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Gap Analysis of Rotavirus Vaccine Impact Evaluations in Settings of Routine Use

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Executive Summary

SCOPE OF ANALYSIS: This report describes the global state of rotavirus vaccine (RVV) use and describes the availability of RVV impact evidence as of November 3, 2016 in countries routinely using RVV. The ***amount of evidence*** that is published or being collected on RVV impact is described and key gaps are identified.

CHANGES FROM PREVIOUS REPORT: In addition to updating data on RVV introductions and number/type of impact studies, this report includes several new sections or analyses:

- Previous reports used ***study*** as the unit of analyses, and summarized the availability of impact evidence at this level. Our impact study database is under redesign and the definition and previous designation of individual studies are undergoing review to best reflect the unique sources of impact evidence. Thus for this report, ***country*** is the unit of analysis as it is the most reliable and accurate unit of analysis.
- Each section now highlights key opportunities from Gavi's perspective, in green "opportunities" boxes
- We have added new, in-depth analyses of:
    - Impact study gaps by Gavi transition status
    - Economic impact study gaps, including by type of economic analyses
    - Future opportunities for impact studies, beginning with an evaluation of existing WHO surveillance infrastructure

KEY STRATEGIC OPPORTUNITIES: Our analyses revealed the following strategic opportunities for Gavi and partners:

- Although there are many ongoing health impact studies that will provide useful information for Gavi graduating countries, the existing key health impact gaps will not likely be addressed in time to be meaningful for certain country-level decision makers in Gavi countries facing imminent post-graduation sustainability decisions. In these cases, supplemental communications and advocacy support emphasizing regional health impact evidence or alternate types of evidence (e.g. pre-vaccine disease burden data) should be an integral part of Gavi strategy.
- Local economic impact evidence may be especially important for countries facing Gavi graduation and worthy of proximal support since the biggest concerns for these countries are economics. The known existing key gaps in local economic impact evidence may be addressed in time to be meaningful for certain country-level decision makers in Gavi countries facing imminent post-graduation sustainability decisions. An assessment of unknown needs and whether the forthcoming information will be sufficient should be made as economic impact evidence is often relatively cheap, quick and easy to produce (compared to health impact evidence).
- To adequately understand the feasibility of using existing WHO surveillance sites for potential impact studies in countries planning to introduce, a significant amount of additional consideration is required. The existing sites and pre-introduction data collected should be evaluated according to a set of standardized quality criteria by a group consisting of a) those familiar with RVV impact evaluations and b) those familiar with the surveillance networks themselves.
    - In particular, sites in Asia and large African countries (e.g. Nigeria and DRC) should be prioritized given the lack of data and imminent introductions there.

Introduction: RVV Use and Impact Evaluations

Monitoring the health and economic impact of a vaccine in a routine use program is considered a core element of vaccine program management and disease control monitoring. Rotavirus vaccine (RVV) impact studies are essential for understanding the effects of the global rollout of RVV that have taken place over the past 10 years. These studies generate the ***evidence*** that can answer key scientific and policy questions about optimizing vaccine use in the prevention of childhood diarrheal disease and mortality.

The uptake of RVV since first licensure in 2006 has resulted in a massive population-level change in immunity; thus it is important to monitor changes in the epidemiology of rotavirus disease specifically, and diarrheal disease generally, along with monitoring for waning of protection and for overall risk and benefit. Two RVV products are currently WHO prequalified, both of which are live, attenuated formulas that are administered orally: RV1 (Rotarix), is a monovalent product made from the G1P[8] strain; and RV5 (RotaTeq), is a pentavalent product containing the G1, G2, G3, G4 and P[8] genotypes. Over 90% of all circulating strains belong to a genotype contained in these two vaccines and both vaccines are broadly cross-protective, even against genotypes not included in the vaccine formulation (that is, it is not necessary to include all genotypes in the vaccines for them to be highly effective); however because the currently licensed RVVs target some, but not all rotavirus genotypes it is critical to monitor for any genetic changes that may occur over time. Furthermore, because the RVVs have shown lower efficacy in high-burden settings than in low-burden settings, ongoing evaluations of rotavirus vaccine impact and effectiveness are especially vital to better understand this phenomenon and inform actions to improve vaccine performance.

In addition to answering ongoing scientific questions described above, RVV impact studies are critical to inform policy decisions. Data on vaccine impact can aid in advocacy efforts at the country level to assure that RVV is considered for investment. In countries that have not yet introduced the vaccine and in countries using RVV that are approaching or entering Gavi graduation (which requires countries to make an increased financial commitment to sustain existing vaccine programs), impact evidence can be a key driver of national and subnational policy. Other contexts where impact data may be relevant include decision making about product choice (i.e. RV1 versus RV5), in program optimization after introduction, in strategy development on new and modified RVVs, and in prioritization of other diarrheal disease control and public health measures.

However, the capacity to undertake vaccine impact monitoring is absent in some countries and insufficient in others, leaving many gaps in vaccine impact evidence. From a global or regional perspective, not every country needs to have an impact study for the technical and policy communities to have credible insights into the impact of RVV. However, there need to be studies in countries representing different epidemiological, political and geographic settings to inform global and regional policies and in countries with similar characteristics in the absence of local data.

In this context, RVV impact studies from low- and middle-income countries (LMICs), especially those with high rotavirus disease burden, are considered important so that the evidence base for introducing and sustaining rotavirus immunization in the highest disease burden settings is robust. We have chosen Gavi status as the stratification for all analyses that follow to highlight the current status and gaps in impact evaluations from the lowest-income strata countries. For the purpose of this analysis, Gavi countries were defined as the original 73 nations that were determined to be eligible for Gavi financial support for vaccine procurement regardless of their current transition status.

This report aims to describe and evaluate the ***availability*** of RVV impact evaluation data by reporting the number of countries with impact studies and key information on RVV products and outcomes assessed in these evaluations. This gap analysis on availability of information is useful for prioritizing the future research agenda, as well as identifying where advocacy resources using alternative messaging/data sources may need to be directed in the absence of local impact evidence. Importantly, however, *this gap analysis does not evaluate the quality or quantity of data from each country for each outcome, nor the actual impact results from the studies.* The availability of data does not exactly correlate with the ability to determine rotavirus impact from such data. Some studies may be underpowered to provide robust analyses for one or more outcomes, or comparators; thus, it is important in interpreting the results below to remember that our analysis is inclusive of any published or ongoing impact studies, regardless of quality.

We begin by providing background information about global RVV introductions to date and the products currently in use, using data from IVAC's VIEW-Hub database (www.VIEW-hub.org). Then, our analysis of gaps in impact data is broken into two sections:

- **The *current* state of vaccine impact evaluations**: This describes the availability of published and ongoing health and economic impact evaluations (and corresponding gaps) in countries that have already introduced RVV, again using data compiled in the VIEW-hub impact study database. Like previous reports, we describe availability and corresponding gaps in impact evaluations by region, product/dosing schedule and outcomes measured. Unlike previous reports, in this iteration we have broken down the available analyses by type of impact evaluation; health impact studies are now separate from economic impact studies, allowing for additional descriptive variables to be reported for economic studies, including type of economic analysis. Additionally, because these countries are not using impact data to inform introduction decisions but are more likely to face policy questions about program sustainability, we have added analyses stratified by Gavi transition status to this section, to provide context on the *urgency* of the need for impact evaluations in the near future.
- ***Future* opportunities to generate impact evidence**: This section describes existing infrastructure that could be leveraged to conduct impact evaluations in countries that have not yet introduced the vaccine. This is the first TASC gap analysis report where the feasibility of additional impact studies is evaluated, and we begin by using data provided by the World Health Organization (WHO) about existing surveillance sites in the Global Rotavirus Laboratory Network (GRLN).

Methods

It is important to note that the list of studies catalogued in this report is not yet comprehensive, but does include the most widely cited publications in the literature and most current studies, including ongoing studies not yet published.

RVV impact studies included in this analysis were gathered from three main **sources**:

1) Publications on vaccine impact cited in *Rotavirus: common, severe, devastating, preventable,* a white paper published by the Rotavirus Organization of Technical Allies (ROTA) Council that provides a comprehensive source of information on rotavirus disease and vaccines through 2015.[1]
2) Literature searches of published studies performed as part of the Gavi-funded Targeted Assessment Study Coordination and Communication project with particular attention on the period post ROTA Council white paper citations (May 1, 2015 to September 30, 2016)
3) Communication with key impact study investigators and funders, including the United States Centers for Disease Control and Prevention (CDC), Gavi, and the Bill and Melinda Gates Foundation, which identified *ongoing* RVV impact studies that do not yet have published results.

Included in our search terms were concepts related to both economic and health impact studies. Importantly, economic evaluations included all cost and economic assessments of rotavirus disease and rotavirus vaccines. Thus, this section includes both impact assessments using empiric data and studies evaluating potential economic impact of vaccine introduction (i.e. projected or modeled data).

We are currently updating our literature database using the above search strategy to identify articles published between 2006, when the first RVV was licensed, and 2015, that may not have been captured in the ROTA Council whitepaper for incorporation into the next iteration of this report.

Published and ongoing RVV impact studies were included in this analysis if they met one of the following **inclusion criteria**:

- They were conducted in a country that was using RVV in its NIP, either nationally or sub-nationally, at the time of the evaluation
- Study is evaluating the economic impact of RVV (regardless of the country's introduction status). This includes predictive/modeled economic studies conducted prior to vaccine introduction, as well as empirical economic studies conducted post-RVV introduction.

Ongoing studies designed to measure RVV health (as opposed to economic) impact in settings where the vaccine has not yet been introduced into the NIP are excluded from the VIEW-hub impact study database, and therefore are also excluded from this report. However, these studies will be included in future reports once the vaccine has been officially introduced, and may also be used in future analyses of additional non-surveillance infrastructure as described in the "Future Steps" section of this report. We are aware that pre-introduction data is being collected in Bangladesh, Nepal, Pakistan, and Viet Nam.

[1] ROTA Council. *White Paper – Rotavirus: Common, Severe, Devastating, Preventable*, 2016 http://rotacouncil.org/resources/Rotavirus-Severe-Preventable-White-Paper-Full.pdf

Unit of Analysis

This report summarizes and characterizes the ***countries*** evaluating RVV impact.

Previous reports used ***study*** as the unit of analyses, and summarized the availability of impact evidence at this level. Our impact study database is under redesign and the definition and previous designation of individual studies are undergoing review to best reflect the unique sources of impact evidence. Thus for this report, ***country*** is the most reliable and accurate unit of analysis.

Context: RVV Introductions and Use

OVERVIEW

- 45% (88) of 194 countries have introduced RVV into routine immunization programs since licensure in 2006 (this includes both national and sub-national introductions)
- A greater proportion of Gavi countries (55%, 40/73) have introduced RVV than non-Gavi countries (40%, 48/121),
- 25% (26) of the 106 countries that have not yet introduced RVV are planning to introduce by 2020
  - 14 of these are Gavi-countries, representing 19% of Gavi countries
- The rate of RVV uptake in LMIC has improved significantly since Gavi began supporting RVV in AFR and Asia in 2009, although RVV introductions in LMIC initially lagged behind those in HIC
- AFR is the region with the most countries using RVV (n=30; 64%)
- RV1 is the predominant product being used (71% of all RVV-using countries) and is being used in all regions; RV5 is used in 19% of RVV-using countries and 8% use both
- AFR and AMR are the only regions with Gavi countries using RV5. All regions have at least 1 country using RV1

KEY REMAINING GAPS

- 67% (90.9 million) of the world's infants do not currently have access to rotavirus vaccines
  - Most of these infants (70%, 56.2 million) are living in Gavi countries
- 14 Gavi countries (80 countries globally) have not yet made a decision to introduce rotavirus
- Introduction of rotavirus vaccine in LMICs (largely driven by Gavi support) has advanced more quickly in the Africa region than in the Asia region, hence there are fewer opportunities to evaluate impact there
  - 38 (81%) of 47 AFR countries, and 19 (I count 10) (50%) of 38 WPR & SEAR countries use rotavirus vaccine in their NIP

OPPORTUNITIES

- Large birth cohort countries who have not yet introduced or are planning introduction (e.g. Indonesia, Nigeria) represent possible opportunities to generate meaningful impact data
- Middle income countries in SEAR/WPR and EUR need additional support for RVV decision-making including understanding health and economic impact evidence from other countries in region

Availability of data on impact of RVV in routine use is dependent on vaccine introduction and rollout (we define impact studies as those performed in settings of routine vaccine use). The global rollout of RVVs into NIPs started after initial licensure in the U.S. in 2006 and uptake of the vaccine has grown steadily. Introductions occurred first in high-income countries primarily in the European and North American regions, followed by Gavi-supported countries in the Africa region. Gavi RVV support began in 2006 for countries in the Americas and Europe and was extended to all 73 Gavi countries in 2009 when results from the RVV efficacy trials from those regions became available.

Low- and middle-income countries (both Gavi and non-Gavi) in the Asia region began introducing later than in Africa; therefore, a lag in the availability of RVV impact evidence from this area is expected. Furthermore, because there are so few Gavi countries in Asia, the opportunities for RVV impact are more limited than in Africa, enhancing the importance of assuring that RVV impact studies are well planned and coordinated in this region.

RVV Introductions: The Global Picture

Currently, 88 countries have introduced RVV, either nationally or sub nationally – 40 of which are Gavi countries (**Figure 1** and **Table 1**). However, uptake of the vaccine is quite heterogeneous across regions. The speed of introduction of RVV in lower-income countries has been driven by Sub-Saharan Africa; with 30 (64%) of 47 AFR countries now using RVV in their NIPs compared to just 10 (26%) of the 38 SEAR and WPR countries in Asia. Globally, product choice is dominated by RV1, which is used in 63 (71%) of RVV-using countries as opposed to 17 (19%) using RV5.

Figure 1: Global introductions of RVV

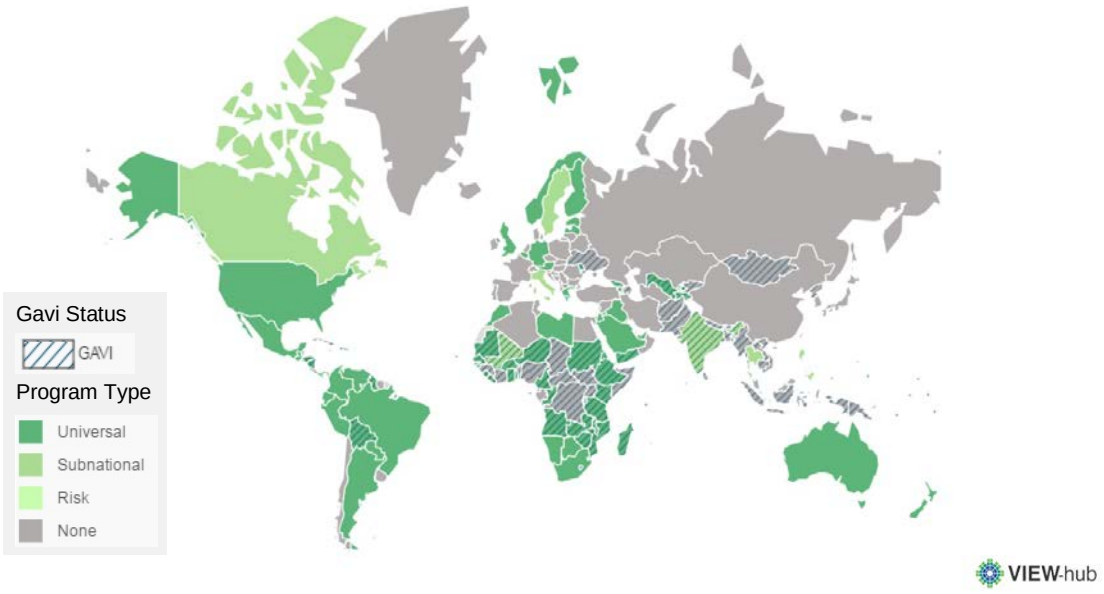


Table 1: Number of countries using RVV in NIP, by WHO region and Gavi status

WHO Region	# Countries in Region		# Countries (% in Region) with Routine RVV Use		# Countries using RVV (% of Introduced)				
					RV1		RV5		RV1 & RV5
	Gavi	Total	Gavi	Total	Gavi	Total	Gavi	Total	Total*
AFR	37	47	25 (67%)	30 (64%)	21 (84%)	26 (87)	4 (16%)	4 (13%)	0
AMR	6	35	5 (83%)	19 (54%)	3 (60%)	15 (79%)	2 (40%)	3 (16%)	1 (5%)
EMR	6	21	3 (50%)	11 (52%)	3 (100%)	8 (73%)	0	3 (27%)	0
EUR	8	53	5 (63%)	18 (34%)	5 (100%)	9 (50%)	0	4 (22%)	5 (28%)
SEAR	9	11	1** (11%)	2** (18%)	1 (100%)	1 (100%)	0	0	0
WPR	7	27	1 (14%)	8 (30%)	1 (100%)	3 (38%)	0	3 (38%)	2 (25%)
Global	73	194	40 (55%)	88 (45%)	34 (85%)	63 (71%)	6 (15%)	17 (19%)	8 (9%)

** No Gavi country uses both RV1 and RV5.*
***Includes India, which uses neither WHO prequalified product, but instead its own indigenous product.*
Note: See Appendix B for the complete list of countries' RVV introduction status, by region.

Forty (55%) of the 73 Gavi countries have introduced RVV. The proportion of Gavi countries using RV1 and using RV5 is similar to the proportions among non-Gavi countries. RV1 is the predominant product being used (71% of all RVV-using countries) and is being used in all regions; RV5 is used in 19% of RVV-using countries and 8% use both. Of the Gavi using countries, 34 (85%) are using RV1, 6 (15%) are using RV5, and none use both. AFR and AMR are the only regions with Gavi countries using RV5; all regions have at least 1 Gavi country using RV1.

RVV Introductions: Current Gaps

Although rapid progress for RVV introduction is shown by counting the number of countries with RVV in their routine schedule, perhaps more relevant is an analysis of the children who have access to these vaccines. *Most* (67%, *90.0 million) of the world's 135.3 million infants currently lack access to the vaccine because they live in one of the 106 countries that have not yet introduced RVV.* Of these, 61.5 million (77%) live in Gavi countries. This is driven by large birth cohort countries (e.g. India, Indonesia) that contribute substantially to the total number of infants eligible for vaccinations that have not introduced RVV. An additional 9.5 million (7% of the world's infant cohort) live in countries that have RVV in their NIP but are not reached by current routine immunization strategies, as evidenced by incomplete DTP3 coverage.

Globally, there are 26 countries that have announced plans to introduce RVV into their NIP in the coming years, 14 (54%) of which are Gavi countries. The remaining 80 have not yet made a decision about RVV introduction (**Table 2**).

Table 2: Introduction plans by 2020 among countries that have not introduced RVV, with Gavi countries highlighted in gold

WHO Region	Countries Planning to Introduce by 2020 (n=26)		Countries With No plans to introduce by 2020 (n=80)	
AFR	Benin Central African Republic DR Congo Cote D'Ivoire Gabon Lesotho	Nigeria Sao Tome and Principe Seychelles South Sudan Uganda	Algeria Cape Verde Chad Comoros Equatorial Guinea Guinea	
AMR	Bahamas		Antigua and Barbuda Barbados Belize Chile Costa Rica Cuba Dominica Grenada	Jamaica Saint Kitts and Nevis Saint Lucia Saint Vincent and the Grenadines Suriname Trinidad and Tobago Uruguay
EMR	Afghanistan Iran, Islamic Republic of Kuwait Oman Pakistan		Egypt Lebanon Somalia Syrian Arab Republic Tunisia	
EUR	Albania Kyrgyzstan		Andorra Azerbaijan Belarus Bosnia and Herzegovina Bulgaria Croatia Cyprus Czech Republic Denmark France Hungary Iceland Ireland Kazakhstan Lithuania Macedonia	Malta Monaco Montenegro Netherlands Poland Portugal Romania Russian Federation San Marino Serbia Slovakia Slovenia Switzerland Turkey Turkmenistan Ukraine
SEAR	Bangladesh Indonesia Myanmar	Sri Lanka Timor-Leste	Bhutan Korea, DRP	Maldives Nepal
WPR	Mongolia Viet Nam		Brunei Darussalam Cambodia China Cook Islands Korea, Republic of Lao PDR Malaysia	Nauru Niue Papua New Guinea Samoa Solomon Islands Tonga Tuvalu Vanuatu

Gold highlight denotes Gavi countries.

Current State: Health Impact Studies in Countries Using RVV

RVV Health Impact Study Gaps by Region

OVERVIEW

- Every WHO region has at least 1 country with an ongoing or published RVV impact evaluation, but 3 regions (EMR, SEAR and WPR) have no Gavi countries with an impact evaluation.
- 45% of Gavi countries and 45% of non-Gavi countries using RVV have an impact study ongoing or published impact study.

KEY REMAINING GAPS

- The limited number of countries with health impact evaluations in Asia (n=4 in SEAR and WPR) is partially due to the fact that only 10 countries (2 Gavi) in these regions have introduced RVV into their NIPs.
    - However, this limited availability of RVV impact data in these regions may in turn impede the pace of country decision making for introduction.

OPPORTUNITIES

- It's critical that potential RVV health impact studies in Asia are planned well in advance of vaccine introduction;; countries in Asia planning introductions should be considered for potential studies *now* (see "Future Opportunities" section below).
- Ongoing impact evaluations in India should be monitored closely as potential sources for critical evidence that could influence regional introductions in other countries, which are currently lagging.
    - Of note: there are unconfirmed reports that national surveillance may no longer continue to receive government funding; if so, this represents a major risk to one of the few potential sources of quality impact data in the region.

Understanding whether there are epidemiologic differences in rotavirus disease or vaccine program impact between regions is key to assessing whether the existing portfolio of evidence is generalizable. All WHO regions have at least one country that is undertaking a RVV impact study[2] but the number and proportion vary substantially by region (**Table 3**).

Table 3: Availability of RVV impact studies evaluating health outcomes among countries using RVV, by WHO region and Gavi status

WHO Region	# Countries in Region		# Countries (% in Region) with Routine RVV Use		# Countries (% of RVV-using Countries) in Region with ≥1 RVV Impact Study	
	Gavi	Total	Gavi	Total	Gavi	Total
AFR	37	47	25 (67%)	30 (64%)	11 (44%)	13 (43%)
AMR	6	35	5 (83%)	19 (54%)	3 (60%)	11 (58%)
EMR	6	21	3 (50%)	11 (52%)	0 (0%)	1 (9%)
EUR	8	53	5 (63%)	18 (34%)	3 (60%)	12 (67%)
SEAR	9	11	1 (11%)	2 (18%)	1 (100%)	2 (100%)
WPR	7	27	1 (14%)	8 (30%)	0 (0%)	2 (25%)
Global	**73**	**194**	40 (55%)	88 (45%)	**18 (45%)**	**41 (47%)**

Not surprisingly, the region with the most impact evaluations is the same region with the greatest number of countries using RVV (AFR, n=13). The Americas (AMR) and Europe (EUR), where RVV

[2] This report summarizes the number of ***countries*** evaluating RVV impact rather than ***studies***. Our impact study database is under redesign and the definition and previous designation of individual studies are undergoing review to best reflect the unique sources of impact evidence. Thus for this report, country is the most reliable and accurate unit of analysis.

was first introduced in 2006, have the greatest proportion of RVV-using countries with impact evaluations (58% and 67%, respectively). Although Gavi support for the vaccine did not begin until 2009, the proportion of RVV-using countries with an impact evaluation is about the same for Gavi countries as for all countries (45% vs 47%, respectively). The regions with fewest impact studies, Eastern Mediterranean (EMR), South-East Asia (SEAR) and Western Pacific Regions (WPR), also have the fewest countries that have introduced RVV.

In Asia, only four countries are evaluating RVV impact (India, Thailand, Australia and Fiji). The epidemiologic, health system, political, and economic characteristics of these countries is not representative of SEAR and WPR regions as a whole, and the introduction strategies are also heterogeneous (two countries have introduced sub-nationally only, and India is using its own domestically produced product), limiting the generalizability of these health impact studies.

In SEAR, only Thailand and India have introduced RVV (although Thailand's was a pilot project that has concluded), but there are impact evaluations in both countries. We have recently[3] been made aware of several studies being planned in India that will have regionally important health impact results. Gavi and partners should monitor the progress of these evaluations closely. We have received unconfirmed reports that national rotavirus surveillance, which forms the foundation of these studies, may not continue to be government-funded in future years. If this is true, it represents a major risk for one of the few and certainly the largest potential sources of meaningful impact data in the region; thus this is an important potential opportunity for Gavi intervention.

Of 8 WPR countries that have introduced RVV, only 2 evaluate impact (Australia and Fiji). Working from the assumption that impact data is a driver of country introduction decision-making, the paucity of impact evidence in Asia may feed a vicious cycle, where lack of regional health impact evidence slows down country RVV decision making further, limiting the opportunities to generate impact data in routine use settings. Considering that Gavi support for RVV was available to countries in Asia and Africa simultaneously, the lag in introductions in Asia reflects delayed decision-making rather than lack of financial support from Gavi.

To accelerate decision-making on RVV in Asia, emphasis on other key evidence, including modeled assessments of potential vaccine impact (both health and economic) and health impact evidence from countries in the region, including those with RVV in use only in the private market (as opposed to introduced in the NIP) may be helpful. We are aware of 2 countries, Japan and Singapore, with impact evidence of this kind in Asia; however, the impact in such high income countries is not likely generalizable to LMICs.

The value of strengthening the infrastructure to generate RVV impact evidence in Asia in countries not yet using RVV should be assessed where such evidence may be important, to assure that once introductions occur, these opportunities for conducting robust impact studies are not lost. The "Future Opportunities" section has a preliminary discussion of existing infrastructure that may be leveraged to assess impact in countries planning to introduce.

EMR is notable for having 11 countries using RVV, but only one (Morocco) country evaluating health impact. This demonstrates that factors other than impact evaluations can drive decision-making. Determining what those factors are and translating them into actionable insights may aid decision making in other countries.

[3] Because we have only recently learned of an ongoing health impact study in India and do not have thorough details yet, the maps and select tables displaying health impact studies do not include India. This information will be updated in future reports.

RVV Health Impact Study Gaps by Gavi Transition Status

OVERVIEW

- Of the 11 Gavi countries using RVV that are already fully self-financing or will have to fully self-finance within 5 years, only 6 (55%) have health impact studies
- We are aware that pre-introduction data is being collected in Bangladesh, Nepal, Pakistan, and Viet Nam

KEY REMAINING GAPS

- Neither of the two African countries (Angola and DRC) that will have to fully self-finance within the next five years has local, in-country RVV impact evidence (e.g. burden data, economic impact evidence, etc.) to support sustainability decisions
    - Angola and DRC will have to rely on impact data from the 13 other countries in the region with health impact studies, and perhaps other types of evidence, to support decision making for sustaining the RVV program

OPPORTUNITIES

- Countries approaching Gavi graduation without local impact data may require enhanced in-country communications and advocacy efforts to support program sustainability; such efforts will need to be proactive and creative in using regional impact data and/or alternate types of supportive evidence.
- Conducting additional health impact evaluations in French-speaking West African countries may address the potential language-based barriers for generalizing studies from the AFR region as a whole; alternatively, active engagement via enhanced communications/advocacy in French-speaking countries may be beneficial.

Because it is not practical or feasible for every RVV-using country to evaluate vaccine impact, further prioritization for impact study investments is needed. For Gavi countries, one metric to assess the importance of impact data is the timeline for self-financing in transition (**Table 4**).

Countries that have entered transition phases require increased self-financing above the $0.20 per dose required during the Initial Self-Financing phase. As each country transitions through the Preparatory and Accelerated Transition phases, these country-shouldered costs will continue to increase annually until each country is responsible for the full cost of the vaccine (currently as high as $10.50 per fully immunized child – which is nearly 18 times the country's initial Gavi-funded cost). Although the timeline for reaching the Fully Self-Financing phase is not entirely calendar-dependent (GNI is the driving factor for the transition between Preparatory and Accelerated Transition Phases), 21 countries will be facing fully self-financing within the next 5-6 years. Only 8 (38%) of these have an RVV health impact evaluation. Countries without local health impact data will be left facing sustainability decisions using only a) regional health impact data, or b) non-impact data (e.g., pre-RVV disease burden estimates, economic impact evaluations, etc.) where available. Given the timelines for Gavi graduation, it is unlikely that quality local health impact data could be obtained in time to inform sustainability decisions. Thus, for countries facing graduation without local health impact data, resources should be directed towards enhanced in-country communications and advocacy activities aimed at sustaining these critical programs.

There are 5 African counties (Angola, Cameroon, DRC, Mauritania and Senegal) that are in sight of graduation without impact studies. Senegal and Mauritania are French speaking countries in West Africa, where there tends to be a lack of influence from English- to French-language settings - so impact evaluations in The Gambia and Ghana may have little value. However, there are two French-speaking countries (Burkina Faso and Mali) with impact evaluations, so these studies may provide sufficient relevant evidence for decision makers in Senegal and Mauritania. Any remaining gaps in

French-language evidence could also be filled with communications and advocacy efforts aimed at translating/promoting existing English-language regional evidence.

In SEAR and WPR, two Gavi countries (India and Kiribati) are in sight of graduation, with Kiribati reaching full self-financing at least one year before India. As described above, there is limited regional evidence to inform sustainability decisions and health impact evidence from India will be an important addition of data from the region.

Table 4: Availability of RVV health impact, by WHO region and Gavi transition status

Region	Non-Gavi countries using RVV	Gavi countries using RVV, by 2016 transition status			
		Initial Self Financing (could reach full self-financing within **7 years** at earliest)	**Preparatory Transition** (*could* reach full self-financing within **6 years** at earliest)	**Accelerated Transition** (*must* reach full self-financing within **5 years**)	**Full self-financing**
AFR	Botswana South Africa Mauritius Namibia Swaziland	Burkina Faso Gambia Malawi Mali Mozambique Rwanda Tanzania Zimbabwe Burundi Eritrea Ethiopia Guinea-Bissau Liberia Madagascar Niger Sierra Leone Togo	Ghana Kenya Zambia Cameroon Mauritania Senegal	Angola DRC	
AMR	Brazil Canada Colombia El Salvador Guatemala Mexico Panama Peru United States Argentina Dominican Republic Ecuador Paraguay Venezuela	Haiti		Bolivia Nicaragua Guyana	Honduras
EMR	Morocco Bahrain Iraq Jordan Libya Qatar Saudi Arabia United Arab Emirates		Djibouti Sudan Yemen		
EUR	Austria Belgium Finland Germany Greece Israel Italy Norway Spain* United Kingdom Estonia Latvia Luxembourg Sweden		Tajikistan	Armenia Moldova Uzbekistan Georgia	
SEAR	Thailand		India		
WPR	Australia Fiji Japan* Singapore* Marshall Islands Micronesia New Zealand Palau Philippines			Kiribati	

Green text indicates countries with a published or ongoing RVV impact study.
**Spain, Japan, and Singapore have not introduced RVV into their NIP; however, each country has one or more impact studies evaluating substantial private market use*

RVV Impact Study Gaps by Product and Outcomes Evaluated

OVERVIEW

- More health impact evidence is being generated for RV1 than RV5 because of greater use of RV1 (32 RV1-using countries vs 14 RV5-using countries), but the proportion of RVV-using countries evaluating impact is greater for RV5-using countries (82% of RV5 using countries vs 51% of RV1 using countries)
- Both RV1 and RV5 are evaluated in Gavi countries (and in Non-Gavi countries).
- Most (93%, 37/40) countries evaluating impact assess all-cause and/or rotavirus specific diarrhea/ gastroenteritis, which are the most common outcomes evaluated (exceptions are Austria, Guatemala, and Italy).
- Herd effects are assessed in many (43%; 17/40) countries with impact evaluations.
- The effect of partial vaccination is assessed in 40% (16/40) countries.

KEY REMAINING GAPS

- Mortality is measured in only 14 (35%) of countries with RVV impact evaluations.
- Intussusception is being assessed in only 13 (33%) countries with RVV impact evaluations – although the marginal value of additional data on this outcome may not be particularly high.

OPPORTUNITIES

- Although mortality studies showing measured (as opposed to modeled) data are difficult to undertake, they are of great value in convincing decision makers of the value of RVV; thus it may be worthwhile to invest in these studies if decisions not to introduce are based at least in part on insufficient health impact evidence.
- Given the variability in the magnitude of the impact of oral vaccines, even between Africa and Asia, generating evidence on less frequently reported outcomes like intussusception and mortality (in addition to more common indicators of impact such as diarrhea) may be important in Asia. This may be even more important given that existing mortality data is mostly from middle-income countries where diarrhea mortality is relatively low, resulting in gaps in data availability in high-mortality settings in Asia and Africa.
    - Given the number of countries planning introductions in the region, there is enormous opportunity to generate new impact data (see "Future Opportunities" section below).

Countries are responsible for choosing the RVV product they will use in their routine immunization programs; for Gavi-eligible countries, this choice is limited to the two currently prequalified oral vaccines: a monovalent human RVV that is administered in two doses (RV1) and a pentavalent bovine-human reassortant RVV that is administered in three doses (RV5). Product selection is usually based on the country's childhood immunization schedule (optimizing the visits already scheduled for infants) and supply constraints (which have affected availability of RV1). It is critical to ensure the availability of robust impact data for each product to encourage healthy markets.

The published/ongoing RVV impact studies were characterized by the type of outcome assessed based on publication review or personal communication with investigators (**Table 5**). Note that the inclusion of these outcomes does not include an evaluation of quality of the research study. As such, measurement of an outcome does not necessarily convey ability to determine RVV impact from such data (e.g., some studies may be underpowered or the design/analysis insufficient).

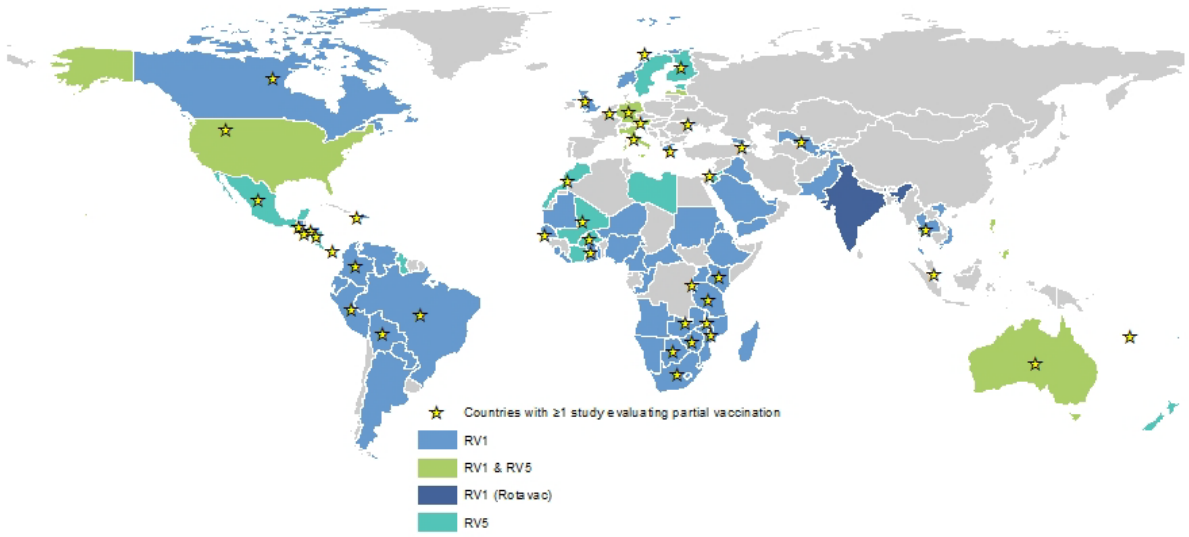
Table 5: Countries with RVV impact studies, by outcome(s) measured

WHO Region	Gavi status (# Countries)	Country (Vaccine currently in use)	All-cause diarrhea	Rotavirus diarrhea	Mortality	Herd effect	Intussusception	Effect of partial vaccination	Other***
Global Total			37	36	14	17	12	17	10
AFR	Gavi (11)	Burkina Faso (RV5)	✓	✓			✓		
		Gambia* (RV5)	✓	✓	✓		✓		✓
		Ghana (RV1)	✓	✓					
		Kenya* (RV1)	✓	✓	✓	✓			✓
		Malawi* (RV1)	✓	✓		✓		✓	✓
		Mali (RV5)	✓	✓	✓		✓		✓
		Mozambique* (RV1)	✓	✓					
		Rwanda* (RV5)	✓	✓			✓		
		Tanzania* (RV1)	✓	✓					
		Zambia (RV1)	✓	✓	✓				
		Zimbabwe* (RV1)	✓	✓					
	Non-Gavi (2)	Botswana (RV1)	✓	✓	✓	✓			
		South Africa (RV1)	✓	✓	✓		✓	✓	
		AFR Total	13	13	6	3	5	2	4
AMR	Gavi (3)	Bolivia (RV1)	✓	✓		✓		✓	✓
		Haiti* (RV1)	✓	✓					
		Nicaragua (RV5)	✓	✓	✓	✓		✓	
	Non-Gavi (8)	Brazil (RV1**)	✓	✓	✓	✓	✓	✓	
		Canada (RV1)	✓	✓				✓	
		Colombia (RV1)	✓	✓		✓		✓	
		El Salvador (RV1)	✓	✓	✓	✓		✓	
		Guatemala (RV1)							
		Mexico (RV5)	✓		✓	✓	✓	✓	
		Panama (RV1)	✓		✓	✓		✓	
		United States (RV1 and RV5)	✓	✓		✓	✓	✓	✓
		AMR Total	11	8	5	8	3	9	2
EMR	Non-Gavi (1)	Morocco (RV5**)	✓	✓				✓	
		EMR Total	1	1	0	0	0	1	0
EUR	Gavi (3)	Armenia (RV1)	✓						
		Moldova (RV1)	✓	✓					
		Uzbekistan* (RV1)	✓	✓					
	Non-Gavi (9)	Austria (RV1 and RV5)		✓	✓	✓		✓	
		Belgium (RV1 and RV5)	✓	✓	✓	✓			✓
		Finland (RV5)	✓	✓		✓	✓	✓	
		Germany (RV1 and RV5)	✓	✓		✓	✓		
		Greece (RV1)	✓	✓					
		Israel (RV5)	✓	✓				✓	✓
		Italy (RV1 and RV5)		✓			✓		
		Norway* (RV1)	✓	✓	✓				
		United Kingdom* (RV1)	✓	✓		✓		✓	
		EUR Total	10	11	3	5	3	4	2
SEAR	Non-Gavi (1)	Thailand* (RV1)	✓	✓					
		SEAR Total	1	1					
WPR	Non-Gavi (3)	Australia* (RV1 and RV5)	✓	✓		✓	✓	✓	✓
		Fiji* (RV1)	✓	✓					
		WPR Total	2	2	0	1	1	1	1

**Indicates countries with one or more ongoing impact study (i.e. a study with ongoing data collection/analysis), with future publication(s) expected.*
***Indicates countries that have used multiple products. Brazil introduced RV5 and later switched to RV1. Morocco introduced RV1 and later switched to RV5.*
****Includes seizures, asymptomatic rotavirus+ cases (e.g. community surveys), genetic diversity/circulating strains, and/or other outcomes measured but not specifically listed here.*

RVV Impact Studies by Product in Use

Figure 2: Countries with studies evaluating RVV impact, by product in use in NIP

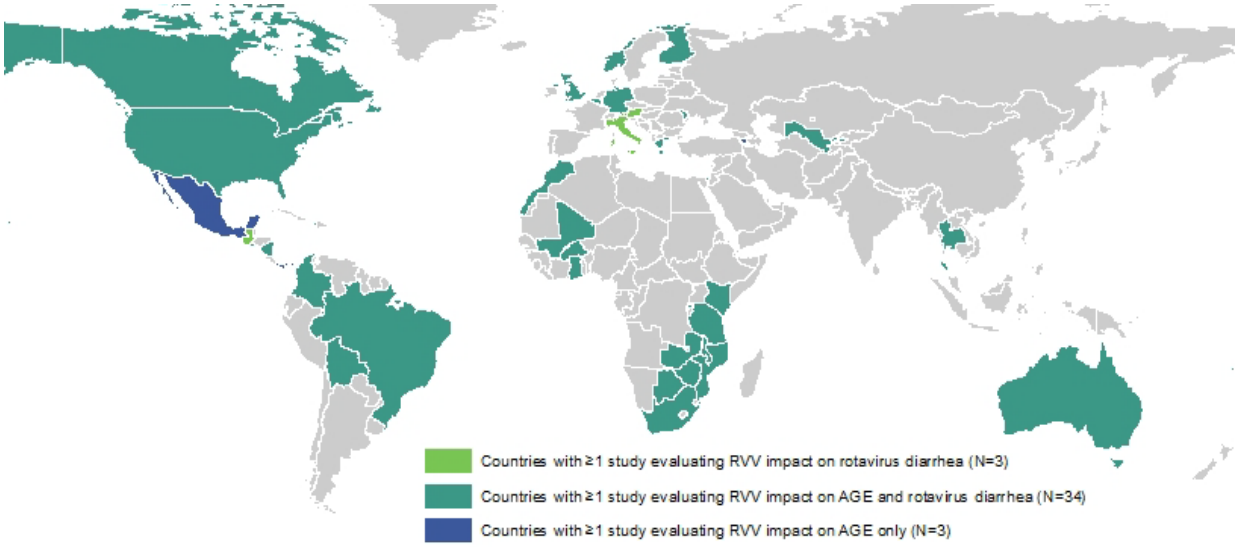


There are more RV1-using countries with health impact studies than RV5-using countries, largely because more countries have introduced RV1 than RV5 (**Figure 2**). Globally, 63 (72%) of the 88 countries that have introduced RVV are using RV1; 32 of these have an impact study compared to 14 of 17 countries using RV5. Although more impact evaluations are being done with RV1, the proportion of RVV-using countries evaluating impact is greater for RV5 (82% vs. 51%).

Similarly among the 40 Gavi countries that have introduced RVV, most (85%) use RV1, of which 13 (38%) have impact evaluations, compared to 4 (67%) of 6 RV5-using countries with impact evaluations.

Measuring RVV Impact on Diarrhea

Figure 3: Countries with studies evaluating RVV impact on diarrhea



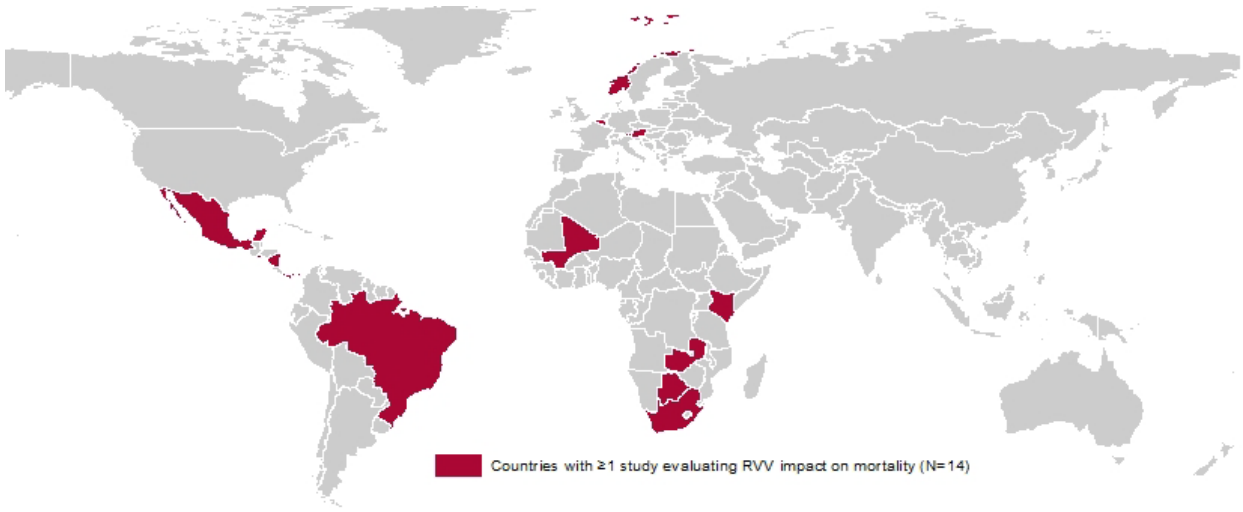
RVV impact studies most often measure the impact on all-cause or rotavirus-specific diarrhea/gastroenteritis. Of the 40 countries with RVV health impact evaluations, all but three

collect data on all-cause diarrhea: 34 evaluate both all-cause and rotavirus-specific diarrhea impact, 3 evaluate all-cause diarrhea only, and 2 evaluate rotavirus diarrhea only (**Figure 3**). There is at least one country in each WHO region with an impact study evaluating diarrhea (either all-cause, rotavirus positive, or both).

Among the 17 Gavi countries with a health impact evaluation, 16 (94%) evaluate impact on both all-cause diarrhea and rotavirus-specific diarrhea; the other measures all-cause diarrhea only.

Measuring RVV Impact on Mortality

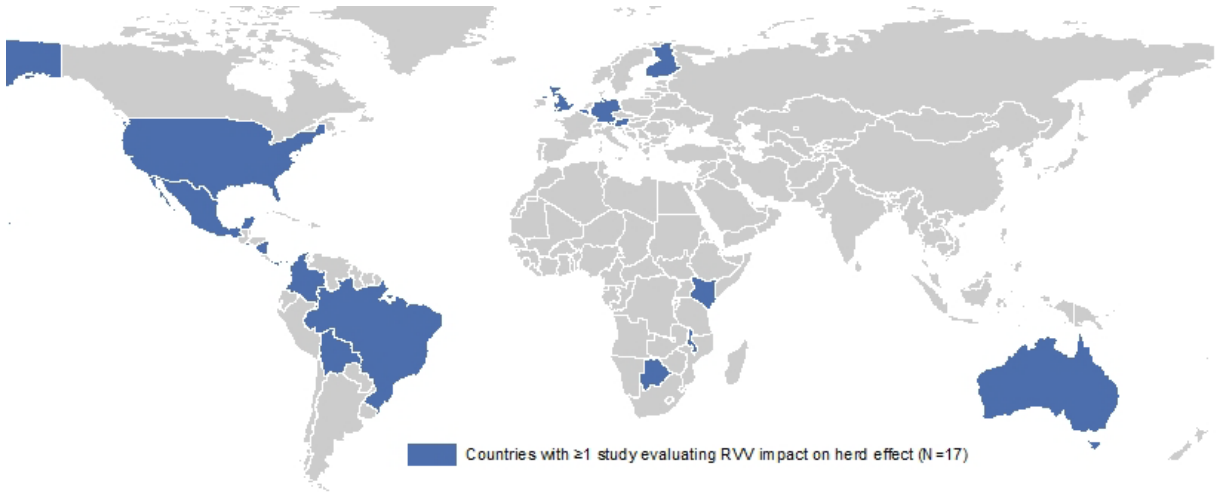
Figure 4: Countries with ≥1 RVV impact study measuring mortality



Globally, 14 (35%) of the 40 countries with an impact evaluation are measuring impact on mortality, 5 of which are Gavi countries (4 in AFR [Gambia, Kenya, Mali and Zambia] and 1 in AMR [Nicaragua]); there are no mortality studies in SEAR, EMR, or WPR (**Figure 4**).

Measuring RVV Herd Effects

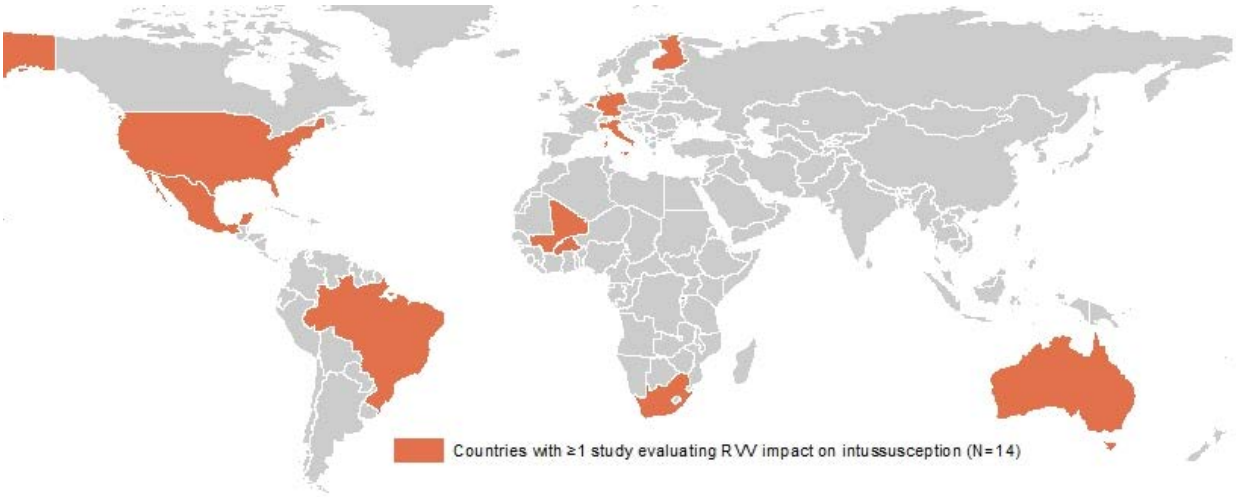
Figure 5: Countries with ≥1 RVV impact study measuring herd effects



Globally, 18 (45%) of the 40 countries with an impact evaluation are evaluating herd effects of the vaccine, 4 of which are Gavi countries (2 in AFR [Kenya and Malawi] and 2 in AMR [Bolivia and Nicaragua]; no evaluation of herd effects is ongoing in EMR or SEAR (**Figure 5**).

Measuring RVV Impact on Intussusception

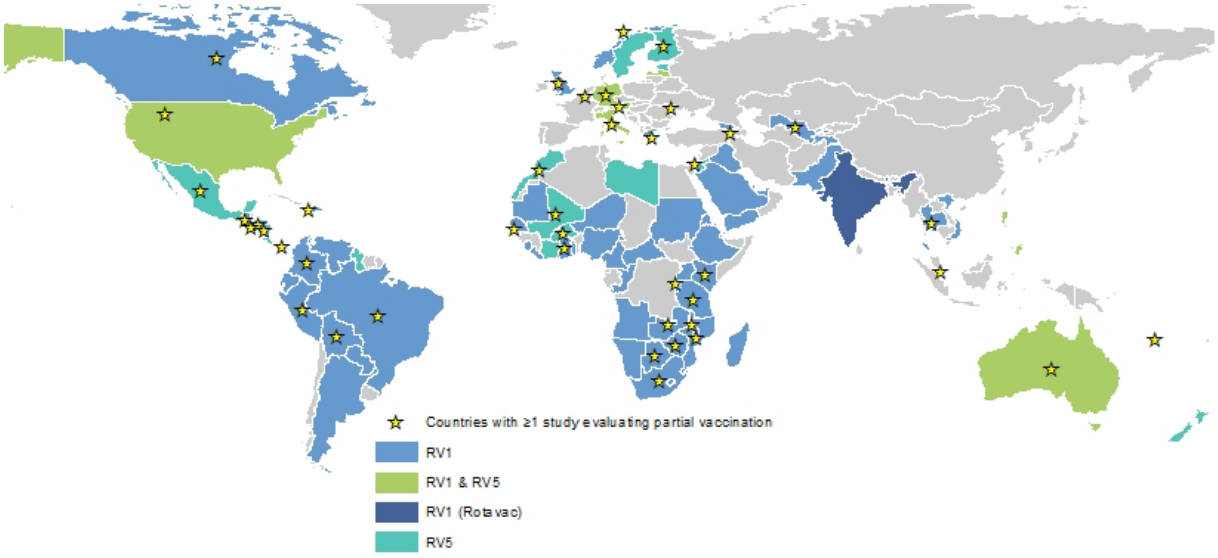
Figure 6: Countries with ≥1 RVV impact study measuring intussusception



Although not generally considered vaccine impact evaluations, studies evaluating RVVs potential effects on intussusception are critical for monitoring vaccine safety (an important component for decision makers). Globally, 12 (30%) of the 40 countries that are evaluating RVV impact evaluate intussusception, 4 of which are Gavi countries (all in AFR: Burkina Faso, Gambia, Mali, and Rwanda); none are being done in SEAR or EMR (**Figure 6**). Of note, Bangladesh, Nepal, Pakistan, and Viet Nam have ongoing RVV studies designed and prepared to measure intussusception cases (which could provide baseline data for an evaluation of changes in intussusception after vaccine introduction), but are not included here because they have not introduced RVV into their NIP.

Evaluating the impact of partial/incomplete rotavirus vaccination

Figure 7: Countries evaluating partial vaccine impact, by product currently in use



Evidence demonstrating RVV effectiveness or impact in children who were only partially vaccinated (i.e., received less than the full number of doses for a complete series) is of interest because it may provide compelling evidence of RVV protectiveness under conditions of low coverage for the last dose of RVV. Of the 40 countries routinely using RVV and which have ongoing/published impact evaluations, 18 are evaluating impact of receiving only partial (or incomplete) rotavirus vaccination (**Figure 7**). There was at least 1 country in every region except SEAR reporting such data, and was available for both RV1 and RV5.

Current State: Economic Impact Studies in Countries Using RVV

OVERVIEW

- **Note: this report is likely an incomplete inventory of the current state of economic impact studies of RVV, as our search strategy was designed primarily to identify health impact studies – see above for methodological details**
- There is a substantial body of evidence on the economic value of RVV and equally important is the evidence on the economic consequences of diarrhea due to RV and other causes
    - Most economic evidence comes from cost-effectiveness and cost-utility analyses (78%)
    - 10% of the evidence relates to budget impact analyses;
    - 5% of the evidence corresponds to cost of illness studies and another 5% from costing analyses;
    - 2% of the evidence comes from an extended cost-effectiveness analysis which looks at the broader economic impact of vaccines
- Few studies globally have assessed the economic consequences of rotavirus disease and the value of RVV
    - About 15% of Gavi countries have evidence from at least one economic study (14% of non-Gavi countries)
    - Most countries with economic impact evidence are not Gavi countries (61%)
    - There are substantial economic evidence coming from studies in Gavi countries (39%)

KEY REMAINING GAPS

- Mainly financial costs of diarrhea (disease expenditure) are reported rather than true economic costs of diarrhea (productivity loss, non-medical costs)
- There are no recent papers on willingness-to-pay, cost minimization or program financing for RVV; this leaves stakeholders short of any independent appraisal of the value of the vaccine for the population and of funding strategies
- Identifying clear-cut evidence of the economic benefits of vaccines against RV in low-resource countries is not straightforward:
    - Country-specific analyses may not be generalizable to other countries
    - Methodological quality of economic evaluations may be variable - we did not perform any quality assessment for this report

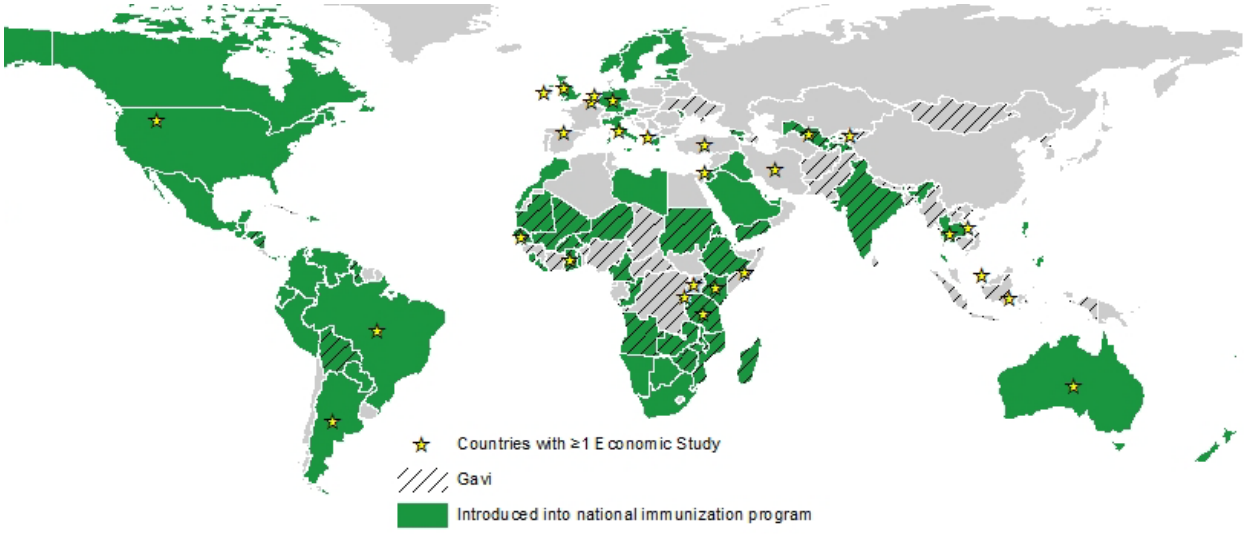
OPPORTUNITIES

- Gavi countries currently transitioning to full self-financing may especially benefit from economic impact studies, which can inform critical decisions about program sustainability
    - Willingness to pay studies, which provide evidence to consider sharing the cost of an increasingly expensive vaccine program with its population, may be particularly important
    - Economic impact studies, when compared to health impact studies, are often less expensive and require less preparation time – meaning they may still be feasible for decision making on the near horizon
- Prioritization of needs assessment for economic impact studies should focus on countries closest to graduation and countries with large birth cohorts

In addition to studies that determine the health impact of vaccines, evidence on the economic impact of vaccines is critical to inform decision making at all levels of vaccine programs. It's particularly important for in-country policy-makers, as information on costs, returns on investment and other economic measures are critical to making well-informed decisions about vaccine introduction.

Figure 8 depicts countries where economic evaluations of RV1 and RV5 have been published. The Americas and Australia are well covered by economic research on RV1 and RV5, as are countries in Africa. However, many countries in Asia lag behind in terms of economic evidence of RV1 and RV5.

Figure 8: Countries with published economic evaluations of RV1 and RV5



Every region in the world has at least one country with a published economic impact study (**Table 6**). Although we did not identify economic impact studies in any Gavi countries in AMR or in any Non-Gavi countries in AFR, that does not imply that such evaluations were not performed, especially in countries that introduced RVV, as they may just not have been published. More non-Gavi countries were reported using economic evidence than Gavi-eligible countries. While there is an ongoing effort to focus more on Gavi eligible countries, only 11 studies in Gavi-eligible settings are available to stakeholders to make decisions and shape a relevant rotavirus vaccine policy.

Table 6: Countries evaluating the economic impact of RV1 and RV5 by region

WHO Region[1]	# Countries in Region		# Countries (%) in Region with ≥1 Economic Impact Study	
	Gavi	**Non-Gavi**	**Gavi**	**Non-Gavi**
AFR (47)	37	10	6 (16.2%)	--
AMR (35)	6	29	--	3 (10.3%)
EMR (21)	6	15	1 (16.7%)	1 (6.7%)
EUR (53)	8	45	2 (25.0%)	10 (22.2%)
SEAR (11)	9	2	1 (11.1%)	1 (50.0%)
WPR (27)	7	20	1 (14.3%)	2 (10%)
Total (194)	73	121	11 (15.1%)	17 (14.0%)

Economic evaluation aims to identify, measure, value and compare the costs and consequences of healthcare programs, and to determine whether or not the benefits of a given program are 'worth the cost.' Economic impact evaluations in our database generally fall into four major categories, based on the method of measurement and valuation of consequences:

- **Cost-effectiveness analysis (CEA)** and **cost-utility analysis (CUA)** are two of most common forms of evaluations. When the addition of a new vaccine to an expanded program on immunization (EPI) schedule is compared with the existing EPI schedule, an incremental approach to CEA is considered to be the most appropriate. In this approach, the additional costs of adding a vaccine to the existing EPI are compared with the additional health benefits. This method of evaluation is preferred because there are common effects of interests (e.g., lives saved, life years gained [LYG], disability-adjusted life-years [DALYs], quality-adjusted life years [QALYs]). **Extended CEA (ECEA)** studies explore the broader economic benefits of a vaccine intervention.

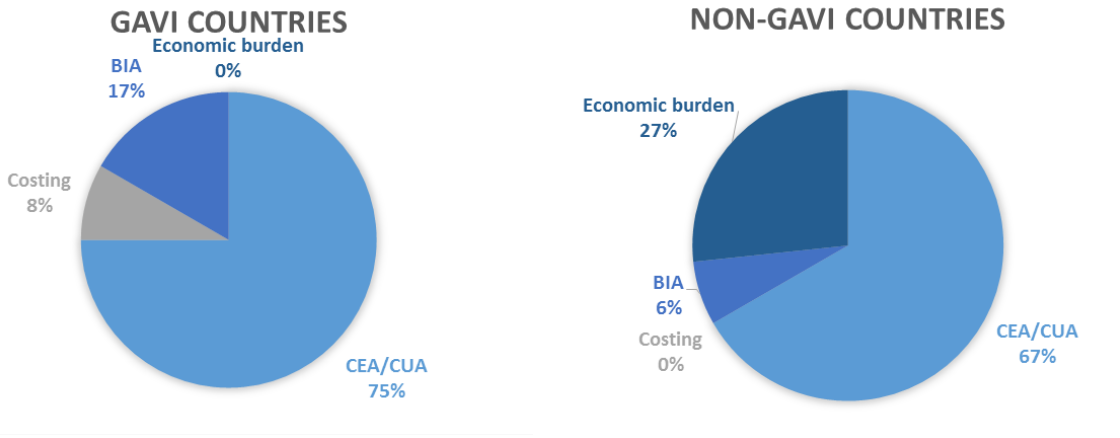
- Another type of evaluation, which is increasing in importance, is **budget impact analyses (BIA)**. BIA most often consider the impact of introducing or sustaining a vaccine program on the country's overall or health-specific budget, including the costs and cost savings that would be incurred as a result of the program (e.g. the cost of the vaccine program as well as the costs saved by hospitalizing fewer patients). Decision-makers need to understand how vaccine will impact the healthcare systems in low and middle-income countries to ensure that sufficient funds are available to fully support its use. Results of these types of analyses can be used for budget planning, forecasting and for computing the financial consequences of adoption and distribution of vaccines and in predicting how a change in mix of vaccines with existing interventions will impact health spending.

- **Costing** studies, while not a type of economic evaluation per se, are important components of the comprehensive economic assessment of disease. A common approach to costing is the **cost of illness study (COI)** or cost burden study that estimates the total costs attributable to a particular disease rather than a particular intervention. The aim of a COI study is to establish the true level of the economic burden imposed by a particular disease so that informed choices can be made regarding health care resource allocation. This form of study identifies those elements of cost that might be reduced by more effective new treatment. One of the benefits of COI studies is identifying the illnesses that consume the most health care resources. This form of studies introduces an estimate of the scale of medical problems in terms of amount of spending and is increasing in importance. There are two distinct approaches to undertaking a COI study which refer to the manner in which costs are attributed to a particular illness: the prevalence approach and the incidence approach:
    - The prevalence-based cost estimates the costs attributable to all individuals suffering from an illness in a given year. In contrast, an incidence-based cost study estimates the present value of the lifetime costs of all individuals newly diagnosed with an illness in a given year.
    - The incidence approach is more precise but has more information needs and is more costly to perform. This approach is generally used to cost infectious diseases because of the short duration and fluctuation of incidence. A simpler approach to costing is to value and measure costs per case or event reported, without considering disease incidence or prevalence.

In our database, most economic studies identified were cost-effectiveness or cost-utility analyses (69%) (**Figure 9**). Such studies assessed the potential economic impact of a specific vaccine intervention by providing average estimates for averted disease treatment costs, then comparing them to the costs of the vaccine. The remaining studies included budget impact analyses (10%), cost-of-illness analyses (5%), cost analyses that looked at costs in healthcare pre and post vaccine introduction (5%) and an extended cost-effectiveness analysis (2%, 1 study). Overall, the lack of

willingness to pay evidence indicates a gap in knowledge that could better inform country-level policies and optimize programs and budgets.

Figure 9: Type of economic evidence by Gavi status, proportion of papers



Abbreviations: CEA = Cost-effectiveness analysis; CUA = cost-utility analysis; BIA = budget impact analyses.

Europe had the largest body of the economic evidence (19 of 29 papers) coming from 9 countries, 2 of which are Gavi-eligible (Kyrgyzstan, Uzbekistan; **Table 7**). Africa had the greatest number (n=4) of Gavi countries reporting economic evidence of vaccines against RV (i.e., CEA/CUA studies).

No single country had every category of economic impact analysis, and the vast majority of countries (n=17; 62%) had only CEA/CUA studies. Only 4 countries (Germany, the Netherlands, the United Kingdom and the United States of America), all high income, had evidence that used more than one type of analysis (**Table 7**).

Table 7: Countries reporting economic evaluations of RVV by type of analysis

Region (# Countries with one or more study)	Gavi Status (# Countries with one or more study)	Country	Cost-effectiveness or cost-utility analysis	Extended cost-effectiveness analysis	Cost analysis	Budget impact analysis	Cost of illness study
Global Total (Number of Papers)			30	1	1	4	8
AFR (6)	Gavi (6)	Ghana				✓	
		Kenya	✓				
		Rwanda			✓		
		Senegal	✓				
		Tanzania	✓				
		Uganda	✓				
	AFR Total		4		1	1	
AMR (3)	Non-Gavi (3)	Argentina	✓				
		Brazil	✓				
		United States	✓		✓		✓
	AMR Total		3		1		1
EMR (2)	Gavi (2)	Iran	✓				
		Somalia	✓				
	EMR Total		2				
EUR (12)	Gavi (2)	Kyrgyzstan	✓				
		Uzbekistan	✓				
	Non-Gavi (10)	Albania	✓				
		Belgium	✓				
		Germany	✓			✓	
		France	✓				
		Ireland	✓				
		Israel	✓				
		Italy	✓				
		Netherlands	✓				✓
		Turkey	✓				
		United Kingdom	✓			✓	
	EUR Total		11			2	1
SEAR (2)	Gavi (1)	Indonesia	✓				
	Non-Gavi (1)	Thailand	✓				
	SEAR Total		2				
WPR (3)	Gavi (1)	Viet Nam				✓	
	Non-Gavi (2)	Australia	✓				
		Malaysia		✓			
	WPR Total		1	1		1	

Although the majority of countries have not evaluated economic impact (or potential impact) of rotavirus vaccine, a significant number of Gavi countries using RVV have entered or will soon enter graduation, during which the country's share of financing for the vaccine will dramatically increase until the country must fully self-finance the full cost of the program. In these situations, decision makers considering the financial aspects of sustainability must have reliable and complete information on the expected costs and economic benefits of RVV to make well-informed decisions.

Of the two Gavi countries already fully self-financing (Honduras and Mongolia), neither has an economic impact study (**Table 8**). Of the 32 countries that have entered Gavi graduation but are not yet fully self-financing, only 5 have economic impact studies to inform future sustainability financing decisions. Although there are studies in other countries in the region, because each country's health and economic system is unique (i.e. some are public, some are private, currencies differ, etc.), country-specific economic data from other countries in the region are unlikely to be informative or meaningful. Thus, it is extremely important for Gavi and partners to assess the need for economic impact studies, prioritizing by urgency (i.e., countries' expected self-financing timeline) and size of birth cohort.

Table 8: Countries using RVV with studies evaluating economic impact, by current Gavi transition status

WHO Region	Status of RVV Introduction into NIP	Non-Gavi Countries Using RVV	Gavi Countries using RVV, by 2016 Gavi transition status			
			Initial Self Financing[1]	Preparatory Transition[2]	Accelerated Transition[3]	Fully self-financing
AFR	Introduced (30)	BOTSWANA MAURITIUS NAMIBIA SOUTH AFRICA SWAZILAND	BURKINA FASO BURUNDI ERITREA ETHIOPIA GAMBIA GUNIEA-BISSAU LIBERIA MADAGASCAR MALAWI MALI MOZAMBIQUE NIGER RWANDA SIERRA LEONE TANZANIA TOGO ZIMBABWE	CAMEROON GHANA KENYA MAURITANIA SENEGAL ZAMBIA	ANGOLA CONGO	
	Not introduced (1)		UGANDA			
AMR	Introduced (19)	ARGENTINA BRAZIL CANADA COLOMBIA DOMINICAN ECUADOR EL SALVADOR GUATEMALA MEXICO PANAMA PARAGUAY PERU UNITED STATES VENEZUELA	HAITI		BOLIVIA GUYANA NICARAGUA	HONDURA

WHO Region	Status of RVV Introduction into NIP	Non-Gavi Countries Using RVV	Gavi Countries using RVV, by 2016 Gavi transition status			
			Initial Self Financing[1]	Preparatory Transition[2]	Accelerated Transition[3]	Fully self-financing
AMR (cont.)		IRAQ JORDAN LIBYA MOROCCO QATAR SAUDI ARABIA UNITED ARAB EMIRATES		SUDAN YEMEN		
	Not introduced (2)	IRAN	SOMALIA			
EUR	Introduced (18)	AUSTRIA BELGIUM **ESTONIA** **FINLAND** **GERMANY** **GREECE** **ISRAEL** **ITALY** LATVIA LUXEMBOURG NORWAY SWEDEN UNITED KINGDOM		TAJIKISTAN	ARMENIA GEORGIA MOLDOVA UZBEKISTAN	
	Not introduced (6)	ALBANIA FRANCE IRELAND NETHERLANDS TURKEY		KYRGYZSTAN		
SEAR	Introduced (2)	THAILAND		INDIA		
	Not introduced (1)				INDONESIA	
WPR	Introduced (8)	AUSTRALIA FIJI MARSHALL MICRONESIA NEW ZEALAND PALAU PHILIPPINES			KIRIBATI	
	Not introduced (2)	MALAYSIA			VIET NAM	

Green cells denote countries that have introduced RVV and have a RVV economic impact study
Blue cells denote countries that have NOT introduced RVV and have a RVV economic impact study
[1] Countries that can reach fully self-financing within **7 years** at earliest
[2] Countries that reach fully self-financing within **6 years** at earliest
[3] Countries that must reach fully self-financing within **5 years**

Future Opportunities: Existing Infrastructure for Potential Impact Studies

OVERVIEW

- Of the 24 countries planning to introduce RVV, 14 have existing WHO surveillance sites collecting information on rotavirus diarrhea
    - These sites are in all WHO regions except for AMR and EUR, which is not in particular need of impact studies
- AFR has the most surveillance infrastructure (8 countries with sites); most other regions each have two

KEY REMAINING GAPS

- Among countries with WHO surveillance sites, a detailed account of the quality and quantity of data, along with a country-specific determination the feasibility of leveraging current infrastructure to measure impact, is not available at this time
- We did not catalogue additional potential sources of data that could be used for impact evaluation (e.g. non-WHO surveillance, existing infrastructure used for burden studies)

OPPORTUNITIES

- Those familiar with existing WHO surveillance sites should devise and apply an objective assessment tool to determine the feasibility for these data to be used for impact assessment(s)
    - It seems likely that countries planning to introduce within one year may not be best suited to measure impact rigorously, as it is likely that improvements in data collection will be required, which takes time
    - Given the lack of RVV impact data from Gavi countries in SEAR, the 5 countries with ongoing surveillance in this region may represent important future targets for impact studies.

Well-designed studies that can quantify the RVV impact with reasonable certainty require several years' lead-time to organize. Therefore, it is important for countries wishing to evaluate impact to consider this well before vaccine introduction. In the near future, countries planning to introduce RVV constitute the list of potential impact study settings. Globally, 28 countries have announced plans to introduce RVV into their NIPs, of which 21 (88%) are Gavi countries.

There is variation in the impact study preparedness and capacity among countries planning to introduce RVV in the next three years. Although the considerations involved in planning impact studies require careful thought, an initial step is to assess a) existing pre-introduction data (and corresponding infrastructure to continue data collection), or b) the ability to collect pre-introduction data before actual introduction (infrastructure to collect data collection, and sufficient time before vaccine rollout to collect meaningful pre-introduction data). Although there are many different mechanisms and types of existing infrastructure that could be leveraged to perform impact studies, for now we focus on existing surveillance sites in the WHO's Global Rotavirus Laboratory Network (GRLN) surveillance network (**Figure 10 and Table 9**). Similar analyses of existing infrastructure that could be leveraged, using literature reviews aimed at identifying disease burden study sites, are possible in the future and are discussed in the "Next Steps" section below.

Figure 10: Countries with WHO GLRN surveillance sites that have not introduced RVV, by vaccine decision status

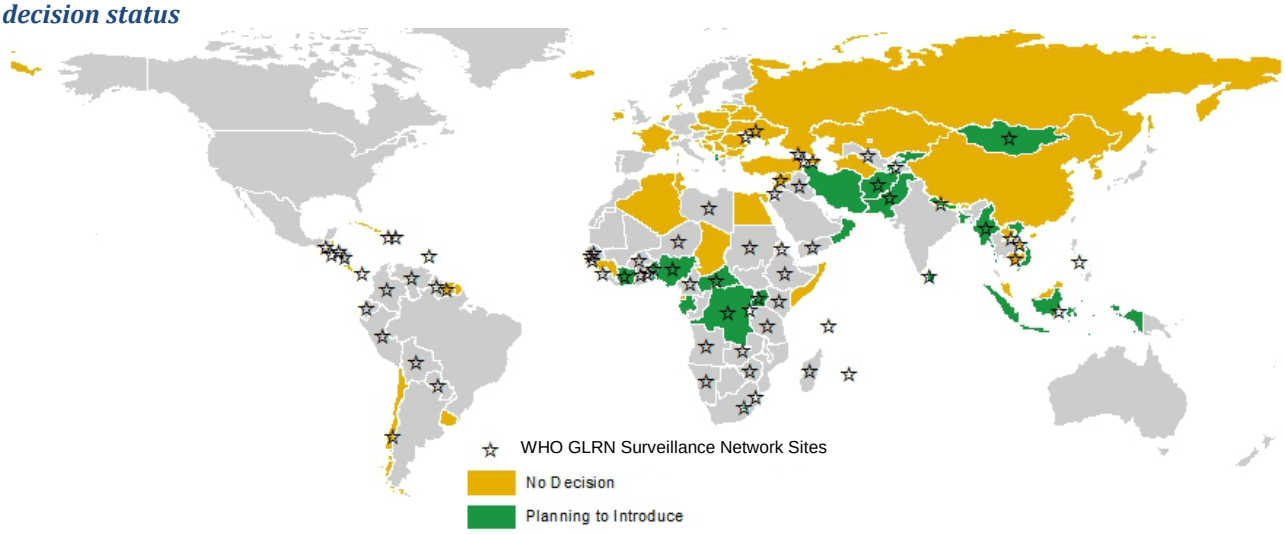


Table 9: Countries planning to introduce RVV by whether or not they have WHO GLRN surveillance sites

Region	Countries Planning To Introduce	
	With WHO GLRN surveillance sites	Without
AFR	Benin Central African Republic The Democratic Republic of the Congo Côte d'Ivoire Lesotho Nigeria Seychelles Uganda	Gabon Sao Tome and Principe Republic of South Sudan
AMR		Bahamas
EMR	Afghanistan Pakistan	
EUR		Albania Kyrgyzstan
SEAR	Bangladesh* Indonesia Myanmar* Nepal* Sri Lanka	Timor-Leste
WPR	Mongolia Viet Nam	

* Bangladesh, Myanmar and Nepal have high-quality non-WHO surveillance systems

Of the 24 countries planning to introduce RVV, 14 have existing WHO surveillance sites collecting information on rotavirus diarrhea and we are currently aware of 3 additional countries planning introductions that have robust existing non-WHO surveillance infrastructure (Nepal, Myanmar, and Bangladesh) (**Table 9**). These sites are in all WHO regions except AMR and EUR which each has only 1 non-Gavi country planning to introduce. AFR has the most surveillance infrastructure (8 countries with sites) followed by SEAR with 5 countries; EMR and WPR each has 2 countries with sites.

Given the lack of RVV impact data from Gavi countries in SEAR, the 5 countries listed here with ongoing surveillance may represent important future targets for impact studies.

Importantly, although we have identified here the countries that have some ongoing data collection for rotavirus events of interest, the suitability of these to measure impact has not been assessed. Although these settings represent opportunities for potential impact studies, additional information about the existing infrastructure is required before they can be considered for impact study implementation. Key considerations should include:

- The number of rotavirus cases detected at the existing sites (including the number of cases for which there are complete case reports – i.e. the number of cases for which key variables of interest are known)
- The number of years of pre-introduction data– which in combination can tell us how many years of post-introduction data collection would be needed to power statistically significant impact results. Because this means there are no distinct "cutoffs" for the amount of pre-introduction data required, we cannot simply apply a rule regarding the number of years of pre-introduction data that exist, or the number of years that remain until the date of planned introduction.
- Completeness of data. Preliminary internal analysis of the WHO surveillance data suggests that it is unlikely that many of the existing sites are currently poised to begin an impact assessment given the quality of data collected to this point, because it is unlikely that immediate post-introduction data collection could be combined with existing pre-introduction data for a robust impact analysis.

Thus, it may be best to approach these particular sites with the assumption that the existing WHO surveillance infrastructure may need several years of improvement/pre-introduction data collection before planned introduction to be successful at evaluating impact – meaning that the countries planning introductions for 2018 and later may be the best targets for future impact evaluations that leverage existing surveillance sites. However, our insight into the quality of existing surveillance data is limited; therefore, a rigorous evaluation of the feasibility and value of using existing WHO surveillance sites should be undertaken by those familiar with the surveillance sites and with impact evaluation methodologies. This should include development of an objective assessment tool that could be universally applied to determine the feasibility for these data to be used for impact assessment(s).

Acknowledgements and Notes

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Various data sources and information were used to generate this report, and are maintained at the Johns Hopkins Bloomberg School of Public Health for use by the International Vaccine Access Center (IVAC) and its affiliated partners.

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Appendix A: Global RVV Introductions, by WHO Region

WHO Region	Country		
AFR	ANGOLA	GUINEA-BISSAU	NIGER
	BOTSWANA	KENYA	RWANDA
	BURKINA FASO	LIBERIA	SENEGAL
	BURUNDI	MADAGASCAR	SIERRA LEONE
	CAMEROON	MALAWI	SOUTH AFRICA
	CONGO	MALI	SWAZILAND
	ERITREA	MAURITANIA	TANZANIA
	ETHIOPIA	MAURITIUS	TOGO
	GAMBIA	MOZAMBIQUE	ZAMBIA
	GHANA	NAMIBIA	ZIMBABWE
AMR	ARGENTINA	EL SALVADOR	PANAMA
	BOLIVIA	GUATEMALA	PARAGUAY
	BRAZIL	GUYANA	PERU
	CANADA	HAITI	UNITED STATES
	COLOMBIA	HONDURAS	VENEZUELA
	DOMINICAN REPUBLIC	MEXICO	
	ECUADOR	NICARAGUA	
EMR	BAHRAIN	LIBYAN ARAB JAMAHIRIYA	SUDAN
	DJIBOUTI	MOROCCO	UNITED ARAB EMIRATES
	IRAQ	QATAR	YEMEN
	JORDAN	SAUDI ARABIA	
EUR	ARMENIA	GERMANY	MOLDOVA, REPUBLIC OF
	AUSTRIA	GREECE	NORWAY
	BELGIUM	ISRAEL	SWEDEN
	ESTONIA	ITALY	TAJIKISTAN
	FINLAND	LATVIA	UNITED KINGDOM
	GEORGIA	LUXEMBOURG	UZBEKISTAN
SEAR	INDIA	THAILAND	
WPR	AUSTRALIA	MARSHALL ISLANDS	PALAU
	FIJI	MICRONESIA, FEDERATED STATES OF	PHILIPPINES
	KIRIBATI	NEW ZEALAND	