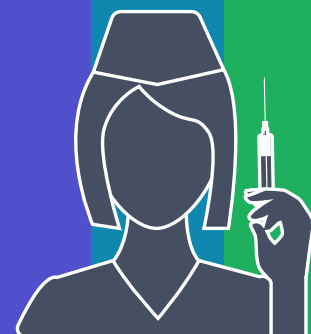


# A compelling public health value proposition for injectable next-generation rotavirus vaccines



While current live, oral rotavirus vaccines (LORVs) are reducing severe diarrhea in all settings, they are not as effective in places with the highest burden. Alternative approaches are in advanced stages of clinical development, including injectable next-generation rotavirus vaccine (iNGRV) candidates. These candidates have the potential to better protect children against disease; be combined with existing routine immunizations; be even more affordable than the current LORVs; and eliminate lingering concerns about safety. However, the relative importance of each of these attributes in driving future uptake of iNGRVs is unclear, even though understanding this would help shape clinical and product development pathways as well as overall commercial interest. Past experiences show that development of an effective vaccine against a World Health Organization-identified priority disease does not automatically result in sufficient commercial interest and country demand. PATH conducted a series of studies to understand the real public health value of iNGRVs to help inform decisions by international agencies, funders, vaccine manufacturers, and countries (Figure 1). This brief provides a comprehensive summary of the results.

## Key takeaways

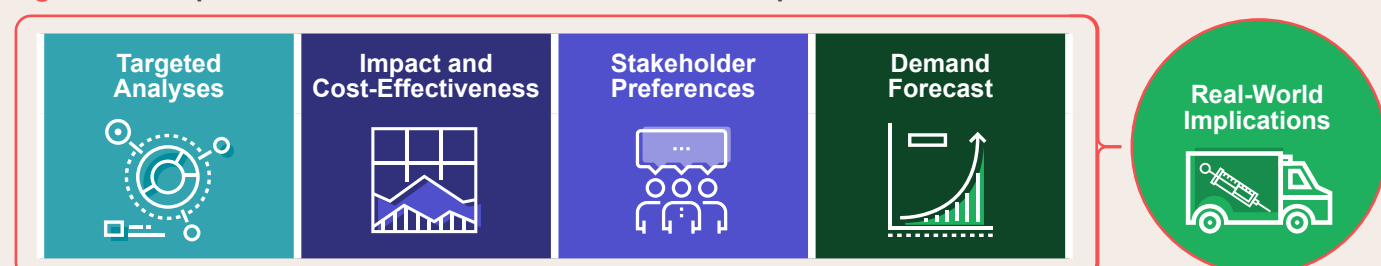
- ◆ Improving the effectiveness of infant rotavirus vaccination, rather than adding an iNGRV booster dose, would offer the most public health benefit.
- ◆ The potential impact, cost-effectiveness, and national stakeholder interest in iNGRVs are each markedly dependent on product profile, especially related to efficacy assumptions and whether it is part of a diphtheria-tetanus-pertussis (DTP)-containing combination vaccine.
- ◆ Demand forecasts suggest a commanding rotavirus vaccine market share for an iNGRV-DTP-containing combination vaccine (iNGRV-DTP), even if an oral NGRV (oNGRV) comes on the market that includes a birth dose and has higher efficacy than current LORVs.
- ◆ These results highlight the potential value of iNGRVs, even if they have similar efficacy to current LORVs, and of accelerating efforts to combine any effective iNGRV in a single formulation with a DTP-containing vaccine.

## Background

Rotavirus causes about one-third of child deaths due to diarrhea globally and millions of hospitalizations each year.<sup>1</sup> Accessing the required care can be challenging in many low- and middle-income countries (LMICs), making rotavirus vaccination critical to saving children's lives. To date, more than 110 countries worldwide have introduced LORVs in their national immunization programs.<sup>2</sup> The globally available LORVs have similar clinical efficacy and are reducing severe disease and deaths where introduced.<sup>3</sup> However, their efficacy is lower in high-burden settings and rotavirus remains a major cause of severe diarrheal disease. Additionally, less than half of the middle-income countries who do not qualify for financial support from Gavi, the Vaccine Alliance, have introduced rotavirus vaccines.<sup>4</sup> **Rotavirus vaccines that are more effective and more convenient to administer could help mitigate the remaining disease burden.**

NGRV approaches currently in late-stage clinical development may address barriers to uptake and access. iNGRV candidates, designed to be given on the same schedule as LORVs, are expected to provide superior efficacy in high-burden settings because they bypass the child's gut. Many scientists think vaccines delivered orally are simply less effective when children are malnourished or have other competing pathogens in their gastrointestinal tract. Even moderately effective iNGRVs may enhance rotavirus vaccine efficacy through co-administration with an LORV or as a booster dose strategy, and they could be available at a lower price. Because iNGRVs are injected, they also have the potential

**Figure 1. Components of the iNGRV Public Health Value Proposition.**



to be combined with other injectable vaccines in the childhood immunization schedule, which would further reduce costs and vaccine delivery concerns. Another alternative approach is oNGRVs that include a dose administered at birth followed by two infant doses, and preliminary evidence from one such candidate still in clinical trials has shown higher efficacy than current LORVs.

Understanding which of these potential advantages—higher efficacy, lower cost, more convenient administration—are the key drivers of stakeholder decision-making can help refine target product profiles to inform vaccine design, clinical evaluation, and donor and vaccine manufacturer investments. Therefore, PATH conducted a series of studies to better understand the full public health value of iNGRVs.<sup>5</sup>

Results



Targeted Analyses

Two targeted analyses aimed to better define the target age group for administering iNGRVs as well as potential future combination options. Regarding target age groups for vaccination, some researchers have proposed focusing on vaccine delivery in young infants while others have suggested that an iNGRV could serve as a booster dose in children already vaccinated with LORVs. PATH conducted a literature review to explore the potential public health impact of a booster dose of iNGRV given at 9 or 12 months of age as a way to counteract the apparent waning in vaccine efficacy seen over time with LORVs in clinical trials. The analyses suggest that **at least 40 percent of the decline in vaccine efficacy calculated from randomized trials is actually due to the increasing natural immunity in the non-vaccinated group due to continued circulation of rotavirus, not diminishing vaccine protection.** Additionally, the literature shows that the vast majority of severe rotavirus disease occurs prior to 9 to 12 months of age when any booster would be administered. Given the marginal incremental value of a booster dose, PATH focused its value proposition efforts on understanding how an iNGRV delivered to young infants can improve protection at that very early age.

Future analyses should focus on delivery of an iNGRV to young infants, either instead of LORVs or alongside them in a co-administration strategy. iNGRV combinations with DTP-pentavalent and DTP-hexavalent vaccines are the most promising to explore in the future.

The second analysis was a market assessment conducted by the firm Linksbridge that focused on vaccine presentation options. It was designed to determine which infant vaccine, in theory, would make the most sense to physically combine with an iNGRV based on its likely market share and longevity. Linksbridge examined trends of DTP-pentavalent, DTP-hexavalent, and inactivated polio vaccine (IPV) use and predicted market shares of each through 2030. The analysis found that the proportion of LMICs giving three doses of standalone IPV in infancy is expected to decrease markedly as polio eradication nears and as hexavalent formulations of DTP containing IPV are more widely adopted. In contrast, **both pentavalent (DTP-Hib-HepB) and hexavalent (DTP-Hib-HepB-IPV) are expected to each account for a substantial market share** over that time period. Given these results, iNGRV combinations with DTP-pentavalent and DTP-hexavalent vaccines are the most promising to explore in the future.



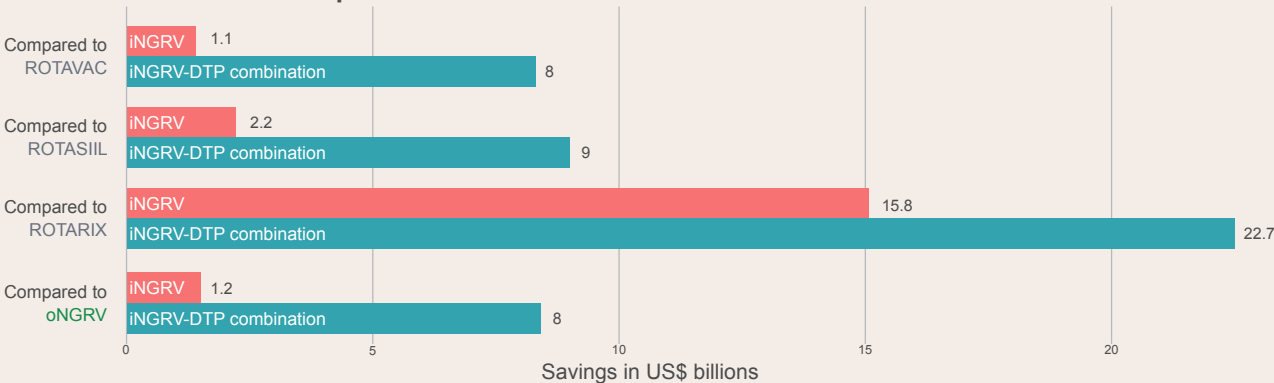
Impact and Cost-Effectiveness

PATH conducted a modeling study to assess the potential impact and cost-effectiveness of different NGRV strategies in 137 LMICs.<sup>6</sup> The study compared hypothetical iNGRVs and oNGRVs with varying levels of efficacy to several currently licensed LORVs to determine scenarios that could bring the highest value. Co-administration strategies were also explored as a way to increase efficacy in case iNGRVs alone do not show superior protection against disease compared to current LORVs. Vaccine attributes such as presentation, cost, and efficacy used in this analysis were modeled on currently available information.

An iNGRV with comparable or superior efficacy to current LORVs is likely to be cost-effective in the majority of LMICs. Strikingly, a vaccine that combines iNGRV with a DTP-containing vaccine into one formulation is also likely cost-effective in all LMICs and is a cost-saving intervention in many.

The results predict that an iNGRV with higher efficacy compared to current LORVs would result in **an additional 200,000 averted rotavirus deaths over 10 years.** Additionally, vaccination programs with a standalone iNGRV would save between US\$1 to 15 billion compared to current LORV vaccination programs over 10 years, with even higher savings with an iNGRV-DTP vaccine (Figure 2).

Figure 2. Vaccination program savings over 10 years in 137 LMICs using iNGRV standalone or iNGRV-DTP combination instead of LORV options.



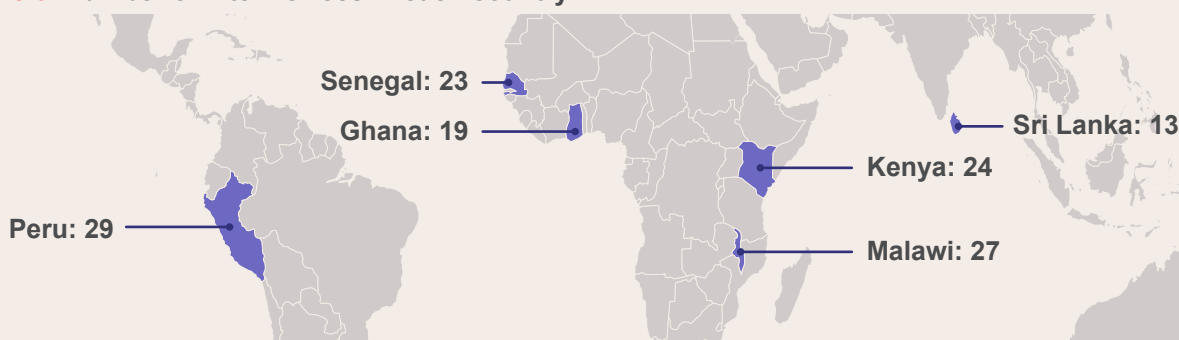
Additionally, the study found that an iNGRV with comparable or superior efficacy to current LORVs is likely to be cost-effective in the majority of LMICs. Strikingly, a vaccine that combines iNGRV with a DTP-containing vaccine into one formulation is also likely cost-effective in all LMICs and is a cost-saving intervention in many. This remains true even if the iNGRV has similar efficacy to current LORVs.



## Stakeholder Preferences

Country-level stakeholders are the ultimate decision-makers on whether to introduce new vaccines into their country's immunization schedules. Yet, vaccine developers do not routinely take their perspectives into account when designing candidate vaccines. PATH led a feasibility and acceptability study in six countries to understand stakeholder preferences for different aspects of hypothetical NGRV products. PATH conducted interviews with **71 national stakeholders and 64 healthcare providers** who administer vaccines in **Ghana, Kenya, Malawi, Peru, Senegal, and Sri Lanka** (Figure 3), as well as interviews with **20 global stakeholders** to gather international perspectives.<sup>7,8</sup> Through a series of comparisons, interviewees were asked to indicate their preference for different rotavirus vaccine options with varying attributes and explain the reasons for their choice.

**Figure 3. Number of interviewees in each country.**



For national stakeholders, vaccine delivery considerations were the most important preference drivers, followed by improved efficacy and lower cost. Nearly half of national stakeholders interviewed preferred a higher efficacy, standalone iNGRV over existing LORVs despite reservations about adding new injections to the vaccination schedule. There was also moderate interest among national stakeholders in co-administration of a standalone iNGRV with existing LORVs to achieve higher overall rotavirus protection, especially in countries with a high rotavirus disease burden. Most strikingly, **an iNGRV-DTP vaccine was by far the most preferred approach among national stakeholders over all oral options including a high-efficacy, neonatal oNGRV due to the ease of delivery and lower cost.** Global and national stakeholders generally had similar perspectives, however national stakeholders expressed more interest than global stakeholders in a standalone iNGRV and LORV-iNGRV co-administration schedules.

Healthcare providers were not given information about efficacy or price differences between the vaccine options in their interviews in order to focus on delivery concerns. Healthcare providers strongly preferred an oral vaccine over an injectable, but several noted limitations of oral administration due to babies spitting up the vaccine and concerns about complete dosing. The majority of healthcare providers had no concerns about an iNGRV-DTP combination vaccine, and even expressed enthusiasm as it would free up cold chain storage and eliminate LORV in the visit schedule.

These results demonstrate that an iNGRV may be a strongly preferred alternative to current LORVs even if its efficacy is no better, as long as it is part of a DTP-combination vaccine. A standalone iNGRV that averts more child deaths and hospitalizations and is less costly to procure may also be preferred by many. In addition, a highly effective neonatal oNGRV would be preferred over a highly effective standalone iNGRV, but not over a highly effective iNGRV-DTP vaccine.

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## Demand Forecast

Linksbridge, in collaboration with PATH, conducted a demand forecast analysis to predict the market share of iNGRVs based on different product profiles and presentations in 107 Gavi-eligible countries and non-Gavi middle-income countries five years after product launch. The model incorporated the preferences identified in PATH's feasibility and acceptability study and were extrapolated to a large group of countries. The forecast also assumed that introduction of an iNGRV in India would be dependent on a local producer. The results predict that an iNGRV-DTP vaccine with efficacy equal to current LORVs would command the largest (84 percent) market share by 2030, with demand reaching approximately 99 million courses for Gavi countries and non-Gavi middle-income countries. Demand for a high-efficacy, standalone iNGRV could reach 50 million courses by 2030 for Gavi countries plus non-Gavi middle-income countries if a high efficacy oNGRV is not also on the market. If co-administered with LORV, an iNGRV-DTP vaccine could command two-thirds of the market, with demand reaching 79 million courses in Gavi countries and non-Gavi middle-income countries by 2030. Taken together, **there is a potentially substantial demand for an iNGRV, whether efficacy is higher than current LORVs or only similar, particularly if it could be integrated with a DTP-containing combination vaccine.**



## Conclusions and real-world implications

These results demonstrate significant themes in the public health value proposition for iNGRVs. Improving infant rotavirus vaccination, rather than focusing on a booster, would offer the most public health benefit. **The potential impact, cost-effectiveness, and national stakeholder interest in iNGRVs are markedly dependent on the product profile**, especially related to efficacy assumptions and whether it is part of a DTP-containing combination vaccine. This combination approach was preferred by the vast majority of country stakeholders, was cost-effective in all LMICs and cost-saving in many, and was projected to dominate the rotavirus vaccine market should it become available in the future. Donors and vaccine developers should invest in accelerating the development of iNGRV-DTP vaccines, and investments should seek to involve multiple manufacturers to avoid supply constraints and monopolies. Additionally, there appears to be some interest in a high-efficacy, standalone iNGRV, though this decreases if a high-efficacy oNGRV is also available. While an iNGRV with efficacy superior to current LORVs is clearly preferable, these results also suggest that an iNGRV with clinical efficacy similar to current LORVs may also have a compelling public health value proposition, particularly if combined with a DTP-containing combination vaccine.

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These comprehensive findings may help to steer donor and vaccine development investments toward the most preferred and cost-effective formulations of iNGRVs, as well as assist in future clinical trial designs and endpoints. They also highlight the importance of structured consultations with a variety of country stakeholders, not just global experts, regarding vaccine preferences. **While it is too early for countries to start considering introduction of NGRVs, the results from this public health value proposition demonstrate that there would likely be a substantial market for iNGRVs.** Global and national rotavirus vaccine policy recommendations, as well as Gavi's strategic planning efforts should be informed by the strong country preferences for alternatives to the currently available LORVs, projections of enhanced cost-effectiveness of most iNGRV candidate formulations, and the high interest across a variety of stakeholders in the integration of rotavirus protection into DTP-containing combination vaccines. The comprehensive findings from this iNGRV value proposition may also be applicable to other new vaccines in development.

## Recommendations

- ◆ Include input of country stakeholders, not just global experts, in the vaccine development process so their vaccine preferences can be considered.
- ◆ Donors and vaccine developers should consider investments to accelerate the development of DTP-pentavalent and DTP-hexavalent vaccines combined with iNGRVs.
- ◆ Future rotavirus vaccine policy recommendations should be informed by the substantial cost-effectiveness and incremental health impact of alternatives to the currently available LORVs, as well as by the product preferences of national and local stakeholders.

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