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Introduction of a hexavalent vaccine containing acellular pertussis into the national immunization program for infants in Peru: a cost-consequence analysis of vaccination coverage

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Abstract

Background Infant vaccination coverage rates in Peru have declined in recent years, exacerbated by the COVID-19 pandemic. Introduction of the fully-liquid diphtheria, tetanus, and acellular pertussis (DTaP)-inactivated polio vaccine (IPV)-hepatitis B (HB)-*Haemophilus influenzae* type B (Hib) hexavalent vaccine (DTaP-IPV-HB-Hib) in Peru's infant National Immunization Program may help improve coverage. We evaluated costs and healthcare outcomes, including coverage, of switching from a pentavalent vaccine containing whole-cell pertussis component (DTwP-HB-Hib) plus IPV/oral polio vaccine (IPV/OPV) to the hexavalent vaccine for the primary vaccination scheme (2, 4 and 6 months).

Methods The analysis was performed over a 5-year period on a cohort of children born in Peru in 2020 ($N=494,595$). Four scenarios were considered: the pentavalent plus IPV/OPV scheme (S1); replacing the pentavalent plus IPV/OPV scheme with the hexavalent scheme (S2); expanded delivery of the pentavalent plus IPV/OPV scheme (S3); expanded delivery of the hexavalent scheme (S4). Vaccine coverage and incidence of adverse reactions (ARs) were estimated using Monte Carlo simulations and previous estimates from the literature. Cases of vaccine-preventable diseases were estimated using a Markov model. Logistical and healthcare costs associated with these outcomes were estimated. Impact of key variables (including coverage rates, incidence of ARs and vaccine prices) on costs was evaluated in sensitivity analyses.

Results The overall cost from a public health payer perspective associated with the pentavalent plus IPV/OPV vaccine scheme (S1) was estimated at $56,719,350, increasing to $61,324,263 (+8.1%), $59,121,545 (+4.2%) and $64,872,734 (+14.4%) in scenarios S2, S3 and S4, respectively. Compared with the status quo (S1), coverage rates were estimated to increase by 3.1% points with expanded delivery alone, and by 9.4 and 14.3% points, if the hexavalent vaccine is deployed (S2 and S4, respectively). In both scenarios with the hexavalent vaccine (S2 and S4), pertussis cases would also be 5.7% and 8.7% lower, and AR rates would decrease by 32%. The cost per protected child would be reduced

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when the hexavalent vaccine scheme. Incidence of ARs was an important driver of cost variability in the sensitivity analysis.

Conclusions Implementation of the hexavalent vaccine in Peru's National Immunization Program has a positive public health cost consequence.

Keywords Vaccination coverage rate, Vaccination coverage gap, Hexavalent vaccination, Diphtheria-tetanus-pertussis, *Haemophilus influenzae* type b, Hepatitis B, Polio, Cost-consequence analysis

Background

Globally, immunization practices have shifted towards reducing the number of injections while maintaining antigenic coverage. This approach began with bivalent vaccines and has progressively advanced through more complex combinations. These combination vaccines offer significant public health benefits, including simplified, more convenient schedules with fewer injections, leading to increased and more timely vaccination coverage [1, 2]. Economic and logistical efficiencies can be gained through reduced costs and resources needed for transport, simplified cold-chain storage and administration [1]. As fewer injections are needed, they can potentially decrease the risk of local reactions and associated pain/discomfort [1].

In Peru, the primary National Immunization Program schedule up to 2022 for infants aged ≤ 6 months included vaccination with the diphtheria, tetanus, whole-cell pertussis (DTwP)-hepatitis B (HB)- *Haemophilus influenzae type b* (Hib) pentavalent vaccine (DTwP-HB-Hib) at 2, 4 and 6 months of age, two doses of polio inactivated vaccine (IPV) at 2 and 4 months of age, and one dose of oral polio vaccine (OPV) at 6 months of age[1] [3]. This program has been instrumental in improving public health, not only protecting those immunized, but also providing population-level protection by reducing community transmission.

In 2012, the World Health Organization (WHO) established the Global Vaccine Action Plan (GVAP) to promote universal vaccination, aiming to achieve over 90% coverage with routine vaccines and eradicate poliomyelitis globally [4]. However, in Peru, vaccination coverage rates have declined since then, a trend further exacerbated by the COVID-19 pandemic [5]. According to figures reported by the Demographic and Family Health Survey (Endes), coverage with the third dose of the pentavalent and polio vaccines in infants aged ≤ 1 year dropped from 78.5% and 81.4% in 2019 to 63.8% and 64.8%, respectively, in 2020 [6, 7]. Vaccine coverage rates have not recovered to their pre-pandemic levels [5]. By the end of 2022, less than 75% of one-year-old infants were fully immunized with the primary doses of the pentavalent and polio vaccines [8]. Furthermore, a case of vaccine-derived poliomyelitis was detected in 2023, alongside seven cases of children affected by post-vaccination polio and vaccine-derived poliovirus between 2003 and 2013 [9]. According to the WHO, such outbreaks typically occur in areas with insufficient polio vaccination coverage, where the virus can regain neurovirulence, increase transmission risk, and cause paralysis similar to that caused by wild poliovirus [10].

A proposed alternative to the pentavalent plus IPV/OPV scheme in Peru would be the introduction of the acellular pertussis-based hexavalent vaccine (DTaP-IPV-HB-Hib) administered at 2, 4, and 6 months [11]. Vaccination with this hexavalent vaccine has been widely adopted in the infant immunization programs of most European countries. In Latin America, the adoption of the hexavalent vaccine into national immunization schedules has been a gradual process, initiated by Panama in 2014 and later extended to Chile, Mexico, Paraguay, and El Salvador [12–15].

Economic analyses have been undertaken to assess the impact of switching to the hexavalent vaccine in Latin American countries deploying the pentavalent-based infant schedule, such as Peru, Chile, Colombia, and Argentina [16–19]. These analyses suggest that the hexavalent scheme would lead to additional expenditure, mainly due to higher acquisition costs, though partly offset with cost savings from improved logistic efficiencies, as well as public health benefits such as reduced vaccine-associated adverse events [16–19].

In this study, we conducted a cost-consequence analysis of introducing the hexavalent vaccine into the primary National Immunization Program for infants in Peru. We assessed its impact on vaccination coverage, health and economic outcomes, and the implications of expanded vaccination access. This research contributes to existing studies in Peru by incorporating cohort data, exploring scenarios of increased coverage, and considering the effects of potential disease outbreaks. The study's value lies in providing evidence-based insights to inform decision-makers on viable immunization options in the country.

[1] Recent modifications to the calendar for 2023 onwards, has eliminated the OPV dose at 6 months of age, replacing it with a third IPV dose.

Methods

Target population and vaccination scenarios

The target population, children born in 2020 eligible for immunization (N = 494,595), was taken from data reported in the Nominal Census of Boys and Girls by the Peruvian Ministry of Health (Minsa) [20].

The primary schedule at the time of this cost evaluation involved three doses of the pentavalent vaccine (2, 4, 6 months of age), two doses of IPV (2 and 4 months of age), and one dose of OPV (6 months of age), delivered primarily at health centers. This status quo was considered the baseline scenario, scenario 1 (S1). Three other scenarios were considered (Fig. 1). Scenario 2 (S2) considered replacing the pentavalent plus IPV/OPV vaccine scheme with the hexavalent vaccine, assuming administration at the same ages and delivery primarily at health centers as in S1. Scenario 3 (S3) considered the pentavalent plus IPV/OPV vaccine scheme, as in S1, but included a broader range of fixed locations for vaccine delivery (health centers and vaccination centers), complemented with mobile strategies (vaccination at strategic locations, door-to-door vaccination, at-home with prior appointment and traveling teams). Scenario 4 (S4) considered the alternative hexavalent vaccine as in S2 but with extended program delivery as in S3.

Outcomes

Three outcomes were evaluated: vaccine coverage, incidence of adverse reactions (ARs), and incidence of three vaccine-preventable diseases (diphtheria, pertussis, and polio disease cases; see below for rationale). The analysis period was 2 years for the first two outcomes and 5 years for the latter, with 2020 as the baseline year for estimates.

For S1, vaccine coverage estimates were derived from information reported by the Demographic and Family Health Survey [7]. This involved summation of coverage estimates for 12 sub-cohorts of children based on their birth month to determine the coverage of the total cohort born in 2020. Monte Carlo simulations were used to estimate the behavior pattern of the target population during the first 2 years of the analyzed period, based on the birth month of the children, the number of doses of each vaccine received, the probability of receiving both vaccines at the same visit and age at the time of vaccination. For S2, the variation in coverage rate with the introduction of the hexavalent vaccine was calculated, considering that there would be a greater opportunity for total protection (being a combined vaccine) and, thus, assuming that all children initiating the schedule in S1 (with any of the vaccines) would receive the hexavalent first dose. The number of infants continuing to the second and third dose were estimated based on a study conducted in Chile by O'Ryan et al. (2020) which, although based on parental

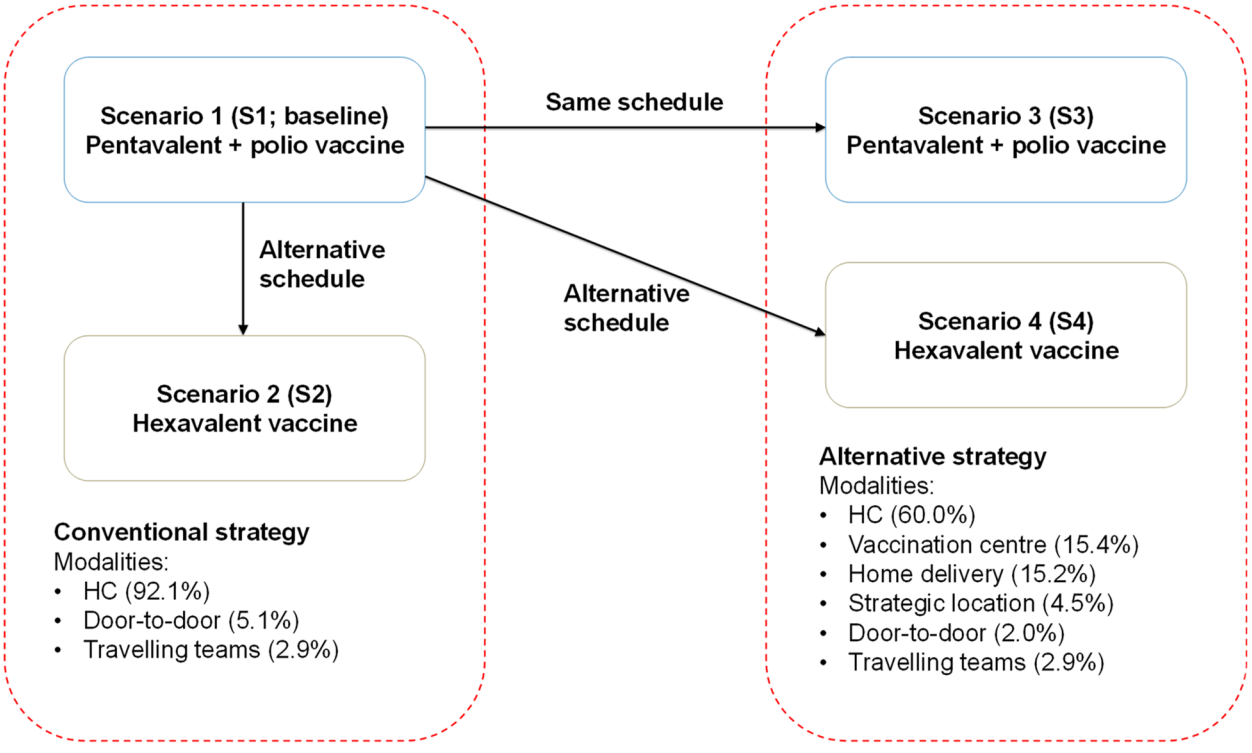

Fig. 1 Scenarios for analysis. The proportion of the target population at a national level for each intervention modality is presented in parentheses. HC, health center

intentions, provided the closest representation of the outcomes resulting from the same vaccination scheme change assessed in our study [21]. On this basis, the greater schedule adherence reported following the first dose with the hexavalent vaccine compared with the pentavalent plus polio vaccines (2.62-fold higher odds of continuation) was replicated for the Peruvian context, and for further subsequent doses. For S3, a study conducted in India was used as a reference [22], estimating variation in coverage rates with the first, second, and third doses of DTP and OPV, as a proxy for the pentavalent vaccine plus IPV/OPV, upon implementing vaccination locations at a closer proximity to the target population. For S4, the same criteria for S2 were used, but based on the number of children immunized with the first dose in S3. To verify the consistency of our estimates, we contrasted these to experts' and healthcare professionals' predictions of variation collected in two focus groups and corroborate that these were aligned. Methods for the implementation of the focus groups are detailed in the Supplementary material.

The most common ARs were identified from the product inserts for each vaccine in this analysis (pentavalent, IPV, OPV and hexavalent product inserts) [23–27]. Average probabilities with which vaccinated infants were estimated to develop these ARs were derived from literature reports (Supplementary Table S1) [28–32]. A Monte Carlo simulation with binomial distribution modelled the number of ARs developed by each child under each vaccination scenario. The model considered the differences in the probability of occurrence of an AR depending on each child's history of ARs, based on findings of Zafack et al. [33]. For all vaccines, those receiving a second or third dose were regarded to have a higher probability of ARs (maximum incidence rate for the vaccine), if they experienced an AR with a previous dose; conversely, the minimum incidence rate was considered for those who did not experience an AR with a previous dose (Supplementary Table S1). The number of iterations considered in the model was equal to the number of children vaccinated with ≥ 1 dose under each scenario.

A Markov model, based on a susceptible-infected-recovered (SIR) epidemic model with vaccine intervention, was used for each of the 12 sub-cohorts of children based on their birth month to estimate the number of diphtheria, pertussis, and polio disease cases under each vaccination scenario (Fig. 2). For hepatitis B and *Haemophilus influenzae* type b, there was no robust national epidemiological information to allow for meaningful estimations. Tetanus was not modelled as it is not a communicable disease. Probabilities of transitioning between states of susceptibility and immunity or infection and subsequent recovery were determined from the previously estimated coverage rates for each scenario and epidemiological surveillance data reported by the National Center for Epidemiology, Prevention and Disease Control of Peru in the period 2000–2020 [34]. Since confirmed cases of pertussis are usually underreported, we used the number of suspected cases instead. We assumed total effectiveness if the schedule was completed, i.e., in the

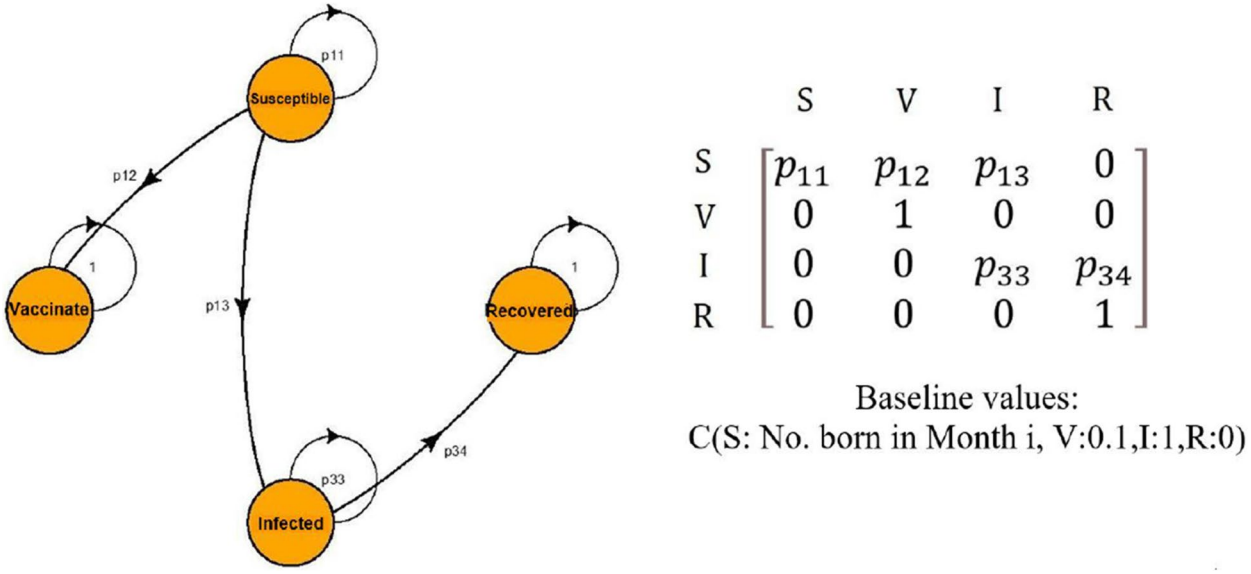

Fig. 2 Markov SIR model for estimating the incidence of vaccine-preventable disease cases. Initially, the target population is considered susceptible to the disease. Having received the third vaccination dose (with a p12 probability), the population transitions to a state of immunity, in which they are not at risk of infection. Children who do not receive the corresponding dose remain susceptible (probability, p11), of which a proportion contract the disease (probability, p13). Finally, this infected population may remain ill (probability, p33) or recover (probability, p34). I, infected; p, probability; R, recovered; S, susceptible; SIR, susceptible-infected-recovered; V, vaccinated

model, children are only no longer susceptible to infection if they received three protective doses. Conversely, children who received fewer doses were not considered protected and thus could develop the disease.

Cost estimation

Cost estimation was undertaken from the perspective of the public health payer, the Peruvian Ministry of Health (Minsa), and encompassed costs for logistics, vaccination administration (including the cost of the vaccines and their administration), AR-related care, and disease care.

Logistics costs included all costs associated with implementation of the vaccine supply chain (Supplementary Table S2). This included planning, acquisition, distribution and storage of vaccines at different levels of the supply chain (national, regional, health network, health center and vaccination locations) across five representative geographical areas, to account for the infrastructural diversity of Peru (Metropolitan Lima, urban coast, rural coast, rural range and jungle). The logistics cost for each setting was approximated by referencing the vaccine supply chain to a health center in an area or strategic point within the healthcare network. Costs per dose of each vaccine at a national level were calculated by weighting the costs for each geographical area according to the area's population.

The other costs linked to provision of health services were estimated using a standard micro-costing approach, where the unit cost of each medical procedure was calculated, considering the costs of human resources, infrastructure, equipment, medical supplies and other administrative and general services needed. Also, vaccine and medication costs required to treat ARs or disease occurrence were included (Supplementary Table S3). Estimates considered the potential variations in the vaccination pattern according to the number of doses received and, in S1 and S3, the level of integration for receiving the pentavalent plus polio vaccines (the extent of co-administration of pentavalent and polio vaccines at the same visit) (Supplementary Table S4 and S5). Different treatment profiles were considered by AR type (Supplementary Table S1) and clinical presentation of the disease (Supplementary Table S6).

All unit costs, both logistical and healthcare-related (Supplementary Tables S2 and S3), were calculated for the baseline year (2020) and projected over the study time frame (5 years), considering inflation reported by the National Institute of Statistics and Informatics (Instituto Nacional de Estadística e Informática, INEI) for 2021, and inflation reported in the Monthly Macroeconomic Expectations Survey Report of the Central Reserve Bank of Peru (Banco Central de Reserva de Perú, BCRP) as of February 2022 for the 2022–2024 period [35, 36]. The overall cost was calculated based on the target population for each cost category, discounted at 5% per year. Finally, the overall cost was divided by the number of children estimated to receive the complete vaccination schedule (assumed to be fully-protected) in each scenario, to determine the total cost per protected child.

All costs are reported in US dollars (USD, $), using an exchange rate equivalent to $1 per S/3,621 (PEN, Peruvian soles), as reported by the Banking Superintendence, Insurance and AFP (Administradoras de Fondos de Pensiones) of Peru for the base year of the estimate [37].

Sensitivity analysis

Univariate sensitivity analyses were performed to evaluate the effect of modifying eight key parameters on the overall cost of implementing each of the alternative scenarios. The following parameters were subject to a ± 20% change in sensitivity analyses: cost of human resources; cost of acquiring cold-chain refrigeration equipment and transport costs for vaccine distribution. The ± 20% variation was based on the range used in a similar study, a cost minimalization analysis of the hexavalent vaccine deployed in a Colombian expanded program [17]. This selected range is considered broad enough to cover variability in costs of the cold chain, transportation and human resources, reflecting current socioeconomic conditions in Peru. Vaccine prices per dose were also varied considering the evolution of their referential acquisition cost reported by the Pan American Health Organization (PAHO) Revolving Fund between 2015 and 2021: IPV, ± 23.3%; pentavalent, ± 11.4%; hexavalent, ± 2.1% and; OPV, ± 4.3% [38, 39].

Coverage rates were varied by ± 3% which, compared to the baseline scenario, were equivalent to increased coverage of 6.9–12.0% points in S2, 0.7–5.4% points in S3, and 11.6–17.0% points in S4. This range was based on two studies that reported coverage variations for DTaP and polio vaccines when a more combined scheme or extramural strategies to enhance routine immunization were implemented. A US-based study that compared the impact of applying a pentavalent vaccine (DTaP/HB/IPV) instead of a trivalent (DTaP), provided a frame of reference for scenarios including the hexavalent vaccine [40]. A systematic review that examined the impact of extramural interventions in low and middle-income countries was considered as a reference for scenarios with expanded delivery [41]. Literature estimates were adjusted when included in the sensitivity analysis to maintain consistency with the study characteristics.

The proportion of children immunized at health centers was varied by ± 5%; the incidence of ARs, to its minimum and maximum values (Supplementary Table S1); and the probability of infection, from half to double the baseline value. Two-way tornado diagrams were created to identify the variables with greatest impact on overall

costs of implementing each of the three alternative scenarios relative to the baseline scenario (S1).

Additionally, a probabilistic sensitivity analysis was conducted on the variable with the greatest impact on the total cost in scenario 2. This analysis was performed on scenario 2 because it allows for the assessment of the efficiency of the vaccination schedule change given the incremental cost compared with other countries that have adopted this scenario. For this purpose, a standard cost-effectiveness threshold needs to be established. In the present study, the threshold was estimated as a reference, considering the Chilean experience. Specifically, the threshold was estimated based on two studies: (i) the incremental cost obtained based on Olivera et al. (2020) scenario 1 [18], adjusting the cost estimation to the old schedule before the introduction of the hexavalent vaccine in Chile in 2018, and (ii) the change in the number of ARs was obtained from the differences in incidences reported by the Chilean pharmacovigilance system from 2019 compared to 2017, as shown in Aguirre-Boza et al. (2021) [42]. The standard efficiency threshold was estimated at (7,855,202 USD/50.926% AR reduction).

Results

Vaccine coverage and health outcomes

Compared to the baseline scenario (S1), S2 and S4 would increase vaccination coverage for the complete infant schedule by 9.4 and 14.3% points, respectively (Fig. 3), and there would be a 3.1% point increase with the expanded vaccine delivery strategies with the pentavalent plus IPV/OPV vaccine (S3). Additionally, children would be more likely to complete the vaccination schedule at the recommended age in scenarios involving the hexavalent vaccine. The proportion of infants fully immunized at 6 months of age would rise from 65.6% in S1 to 74.0% and 78.3% in S2 and S4, respectively.

AR rates would decrease by 32% and there would be approximately 13% fewer children developing ARs with a hexavalent vaccine scheme (S2 and S4), than with the pentavalent plus IPV/OPV vaccine combinations in S1 and S3 (Fig. 4). In all scenarios, only a limited number of diphtheria and polio cases would be expected with no difference between the scenarios assessed (Fig. 5). However, the introduction of the hexavalent vaccine could imply a reduction in the number of children who develop pertussis by 5.7% (19 cases) and 8.7% (29 cases) in S2 and S4, respectively.

Costs associated with vaccination

The overall cost associated with the pentavalent plus IPV/OPV scheme in S1 amounts to $56,719,350, which would increase to $59,121,545 (+4.2%) in S3 with expanded vaccine delivery strategies with the pentavalent plus IPV/OPV vaccine (Fig. 6a). The estimated overall cost of introduction of the hexavalent vaccine in S2 would amount to $61,324,263 (+8.1% increase vs. S1); in S4 this cost could increase to $64,872,734 (+14.4% increase vs. S1) with expanded vaccine delivery strategies of the hexavalent vaccine. The increased cost of introduction of the hexavalent vaccine in both S2 and S4, largely attributable to cost of vaccine administration, are partly offset by costs savings associated with logistics and care

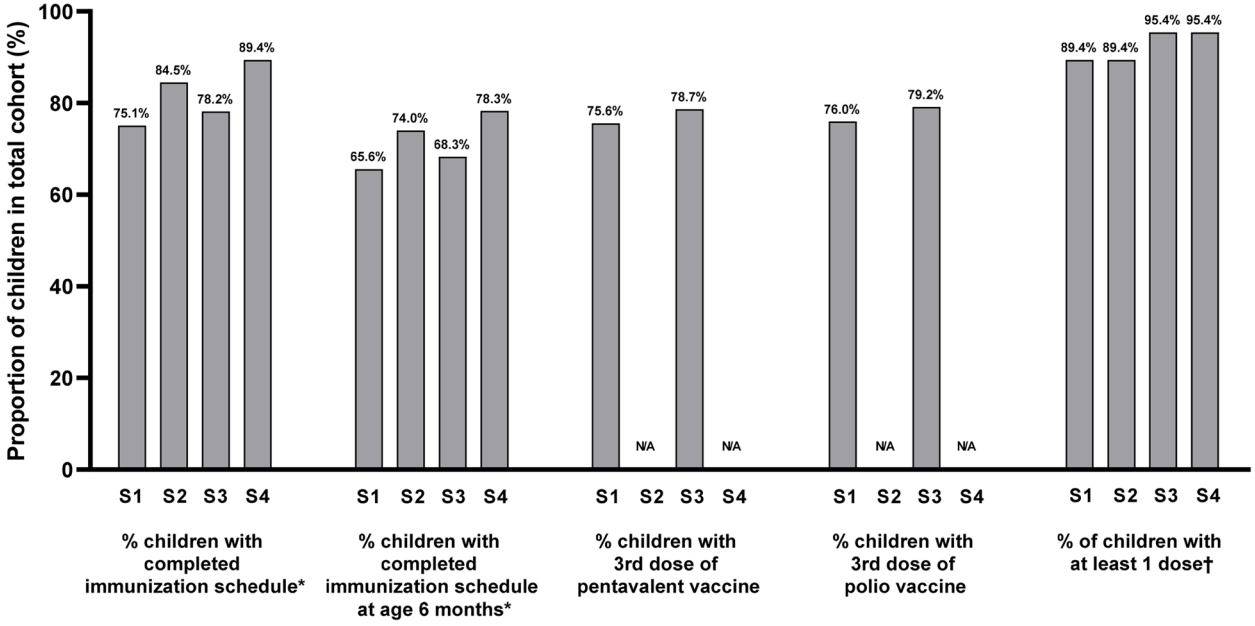

Fig. 3 Vaccine coverage. *Completion of schedule: 3rd pentavalent dose and 3rd dose of the polio vaccine in S1 and S3; 3rd dose of hexavalent vaccine in S2 and S4.†at least one dose of the pentavalent or polio vaccine in S1 and S3; at least one dose of the hexavalent vaccine in S2 and S4.

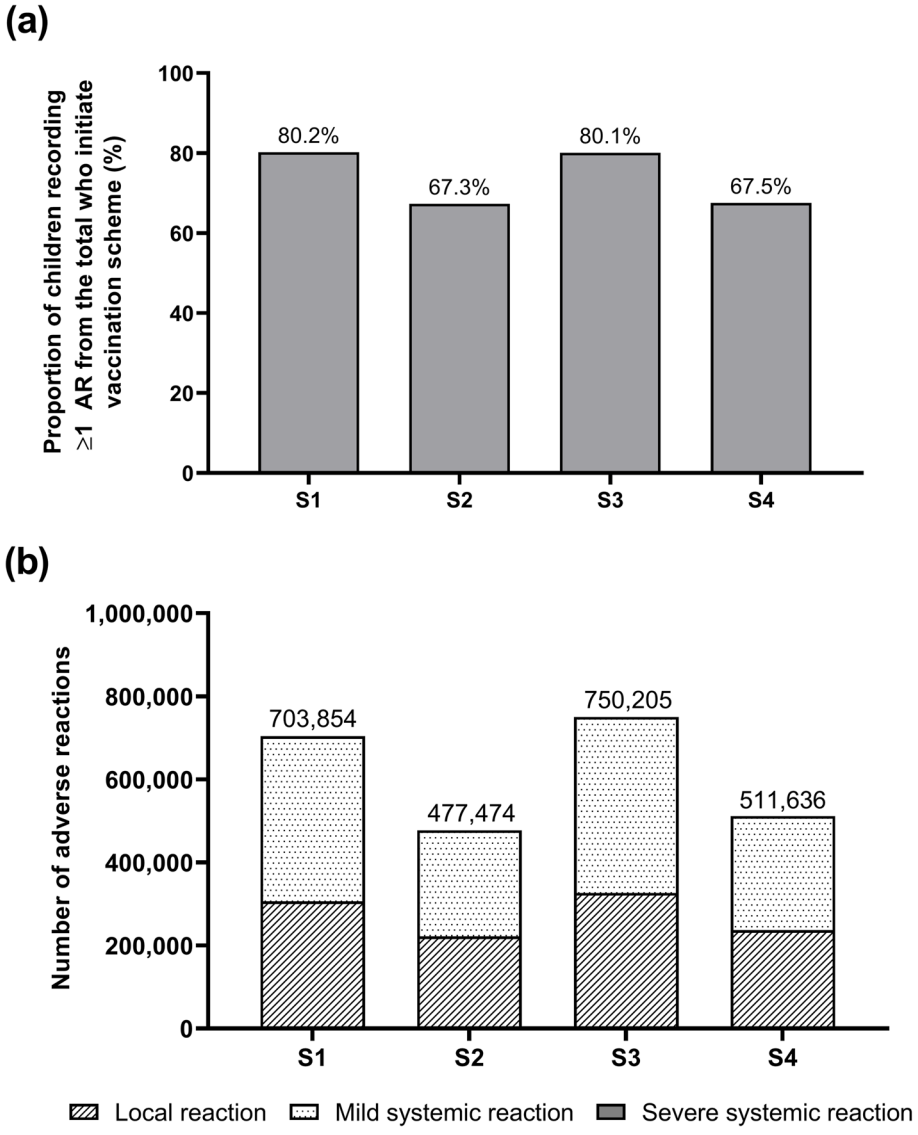

Fig. 4 Adverse reactions. **a** Proportion of children who initiate vaccination scheme recording at least one AR, and **b** Total number of local, mild systematic and severe systemic reactions

of ARs and disease cases (Fig. 6b). Additionally, the costs per protected child would be lowest in scenarios with the hexavalent vaccine, $146.65 in S2 and $146.72 in S4, compared to $152.75 in S1 and $152.95 in S3.

Sensitivity analysis

For all scenarios, the incidence of ARs was an important driver of cost variability in the sensitivity analysis (Fig. 7). In scenarios involving the hexavalent vaccine (S2 and S4), the coverage rate was also a significant factor influencing cost variability. However, it is noteworthy that even under the most conservative scenario evaluated (a reduction of 3% on the estimated hexavalent vaccine coverage) the nature of the results was not affected. The cost per child protected continued to be less than in scenarios with the pentavalent plus IPV/OPV vaccine: $147.11 in S2 and $146.80 in S4.

In our study context, the probabilistic sensitivity analysis used the change in the number of ARs as the measure of efficiency. The results of all simulations show that all simulated points were below the estimated threshold. This illustrates an incremental cost between $4,600,000 and $4,800,000 for a 32% reduction in ARs (Fig. 8).

Discussion

Infant vaccine coverage has been decreasing in Latin American countries in recent years, including Peru [5]. These gaps in coverage were further exacerbated by restriction measures to control the COVID-19 pandemic [5–7]. In the current analysis, we evaluated both costs

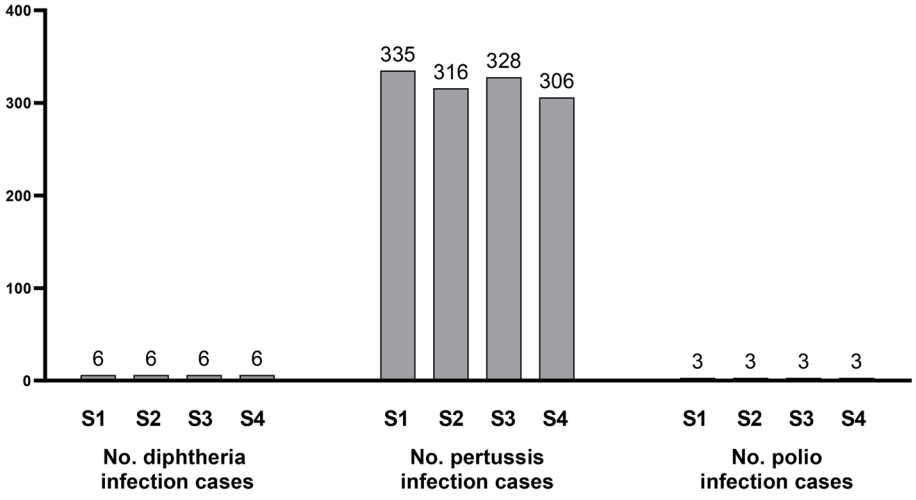

Fig. 5 Disease outbreaks

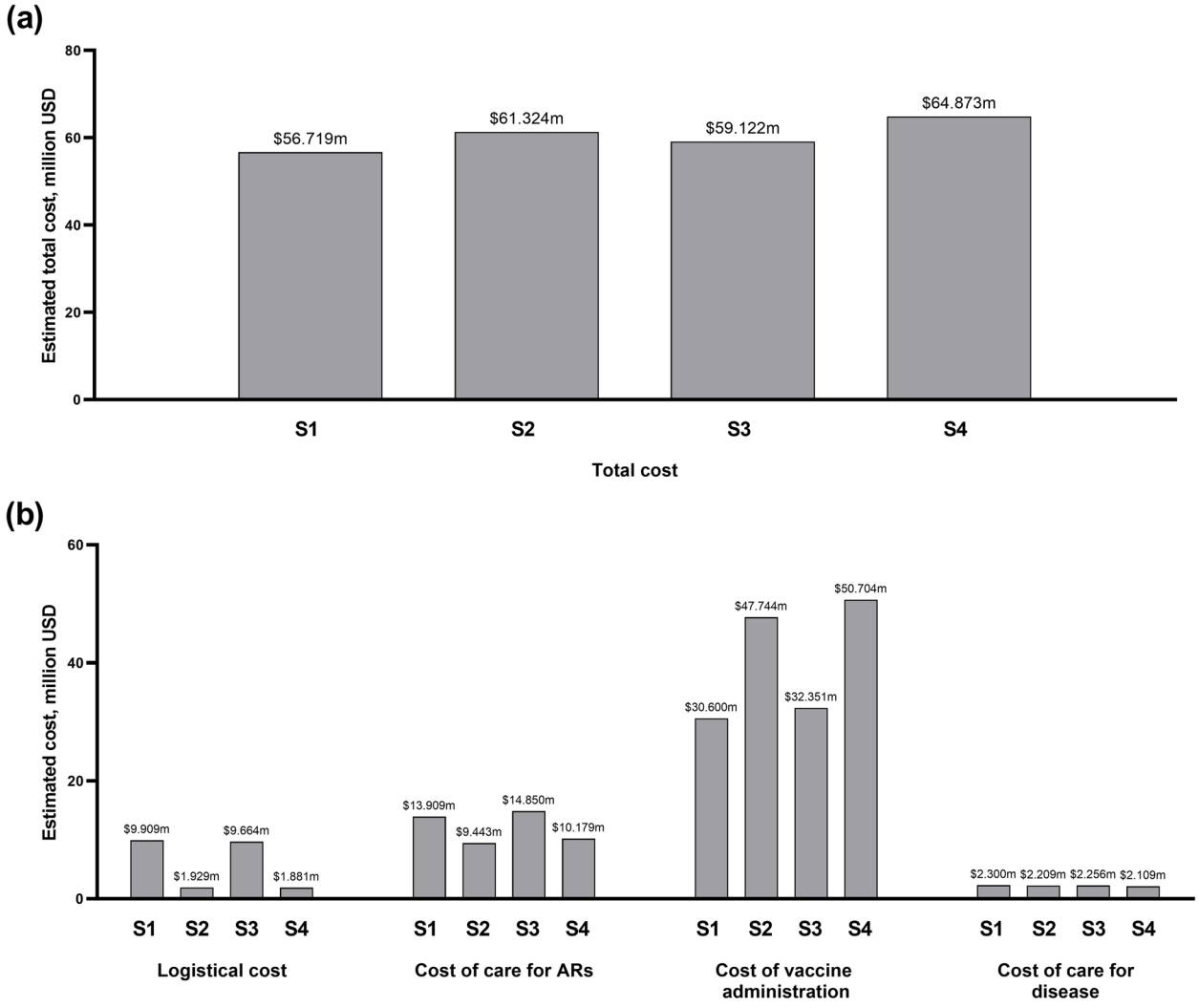

Fig. 6 **a** Total estimated cost and **b** breakdown by cost category

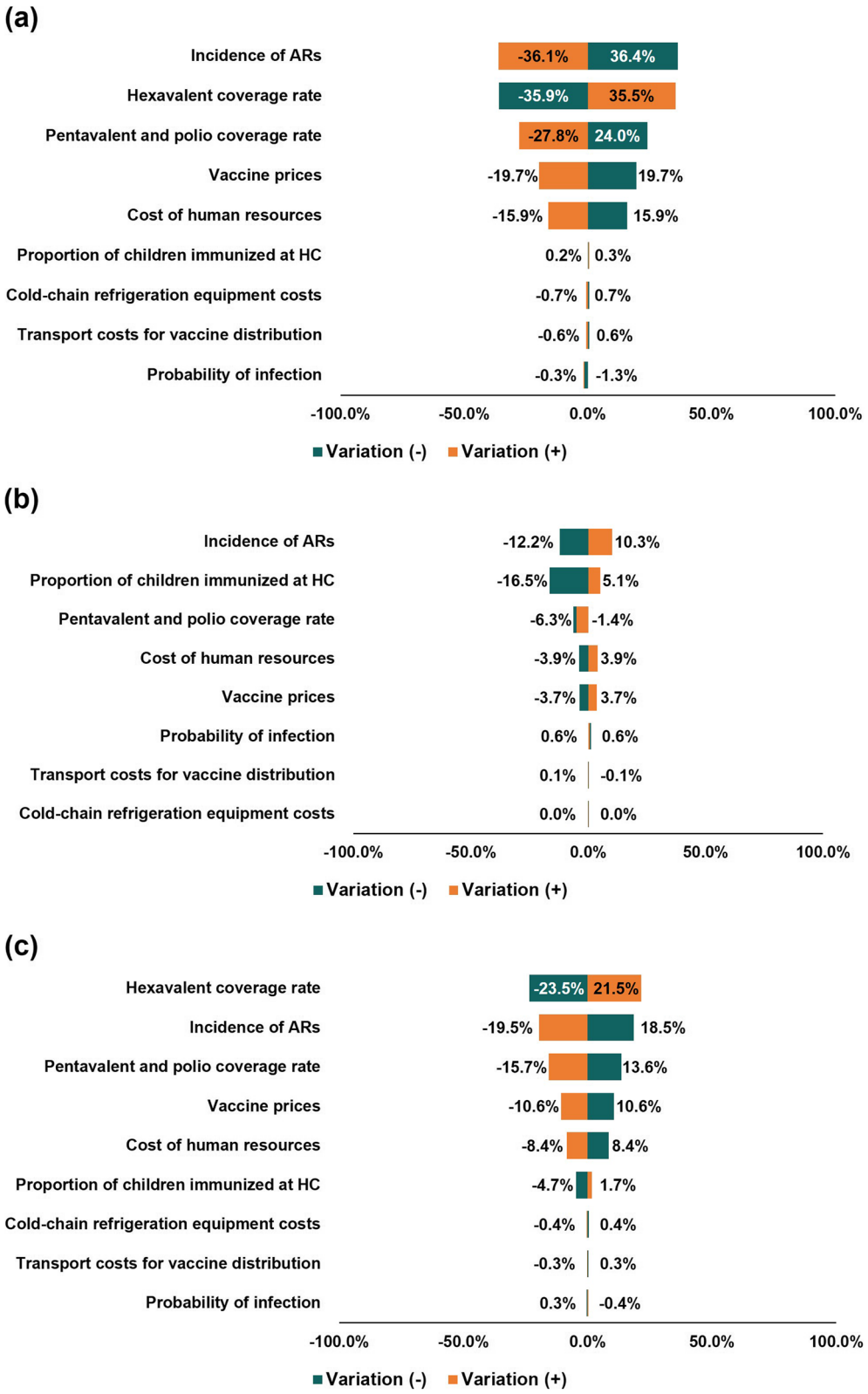

Fig. 7 Univariate sensitivity analysis (two-way tornado) – alternative scenario costs relative to baseline scenario. **a** S2 vs. S1, **b** S3 vs. S1, and **c** S4 vs. S1

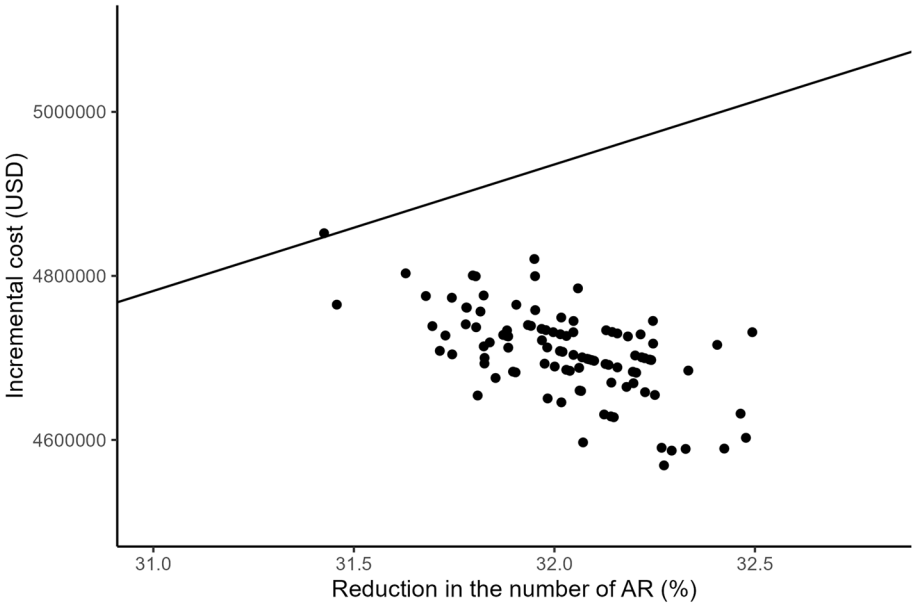

Fig. 8 Probabilistic sensitivity analysis – incremental cost and reduction in the number of adverse reactions (%) S2 vs. S1

and healthcare outcomes of replacing the pentavalent and IPV/OPV vaccines with the hexavalent vaccine for primary immunization, and the impact of expanded program delivery strategies. A key consideration was that the introduction of the hexavalent vaccine, covering diphtheria, tetanus, pertussis, *Haemophilus influenzae* type B, hepatitis B, and polio, administered at 2, 4, and 6 months, would not disrupt other vaccines in the national immunization schedule, such as the monovalent hepatitis B vaccine administered at birth. This approach is consistent with practices observed in other countries, where only the pentavalent and polio vaccines were replaced by the hexavalent vaccine, leaving the rest of the immunization schedule unaffected [14, 15].

Our results indicate that scenarios with the hexavalent vaccine would lead to approximately 10% points higher coverage for the complete infant schedule compared with the pentavalent plus IPV/OPV vaccination schemes (S2 vs. S1 and S4 vs. S3). Although the increase in coverage in scenarios with the hexavalent vaccine came with increased overall costs, largely attributable to vaccine administration, these are partly offset by costs savings associated with logistics and care of ARs and disease cases. This is consistent with the previous cost minimization analysis of the hexavalent vaccine in Peru [16]. Notably, our analysis shows that the hexavalent vaccine would reduce the cost per protected child, suggesting a greater efficiency in use of resources.

In the scenarios involving hexavalent vaccine deployment, the anticipated reduction in ARs with the hexavalent vaccines would be particularly important to vaccine compliance. It is thought that replacement of the pentavalent vaccine, which contains a wP component, with the hexavalent vaccine containing an aP component, would lead to fewer or milder ARs [31]. Mohammed and Atomsa (2013) previously showed that a child is 2.6-times more likely to not complete the vaccination schedule if their parents are concerned about occurrence of ARs [43]. Consistent with this, O'Ryan et al. (2020) found 2.62-fold higher odds of receiving additional doses after the initial dose with the hexavalent vaccine compared with the pentavalent plus polio vaccines [21]. Proximity of the vaccination center or location relative to the vaccinees' residence is also a major factor. In Peru, one of the main reasons for vaccine non-compliance in children is the distance between the vaccination facility and their home [44]. Similarly, a study in Ethiopia showed that a child is 2.7-times more likely to be fully immunized if the vaccination center is less than 30 min away, compared to those living more than 60 min from the health center [45]. In our study, expanding the locations for administration of the pentavalent plus IPV/OPV schedule would increase complete coverage by 3.1% (from 75.1% in S1 to 78.2% in S3) [45]. This is in line with similar studies in India and Pakistan, which reported greater coverage when vaccination locations were expanded to ensure greater proximity to the target population [22, 46].

In a multi-country modelling analysis, Khan et al. (2022) found that use of a pentavalent (DTwP-HB-Hib) vaccine increased global coverage for the third dose of DTP (DTP3) by 3% and both third doses of HB and Hib by 10% compared to when the separate vaccines were used [47]. This is attributed to the simplified pentavalent schedule with fewer injections [47]. It is therefore reasonable to assume that simplification with the hexavalent vaccine in Peru would lead to greater coverage rates than

the pentavalent plus IPV/OPV schedule. Various studies suggest that the hexavalent vaccine is conducive to vaccinee compliance, a major factor in improving timely coverage of the full schedule [21, 48–50]. A study in Germany found that the proportion of children vaccinated at the recommended age against polio increased from 8.3 to 29.7% by replacing IPV and OPV with the hexavalent vaccine [48]. In a US-based study, children receiving the hexavalent vaccine were found to have better punctuality rates, i.e. 2.2-times more likely to complete the vaccination schedule at the recommended age compared to those receiving single-antigen vaccines [49]. The delay in vaccination appeared associated with parental fear of multiple injections simultaneously. A study in Chile, assessing the switch from a pentavalent-polio schedule to the hexavalent regimen in infants, reported greater parental satisfaction and intent to return to the vaccination center to receive the subsequent dose of the vaccine. With administration of the hexavalent vaccine, the parents stated the 'stress-free' experience, ease, convenience, and minimal impact on their daily routine being some of the reasons [21]. A similar study in Malaysia of parental perceptions of switching from a pentavalent schedule plus a stand-alone HB vaccine to a hexavalent regimen found that 95.6% of parents felt that switching could increase vaccination compliance, due to reduced pain and discomfort in their children [50].

Although the current national immunization schedule has excluded the OPV vaccine since 2023, it is anticipated that the results would remain consistent if an IPV-only scheme were to be evaluated. A study conducted in Chile, which has comparable economic and social conditions as Peru, has shown similar outcomes for both IPV-only and IPV + OPV schemes [18]. However, further investigation is needed to address the unique characteristics of the Peruvian context.

There are a number of limitations with our analysis. We used a methodological approach to estimate potential coverage rates with the introduction of the hexavalent vaccine and expanded vaccination delivery modalities considering the scarce evidence available within a context similar to Peru, which may deviate from actual outcomes. Coverage estimation with the hexavalent vaccine was based on parents' reported intention to continue the schedule if their children received a dose of the hexavalent vaccine rather than the pentavalent plus polio vaccines, which may overestimate coverage. To overcome this limitation, two focus groups were conducted, to examine the consistency of the estimates. Moreover, sensitivity analyses supported the robustness of the results. Similarly, coverage under expanded delivery modalities was estimated using a previous study undertaken in India, which only considered the implementation of vaccination centers but did not extend delivery to infants at home. Although this may underestimate the results, the impact should be minor as only a low proportion of children in this scenario in our study (Fig. 1) were considered reachable through this type of intervention (door-to-door and at-home delivery). Another limitation is that the vaccination model developed only considers children up to the age of 24 months for immunization. Yet, the likelihood of catch-up with missed vaccinations in children decreases significantly over time. It was also only possible to model the occurrence of three of the targeted vaccine-preventable diseases, due to limitations in the Peruvian epidemiological surveillance system. The exclusion of some diseases (HB, Hib and tetanus) could underestimate the costs of care for new cases under the pentavalent plus IPV/OPV vaccine scheme. However, we included suspected pertussis (the disease with the highest incidence) to limit underestimation. The health cost estimates assumed medical care under optimal treatment standards, i.e., expected or ideal cost of care according to protocols and clinical practice guidelines established for the country. This means a sufficient number of competent healthcare staff, fully equipped facilities in accordance with current regulations, and receipt of all prescribed medications, which may not reflect actual practice.

In conclusion, introduction of the hexavalent vaccine could result in increased total costs, largely attributable to vaccine administration (cost of vaccines and inoculation), which are partly offset by costs savings associated with logistics and care of ARs and disease cases. The hexavalent vaccine would also lead to a greater efficiency in the use of resources, with lower costs per protected child compared to the baseline pentavalent plus IPV/OPV vaccine scenario. These findings suggest that implementation of the hexavalent vaccine in Peru would also be a more efficient alternative for closing infant vaccination coverage gaps than expanding program delivery of the pentavalent plus IPV/OPV vaccination scheme.

Abbreviations

ARs	Adverse reactions
BCRP	Central Reserve Bank of Peru
DTaP	Diphtheria, tetanus and acellular pertussis
DTwP	Diphtheria, tetanus and whole-cell pertussis
Endes	Demographic and Family Health Survey
GVAP	Global Vaccine Action Plan
HB	Hepatitis B
Hib	*Haemophilus influenzae* type b
INEI	National Institute of Statistics and Informatics
IPV	Inactivated polio vaccine
Minsa	Peruvian Ministry of Health
OPV	Oral polio vaccine
PAHO	Pan American Health Organization
PEN	Peruvian soles
SIR	Susceptible-infected-recovered
USD	US dollars
WHO	World Health Organization

Supplementary Information

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Supplementary Material 1.

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Authors' contributions
JS and AS led the conception and design of the study. MLR, MI and DR contributed to the methods design, data acquisition, analysis and interpretation of coverage rates, ARs and costs estimations. For the incidence of vaccine-preventable diseases, CM developed the epidemiological model, collected the data and performed the analysis. MLR and MI drafted the article and AS revised it critically for important intellectual content. All authors participated in the drafting and revision of this report and approved the final version for publication.

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Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
The data used for the study is publicly available and therefore ethics approval was not required.

Consent for publication
Not applicable.

Competing interests
All authors are employees of Videnza Consultores who were contracted by Sanofi to conduct this research.

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