (1)	0.5 (42)

Data were based on one dose of a single antigen or combination vaccine. [a] Cases reported by parents/caregivers where the child of the parent/caregiver experienced any AR. Data were based on the parent/caregiver survey. [b] Calculations based on the cases where the child of the parent/caregiver experienced any AR and medical advice was sought. Data were based on the parent/caregiver and physician survey. **AR**: adverse reaction.

3.3. Physician-Reported Direct Medical Costs to Manage ARs Associated with Childhood Vaccinations

Although few hospitalizations were reported, these cases were the largest contributor to total direct medical costs, of up to 8 900 000 VND per AR across the ARs examined (**Table 2**). Across ARs, HCP visits also significantly contributed to overall costs, and ranged between 621 250 and 1 800 000 VND per AR. Compared to hospitalization and HCP visits, overall treatments and test/assessment costs were minimal, and ranged between 774 and 28 789 and between 2 457 and 81 500 VND, respectively.

When looking at specific AR-related costs, injection site pain incurred high direct medical costs owing to an estimated 8 900 000 VND contribution from hospitalization expenses (n=1 physician). Rash, fever, and persistent crying incurred moderate direct medical costs also due to substantial contributions from hospitalization expenses, which were estimated at 3 550 000 VND (n=1), 3 850 000 ± 1 739 253 VND (n=6), and 3 550 000 VND (n=1)

per case, respectively. ARs of diarrhea, irritability, and injection site swelling cost the least to manage, partially owing to the lack of reported hospitalization by physicians.

Table 2: Direct Medical Costs Associated with the Management of Post-Vaccination ARs in Vietnam per AR – Breakdown Cost per Case

	HCP visits ^a			Treatment ^b			Tests/assessments ^c			Hospitalization ^d		
	VND	SD	n	VND	SD	n	VND	SD	n	VND	SD	n
Injection site pain	671 905	331 841	42	15 429	52 562	42	7 810	35 349	42	8 900 000	-	1
Injection site redness	689 688	469 217	32	7 838	10 838	32	2 457	14 407	32	1 800 000	-	1
Injection site swelling	710 625	539 324	32	7 375	8 899	32	0	0	32	-	-	-
Fever	621 250	113 051	40	10 109	6 393	40	49 288	106 723	40	3 850 000	1 739 253	6
Drowsiness	1 800 000	-	1	1 719	-	1	81 500	-	1	1 800 000	-	1
Irritability	733 571	319 918	14	774	2 749	14	35 071	76 756	14	-	-	-
Persistent crying	957 778	996 729	9	3 344	5 329	8	64 111	129 021	9	3 550 000	-	1
Loss of appetite	948 333	671 851	6	9 093	18 185	4	27 333	66 953	6	1 800 000	-	1
Vomiting	947 143	455 584	7	2 630	1 862	6	0	0	7	1 800 000	0	2
Diarrhea	737 059	346 460	17	5 024	8 072	17	24 088	56 220	17	-	-	-
Rash	706 667	460 818	18	28 789	50 105	18	27 333	62 891	18	3 550 000	-	1

[a] Calculated based on the following equation: number of visits to HCP x unitary cost per visit. Costs for each HCP were combined. Response options included PCP/GP, A&E department, pediatrician/pediatric specialist, other hospital specialist, pharmacist*, nurse, and other*. [b] Calculated based on the following equation: number of treatments required per day x number of days medication was taken x unitary cost per treatment. Costs of each treatment were combined. Response options included cold compress or bath*, heating pad*, analgesic medication, antipruritic medication (except antihistamines), antipyretic medication, anti-diarrhea medication, antihistamines, IV fluid, anaphylaxis medication, anti-emetic medication, oral rehydration salts, dietary changes*, other*, and no treatment*. [c] Calculated based on the following equation: number of tests/assessments x unitary cost. Costs for each test/assessment were combined. Response options included patient examination*, blood test, urine analysis, other laboratory tests*, X-ray, CT scan, MRI, lumbar puncture, and other*. [d] Calculated based on the following equation: number of night stays x unitary cost per night. * No unitary cost data were available or applicable. **A&E**: Accident & Emergency; **AR**: adverse reaction; **CT**: computed tomography; **GP**: general practitioner; **HCP**: healthcare professional; **IV**: intravenous; **MRI**: magnetic resonance imaging; **PCP**: primary care physician; **SD**: standard deviation; **VND**: Vietnamese Dong.

3.4. Parent/Caregiver-Reported Indirect Costs to Manage ARs Associated with Early Childhood Vaccination

According to parents/caregivers, the management of fever, the local ARs (injection site pain, redness, and swelling), and irritability incurred indirect costs, with an average total varying from 941 000 to 3 962 455 VND per AR case. No indirect costs were reported for the other six ARs of interest (**Figure 1**).

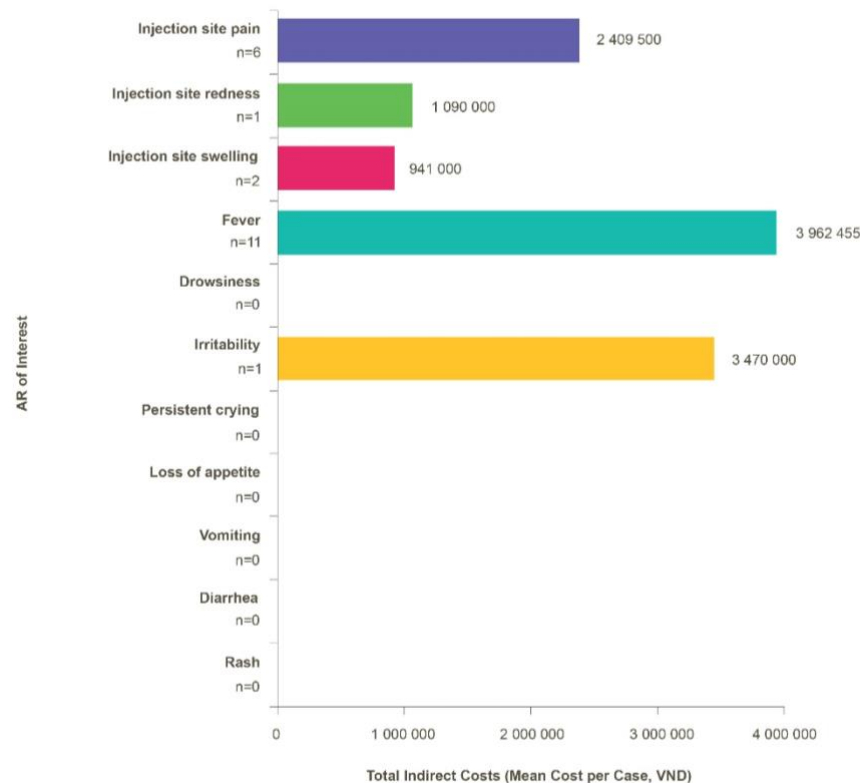


Figure 1: Total Indirect Costs to Manage Specific ARs in Vietnam, Mean Cost per Case
AR(s): adverse reaction(s); **VND**: Vietnamese Dong.

The average total absenteeism costs were 1 137 368 VND (n=38), with an average of 22.7 hours of lost work time per AR case (reported by n=38 parents/caregivers) in the two weeks following their child's vaccination. Total average out-of-pocket treatment costs were 284 359 VND (n=39), and childcare, travel, parking, tests, and other costs totaled an average of 2 001 432 VND (n=44) (**Appendix A2**).

3.5. Costs of the Management of ARs with DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib

Single doses of the two hexavalent vaccines containing acellular pertussis approved for childhood vaccination in Vietnam, DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib, were compared using a newly developed mathematical projection tool. The model assumed a 2023 Vietnamese birth cohort of 1 418 890 individuals, and 69% vaccination coverage for both vaccines (GSK, 2023), (*World Population Prospects 2022: Summary of Results*, 2022).

A primary dose of DT3aP-HBV-IPV/Hib resulted in 420 985 fewer ARs compared with DT2aP-HBV-IPV-Hib (**Table 3**), representing an 8% reduction in overall ARs. When estimating HCRU, there were 175 149 (-11%), 175 149 (-11%), 175 149 (-11%), and 1 566 (-13%) fewer HCP visits, prescribed treatments, tests/assessments, and hospitalizations, respectively, predicted with DT3aP-HBV-IPV/Hib compared with DT2aP-HBV-IPV-Hib.

The reduction in occurrence of ARs with a primary dose of DT3aP-HBV-IPV/Hib lead to a reduction of ~134 billion VND in direct medical costs to manage ARs, compared with DT2aP-HBV-IPV-Hib, marking an overall cost reduction of -11% (**Table 3**). The projection tool estimated that DT3aP-HBV-IPV/Hib reduced HCP visit costs by ~121 billion VND, treatment costs by ~1.70 billion VND, test/assessment costs by ~5.67 billion VND, and hospitalization costs by ~5.85 billion VND, compared with DT2aP-HBV-IPV-Hib.

When looking at the indirect costs to parents/caregivers, significant reductions were also predicted with a primary dose of DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib. The projection tool estimated reductions of ~182 billion VND in absenteeism expenses, ~44 billion VND in out of pocket treatments, and ~219 billion VND in additional costs (which included childcare, travel, parking, tests, and other costs) with DT3aP-HBV-IPV/Hib over DT2aP-HBV-IPV-Hib, marking an overall ~441 billion VND (-14%) reduction in indirect costs.

Table 3: Reduction in HCRU and Indirect Costs from Vaccination with DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib

Management of AR outcomes	DT3aP-HBV-IPV/Hib	DT2aP-HBV-IPV-Hib	DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib	
			Absolute difference	Percent difference, %
Overall number of ARs	4 591 670	5 012 655	-420 985	-8
HCRU				
HCPs visits	1 422 243	1 597 392	-175 149	-11
Hospitalizations	10 373	11 939	-1 566	-13
Treatments	1 422 243	1 597 392	-175 149	-11
Tests/assessments	1 422 243	1 597 392	-175 149	-11
Total direct costs, VND	1 121 121 378 507	1 255 368 940 794	-134 235 569 119^e	-11
HCPs visits ^a	1 030 403 783 290	1 151 433 225 678	-121 029 442 389	-11
Hospitalizations ^b	38 458 525 210	44 305 307 065	-5 846 781 855	-13
Treatments ^c	13 284 130 480	14 981 605 933	-1 697 475 453	-11
Tests/assessments ^d	38 974 939 528	44 648 802 119	-5 673 862 591	-13
Total indirect costs, VND	2 758 084 293 535	3 202 878 972 838	-441 465 963 364^e	-14
Absenteeism	1 111 728 802 565	1 293 732 127 781	-182 003 325 216	-14
Out-of-pocket treatments	308 422 438 585	352 128 656 082	-43 706 217 497	-12
Others	1 337 933 052 384	1 557 018 188 975	-219 085 136 591	-14

[a] Calculated based on the following equation: number of visits to HCP x unitary cost per visit. Costs for each HCP were combined. Response options included PCP/GP, A&E department, pediatrician/pediatric specialist, other hospital specialist, pharmacist*, nurse, and other*. [b] Calculated based on the following equation: number of night stays x unitary cost per night. [c] Calculated based on the following equation: number of treatments required per day x number of days medication was taken x unitary cost per treatment. Costs of each treatment were combined. Response options included cold compress or bath*, heating pad*, analgesic medication, antipruritic medication (except antihistamines), antipyretic medication, anti-diarrhea medication, antihistamines, IV fluid, anaphylaxis medication, anti-emetic medication, oral rehydration salts, dietary changes*, other*, and no treatment*. [d] Calculated based on the following equation: number of tests/assessments x unitary cost. Costs for each test/assessment were combined. Response options included patient examination*, blood test, urine analysis, other laboratory tests*, X-ray, CT scan, MRI, lumbar puncture, and other*. [e] Given iterations of rounding across calculations, the sum of each cost item does not perfectly match the total cost of the respective cost category (direct and indirect), with a minor variation of <1%. * No unitary cost data were available or applicable. A&E: Accident & Emergency; AR: adverse reaction; CT: computed tomography; GP: general practitioner; HCP: healthcare provider; HCRU: healthcare resource utilization; IV: intravenous; MRI: magnetic resonance imaging; PCP: primary care physician; VND: Vietnamese Dong.

3.6. Emotional Impact on Parents/Caregivers of Managing Early Childhood ARs

Rash (100%, n=1 parent/caregiver), diarrhea (100%, n=1), fever/high temperature (85%, n=20), and loss of appetite (71%, n=7) were the ARs parents/caregivers reported as causing the greatest emotional concern following vaccination (Figure 2). Injection site redness (39%, n=18) and injection site swelling (33%, n=15) were the least emotionally concerning ARs for parents/caregivers.

When looking at vaccine compliance, 95% of parents/caregivers would continue with a vaccination schedule as normal, and only 5% stated that they were hesitant to continue all vaccinations, despite their child experiencing

an AR. No parents/caregivers stated that they would refuse to continue with any vaccinations due to ARs experienced by their child. Additionally, 80% of parents/caregivers would not change the timing of future childhood vaccinations. Of the 5% of parents/caregivers that expressed uncertainty, 57% expressed hesitancy towards co-vaccinations of different vaccines during the same appointment, whereas no parents/caregivers reported hesitation towards multivalent vaccines alone; 43% of parents/caregivers expressed the hesitancy towards both co-vaccination and multi-valent vaccinations.

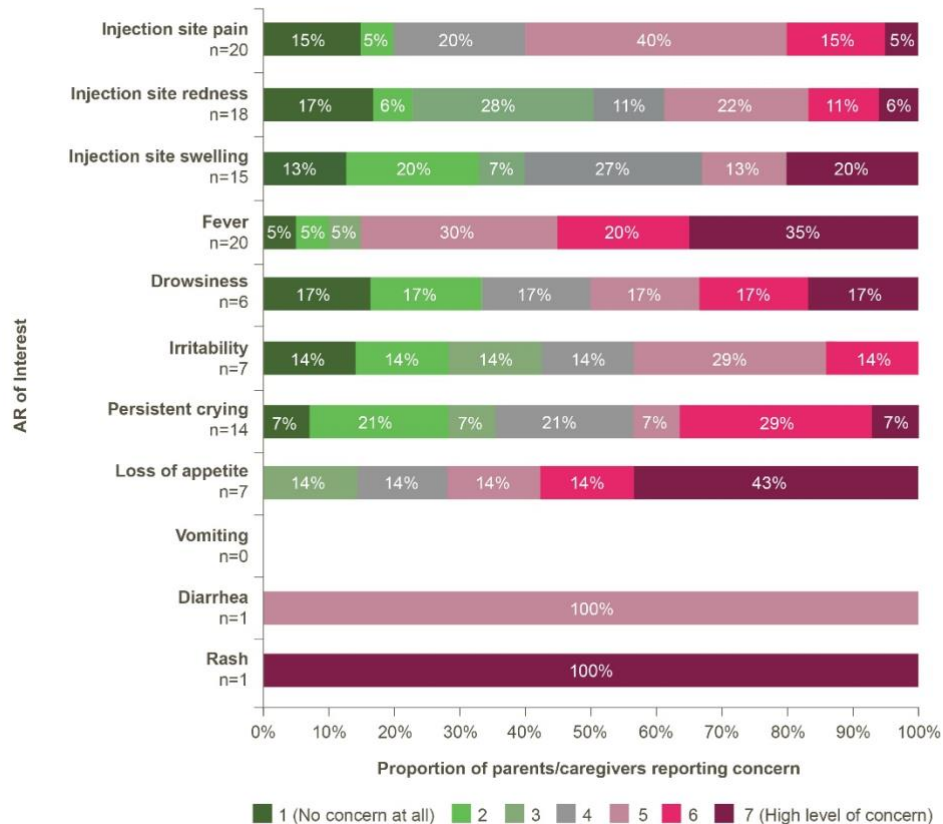


Figure 2: Parent/Caregiver Reported Levels of Emotional Concern Following AR(s)

Scores ≥ 5 are described as concerning. n represents the number of parents/caregivers who experienced in AR in question. Numbers are rounded up. AR: adverse reaction; ARR: absolute risk reduction.

3.7. Sensitivity Analysis

SAs were performed on AR-specific data, i.e., the proportion of each AR for DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib, as well as the ARRs. These results are presented in terms of variations in the direct medical costs saved (**Appendix A3**). As expected, the model is significantly more sensitive to the variation of the ARs' incidences compared with the ARR. This finding confirms the robustness of the analysis.

4. Discussion

To our knowledge, this is the first study which explored the management of ARs associated with early childhood vaccinations in Vietnam. This is also the first study to estimate the reduction in direct medical costs as well as indirect costs to parents/caregivers, which may arise due to the management of fewer ARs when vaccinating with a primary dose of DT3aP-HBV-IPV/Hib over DT2aP-HBV-IPV-Hib in Vietnam.

According to this survey administered to parents/caregivers of children receiving a dose of an early childhood vaccine, fever and the local ARs (injection site pain, redness, and swelling) were the most frequent cause for parents/caregivers to seek medical advice. The results of this study corroborate findings from a 2015 review of ARs associated with early childhood vaccinations (infants aged <2 years) in the US. The review examined a

comparable scope of vaccines, and similarly identified that fever and injection site pain and swelling were the most commonly reported ARs by parents/caregivers (Saleh et al., 2017).

A survey was also administered to physicians who manage ARs associated with early childhood vaccinations. Based on the physician survey and unit cost data, hospitalizations were estimated to be the largest contributor to the total direct medical costs required to manage post-vaccination childhood ARs, despite low hospitalization rates. This study found that vaccination with a primary dose of DT3aP-HBV-IPV/Hib over DT2aP-HBV-IPV-Hib in Vietnam was estimated to reduce post-vaccination related hospitalizations by 11%, and consequently the associated costs. A vaccine which leads to fewer AR-related hospitalizations would in turn reduce the HCRU burden needed to manage the ARs. These projections were based on a single dose of DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib, however, multiple doses of both vaccines are required to complete the vaccination course, suggesting that cost reductions with DT3aP-HBV-IPV/Hib compared with DT2aP-HBV-IPV-Hib could be even greater when considering the full vaccination course (*WHO Recommendations for Routine Immunization*, 2024).

In accordance with the markedly lower odds ratios of developing local and systemic ARs with DT3aP-HBV-IPV/Hib compared with DT2aP-HBV-IPV-Hib found previously (Mukherjee et al., 2021), the mathematic projection tool utilized here estimated significant reductions in the occurrence of local and systematic ARs with DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib in Vietnam. Similar reductions in AR occurrence were predicted when corresponding mathematical projection tools were applied to Europe and Southeast Asia (George et al., 2023; Mohy et al., 2024). Subsequently, the estimated HCRU to manage post-vaccination ARs in Vietnam was lower for DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib, and associated direct medical costs were reduced per primary dose. When looking at indirect costs incurred by parents/caregivers when managing AR(s) experienced by their child, parents/caregivers reported money lost from absenteeism, expenditure on out-of-pocket treatments, and additional costs including childcare, travel, parking and more, totaling an average of ~3 million VND per parent/caregiver per AR. However, reductions of these costs proved possible with DT3aP-HBV-IPV/Hib, such that indirect costs were reduced by 14% compared with DT2aP-HBV-IPV-Hib.

Vaccine hesitancy was identified as one of the top ten threats to global health by the WHO in 2019, highlighting the importance of managing this uncertainty (*World Health Organisation: Ten threats to global health in 2019*, 2019). Negative past experiences with vaccines have been indicated to increase parental vaccine hesitancy at a global level (Obohwemu et al., 2022), and a 2019 survey of Chinese parents identified that perceptions of vaccination safety, and risks of severe side effects, strongly influenced vaccination decisions (Li et al., 2022). In this study, although rashes, diarrhea, and fever caused significant emotional concern among parents/caregivers in Vietnam, the majority would continue with vaccination schedules as normal and would not delay future vaccinations. Having physicians inform parents/caregivers of the expected post-vaccination ARs may reduce safety and emotional concerns (Ventola, 2016). Parents/caregivers in Vietnam showed higher vaccine hesitancy towards co-vaccination compared with multivalent vaccination. This is reflected in the literature, with higher compliance rates reported for multivalent vaccinations compared with single antigen vaccines only, due to lower overall perceived risks and logistical convenience (Kurosky et al., 2017; Marshall et al., 2007). Furthermore, the use of co-vaccinations or multivalent vaccinations with low risks of ARs following vaccination can improve vaccine uptake (Happe et al., 2007). These results emphasize the importance of developing multivalent vaccines with low risks of ARs, to improve compliance and perceptions of vaccine safety.

This study was associated with some limitations. Regarding the surveys, it was not possible to determine the HCRU impact and the associated costs of patients experiencing a combination of simultaneous ARs. As with all online surveys, the presentation and framing of questions may influence respondents. Additionally, once the predefined sample quotas were met the survey closed, which may have introduced bias between respondents, as fast respondents may differ from those who delayed their response. This study may have benefitted from subgroup analyses exploring the impact of parent/caregiver experience in managing post-vaccination ARs, North versus South Vietnam physicians, parent/caregiver demographics, and infant age as these characteristics may alter preferences and therefore, management of post-vaccination ARs. The mathematical projection tool was limited to ARs analyzed in the Mukherjee et al. (2021) review, and therefore diarrhea and rash were excluded from the calculation. According to the physician survey, rashes incurred moderate hospitalization HCRU and contributed

substantially to the overall direct medical costs. Therefore, it would have been of interest to include rashes in the mathematical projection tool. HCRU was estimated from the physician survey and was consequently subject to recall bias as no databases nor patient records were accessed. Furthermore, in several cases HCRU was estimated based on a small sample of answers, which may reduce confidence in the reported values. As the sample size varied across ARs analyzed, the statistical power also varied. As aforementioned, multiple doses of DT3aP-HBV-IPV/Hib and DT2aP-HBV-IPV-Hib are recommended. However, this study did not calculate the total number of ARs experienced over the full vaccination course, and instead only considered the number of children receiving at least one dose, potentially skewing the estimated burden and costs of AR management. If a child experiences an AR with the first dose, it is reasonable to expect similar reactions with subsequent doses, suggesting that the total burden and costs might be underestimated. Conversely, if no AR occurs with the initial dose, it can be assumed that no reactions would occur with subsequent doses, leading to potential overestimation of burden and costs. However, since these over- and underestimations could counterbalance, the assumption of considering at least one dose may still be an acceptable input for analysis.

5. Conclusions

Vaccines are important to reduce the burden of disease. Multi-antigenic vaccines are a proven approach to reduce this burden across multiple diseases simultaneously. To our knowledge, this study is the first to highlight the significant reduction in HCRU and costs related to the management of ARs following a primary early childhood dose of DT3aP-HBV-IPV/Hib versus DT2aP-HBV-IPV-Hib in Vietnam, and also represents the first estimation of the cost of post-vaccination AR management in Vietnam. Decision bodies may consider the financial and societal benefits of selecting vaccines with fewer ARs in their holistic evaluation and decision-making process for vaccines, and how these benefits may improve vaccine adherence.

Author contributions: Substantial contributions to study conception and design: AMo, GN, MD, MN, AMa, and DVO; substantial contributions to analysis and interpretation of the data: AMo, GN, MD, VG, GC, EH, MN, ED, AMa, and DVO; drafting the article or revising it critically for important intellectual content: AMo, GN, MD, VG, GC, EH, MN, ED, AMa, and DVO; final approval of the version of the article to be published: AMo, GN, MD, VG, GC, EH, MN, ED, AMa, and DVO.

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Conflicts of interest: AMo, MD, ED, AMa, and DVO: employees of and hold financial equities in GSK; GN: employee of, holds financial equities in, and has received grants/contracts from GSK; VG: receives consultant fees from Amaris Consulting, working as a contingent worker for GSK; GC and EH: the authors declare no conflict of interest; MN: employee of GSK. The funding sponsor had a role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, and in the decision to publish the results. Conflicts of interest are as reported during analysis and development of the manuscript.

Ethics approval: This study complied with all applicable laws regarding participant privacy and all participants provided informed consent prior to inclusion in the study. Study results are in tabular form and presented as aggregate analyses that omit subject identification; therefore, ethics committee or IRB approval was not required. Study documents were nevertheless submitted to a single central IRB (WCG IRB). The IRB reviewed the protocol, consent forms, data collection materials as well as a study specific form, which included a summary of the study, documents submitted and relevant certificates (CV and ethical training certification). Approval was granted from the WCG IRB on 16th June 2023 (decision ID: 20232715).

Data availability statement: All data generated or analyzed during this study are included in this published article/as supplementary information files.

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Appendix A

A1. Published Unit Cost Data

Item^a	Cost in Vietnamese private healthcare (VND)
HCP Visits	
General practitioner visit	440 000
Pediatric specialist visit	690 000
Other hospital specialist visit	690 000
Pharmacist visit	NA
Nurse (hospital) visit	240 000
Emergency room visit	1 800 000
Tests/Assessments	
Blood test	164 000
Urinalysis	81 500
X-ray	250 000
CT scan	2 150 000
MRI	2 750 000
Lumbar puncture	1 680 000
Treatments^b	
Analgesic and Antipyretic	(Paracetamol) 1 718.64
Antipruritic	(Hydrocortisone) 34 652.00
Anti-diarrhea medication	(Racecadotril sachet) 402.24
Antihistamine	(Desloratadine) 2 691.67
IV fluid	(Sodium chloride) 36 265.78
Anaphylaxis medication	(Epinephrine IM) 125.54
Sedative	(Midazolam IV) 81.70
Anti-emetic medication	(Metoclopramide) 538.01
Oral rehydration salts	(Hydration sachets) 82.00
Hospitalization	
Room per day	3 550 000 (double room)

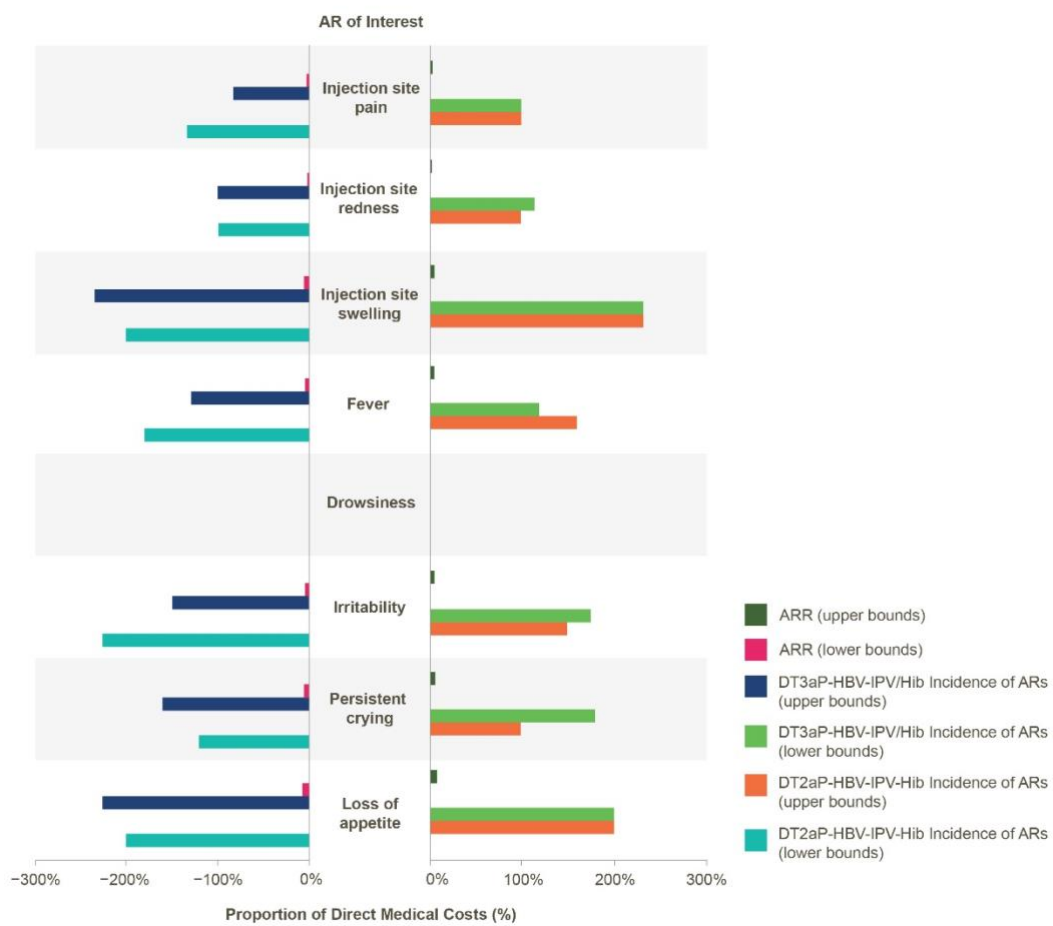
[a] Published unit cost data provided by a third-party agency, Weber, a consultancy firm specialized in HCRU data. Weber used published scientific literature and official databases to identify published unit costs for HCP visits, prescribed treatments, tests/assessments, and hospitalization. Weber used the most recent published data available and provided all references for unit cost data. [b] Treatment costs per administration. CT: computed tomography; HCP: healthcare professional; IV: intravenous; MRI: magnetic resonance imaging; NA: not applicable; VND: Vietnamese Dong.

A2. Indirect costs to parents/caregivers in Vietnam per case – Mean cost per case

Expense to Parent/Caregiver	VND	SD	n
Absenteeism	1 137 368	1 808 279	38
Tests	408 455	1 198 880	44
Parking	51 955	183 656	44
Travel	352 955	806 424	44
Childcare	715 682	2 298 885	44
Other	472 386	1 662 303	44

SD: standard deviation; VND: Vietnamese Dong

A3. Sensitivity Analyses of the Eight Adverse Reactions Analyzed in Vietnam



AR: adverse reaction; ARR: absolute risk reduction.