IVAC
International Vaccine Access Center

February | 2017

Gap Analysis of PCV Impact Evaluations in Settings of Routine Use

VIEW-hub.org

International Vaccine Access Center, Johns Hopkins Bloomberg School of Public Health

Table of Contents

Executive Summary

SCOPE OF ANALYSIS: This report summarizes the use of pneumococcal conjugate vaccine (PCV) and impact evidence as of November 2016 in countries routinely using PCV10 or PCV13. The amount of impact evidence (as opposed to the results) that is published or being collected is described and key gaps are identified, contextualized by current and anticipated country PCV introductions.

SOURCE OF DATA: International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. VIEW-hub. www.view-hub.org. Accessed: November 2016

CURRENT PCV USE: As of November 2016, 139 countries have introduced PCV in their routine immunization program; 52% (72) of which have an impact evaluation, including at least one country in every WHO region.

STRATEGIC GAPS & OPPORTUNITIES IDENTIFIED:

PCV use:

- PCV Catch up: opportunities in humanitarian emergency/displaced populations to assess impact of reduced dose schedules or catch-up should be considered; however, such activities should never act as an impediment to carrying out vaccination programs
    - Evidence may be relevant for countries with lagging coverage to accelerate herd effect
- Large birth cohort countries with limited rollout or coverage would benefit from prioritizing PCV use in highest under-5 mortality subnational areas
    - Impact in high mortality areas would be larger than in low mortality areas
- A lag in PCV uptake in middle-income countries is likely attributable to the cost of PCV, as these countries don't have access to Gavi prices and many don't have the benefit of pooled procurement mechanisms. Extending supportive platforms for procurement of vaccines, including PCV, to alleviate tension between cost and uptake is a priority.
    - Communications around ongoing efforts should remain a priority, such as the V3P price database which publicizes the vaccine prices and has led to increased bargaining power for countries without a financing mechanism
    - More information is needed on what countries need to make the decision to introduce vaccines. Determining decision-making patterns may help to move the levers on introductions and help to strategically allocate resources to generate the most useful evidence in the future.
    - Economic evaluations demonstrating the return on investment and the full value of vaccines in these settings may be relevant for supporting introductions and sustained use. However, timing of introduction decisions appears to align with availability of budget for vaccine procurement. When budget is available there may be opportunities to use economic evaluations to support PCV introduction decisions. Identifying financing and/or procurement mechanisms for countries to access PCV at lower cost remains important to ensuring available budget space for introductions and use over time.

Impact evaluations of PCV use:

- There is a concern that the 3+0 schedule may not induce maximum herd effect in areas with high burden and intense pneumococcal transmission such as in many AFR countries and there is lack of evidence whether a 2+1 schedule would improve herd effects. Should an AFR country switch from 3+0 to 2+1, the opportunity to evaluate and compare impact on NP carriage and herd effect to the 3+0 schedule may address the question of whether the 2+1 schedule should be

preferentially recommended in these settings.

- Advocacy and communication: it may be important to assure that regional PCV impact data are widely shared, understood and are contributing to local decision-making
    - In AFR this should be targeted across French and English speaking countries and for large birth cohort countries that lack local data
    - Ensure Gavi countries are aware of regional data, including from non-Gavi countries
    - For Gavi-transitioning countries, take concerted efforts to assure that EPI program and MOH staff are aware of data to support PCV programs throughout self-financing
- Evaluate the need among countries in the Preparatory and Accelerated Transition phase for generation of evidence to support sustained PCV use in self-financing phase
- Assess the role that NITAGs may play in decision-making to sustain PCV and assure that they have a strong understanding of the available data that are packaged for their deliberations/use

1. Introduction: PCV Use and Impact Evidence

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. Impact evaluations are essential for understanding the value of global PCV use over the past 16 years (6 years in Gavi countries), including the optimization of its use. Because of the rapid pace of PCV introduction, the progress toward universal vaccine coverage, its ability to induce large scale population immunity, and currently licensed PCV products target some, but not all, serotypes of *Streptococcus pneumoniae*, PCV impact should be monitored to assess changes in the epidemiology of pneumococcal disease. Impact evaluations can answer questions about which 3-dose schedule is better (2 primary doses plus a booster (2+1) vs 3 primary doses and no booster (3+0)), the value of catch-up, the magnitude of serotype replacement with these expanded serotype vaccines (compared with PCV7) in relation to the reduction of vaccine type disease, and the importance of understanding serotype distribution of the remaining disease in the post PCV era.

PCV impact evaluations provide the ***evidence*** required to optimize national immunization programs (NIP) and drive the strategy on pneumococcal disease control strategies. Results can also influence countries that have not yet made a decision on PCV introduction, and in countries that will soon move toward self-financing (i.e. graduate from Gavi support) of their NIP. The availability of published PCV impact evaluations is expected to continue increasing rapidly as countries gain sufficient years of post introduction data required to analyze vaccine impact.

The capacity to undertake vaccine impact monitoring does not exist in all countries and may be insufficient or unknown in many others. From a global or regional perspective, not every country needs to have an impact evaluation to have credible insights into the impact of PCV. However, there need to be data generated across different epidemiologic, political and geographic settings in order to inform disease prevention and control policies in countries with similar epidemiological settings, particularly where there is an absence of local data and/or capacity. And there needs to be effective communication of the available data.

There remains a misalignment between the aspiration for optimal public health program monitoring at the country level and the availability of human and financial resources to conduct such activities. Further scrutiny of evidence across all regions aims to strategically assess epidemiologic gaps in the portfolio of available PCV impact evaluations, and better inform decisions on public health monitoring across heterogeneous settings. Analyses, conducted by region, may identify key gaps in impact evidence across epidemiologic and geographic settings, and aim to inform strategic allocation of resources to fill these gaps.

In this context, PCV impact evaluations from low- and middle-income countries (LMICs), especially those with the highest under-5 mortality, are important as they will expand the evidence base for sustaining PCV immunization in the highest disease burden settings. We have chosen Gavi status as the stratification for all analyses in this report, to highlight the current status and gaps in impact evidence within the lowest-income countries. For the purpose of these analyses, Gavi-countries were defined as the 73 nations that were originally eligible for Gavi-financial support for vaccine procurement regardless of current transition status. Regardless of transition status, all 73 countries remain eligible to access tail price PCV through UNICEF under the Gavi Advanced Market Commitment (AMC).

This gap analysis is useful for prioritizing the research agenda, and for identifying where advocacy resources may need to be directed in the absence of available impact evidence. This report describes and evaluates the ***availability*** of evidence on PCV10 and PCV13 by reporting on the ***number of countries*** evaluating impact with consideration of key information on PCV products, schedules, and

outcomes assessed; ***it does not summarize the results or quality*** of that evidence. As such, the availability of data will not correlate fully with the ability to determine PCV impact from such evidence. For example, some evaluations may be underpowered to provide robust analyses of impact for one or more outcomes, comparators, etc. Thus, it is important when interpreting this report to remember that all published or ongoing impact studies are included, regardless of ability to meaningfully measure impact.

We begin by providing background about global PCV vaccine introductions as of November 2016 and the products currently in use, using data from IVAC's VIEW-Hub database (www.VIEW-hub.org) to provide context.[1] Then, our analysis of gaps in impact data is summarized as follows:

- ***The current state of vaccine impact evidence***: This section describes the availability of published and ongoing health and economic impact evidence in countries that have already introduced PCV, using the VIEW-hub impact study database. We describe availability and corresponding gaps in evidence by region, product/dosing schedule, and outcomes measured. We have broken down the analyses by type of impact evaluation (published or ongoing); health impact studies are separated from economic impact studies, allowing for additional descriptive variables to be reported for economic studies, including type of analysis.
    - The report section on economic analysis aims to summarize the available information; it does not distinguish between projected and measured impact (based on local disease burden and cost information).
    - Because many countries that are transitioning out of Gavi-financial support may use impact data to respond to policy questions regarding sustaining use and optimizing programs, we have added analyses stratified by Gavi transition status to provide context on the potential *urgency* for impact evidence to inform next stage decision-making.

- ***Future opportunities to generate impact evidence***: This section describes the ongoing efforts to collect pre-introduction data to highlight the existence of additional surveillance infrastructure as a possible platform for future impact evaluations.

1.1 Methods & Approach

Source of Data

All information on vaccine introductions and impact evaluations comes from the IVAC Johns Hopkins Bloomberg School of Public Health VIEW-hub (www.view-hub.org). VIEW-Hub is a public web-based data access and visualization platform on vaccine introductions and impact evidence, of which PCV is one of the vaccine antigens of interest. Additional information on individual countries and studies reported on VIEW-Hub and thus in this report are available upon request to the lead coordinator of VIEW-Hub (Kirthini Muralidharan: kmurali2@jhu.edu). The data presented herein were accessed from VIEW-Hub on November 3, 2016.

Inclusion and exclusion criteria

Published and ongoing PCV impact evaluations were eligible if:

[1] International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. VIEW-hub. www.view-hub.org. Accessed: November 2016

- They took place in a country using PCV in its NIP, either nationally or sub-nationally (with the exception of economic impact evaluations)
    - Ongoing evaluations designed to measure PCV impact in settings where the vaccine has not yet been introduced into the NIP were excluded. Such evaluations are monitored for future inclusion once the vaccine has been officially introduced. We are aware of such studies in Mongolia and Viet Nam.
- They evaluated PCV10 or PCV13
    - PCV7 impact information is abstracted in VIEW-Hub only if PCV10 or PCV13 was also evaluated. Papers and studies that evaluated PCV7 only are not included in VIEW-Hub for abstraction.
- Published sources: extensive literature search for the period 2009-10/31/2016
- Unpublished sources:
    - **Low- and middle-income countries (LMIC):** systematically identified through[2]
        - Gavi-funded studies list
        - BMGF-funded studies list
        - CDC collaborations list
        - GREEN (Latin America Collaboration)
        - Communications with other partners
    - **High-income countries (HIC):** Opportunistically identified and includes published PCV7 surveillance that extends to the PCV10/13 use period
- Economic evaluations included all cost and economic assessments of pneumococcal disease and PCVs. Thus this section includes both impact assessments and modeled economic impact of vaccine introduction (i.e. projected data).

Although WHO-coordinated invasive bacterial disease (IBD) surveillance is performed in many countries that have introduced PCV, these data are not necessarily being used to assess PCV impact. We briefly describe the available WHO IBD surveillance data; however, such data were included in our formal analyses only if they were published or are part of an ongoing evaluation specifically designed to measure PCV impact.

Unit of Analysis

This report summarizes the number of ***countries*** evaluating PCV impact and key information on such evaluations. Since there may be multiple reports or analyses of data from a single study, a process is required to distinguish separate studies versus separate reports from the same study. The definition of "study" is undergoing review to best reflect the unique sources of impact evidence. While the number of studies is not expected to change meaningfully, in this report we describe impact by country, as it is currently the most reliable and accurate unit of analysis.

[2]Ongoing evaluations in EMR, SEAR, and AFR were included to a high a degree of certainty. Ongoing evaluations in the PAHO region are included, but verification of these data is ongoing through collaboration with the PCV Technical Coordination Project.

2. Context: PCV Introductions and Use

KEY GAPS

- 60% (81.6 million) of the world's infants do not currently have access to PCV
  - Most of these infants (63%, 51.5 million) are living in Gavi countries
- 8 Gavi-countries (37 overall) are not expected to have made a decision to introduce PCV by 2020
- Introduction of PCV in LMIC (largely driven by Gavi support in LICs) has advanced more quickly in AFR than in the Asian regions (WPR and SEAR)
  - 38 (81%) of 47 AFR countries compared to 20 (53%) of 38 WPR & SEAR countries use PCV today

OVERVIEW

- 139 (72%) of 194 countries have introduced PCV into routine immunization programs
- 57 (78%) of the 73 Gavi countries have introduced PCV
- 18 (33%) countries among those not using PCV at present are planning to introduce by 2020
  - 8 of these are Gavi-countries (India, Haiti, Indonesia, Cuba, Bhutan, Comoros, Guinea, Tajikistan), 2 are approved for Gavi financial support (India and Haiti)
- Gavi support for PCV began in 2010 and has reached over 75% of countries in only 6 years; PCV introductions in HIC began in 2000 and reached 75% of countries in 13 years.

OPPORTUNITIES

- India is beginning PCV rollout in a limited number of states Q1/Q2 2017; rollout in states with the highest mortality (and highest pneumococcal burden) offers the greatest opportunity for demonstrating health impact rapidly
  - Other large birth cohort countries with limited rollout or coverage have similar opportunities for rapid impact from prioritizing PCV use in highest under-5 mortality subnational areas
- Indonesia is beginning a pilot PCV program; high quality PCV impact evaluation could support decisions for broader rollout
- Displaced populations (humanitarian emergency, civil war) are increasing; consideration to assess evidence for PCV catch-up programs and alternate PCV strategies in these circumstances is important, but should never be an impediment to the delivery of immunizations to high-risk individuals
- It is important to ascertain the key parameters driving decisions regarding PCV introduction in MICs, where gaps in PCV use remain large compared to LIC and HIC.
  - Such countries may need additional support for PCV decision-making including support for financing and procurement of PCVs and advocacy efforts utilizing available health and economic impact evidence from similar epidemiologic settings.

Availability of data on PCV impact depends on the timing of vaccine introduction and rollout (we define impact evaluations as those performed in the context of routine vaccine use). Introductions occurred first in high-income countries (primarily North America and Europe), followed by Gavi-supported countries in the Africa region. Because there are so few Gavi countries in the Asia regions (WPR and SEAR) and because both Gavi and non-Gavi LMICs in Asia began introducing PCV later, a lag in the availability of PCV impact evidence from Asia is expected and is more limited than in Africa. The limited data in Asia underscores the importance of assuring that PCV impact studies in this region is well planned and coordinated; this includes the importance of a PCV impact assessment plan for India, which will be introducing PCV in a few states Q1/Q2 of 2017.

2.1 PCV Introductions: The Global Picture

At present 72% (139) of the 194 countries globally have introduced PCV, 57 of which are Gavi-countries (78% of the 73 eligible countries). Introduction of PCV began in the United States in 2000 after licensure of the 7-valent PCV and uptake in HIC continued rapidly. It was not until Gavi support began in 2010 that PCV introductions in low-income countries (LIC) began.[3]

Figure 1: Global introductions of PCV

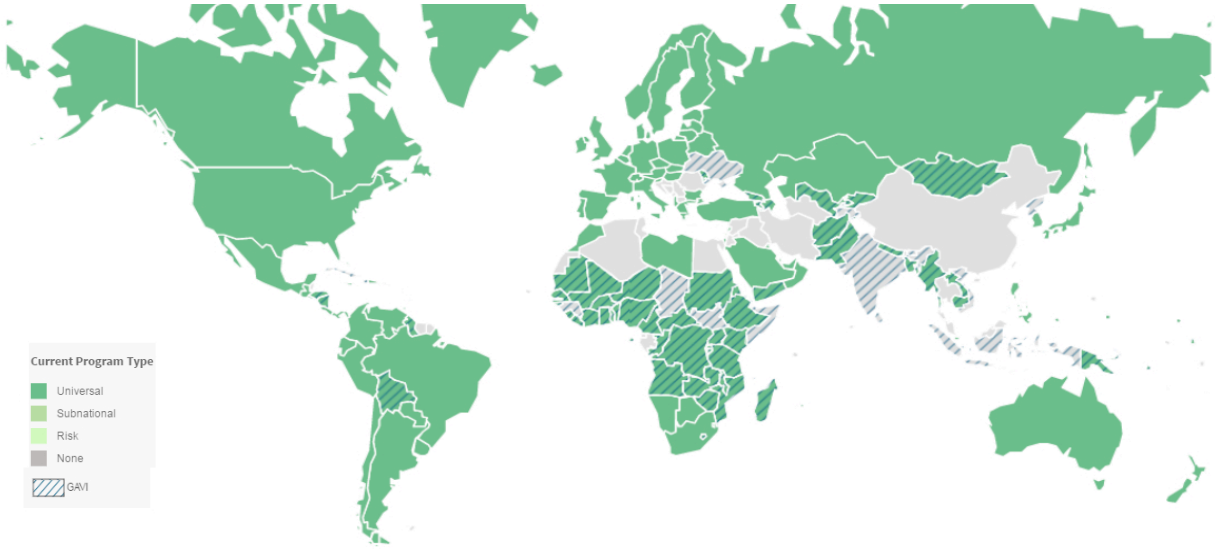


Table 1: Number of countries that have introduced PCV by vaccine program type and Gavi-status

Countries (#)	Global Introductions (138 Countries)			
	Program Type			Total Introductions
	Universal Use	At-Risk Populations	Subnational Use	
Gavi (73)	55	-	2	57
Non-Gavi (121)	74	5	3	82
All Countries (194)	129	5	5	139

Note: See Table 5 for the complete list of countries that have introduced PCV, by region.

Although global success of Gavi-support for PCV introductions is apparent in LIC as 57 (78%) of the eligible countries have introduced the vaccine, middle-income-countries (MIC) that do not have access to a similar financial (or procurement) support mechanism have struggled to introduce and/or sustain PCV in their NIP. This is evident in the number of MIC that have introduced globally as compared to the number of LIC and HIC.

The lag in introductions in MIC is likely due to vaccine price challenges when accessing supply outside of a regional or institutional market commitment and ineligibility for financial support for procurement (i.e. from Gavi). It may also be due to a lack of available data (either locally or from comparable epidemiologic settings) or a lack of awareness of existing useful information to support decision-making. Understanding the key parameters to PCV introduction decisions in countries across income strata, especially for MIC, will help to inform strategic allocation to improve uptake and sustained use in the future.

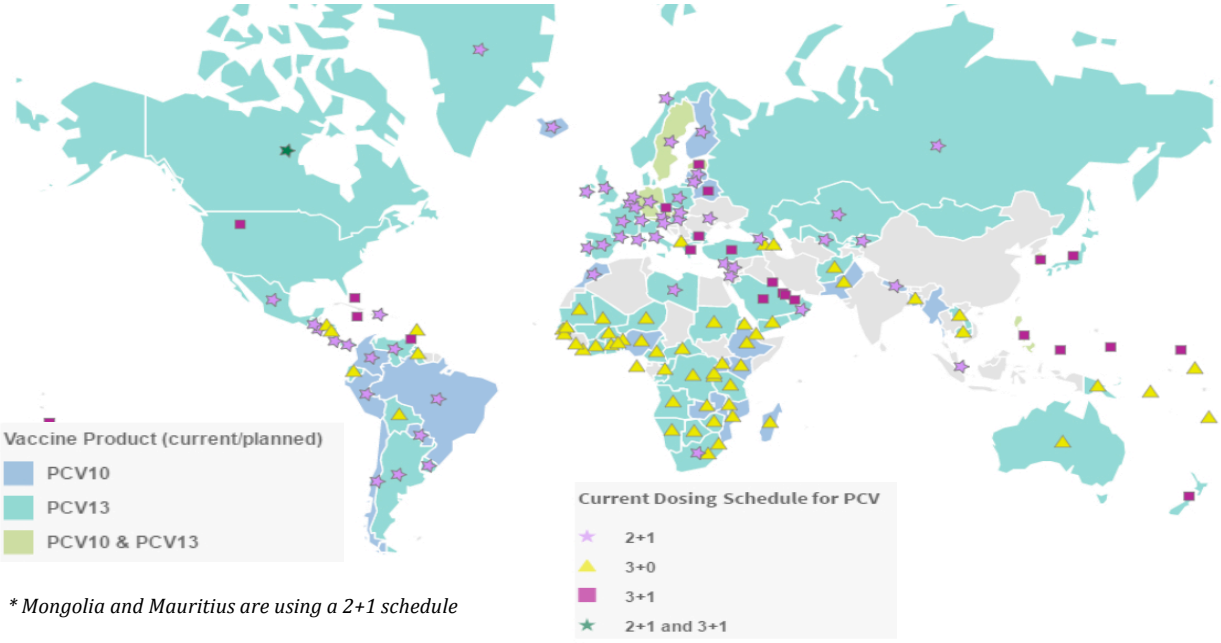
[3] Countries are eligible for Gavi support if their average gross national income (GNI) over the past three years is equal to or below the eligibility threshold amount (USD 1,580). Such countries are eligible to apply for New Vaccine Support (NVS) and/or Health Systems Strengthening (HSS) support.

2.2 PCV Products & Dosing Schedules in Use Globally

There are both programmatic and epidemiologic considerations surrounding product and schedule use. Such factors are important for countries introducing or maintaining their PCV NIPs to sustain and optimize vaccine impact. Both the 10-valent and 13-valent PCV products are currently licensed. Recommended dosing schedules (for both products) include 3- or 4-dose schedules that have either 2 or 3 primary doses in the first 6 months of life and 0-1 booster doses in the 2nd year of life, i.e., 3+1, 3+0 or 2+1[4].

Countries choose a PCV product and dosing schedule for their NIP. However, guidance for decision-making is limited, and unsupported assumptions of effectiveness, budget, and/or product-specific supply constraints may influence product (and schedule) choice for countries and/or Gavi. A summary of current use patterns and impact evidence on products and schedules may help to inform what impact evidence exists on these factors, and inform future PCV decision-making.

Figure 2: Countries using PCV, by product and dosing schedule currently in use



** Mongolia and Mauritius are using a 2+1 schedule*

Table 2: Number of countries currently using each PCV product and dosing schedule, by Gavi status

	Product			Dosing Schedule		
Gavi Status (n)	PCV10	PCV13	PCV10 & 13	2+1	3+0	3+1
Gavi (57)	14	43		6	51	
Non-Gavi (82)	19	55	8	51	8	24
Total (139)	33	98	8	57+	59	24

+Canada uses both a 2+1 and 3+1 schedule, and is included in both columns

Most Gavi countries use a 3+0 PCV schedule; there are 6 Gavi countries using a 2+1 schedule: Nepal, Georgia, Kyrgyzstan, Moldova, Mongolia, and Uzbekistan. Nepal (2+1) and Bangladesh (3+0) altered the PCV primary dose interval to accommodate the administration of IPV at age 14 weeks into their infant routine immunization schedules. Nepal's schedule is 6w/10w/9m and that of Bangladesh is 6w/10w/18w. Both Nepal and Bangladesh are evaluating an altered 3+0 (in terms of timing between doses) schedule in their PCV impact evaluation.

[4] World Epidemiologic Record, No. 14, 2012, 87, 129–144. Pneumococcal vaccines WHO position paper – 2012

2.3 PCV Introductions: Current Gaps

Although rapid progress for PCV introduction is indicated via the number of countries with PCV in their NIP, more relevant is an analysis of the number of children who have access to these vaccines (i.e. live in a country that has introduced PCV into the routine schedule **and** are being vaccinated).

Of the world's 135.3 million infants:

- 60% (81.6 million) do not have access to PCV either because the country has not introduced the vaccine or because of incomplete vaccine coverage
- 48% (65.5 million) of infants live in countries that have not yet introduced PCV
    - Almost 39 million of them live in Gavi countries
    - Large birth cohort countries (e.g. India, Indonesia) contribute substantially to the total number of infants yet to have access to PCV
    - **There is enormous opportunity to increase the number of infants with access to PCV by targeting introductions in these larger countries and focusing the phased introductions on sub-regions with the highest under-5 mortality.**[5]

- 12% (16.1 million) of infants do not have access to PCV despite living in countries that have PCV in their NIP because they are not reached by current routine immunization strategies, as evidenced by incomplete DTP3 coverage.
    - 12.5 million (78%) of these children live in Gavi countries
    - Those who are not reached by routine immunizations are usually the most marginalized and impoverished, which puts them at highest risk of pneumococcal disease.
    - **This highlights the importance of equity in vaccination programs.** As the gap in coverage of PCV in countries is increasingly quantified and characterized, **the hardest to reach populations must be addressed in order to improve global access to PCV**.

Anticipated progress: India and Haiti are approved for Gavi support (with/without clarification).

India has the largest infant birth cohort of any single country, thus introduction of PCV into its NIP would achieve significant gains in global PCV access. With Gavi's catalytic support, India will introduce PCV in a phased manner starting with 5 states in early 2017 included in the government of India plan for PCV and one state that announced introduction on its own (Haryana, pending discussions with Pfizer to determine availability of supply). PCV introduction in India is expected to begin in Q1/Q2 2017 in several districts of Uttar Pradesh, half of Bihar, and the entire state of Himachal Pradesh in 2017; scale up continues in 2018 in the rest of Bihar, MP, more districts in UP and some districts of Rajasthan. In 2019 Rajasthan and more districts of UP will be added.

No decision: 37 countries have not yet made a decision about introducing PCV (within a 3-year time frame), including 8 Gavi countries (Chad, Korea DPR, Somalia, Sri Lanka, South Sudan, Timor-Leste, Ukraine, and Viet Nam[6]). These 8 Gavi countries comprised a birth cohort of 4.3 million infants in 2015.

---

[5] High under-5 mortality sub-regions should be targeted, as exact measures of pneumococcal disease burden by sub-region may not be available to inform strategic rollout of PCVs.

[6] Although they are Gavi countries, Timor-Leste, Vietnam, Sri Lanka and Ukraine have transitioned out from eligibility for Gavi financial support for PCV introductions.

Table 3: Year 2020 PCV introduction plans, by region, among countries that have not introduced PCV (Gavi countries highlighted in gold)[7]

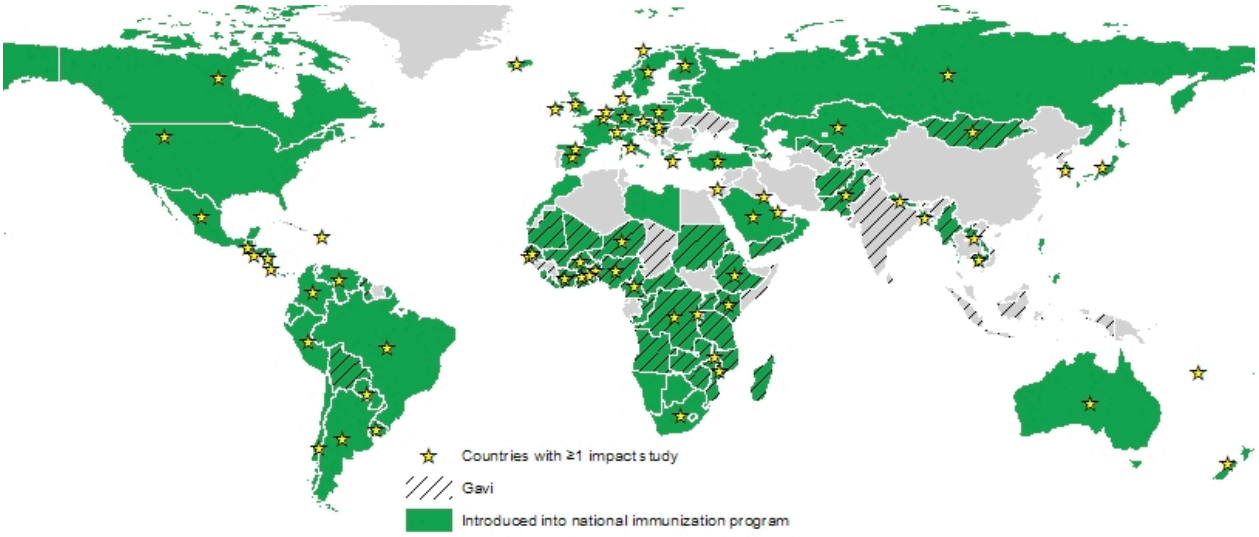
WHO Region	Countries Planning to Introduce	Countries With No Plans to Introduce
AFR	CAPE VERDE COMOROS EQUATORIAL GUINEA GABON GUINEA SEYCHELLES	ALGERIA CHAD SUDAN, REPUBLIC OF SOUTH
AMR	BELIZE CUBA HAITI SURINAME	ANTIGUA AND BARBUDA DOMINICA GRENADA SAINT KITTS AND NEVIS SAINT LUCIA SAINT VINCENT AND THE GRENADINES
EMR	IRAQ JORDAN	EGYPT IRAN, ISLAMIC REPUBLIC OF SOMALIA SYRIAN ARAB REPUBLIC TUNISIA
EUR	TAJIKISTAN TURKMENISTAN	BOSNIA AND HERZOGOVINA CROATIA MACEDONIA, THE FORMER YOGOSLAV REPUBLIC OF MALTA MONTENEGRO ROMANIA SAN MARINO SERBIA UKRAINE
SEAR	BHUTAN INDIA INDONESIA	KOREA, DEMOCRATIC PEOPLE'S REPULIC OF MALDIVES SRI LANKA THAILAND TIMOR-LESTE
WPR	SAMOA	BRUNEI DARUSSALAM CHINA COOK ISLANDS MALAYSIA NAURU TONGA TUVALU VANUATU VIET NAM

[7] International Vaccine Access Center (IVAC), Johns Hopkins Bloomberg School of Public Health. VIEW-hub. www.view-hub.org. Accessed: November 2016

3. Health Impact Evaluations in Countries Using PCV

Of the 139 countries that have introduced PCV, 72 (52%) have an ongoing or published health impact evaluation, with at least 1 country in every WHO Region. Twenty-four of these impact countries are Gavi-countries (indicated by hash-marks in **Figure 3**).

Figure 3: Countries using PCV in their NIP and evaluating PCV impact



Note: not included are countries conducting pre-introduction baseline/preparatory studies (such as Viet Nam). These countries will be added once the country has decided to introduce PCV.

3.1 PCV Impact Evaluations by Region

OVERVIEW

- At least 1 country in every WHO region has an ongoing or published PCV impact study
- 44% of Gavi countries and 59% of Non-Gavi countries using PCV have a PCV impact evaluation

KEY GAPS

- Of 6 Gavi countries in EUR using PCV, none have a PCV impact evaluation
- Of 17 countries in AFR, only 3 in French-speaking Africa are evaluating disease impact

OPPORTUNITIES

SEAR/WPR:

- Countries yet to introduce PCV could be supported to collect pre-PCV baseline data, in particular large birth cohort countries or those imminently introducing in SEAR

AFR:

- Advocacy and communication efforts may assure that regional PCV impact data are widely shared and are contributing to decision-making, especially across Franco- and Anglophone countries

EMR:

- Humanitarian emergencies in this region may thwart planned introductions and impact evaluations; data on PCV catch-up and reduced schedules may support PCV use in these settings

EUR:

- Assessment of information that could be provided by countries that are not yet using PCV and have capacity to initiate an evaluation study prior to introduction is needed, with focus on strategic choices that may add to regional evidence
- Consider economic evaluations, especially return on investment studies, in Gavi countries to support planning for transitions to self-financing; such evidence may also support decisions on introduction from non-Gavi (MIC) in region
- Advocacy and communication efforts to assure that Gavi countries in the region are fully aware of and using the regional impact data, including from non-Gavi countries

AMR:

- PCV Catch up: consider opportunities in humanitarian emergency/displaced populations to assess reduced dose schedules or catch-up impact; however, attempts to collect such data should not be an impediment to implementation of vaccine campaigns and programs in these populations
    - This may be relevant for countries with lagging coverage to accelerate herd effect
- Advocacy and Communication: especially for transitioning countries, a concerted effort to assure that EPI and MOH staff have a strong understanding of the regional and available global impact data to assure that support for PCV programs continue through the self-financing transition

Because geographic regions can be epidemiologically heterogeneous, further examination of differences among them is important for strategically assessing gaps in PCV impact data. As intra-regional differences can be important too, particularly across income strata, stratification by Gavi-status is also reported.

Table 4: Number of countries using PCV in NIP and evaluating impact, by WHO region and Gavi status

WHO Region	# Countries in Region		# Countries (% in Region) with Routine PCV Use		# Countries (% of PCV-using countries) in Region with ≥1 PCV10 or PCV13 Impact Study	
	Gavi	**Non-Gavi**	**Gavi**	**Non-Gavi**	**Gavi**	**Non-Gavi**
AFR (47)	37	10	33 (89%)	5 (50%)	16 (48%)	1 (20%)
AMR (35)	6	29	4 (67%)	21 (72%)	1 (25%)	15 (71%)
EMR (21)	6	15	5 (83%)	9 (60%)	1 (20%)	3 (33%)
EUR (53)	8	45	6 (75%)	36(80%)	**0 (0%)**	24 (67%)
SEAR (11)	9	2	3 (33%)	**0 (0%)**	2 (67%)	**0 (0%)**
WPR (27)	7	20	6 (86%)	11 (55%)	4 (67%)	5 (45%)
Total (194)	73	121	57 (78%)	82 (68%)	24 (42%)	48(59%)

**Viet Nam (in SEAR) has a pre-PCV study in place to collect baseline data, but has not yet introduced PCV intro their NIP, and thus is not counted here.*

Although at least one country in every WHO region is conducting a PCV impact evaluation, the number of studies varies substantially by region. Most countries conducting PCV impact evaluations are in EUR (n=24) and AMR (n=16); however, these regions have the fewest Gavi countries (n=12). We expected there to be more impact evaluations in countries of AFR compared to those in Asia because countries in AFR have a longer experience with PCV than those in Asia (introduction in AFR began in 2010 vs. 2013 in Asia). The available data reflects this, as 18 AFR countries are evaluating PCV impact compared to only 2 SEAR and 9 WPR countries. By contrast, SEAR and EMR are the two regions with the fewest countries with a PCV impact evaluation. This section summarizes the progress to date (i.e. existing studies) and the opportunities (i.e. PCV countries without an evaluation and countries yet to introduce PCV) by region and with an emphasis on Gavi countries.

Across the WHO regions, a lag in PCV uptake in MIC was observed and attributed to the high-cost of PCV, as these countries have no access to a purchasing mechanism for vaccines and must negotiate directly with manufacturers. LIC have access to Gavi and UNICEF purchasing mechanisms, and PAHO nations to a regional pooled purchasing mechanism. Identifying a supportive platform for procurement of vaccines, including PCV, in these MIC may alleviate the tension between cost and uptake. This is a high priority for moving the needle on remaining pneumococcal disease burden and mortality.

AFR:

- **Progress**: 33 of 37 Gavi countries have introduced PCV; of these 17 have an impact evaluation. Nine countries (Algeria, Cape Verde, Chad, Comoros, Equatorial Guinea, Gabon, Guinea, Seychelles, and South Sudan) have yet to introduce PCV in the region; 4 are Gavi-eligible.
- **Opportunities**: The capacity for measuring disease in Africa present challenges to having PCV impact evaluations. There are 16 countries that have introduced PCV but are not evaluating PCV impact. Among them are some large birth cohort countries and high under-5 mortality settings.[8] In such countries, economic evaluations to demonstrate the value of PCV may support sustained use in NIPs, particularly as many transition from Gavi support.
    - Although a larger number of countries in French-speaking Africa (Benin, Burkina Faso, Cameroon, Congo, DRC, Cote D'Ivoire, Niger, Rwanda, Senegal, Togo) have a PCV impact evaluation, than in English-speaking countries (Ethiopia, Gambia, Ghana, Kenya, Malawi, Mozambique[9]), almost all are assessing only bacterial meningitis (likely due to their location in the Meningitis Belt) and may not be specifically designed or powered to evaluate PCV impact. Furthermore, data from English-speaking African countries are published more

[8] The 16 countries in AFR using and not evaluating PCV impact: Angola, Burundi, CAR, Eritrea, Guinea-Bissau, Lesotho, Liberia, Madagascar, **Mali**, Mauritania, Sao Tome and Principe, Sierra Leone, **Tanzania**, **Uganda, Zambia**, Zimbabwe

[9] Mozambique's official language is Portuguese, not English.

frequently and shared globally. Although there are no systematic epidemiologic differences, the degree of data sharing and communication is somewhat segregated along language lines, so the communication of data from English speaking African countries appears to be low in French speaking African countries. Some intentional advocacy and communication activities across countries and languages regarding PCV impact study results may be beneficial.

AMR:

- **Progress**: 25 countries in the region have introduced PCV, 16 of which have an impact evaluation. Four of 6 Gavi countries have introduced PCV and only Nicaragua has an impact assessment in the region.
- **Opportunities**:
  - 2 Gavi countries (Haiti and Cuba) are planning to introduce by 2020 (Haiti in early 2017) and may require local data to support this decision and for sustained use overtime. They may present an opportunity to collect pre-introduction baseline data in settings that are unique for geographic, economic or political reasons.
    - In Cuba, pre-introduction data is currently being collected on invasive disease via a network of hospitals supported through the MOH and on NP carriage in various geographic areas and age groups.[10]
    - In Haiti, meningitis surveillance was initiated and may provide a platform for future impact evaluations. At present, it is unclear if the meningitis data will be robust enough for an impact evaluation, and should be considered as infrastructure for such efforts. Haiti is also building capacity for a baseline NP carriage study in children with leadership from CDC. A repeat NP carriage study could be done at some point to evaluate change post-introduction in Haiti. Evidence from humanitarian emergency and displaced population settings may also be possible in Haiti and inform future use of the vaccine in the country.
  - The three Gavi PCV-using countries (Bolivia, Guyana, and Honduras [which is fully self-financing]) do not have health impact evaluations; economic evaluations are summarized in Section 6.[11]
  - Additional opportunities for improved access and impact evaluations in countries that have not achieved PCV coverage levels that would increase population level impact may also exist, such as in the Dominican Republic where coverage has remained under 30% since introduction.

EMR:

- **Progress**: Five of 6 Gavi countries have introduced PCV and 1 (Pakistan) has an impact evaluation. Nine of 15 non-Gavi countries have introduced PCV, of which 3 (Saudi Arabia, Qatar, and Kuwait) have impact evaluations.
- **Opportunities**: 4 Gavi countries using PCV (Afghanistan, Djibouti, Sudan, and Yemen) have no impact evaluation; 1 Gavi country (Somalia) has no plans for introduction by 2020. Pakistan is the only Gavi country in the region with an impact evaluation and continued support for this ongoing effort may be a priority. Among the non-Gavi countries in the region, Egypt presents an opportunity in a large birth cohort country to collect pre-introduction baseline data in hopes of a future introduction; however, Egypt has no public plans for a PCV introduction by 2020. Communications and advocacy efforts should be made to establish a strong understanding of

---

[10] Toledo ME et al. Prevalence of Pneumococcal Nasopharyngeal Carriage Among Children 2-18 Months of Age: Baseline Study Pre Introduction of Pneumococcal Vaccination in Cuba. *Pediatr Infect Dis* 2017;36:e22-28

[11] Post-introduction economic evaluation of pneumococcal conjugate vaccination in Ecuador, Honduras, and Paraguay/ Evaluacion economica tras la introduccion de la vacunacion antineumococica conjugada en Ecuador, Honduras y Paraguay. *Rev Panam Salud Publica*. DO Constenla. 2015;38:388-95

the data available regionally and globally for decision-makers in the region, and the gaps in evidence that may be prioritized for collection in countries that have yet to introduce PCV.

EUR:

- **Progress**: 6 of 8 Gavi countries have introduced PCV (Armenia, Azerbaijan, Georgia, Kyrgyzstan, Moldova, and Uzbekistan); none have a PCV impact evaluation. Thirty-six non-Gavi countries have introduced PCV, 24 of which have an impact evaluation.
- **Opportunities**: 2 Gavi countries (Ukraine and Tajikistan) have yet to introduce PCV; Ukraine is fully self-financing and has no plans for introduction. Tajikistan plans to introduce by 2020, and presents an opportunity for pre-introduction baseline data collection prior to the use of PCV. Among non-Gavi countries in the region, more than 75% of the impact evidence comes from HIC, a large number of MIC that have introduced PCV may require data from local or similar settings to support sustained PCV use due to increasingly limited resources for EPI programs. Furthermore there are 8 non-Gavi countries that have not yet introduced PCV (Bosnia, Croatia, Macedonia, Malta, Montenegro, Romania, San Marino, Serbia, and Turkmenistan), that have limited evidence to utilize in decision-making for PCV introduction from countries with similar economic and epidemiologic contexts in their region. When budget is available, economic evaluations may present an opportunity for generating supportive evidence for decision-making on introductions and sustained use.

SEAR:

- **Progress**: 3 of 9 Gavi countries have introduced PCV (Bangladesh, Nepal, and Myanmar); Bangladesh and Nepal have PCV impact evaluations, both of which will be providing data on a range of outcomes. Neither of the 2 non-Gavi countries in the region has introduced PCV (Maldives and Thailand).
- **Opportunities**: As they are the only two studies in SEAR, ongoing support to Bangladesh and Nepal may be important to establishing regional impact evidence. Myanmar has PCV but without an evaluation; Bhutan, India, Indonesia, Democratic People's Republic of Korea, Sri Lanka, and Timor-Leste are the 6 Gavi countries yet to introduce PCV, and represent a significant portion of the global birth cohort. India has been approved for Gavi-catalytic support for PCV introduction in 5 states, which will begin in early 2017, and several studies in India are either underway or in planning stages; impact evaluations in introducing states may support a rapid nationwide rollout.

WPR:

- **Progress**: 6 of 7 Gavi countries have introduced PCV; of these 4 have an impact evaluation (Cambodia, Lao PDR, Mongolia, and Papua New Guinea). Viet Nam is the only Gavi country yet to introduce PCV in WPR, and is collecting pre-introduction baseline data as part of a future impact evaluation. In addition, 5 non-Gavi countries have impact evaluations (Australia, Fiji, Japan, Korea, and New Zealand). This region is quite strong on the support of PCV impact data, as there is evidence being generated or available from a range of income strata and epidemiologic settings.
- **Opportunities**: Supporting Viet Nam's introduction of PCV is ongoing. Two Gavi PCV using countries do not have an impact evaluation (Kiribati and Solomon Islands).

3.2 PCV Impact Evaluations by Gavi-Transition Status

OVERVIEW

- There are countries with PCV impact evaluations in all transition phases, except fully self-financing
- 10% of accelerated transition phase countries have a PCV impact evaluation
- 68% PCV-using Gavi countries in the preparatory transition are evaluating PCV impact
- 25% countries in the initial transition phase are evaluating PCV

KEY GAPS

- Only 10% of countries in the accelerated transition phases (i.e. those most imminently transitioning away from Gavi support), have impact evaluations
- Numerous large birth cohort countries in the initial transition phase have no PCV impact evaluation

OPPORTUNITIES

- AFR, initial transition phase: assess the needs of large countries for evidence to support sustained use of PCVs (e.g. Mali, Uganda, Zimbabwe, CAR, Tanzania) and establish a plan for either leveraging regional data with advocacy and communication
- EUR, Gavi countries: consider a concerted advocacy/communication activity to assure that local, regional and global data are feeding into the transition planning/process
- Assess the role that NITAGs may play in the decision making to sustain PCV use in NIP and assure that they have data in appropriate 'packaging' for their deliberations/use
- Assess systematically the patterns in available data and PCV introduction decision-making to determine the key parameters for vaccine uptake and to strategically allocate resources in the future

Countries using PCV are summarized by Gavi transition status and availability of a PCV impact evaluation (**Table 5**). Countries that are transitioning out of Gavi support and toward self-financing of their NIP may be at higher risk for sustaining PCV, as resources are limited for all vaccinations in the program. Thus, these countries may be influenced by evidence of impact to support and justify continuation of their PCV programs. Although all countries may not require local data to support decision-making, it will likely be critical to assure that local advocates are aware of available evidence and have it packaged to support their efforts within EPI, Ministries of Health, Ministries of Finance and other decision making bodies for continued PCV use.

Approximately 25% of PCV-using Gavi countries in the initial self-financing phase (i.e., still eligible to apply for Gavi funding) are evaluating PCV impact. The percent is smaller among those in the preparatory and accelerated transition phases, indicating a gap in local evidence, considering policy makers rely on impact evidence to make policy and program decisions to sustain PCV programs. In such countries (if local evidence is not being collected), concerted advocacy and communications on evidence from similar epidemiologic settings may be important.

Two Gavi countries, Mongolia and Honduras, are fully self-financing[12]. Although Honduras has no health impact evaluation, there was an economic model projecting cost-effectiveness of PCV in the country, which may have been influential to the decision for sustained use however such influence has not been investigated. An evaluation could be done to assess the utility of the economic model in decision-making, and whether lack of local health impact data was problematic. Mongolia has an ongoing PCV impact evaluation.

[12] As of 2017: Guyana, Honduras, Kiribati, Moldova and Mongolia are fully self-financing Gavi countries.

Among those countries in the accelerated transition phase, European countries seem to be at high risk for having a lack of impact evidence that is representative of their epidemiologic and geographic settings. Although 10% of these countries have an ongoing or published impact evaluation, all of these are economic studies (i.e. none of the countries in this category have a health impact evaluation). This may present an area of high risk as they transition towards self-financing; however, the key parameters to decision-making on sustained PCV use are not well understood and/or documented. Efforts to assess these factors and the influence of available health and economic evidence on decision-making may be important to future strategic resource allocation for continued introductions and sustained use.

Countries that are in initial self-financing phase may not present an imminent need for impact evidence to defend their PCV program, as they are not going to be responsible for the financing in the next year(s). However, there are some large birth cohort countries that represent a big portion of global infants and should be recognized. This is particularly true in AFR, which is also a region where capacity may be limited at this point. In such countries advocacy and communications to improve awareness and utility of available evidence (from the region or similar epidemiologic settings) may be feasible.

Table 5: Countries using PCV in NIP and evaluating impact, by WHO region and Gavi transition status (as of November 2016). Green shading indicates countries with a published or ongoing PCV impact evaluation.

WHO Region	Non-Gavi Countries Using PCV		Gavi Countries using PCV, by 2016 Gavi transition status				
			Initial Self Financing *could* reach fully self-financing within **7 years** at earliest		**Preparatory Transition** *could* reach fully self-financing within **6 years** at earliest	**Accelerated Transition** *must* fully self-finance within **5 years**	**Fully self-financing**
AFR (18/38)	SOUTH AFRICA BOTSWANA MAURITIUS NAMIBIA SWAZILAND		BENIN BURKINA FASO DR CONGO ETHIOPIA GAMBIA MALAWI MOZAMBIQUE NIGER RWANDA TOGO	BURUNDI CENTRAL AF. REP. ERITREA GUINEA-BISSAU LIBERIA MADAGASCAR MALI SIERRA LEONE TANZANIA UGANDA ZIMBABWE	CAMEROON CÔTE D'IVOIRE GHANA KENYA NIGERIA SENEGAL LESOTHO MAURITANIA SAO TOME & PRINCIPE ZAMBIA	CONGO ANGOLA	
AMR (16/25)	ARGENTINA BRAZIL CANADA CHILE COLOMBIA COSTA RICA DOMINICAN REPUBLIC EL SALVADOR GUATEMALA MEXICO PARAGUAY	PERU UNITED STATES URUGUAY VENEZUELA BAHAMAS BARBADOS ECUADOR JAMAICA PANAMA TRINIDAD AND				NICARAGUA BOLIVIA GUYANA	HONDURAS
EMR (4/14)	KUWAIT QATAR SAUDI ARABIA BAHRAIN LEBANON	LIBYA MOROCCO OMAN UNITED ARAB EMIRATES	AFGHANISTAN		PAKISTAN DJIBOUTI SUDAN YEMEN		
EUR (24/42)	BELGIUM CZECH REPUBLIC DENMARK FINLAND FRANCE GERMANY GREECE HUNGARY ICELAND IRELAND ISRAEL ITALY KAZAKHSTAN NETHERLANDS NORWAY POLAND PORTUGAL RUSSIA	SLOVAKIA SPAIN SWEDEN SWITZERLAND TURKEY UNITED KINGDOM ALBANIA ANDORRA AUSTRIA BELARUS BULGARIA CYPRUS ESTONIA LATVIA LITHUANIA LUXEMBOURG MONACO SLOVENIA			KYRGYZSTAN	ARMENIA AZERBAIJAN GEORGIA MOLDOVA UZBEKISTAN	
SEAR (2/3)			NEPAL		BANGLADESH MYANMAR		
WPR (8/16)	AUSTRALIA FIJI JAPAN REPUBLIC OF KOREA NEW ZEALAND	MARSHALL ISLANDS MICRONESIA NIUE PALAU PHILIPPINES SINGAPORE	CAMBODIA		LAO PDR SOLOMON ISLANDS	PAPUA NEW GUINEA KIRIBATI	MONGOLIA

3.3 PCV Impact Evaluations by Dosing Schedule

OVERVIEW

- Among the 72 (38%) countries that are evaluating PCV impact, 38 countries (53%) are currently using a 2+1 schedule, 24 countries (33%) are using a 3+0 schedule, and 10 countries (15%) are using a 3+1 schedule.
  - 25 (35%) are Gavi countries, 23 (92%) of which are evaluating a 3+0 schedule (Nepal and Mongolia are the only exceptions and are using a 2+1 schedule)

KEY GAPS

- No Gavi countries in AFR are using a 2+1 schedule.
- 2 (33%) of 6 Gavi-countries using a 2+1 schedule are evaluating impact.
  - Limited evidence of impact in high mortality settings of reduced priming doses and the ability to effectively administer a booster dose in resource-constrained programs is currently available

OPPORTUNITIES:

- Seek an opportunity to evaluate 2+1 in AFR in high transmission/burden setting and compare impact on NP carriage and herd effect to that with a 3+0 schedule
  - This is a priority due to the concern that a 3+0 schedule does not elicit the degree of herd protection required in a high transmission/burden setting and there is lack of evidence whether a 2+1 schedule would improve herd effects
- Opportunities to measure the impact of a 2+1 schedule on NP carriage, disease, and herd effects are a priority in the EUR region and may lend to the evidence base to support decision-making in other regions, in MIC yet to introduce PCV or for sustained use.

All schedules are being evaluated and both 3-dose schedule types (2+1 and 3+0) are being evaluated in Gavi countries (**Table 6**). However, only 2 of 6 Gavi countries, Nepal and Mongolia, using a 2+1 schedule are evaluating PCV impact. The under-5 mortality rates (U5MR) of these countries are low (36 and 22 per 1,000 live births, respectively) and thus may not contribute to the evidence of PCV impact on mortality representative of the highest burden countries. The 4 Gavi countries with a 2+1 schedule that are not evaluating impact are Georgia, Kyrgyzstan, Moldova and Uzbekistan (**Figure 4** and **Table 7**); their U5MR are low, ranging 11 to 34 per 1,000 live births.[13]

At present, there is limited evidence available to demonstrate the impact of only 2 primary doses in the highest under-5 mortality settings (i.e. the highest quintile) and of the ability to effectively administer a booster dose in resource-constrained programs.

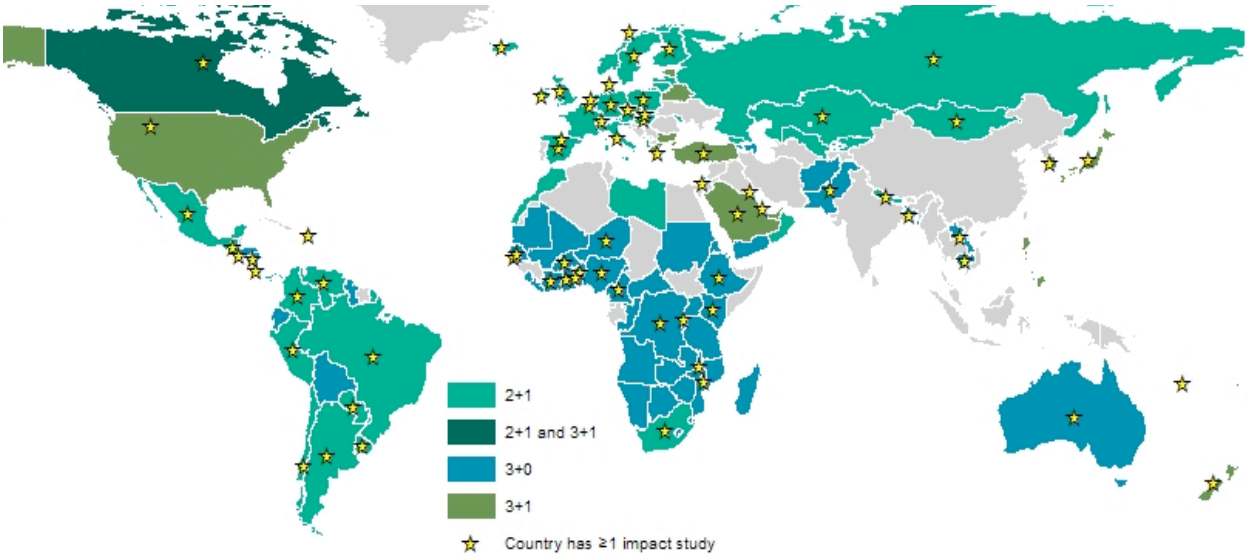
Table 6: Number and percent of countries evaluating PCV impact, by current NIP dosing schedule

Gavi Status	Countries Evaluating PCV	Countries with PCV impact evaluations by current PCV dosing schedule in NIP			
		2+1 n=56[3]	3+0 n=59	3+1 n=23	2+1 & 3+1 n=1
Gavi	24[1]	2/6 (33%)	22/51 (43%)	0	0
Non-Gavi	48	35/50 (70%)	2/8 (25%)	10/23 (43%)	1/1 (100%)[2]
All	72	37/56 (66%)	24/59 (41%)	10/23 (43%)	1/1 (100%)

[1]Viet Nam has a study designed to measure PCV impact, but has not yet introduced PCV into its NIP.
[2]Canada is using both 2+1 and 3+1 schedules, depending on the province
[3] All countries using that schedule

13 World Bank Statistics 2015: http://data.worldbank.org/indicator/SH.DYN.MORT

Figure 4: Countries evaluating PCV10 or PCV13 impact, by dosing schedule currently in use



Of particular interest are countries evaluating alternate interval dosing schedules, which have been implemented due to logistics or programmatic issues that interfere with the recommended dosing timing of 3+1, 3+0, or 2+1 schedules. Recommendations are 2 months between primary doses (e.g., 6-14w) in 2+1 schedules and no less than 1 month between primary doses (e.g., 6-10-14w) in 3+0 schedules for Gavi countries.

Both Nepal and Bangladesh are evaluating unique schedules, which change the timing of a PCV dose because of concerns with giving 3 injections at the 14-week routine immunization visit (i.e., IPV is administered at 14w). Bangladesh is evaluating a 6w-10w-18w schedule (3+0), lengthening the window between the 2nd and 3rd doses of PCV. Nepal is evaluating a 6w-10w-9m, schedule (2+1), shortening the recommended window between the 2 primary doses from 8 to 4 weeks. The results of these impact evaluations could have implications for the dosing schedule (and timing of doses) decisions for PCV in other countries. However, because these studies do not compare different dosing schedules directly, the evaluation of non-inferiority or superiority of various dosing schedules may not be able to be made. Results from these studies may be able to state impact on specific endpoints measured from the dosing schedule evaluated, if they are powered adequately.

Table 7: Countries with a PCV10 or PCV13 impact study, by current product and dosing schedule (Gavi countries are highlighted in gold)

WHO Region	Dosing Schedule					
	2+1		3+0		3+1	
AFR		**PCV13** SOUTH AFRICA	**PCV10** ETHIOPIA KENYA MOZAMBIQUE NIGERIA	**PCV13** BENIN BURKINA FASO CAMEROON DR CONGO CÔTE D'IVOIRE GAMBIA GHANA MALAWI NIGER RWANDA SENEGAL TOGO		
AMR	**PCV10** BRAZIL** CHILE COLOMBIA PARAGUAY PERU	**PCV13** ARGENTINA CANADA* COSTA RICA DOMINICAN REPUBLIC EL SALVADOR GUATEMALA MEXICO URUGUAY VENEZUELA		**PCV13** NICARAGUA		**PCV13** UNITED STATES CANADA*
EMR			**PCV10** PAKISTAN			**PCV13** KUWAIT QATAR SAUDI ARABIA
EUR	**PCV10** BELGIUM FINLAND ICELAND NETHERLANDS**	**PCV13** DENMARK FRANCE HUNGARY IRELAND ISRAEL ITALY KAZAKHSTAN NORWAY POLAND PORTUGAL RUSSIA SPAIN SWITZERLAND UNITED KINGDOM GERMANY° SLOVAKIA° SWEDEN°				**PCV13** CZECH REPUBLIC GREECE TURKEY
SEAR	**PCV10** NEPAL		**PCV10** BANGLADESH			
WPR		**PCV13** MONGOLIA	**PCV10** FIJI	**PCV13** CAMBODIA LAO PDR PAPUA NEW GUINEA AUSTRALIA	**PCV10** NEW ZEALAND***	**PCV13** KOREA° JAPAN

**Canada's PCV dosing schedule varies by province/territory; some use a 2+1, while others use a 3+1 dosing schedule.*
***The Netherlands and Brazil switched from a 3+1 dosing schedule to a 2+1 schedule in Nov 2014 and Apr 2016, respectively.*
****New Zealand has conducted impact evaluation of PCV10, later switched to PCV13, and is now using PCV10 (again)*
❖ Viet Nam has study designed to measure PCV impact, but has not yet introduced into their NIP; they are not listed here.
°Countries use(d) both PCV10 and PCV13, but the evaluation focuses on PCV13

3.4 PCV Impact Evaluations by Product and Outcome(s) Evaluated

OVERVIEW

- A similar proportion of PCV10- and PCV13-using countries are evaluating impact (52-53%)
- Both PCV10 and PCV13 are being evaluated in Gavi countries (and in Non-Gavi countries)
- PCV13 is evaluated in 55 (3x) more countries than PCV10, it is also used in 106 (3x more) NIP
- IPD, pneumonia and NP carriage are all commonly evaluated outcomes in countries conducting PCV evaluations (68%, 59% and 47%, respectively).
    - Every WHO region has countries evaluating PCV impact on IPD, pneumonia, and NP carriage.
- Herd effects are commonly being evaluated (55% (n=32) of countries evaluating PCV impact),
    - At least 1 evaluation exists in every region, 55 assess PCV13 and 17 assess PCV10

KEY GAPS

- PCV10: 2 countries in SEAR; 1 country in EMR and 1 in WPR are evaluating impact
- PCV10 has fewer assessments of NP, herd effects or mortality compared to PCV13 assessments
- PCV impact on pneumonia and IPD are being conducted in 9 and 12 countries in Africa, respectively, mostly in southern and eastern Africa
- Impact of PCV on mortality is being measured in 24 (33%) countries that are evaluating PCV impact.
    - Data on PCV impact on mortality are being collected in studies in AFR, AMR, EUR, SEAR, and WPR; however, no data on this outcome is being collected in EMR.
- PCV10 or PCV13 impact on mortality has been published in: AMR (Brazil, Canada, Nicaragua, and United States); EUR (Denmark, Spain, and Sweden); and WPR (New Zealand).
    - None of these countries are high under-5 mortality settings

OPPORTUNITIES

- More evidence to quantify PCV10 impact on NP carriage would enhance the modeling and expected serotype specific changes and indirect effects
- Evaluating PCV impact on multiple outcomes, including NP carriage, in a single setting to allow triangulation of impact
- Seek opportunities for further pneumonia and IPD assessments in western Africa
- Assure that studies with pneumonia outcomes are leveraging WHO Chest Radiography in Epidemiologic Studies (CRES) resources to assure that study results can be compared across studies
    - Improvement of WHO definitions for CXR readings and improved CXR reading training capacity through WHO CRES expected in 2017
- Systematic assessment of PCV impact by outcome is expected from the PCV Review of Impact Evidence (PRIME) Project at the end of 2017

The two PCV products currently prequalified by WHO, PCV10 (Synflorix®, GSK) and PCV13 (Prevenar®, Pfizer) have overlapping but not identical serotype compositions (type 3, 6A and 19A are in PCV13, but not in PCV10) and thus aim to elicit direct immunity to a different number of serotypes. The impact of each product is not linearly proportional to the number of serotypes included in the product[14], particularly when taking both direct and indirect effects into account, because not all serotypes are equally likely to cause disease. The differences by PCV product are not consistent in across studies, making it essential to evaluate the impact of both products across a

[14]An adequate synthesis of the biologic and epidemiologic evidence on PCV performance and impact for the two PCV products across dosing schedules is being generated via the PCV Review of Impact Evidence (PRIME) Project, and will be available in October 2017 as part of the SAGE Working Group evaluation of PCV

variety of geographic and epidemiologic to best answer questions on PCV impact and inform decision-making on product.

The amount of available evidence on PCV10 and PCV13 impact varies by outcome across the globe. **In general, the most common outcomes evaluated for PCV impact are IPD and pneumonia.** Countries that have evidence on multiple outcomes may allow for triangulation of impact across endpoints, and an assessment of relationships between NP colonization and disease. It is unclear how many of these studies will have a sufficient amount of data for a valid assessment of any particular outcome, as the quality of the evidence generated in these studies has not been fully evaluated as part of this gap analysis. That assessment is ongoing in the PCV Review of Impact Evidence (PRIME), systematic review project, which will be reviewed by the SAGE WHO Working Group on PCVs whom are expected to deliberate in Q4/2017.

Figure 5: Countries evaluating PCV10 or PCV13 impact, by product currently in use

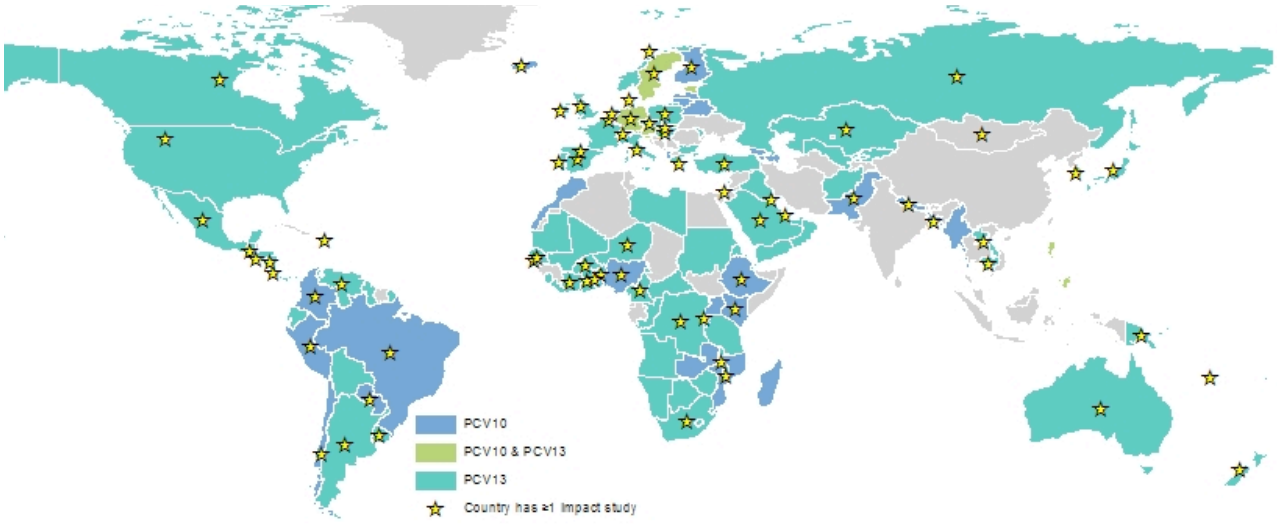


Table 8: Number and percentage of countries evaluating PCV use, by current product in NIP

	Current product in NIP*			
	PCV10 (n=33, 24%)**	**PCV13 (n=98, 70%)**	**PCV10 and PCV13 (n=8, 6%)**	**Total (n=139, 100%)**
Gavi Countries	7 (21%***)	17 (18%)	0 (0%)	24 (17%)
Non-Gavi Countries	10 (30%)	34 (35%)	4 (50%)	48 (35%)
All Countries	17 (52%)	51 (53%)	4 (50%)	72 (53%)

**Stratifies countries using and evaluating PCV impact by the current product in their NIP, not by the product(s) evaluated in the impact studies. The product(s) currently used in the NIP are often the same as the product(s) evaluated, however some countries have switched products and may or may not have evaluated all products currently and previously used.*
***All countries using the product in the NIP.*
**** Percent of all countries using the product (column header n)*

Thirty-three (24%) of the 139 countries that have introduced PCV are using PCV10, of which 17 (52%) are evaluating impact (**Figure 5** and **Table 8**). Ninety-seven (70%) of the 139 countries that have introduced PCV are using PCV13 of which 51 (53%) have ongoing or published impact studies. Eight (6%) countries are using both PCV10 and PCV13, of which 4 (50%) are evaluating impact. Seven (50%) of the 14 Gavi countries using PCV10 are evaluating impact, and 17 (40%) of the 42 Gavi countries using PCV13 are evaluating impact.

Table 9: Number and percentage of countries using and evaluating PCV, by current product in NIP and Gavi-status and region

WHO Region (number of countries using PCV)	PCV10 (n=33)		PCV13 (n=106)	
	Gavi	Non-Gavi	Gavi	Non-Gavi
AFR (38)	4/7* (57%)	0/0	12/26 (46%)	2/5 (40%)
AMR (25)	0/0	5/7 (71%)	1/4 (25%)	10/14 (71%)
EMR (14)	1/1 (100%)	0/1 (0%)	0/4 (0%)	3/8 (38%)
EUR (42)	0/3 (0%)	4/9 (44%)	0/3 (0%)	20/27 (74%)°
SEAR (3)	2/3 (67%)	0/0	0/0	0/0
WPR (17)	0/0	1/2 (50%)	4/6 (67%)	4/9 (44%)
Total (139)	7/14 (50%)	10/19 (53%)	17/44 (39%)	38/62 (58%)°

*Number evaluating product/number using product. All countries using PCV10 and PCV13 are included in PCV13.
°*Four countries use both PCV10 and PCV13 but their evaluation focuses on the impact of PCV13.*

Table 10: Number of countries evaluating impact by outcome, region and product

WHO Region (# of countries evaluating/using PCV)	PCV10 (n=17/33)					PCV13 (n=55/106)				
	IPD	**Pneumonia**	**NP Carriage**	**Mortality**	**Herd Effect**	**IPD**	**Pneumonia**	**NP Carriage**	**Mortality**	**Herd Effect**
AFR (17/38)	3/4* (75%)	3/4 (75%)	3/4 (75%)	1/4 (25%)	1/4 (25%)	5/13 (38%)	6/13 (46%)	7/13 (54%)	3/13 (23%)	5/13(38%)
AMR (16/25)	3/5 (60%)	4/5 (80%)	2/5 (40%)	4/5 (80%)	2/5 (40%)	7/11 (64%)	8/11 (73%)	3/11 (27%)	5/11 (45%)	7/11 (64%)
EMR (4/14)	1/1 (100%)	1/1 (100%)	1/1 (100%)	0/1 (0%)	1/1 (100%)	3/3 (100%)	0/3 (0%)	0/3 (0%)	0/3 (0%)	2/3 (67%)
EUR (24/42)	3/4 (75%)	2/4 (50%)	2/4 (50%)	2/4 (50%)	3/4 (75%)	16/20 (80%)	14/20 (70%)	13/20 (65%)	4/20 (20%)	15/20 (75%)
SEAR (2/3)	2/2 (100%)	2/2 (100%)	1/2 (50%)	1/2 (50%)	0/2 (0%)	**0**	**0**	**0**	**0**	**0**
WPR (9/17)	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)	1/1 (100%)	6/8 (75%)	6/8 (75%)	7/8 (88%)	3/8 (38%)	6/8 (75%)
Total (72/139)	13/17 (76%)	13/17 (76%)	10/17 (59%)	9/17 (53%)	8/17 (47%)	41/55 (75%)	34/55 (62%)	30/55 (55%)	15/55 (27%)	35/55 (64%)

* Denominator is number of impact studies for the given region and product.
°*Four countries use both PCV10 and PCV13 but their evaluation focuses on the impact of PCV13.*

SEAR has no impact evaluation of PCV13 since the 2 countries that have introduced in the region Bangladesh and Nepal are using PCV10 and have ongoing evaluations of PCV10 (**Table 10**). EMR has 4 countries evaluating PCV impact, 3 of which use PCV13. WPR has 9 countries with impact evaluations, 1 country using PCV10, 7 using PCV13, and 1 using both PCV10 and PCV13. AFR, AMR, and EUR have at least one country using each PCV product and evaluating impact.

Table 11: Countries using PCV10 and PCV13 evaluating impact, by outcome(s) measured

WHO Region (# Countries with PCV impact evaluation)	Gavi Status (# Countries with PCV impact evaluation)	Country (Vaccine Product Currently in Use)	Ongoing Study^	IPD	Pneumonia	NP carriage	Herd effect	Mortality	Evaluate Impact of Partial Vaccination	Other❖
Global Total (Number of Countries)			63	50	47	40	43	24	22	72
AFR (17)	Gavi (16)	Benin (PCV13)	✓							✓
		Burkina Faso (PCV10)	✓		✓	✓	✓	✓	✓	✓
		Cameroon (PCV13)	✓							✓
		DR Congo (PCV13)	✓			✓				✓
		Cote D'Ivoire (PCV13)								✓
		Ethiopia (PCV10)	✓			✓				✓
		Gambia (PCV13)	✓	✓	✓	✓	✓	✓	✓	✓
		Ghana (PCV13)	✓			✓				✓
		Kenya (PCV10)	✓	✓	✓	✓	✓	✓	✓	✓
		Malawi (PCV13)	✓	✓	✓	✓	✓	✓		✓
		Mozambique (PCV10)	✓	✓	✓	✓				✓
		Niger (PCV13)	✓							✓
		Nigeria (PCV10)	✓	✓	✓					✓
		Rwanda (PCV13)		✓	✓					✓
		Senegal (PCV13)	✓							✓
		Togo (PCV13)	✓	✓	✓	✓	✓			✓
	Non-Gavi (1)	South Africa (PCV13)	✓	✓	✓	✓	✓		✓	✓
	Total		15	8	9	10	6	4	4	18
AMR (16)	Gavi (1)	Nicaragua (PCV13)			✓		✓	✓		✓
	Non-Gavi (15)	Argentina (PCV13)	✓	✓	✓	✓	✓	✓	✓	✓
		Brazil (PCV10*)	✓	✓	✓	✓	✓	✓	✓	✓
		Canada (PCV13*)	✓	✓	✓	✓	✓	✓		✓
		Chile (PCV10)	✓	✓	✓		✓	✓		✓
		Colombia (PCV10)	✓	✓	✓			✓		✓
		Costa Rica (PCV13)	✓	✓	✓		✓	✓		✓
		Dominican Republic (PCV13)	✓	✓						✓

		El Salvador (PCV13*)	✓							✓
		Guatemala (PCV13)	✓		✓					✓
		Mexico (PCV13)	✓	✓	✓		✓			✓
		Paraguay (PCV10)				✓				✓
		Peru (PCV10*)	✓		✓			✓		✓
		United States (PCV13)	✓	✓	✓	✓	✓	✓	✓	✓
		Uruguay (PCV13)	✓	✓	✓		✓			✓
		Venezuela (PCV13*)	✓							✓
		Total	14	10	12	5	9	9	3	16
EMR (4)	Gavi (1)	Pakistan (PCV10)	✓	✓	✓	✓	✓		✓	✓
	Non-Gavi (3)	Kuwait (PCV13*)		✓			✓			✓
		Qatar (PCV13*)	✓	✓			✓			✓
		Saudi Arabia (PCV13)		✓						✓
		Total	2	4	1	1	3		1	4
EUR (24)	Non-Gavi (24)	Belgium (PCV10*)	✓	✓			✓			✓
		Czech Republic (PCV13)	✓	✓	✓		✓		✓	✓
		Denmark (PCV13)	✓	✓		✓	✓	✓	✓	✓
		Finland (PCV10)	✓	✓	✓		✓	✓	✓	✓
		France (PCV13)	✓	✓	✓	✓	✓	✓	✓	✓
		Germany (PCV10 & PCV13)	✓	✓	✓		✓		✓	✓
		Greece (PCV13)	✓	✓	✓		✓			✓
		Hungary (PCV13*)				✓				✓
		Iceland (PCV10*)	✓			✓				✓
		Ireland (PCV13)	✓	✓	✓	✓	✓		✓	✓
		Israel (PCV13)	✓	✓	✓	✓	✓			✓
		Italy (PCV13)	✓	✓	✓	✓	✓		✓	✓
		Kazakhstan (PCV13)	✓		✓	✓				✓
		Netherlands (PCV10*)	✓	✓	✓	✓	✓	✓	✓	✓
		Norway (PCV13*)	✓	✓	✓	✓	✓		✓	✓
		Poland (PCV13*)			✓		✓			✓
		Portugal (PCV13)	✓	✓	✓	✓	✓			✓

		Russia (PCV13)	✓							✓
		Slovakia (PCV10 & PCV13)	✓	✓						✓
		Spain (PCV13*)	✓	✓	✓		✓	✓	✓	✓
		Sweden (PCV10 & PCV13)	✓	✓		✓	✓	✓	✓	✓
		Switzerland (PCV13)	✓	✓	✓	✓	✓			✓
		Turkey (PCV13*)		✓		✓				✓
		United Kingdom (PCV13*)	✓	✓	✓	✓	✓		✓	✓
		Total	22	19	16	15	18	6	12	24
SEAR (2)	Gavi (2)	Bangladesh (PCV10)	✓	✓	✓			✓		✓
		Nepal (PCV10)	✓	✓	✓	✓				✓
		Total	2	2	2	1		1		2
WPR (9)	Gavi (4)	Cambodia (PCV13)	✓			✓				✓
		Lao PDR (PCV13)	✓		✓	✓	✓			✓
		Mongolia (PCV13)		✓	✓	✓	✓		✓	✓
		Papua New Guinea (PCV10)		✓	✓	✓				✓
	Non-Gavi (5)	Australia (PCV13*)	✓	✓		✓	✓	✓	✓	✓
		Fiji (PCV10)	✓	✓	✓	✓	✓	✓		✓
		Japan (PCV13*)	✓	✓	✓		✓			✓
		Korea (PCV10 & PCV13*)	✓	✓	✓	✓	✓	✓	✓	✓
		New Zealand (PCV13*)	✓	✓	✓	✓	✓	✓		✓
		Total	7	7	7	8	7	4	3	9

Note: Outcome measured means that a study explicitly states that the outcome was measured in the study population and/or data was reported for the outcome. Viet Nam has a study designed to measure PCV impact and collecting pre-introduction data, but has not yet introduced the vaccine into its NIP and is therefore not included here.

❖ *Other outcomes not specifically listed here, such as acute otitis media (AOM), mastoiditis, empyema, antibiotic non-susceptibility, etc.*

^ *Indicates countries with one or more ongoing impact study (i.e. a study with ongoing data collection/analysis), with future publication(s) expected.*

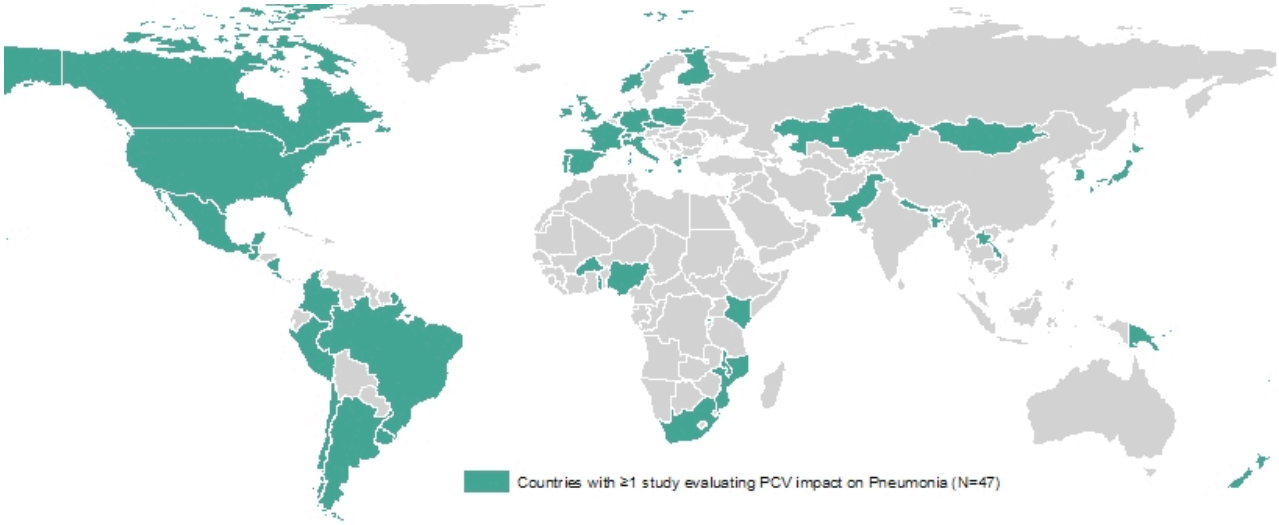
* *Indicates countries that have previously used other products, usually PCV7.*

3.5 PCV Impact Evaluations: Pneumonia

Forty-seven (65%) of the 72 countries with a PCV impact evaluation are measuring pneumonia, one of the most commonly measured, and most important outcomes. Among the countries with PCV impact evaluations pneumonia is evaluated in 9 (50%) AFR countries, 12 (75%) AMR countries, 1 (25%) EMR countries, 16 (67%) EUR countries, 2 (100%) SEAR countries and 7 (78%) of WPR countries.

Although 47 countries are evaluating impact of pneumonia, there are gaps in available evidence from countries in Africa and Asia where the highest under-5 mortality rates occur globally. Among the 10 highest burden pneumonia mortality countries (India, Nigeria, Pakistan, Democratic Republic of Congo, Angola, Ethiopia, Indonesia, Chad, Afghanistan, and Niger), 7 have introduced PCV and only 1 (Pakistan) has a pneumonia impact ongoing evaluation. Furthermore, although Nigeria is using PCV, its coverage is estimated at only 13% nationally, thus the majority of the infants in that country do not actually receive PCV[15]. Focusing on Gavi countries, 15 (63%) of the 24 Gavi countries evaluating PCV impact are collecting data on pneumonia, and represent all regions except EUR.

Figure 6: Countries with a PCV10 or PCV13 study evaluating impact on pneumonia

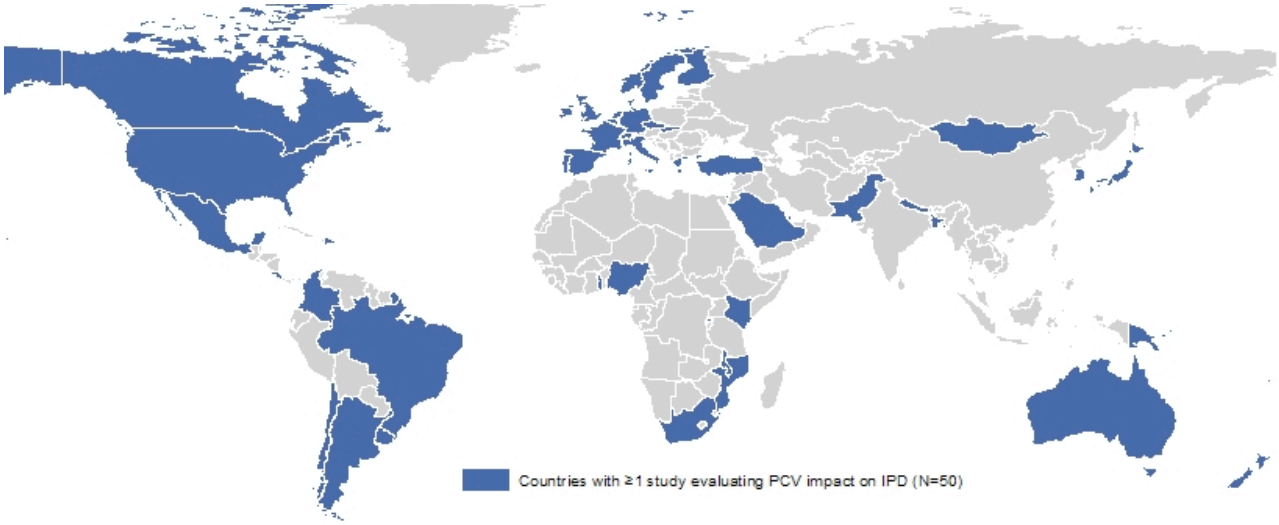


[15] 2016 Pneumonia & Diarrhea Progress Report http://www.jhsph.edu/research/centers-and-institutes/ivac/resources/IVAC-2016-Pneumonia-Diarrhea-Progress-Report.pdf

3.6 PCV Impact Evaluations: IPD

Fifty (69%) of the 72 countries evaluating PCV impact are measuring IPD. This includes 8 (44%) of AFR countries, 9 (56%) of AMR countries, 4 (100%) of EMR countries, 20 (83%) of EUR countries, 2 (100%) of SEAR countries and 8 (89%) of WPR countries with a PCV impact evaluation. Focusing on Gavi countries, 12 (50%) of the 24 Gavi countries evaluating PCV impact are collecting data on IPD, representing all but two regions, AMR and EUR.

Figure 7: Countries with ≥1 PCV10 or PCV13 study evaluating impact on IPD

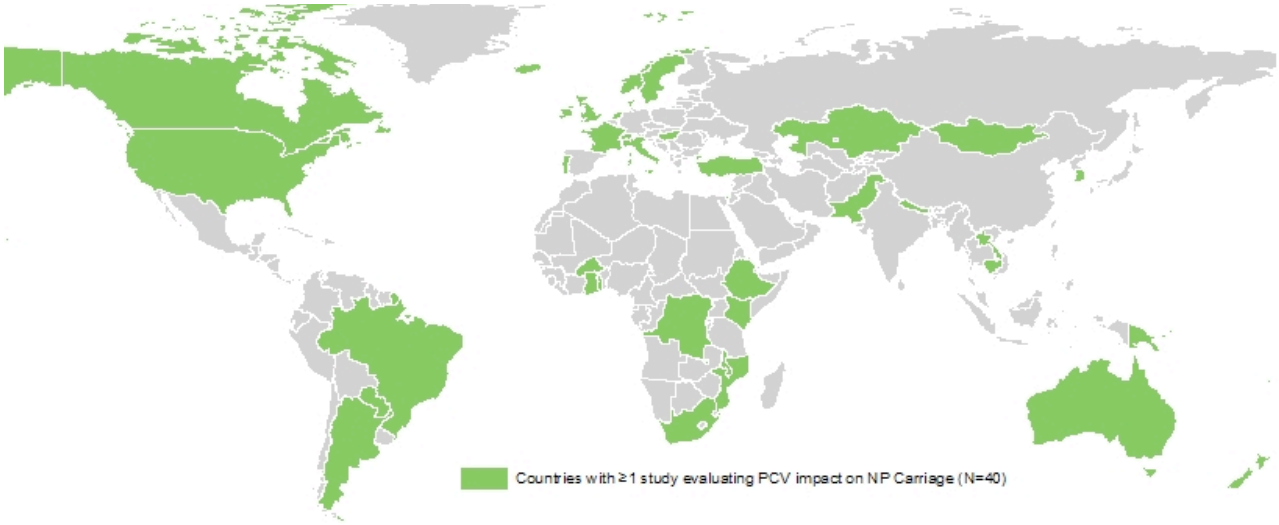


3.7 PCV Impact Evaluations: Nasopharyngeal Carriage

Forty (56%) of the 72 countries evaluating PCV impact are measuring pneumococcal nasopharyngeal (NP) carriage. This includes 10 (56%) of AFR countries, 5 (31%) of AMR countries, 1 (25%) of EMR countries, 15 (62%) of EUR countries, 1 (50%) of SEAR countries, and 8 (57%) of WPR countries with a PCV impact evaluation. Focusing on Gavi countries, 14 (58%) of the 24 Gavi countries evaluating PCV impact are collecting data on NP carriage representing all but two regions, AMR and EUR.

Of particular interest are sites that contemporaneously measure NP carriage and a disease outcome since these improve our understanding of the relationship between carriage and disease, as well as the way in which PCV can amplify its effect through this relationship (**Table 11**). There are 33 such countries (11 in Gavi countries), at least one country in every region, studying NP carriage plus either IPD or pneumonia.

Figure 8: Countries with a PCV10 or PCV13 study evaluating impact on NP carriage



Note: Viet Nam also has an ongoing PCV studies designed and prepared to measure impact on NP carriage, but are not shown here because it has not introduced PCV into its NIP.

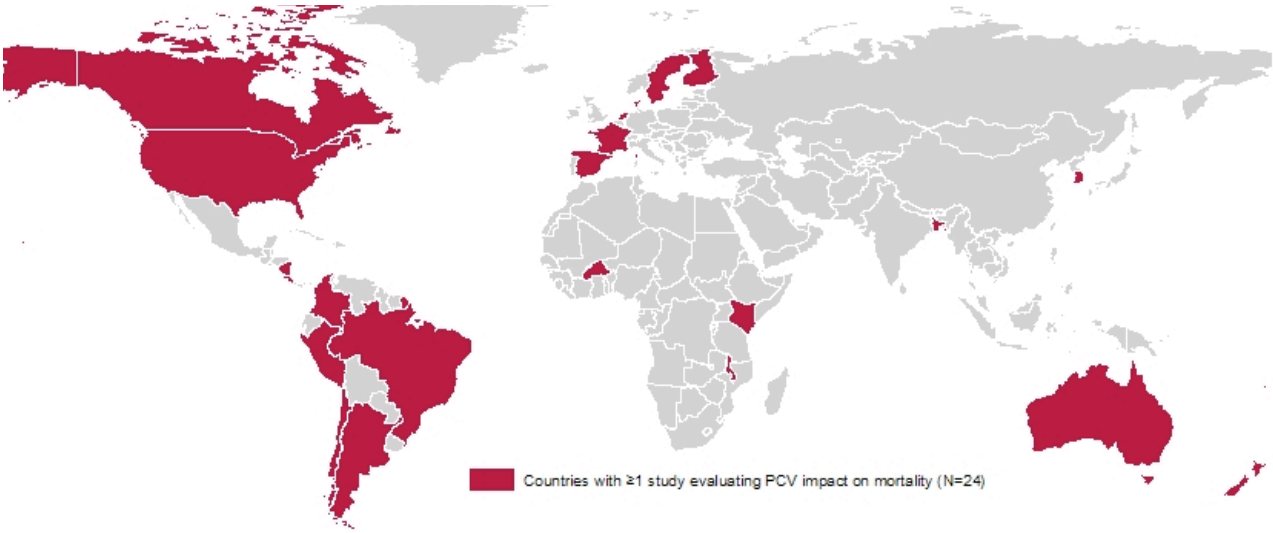
3.8 PCV Impact Evaluations: Mortality

Twenty-four (33%) of the 72 countries with PCV impact evaluations measure mortality as an outcome. These include 4 (22%) AFR countries, 9 (56%) AMR countries, 0 EMR countries, 6 (25%) EUR countries, 1 (50%) SEAR country and 4 (50%) WPR countries with a PCV impact evaluation. Six (25%) of the 24 Gavi countries evaluating PCV impact are collecting data on mortality, from AFR, AMR, and SEAR, but not EMR, EUR, or WPR.

Evaluations of PCV10 or PCV13 impact on mortality have been published in three regions: AMR (Brazil, Canada, Nicaragua, and the United States); EUR (Denmark, Spain, and Sweden); and WPR (New Zealand)[16]; only 1 was from a Gavi country (Nicaragua).

No evaluation on mortality is being done in a high mortality setting.

Figure 9: Countries with a PCV10 or PCV13 study evaluating impact on mortality

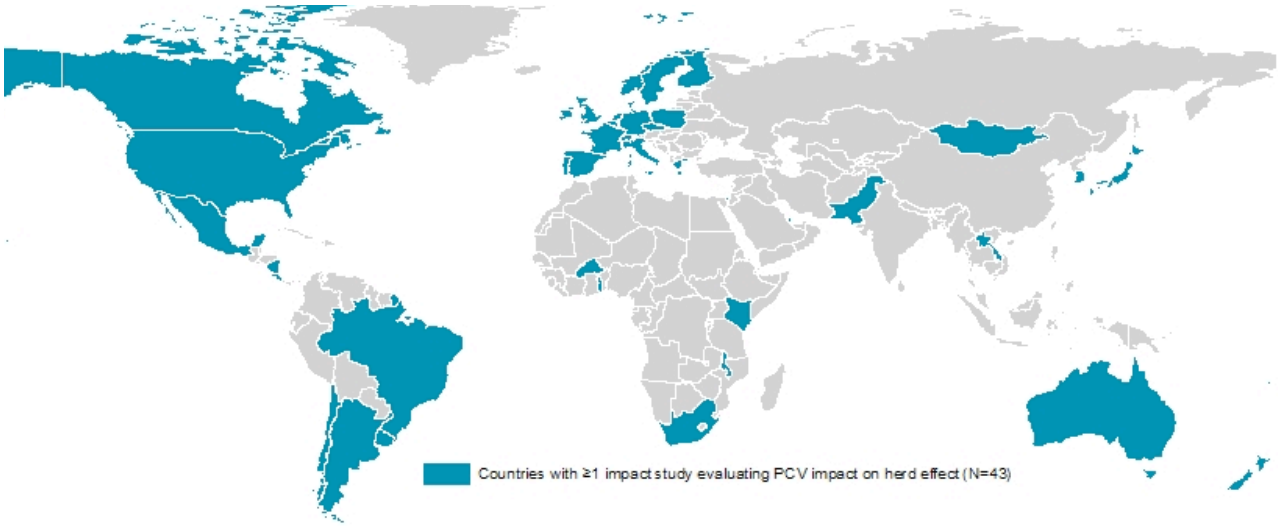


[16] Note: Data on impact of PCV9 on mortality in Gambia was published, however this study did not meet our criteria for inclusion in this analysis (i.e., we excluded results reported from impact of an unlicensed product or studies that were not of PCV in routine use).

3.9 PCV Impact Evaluations: Herd Effects on Disease and NP Colonization

Forty-three (60%) of the 72 countries with PCV impact studies are measuring herd effects of PCV (i.e., reductions in disease or colonization in unvaccinated portions of the population, including unvaccinated children and non-age-eligible older individuals). This includes 6 (33%) AFR countries, 9 (56%) AMR countries, 3 (75%) EMR countries, 18 (75%) EUR countries, 1 (50%) SEAR countries and 7 (78%) WPR countries with a PCV impact evaluation. Eight (33%) of the 24 Gavi countries evaluating PCV impact are collecting data on herd effects of PCV vaccination, from AMR, AFR, SEAR, and WPR regions but not EMR or EUR.

Figure 10: Countries with ≥1 PCV10 or PCV13 impact study measuring herd effects



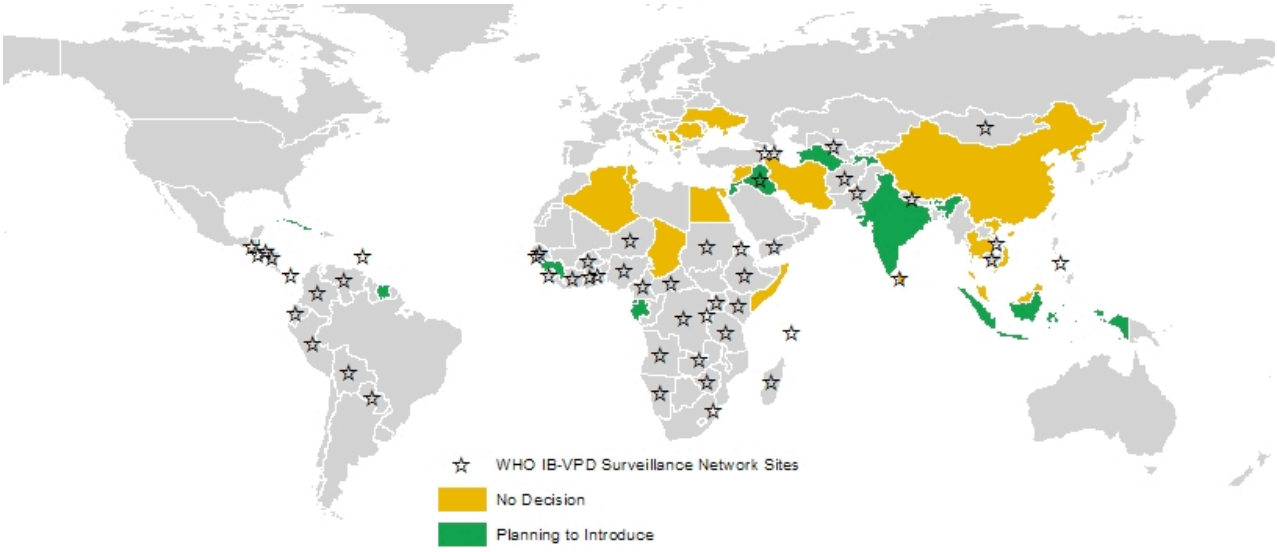
3.10 PCV Impact Evaluations: Other Outcomes

In addition to the outcomes mapped above, all 72 countries evaluating PCV impact are measuring other outcomes, 24 of which are Gavi countries. These outcomes include acute otitis media, mastoiditis, empyema, and antibiotic non-susceptibility, among others. Such outcomes are important in specific settings, particularly as vaccine serotype invasive disease reaches near elimination levels after sustained PCV use and these other outcomes may contribute to the economic and health impact case for sustained PCV use.

4. The World Health Organization (WHO)-coordinated Global Invasive Bacterial Vaccine-Preventable Disease (IB-VPD) Surveillance Network

Since 2008, the WHO-coordinated global IB-VPD surveillance network has been building an infrastructure to provide quality data for decision makers to assist with planning of appropriate public health programs. The WHO IB-VPD surveillance network has an associated laboratory network that contributes to achieving objectives to document presence of disease and identify circulating serotypes and measure serotype distribution before vaccine introduction. In the post-vaccine introduction period, the laboratory network will generate data to assess disease trends over time and monitor changes in circulating strains/serotypes in different countries and regions. In January 2016, the network included 117 Sentinel Hospital Laboratories (SHL), 20 National Laboratories (NL), 9 Regional Reference Laboratories (RRL), and 1 Global Reference Laboratory (GRL).[17]

Figure 11: Countries with WHO IBD surveillance (stars) and countries not yet using PCV (colored) by planned introduction status



[17] http://www.who.int/immunization/monitoring_surveillance/burden/laboratory/IBVPD/en/

5. Future Opportunities: Existing Infrastructure for Health Impact Evaluation of Upcoming PCV Introductions

High quality studies to measure the impact of PCV with reasonable certainty require several years' of surveillance pre-PCV introduction. It takes time to ramp up surveillance activities to a steady state level and to assess the magnitude of monthly and annual fluctuations in disease due to secular trends or due to surveillance design artifact. These fluctuations need to be quantified so they can be accounted for when monitoring disease post-PCV to distinguish impact of PCV from changes due to these other factors. It is therefore important for countries wishing to evaluate PCV impact to begin surveillance well before vaccine introduction.

In the near future, countries planning to introduce PCV constitute the list of potential new impact study settings. Globally, 23 countries have announced plans to introduce PCV into their NIPs; of which 8 (35%) are Gavi countries (India, Haiti, Cuba, Bhutan, Comoros, Guinea, Indonesia, Tajikistan) among them 2 have been approved for Gavi-support (India and Haiti) and two (India and Indonesia) are countries with very large birth cohorts.

Among these countries planning to introduce by 2020, there are varying degrees of preparedness and capacity to undertake PCV impact evaluations. Although the considerations involved in planning impact studies require careful thought, an initial step in the process of evaluating countries' future capacity to undertake vaccine impact evaluation will involve identifying the countries with either 1) existing pre-introduction data (and corresponding infrastructure to continue data collection), or 2) the ability to collect pre-introduction data before introduction (infrastructure to collect data collection, and sufficient time before vaccine rollout to collect meaningful pre-introduction data).

In settings with little infrastructure or capacity to measure disease overtime, or not enough time for sufficient years of baseline data to be collected, NP carriage studies post introduction may provide some important evidence of impact. Such may not be the ideal impact evaluation, but may contribute data supporting the use of PCVs as a proxy for disease measures overtime.

5.1 Health Impact Evaluations with Ongoing Data Collection in the Pre-PCV Era

We are aware of 4 studies in Asia that are specifically designed/funded to assess PCV impact, but are in countries that have not yet introduced the vaccine. These studies do not yet appear in any maps or tables in this report, as our definition of impact study requires that the vaccine be in use in the NIP. We describe them here.

Viet Nam: A community-randomized study is ongoing in Nha Trang, Viet Nam[18] where PCV10 is being evaluated in multiple dosing schedules (3+0, 2+1, 1+1, 0+1) to evaluate both nasopharyngeal carriage and pneumonia. Pre-introduction data is currently being collected, and results are expected in 2021. Importantly, the study aims to investigate the impact of alternate dosing schedules including reduced dosing schedules in a PCV naïve setting in Asia. Children under 2 are being evaluated in this study, except for the 0+1 arm, which includes children from 19-36 months of

[18] Vietnam impact evaluation is funded by the Bill & Melinda Gates Foundation. A complementary individual randomized study to evaluate immune response and NP carriage from the same dosing schedules for both PCV10 and PCV13 is ongoing in Ho Chi Minh City, preliminary results were presented at ISPPD-10 and final results are expected at the end of 2018. This complementary study is not included in our analyses as it was conducted outside of the context of national introduction of the vaccine.

age, to measure direct effects of PCV10. Mothers of children enrolled in the study are being evaluated for carriage to estimate indirect effects of the vaccine. This study may not inform decisions on national roll out as it was designed to evaluate alternate and reduced dosing scheduled which are not currently included in WHO recommendations.

Mongolia: Ongoing invasive bacterial disease surveillance (partially supported by the WHO-coordinated Global IB-VPD Network) in Mongolia is being used to establish pre introduction data on IPD. Mongolia has just recently introduced PCV13 in a 2+1 schedule, and thus post-introduction data is starting to be measured. In addition, nasopharyngeal carriage surveillance among patients whom are hospitalized with acute respiratory infections is ongoing to evaluate both direct and indirect impact of PCV13 in Mongolia. Pre introduction carriage results in both respiratory patients and healthy individuals under 5 years of age were presented at ISPPD-10. Results on post introduction data and evaluation of impact of PCV13 are expected in 2019.

India: India, a key country in Asia and the largest birth cohort country globally, is planning to introduce PCV13 in early 2017 and is actively constructing a plan for both the vaccine's rollout and evaluation of impact of the vaccine. At present we are aware of ongoing surveillance through the BASIS project, which characterizes the serotype distribution of *Streptococcus pneumoniae* causing invasive disease among children younger than five years of age in India. The BASIS project builds on the recently completed ASIP study to continue surveillance for invasive pneumococcal disease to provide the evidence-base in India for selection of an appropriate pneumococcal conjugate vaccine and baseline information to evaluate the impact of vaccine introduction on serotype distribution. This platform can be built upon in the future to evaluate PCV13 impact once the vaccine has been introduced into the national (or state-based) immunization program[19]. There is also a pneumonia study being conducted in northern India (UP and Bihar) with pre-PCV data being collected now. Patients have CXRs obtained and NP specimens from the nasopharynx. Additionally ICMR, in partnership with additional investigators and institutions, is evaluating potential impact study approaches.

Indonesia: Indonesia, another large birth cohort country in Asia, is in the early stages of planning an impact evaluation in Lombok. We do not have details regarding the specific outcomes that will be measured in this evaluation or the study design. Indonesia is expected to introduce PCV in 2017 but without Gavi support.[20]

5.2 World Health Organization (WHO)-coordinated Global Invasive Bacterial Vaccine-Preventable Disease (IB-VPD) Surveillance Network

Although there are many different types of existing infrastructure that could be leveraged to perform impact studies, for now we focus on existing surveillance sites in the WHO-coordinated IB-VPD Surveillance Network. Similar potential analyses of existing infrastructure to be leveraged, such as literature reviews aimed at identifying disease burden study sites, are possible but have not been conducted to date.

Of the 22 countries planning to introduce PCV, only 2 have existing WHO IBD surveillance sites, 1 in AFR and 1 in EMR (**Table 12**). As there are already impact evaluations in both AFR and EMR, building upon the WHO IBD sites in these regions presents a limited opportunity.

---

[19] There is at least one randomized controlled trial that is currently going on in India to evaluate various dosing schedules (3+0, 2+1, and 1+1) to determine the effects of PCV10 and PCV13 on nasopharyngeal carriage and immune response in a PCV naïve setting with high burden. These results are expected in 2018.
All studies we have described in this report in India are funded by the Bill & Melinda Gates Foundation.

[20] Based on communication with Gavi , October 19, 2016

Table 12 reports on 9 (of 38) countries in Asian regions (WPR and SEAR) that are planning to introduce by 2020 with WHO IB-VPD sites, which highlights the lag in PCV introductions in the region and an opportunity to build on the infrastructure of the WHO IB-VPD sites in these countries to collect pre-introduction data to incorporate into a pre/post impact evaluation in the future.

Table 12: Countries that are planning to introduce PCV by date of expected introduction through 2020, those highlighted in green have a WHO IBD surveillance site

	Countries Planning To Introduce, By Planned Intro Date
Region	2016
AFR	Cape Verde Seychelles Comoros Guinea Chad
AMR	Belize Suriname Cuba Haiti
EMR	Iraq Syrian Arab Republic
EUR	Turkmenistan Tajikistan
SEAR	Indonesia India* Bhutan Korea, Democratic People's Republic of
WPR	Samoa Tonga Tuvalu Vanuatu

**India does not have a WHO IBD site but has ongoing IBD surveillance through the BASIS project*

For all countries planning PCV introduction with IB-VPD sites, no assessment is made on the capacity within these countries to be able to leverage these data assess impact. Although these settings represent opportunities for potential impact studies, a significant amount of additional information about the existing infrastructure is required before they can be considered viable. Key considerations in this endeavor include the number of 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) and the number of years of pre-introduction data that exist – which in combination can tell us how many years of post-introduction data collection would be needed to power statistically significant impact results.

Because there are no distinct "cutoffs" for the amount of pre-introduction data required, we cannot simply apply a rule of thumb regarding the number of years of pre-introduction data that exist, or the number of years that remain until the date of planned introduction[21]. 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.

[21] There is a WHO framework for designing PCV impact evaluations: http://www.who.int/immunization/research/meetings_workshops/pcv_impact_sept13/en/

6. Economic Impact Evaluations in Countries Using PCV

OVERVIEW

- Economic studies play a key role in vaccination policies geared to improve health
  - No distinction between projected (i.e., modeled) economic benefit and measure economic impact has been made in this analysis
- Economic evaluations are usually conducted prior to vaccine introduction as a tool to guide decision-making; new evidence is showing a gradual increase in post-vaccine introduction economic studies to document impact and may play a key role in sustainability of PCV use
- The majority of completed and ongoing studies came from non-GAVI eligible countries (56/68 studies, 82%); 35 (51%) were from HIC
  - 11 (16%) economic studies focused on Gavi countries
- Financial costs (healthcare for the disease event) are most commonly reported rather than total economic costs of disease (including productivity loss, non-medical costs)
  - CEAs are likely underestimating the value of PCV
- An overwhelming majority of the evidence was found to be CEA or cost-utility analyses, comprising 75% of all economic impact studies

KEY GAPS

- PCV health economic evidence in Gavi-eligible countries is limited
- Few papers on willingness-to-pay are available in Gavi-eligible countries, limiting insights on how individuals in LMIC value vaccines
- No country has every category of economic impact analysis completed; only three countries (the U.S., Nepal and the Philippines) have used more than one type of analysis
- Clear evidence of the economic benefits of PCV in low-resource countries is not straightforward:
  - Country-specific analyses from HIC or MIC settings may not be relevant;
  - PCV has obvious clinical benefits that often did not undergo a robust economic evaluation;
  - Methodological quality of economic evaluations is variable
- Limited health economic information on PCV from countries transitioning from Gavi support, which may be the most vulnerable for sustainability

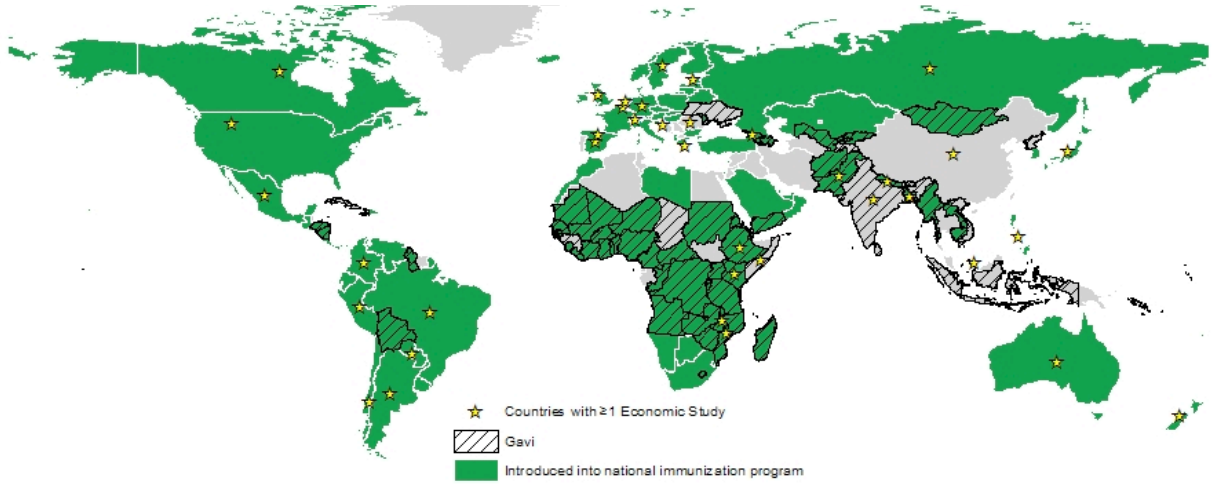
OPPORTUNITIES

- Evaluate the need for health economic studies of PCV among countries in the Preparatory and Accelerated Transition phase to support sustained PCV use
- Leverage countries that are conducting PCV health impact studies to add economic impact studies
- Enhance capacity to assess and use health economic impact data through NITAGs and other means
- Assure that advocacy and communication activities include information on health economics of PCV and are being widely disseminated and included in policy decision-making

In addition to studies that determine the health impact, evidence on the economic impact of vaccines is critical to inform vaccine program decision-making. It's particularly important for in-country policy-makers, as information on costs, returns on investment and other economic measures are critical to making the case among competing national priorities for financial and human resources.

Figure 12 depicts countries where economic evaluations of PCV10 and PCV13 have been published. AMR and EUR are well covered by economic research on pneumococcal vaccines and syndromes, as some countries in Asia (e.g. China, Japan and the Philippines). However, many countries in Asia (India, Pakistan, Nepal, and the Russian Federation) have limited economic evidence. Only 10% of the studies completed (4 of 42 completed studies) come from AFR, namely in Ethiopia, Kenya, Malawi and Somalia, and only 8% of ongoing studies (2 of 26) are from this region (in Kenya and Mozambique). No economic evidence was found in West Africa.

Figure 12: Countries with published economic evaluations of PCV10 and PCV13



Every region in the world has at least one country with an economic impact study. However, no Gavi countries in WPR and no Non-Gavi countries in AFR, EMR or SEAR have an economic impact evaluation (**Table 13**). Economic studies were mainly conducted in countries that are not eligible for GAVI support; 10 studies in Gavi-eligible settings are available to stakeholders to make decisions and shape a relevant pneumococcal vaccine policy.

Table 13: Countries evaluating PCV economic impact, by region

WHO Region	# Countries in Region		# Countries (%) in Region with ≥1 Economic Impact Study of PCV	
	Gavi	**Non-Gavi**	**Gavi**	**Non-Gavi**
AFR (47)	37	10	4 (11%)	
AMR (35)	6	29		9 (7%)
EMR (21)	6	15	2 (33%)	
EUR (53)	8	45	1 (13%)	13 (29%)
SEAR (11)	9	2	3 (33%)	
WPR (27)	7	20		6 (30%)
Total (194)	73	121	10 (14%)	28 (23%)

Definitions of types of economic evaluations

Economic evaluations aim 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 the most common forms of evaluations. When the addition of a new vaccine to an 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 is a preferred method of due to common effects of interests (e.g., lives saved, life years gained [LYG], disability-adjusted LY [DALYs], quality-adjusted LY [QALYs]).

Benefit cost analyses (BCA) are increasingly seen to quantify the full value of vaccines but have rarely been conducted for PCV.

Budget impact analyses (BIA) are increasing in importance. BIA 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). 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 the mix of vaccines with existing interventions will impact health spending.

Willingness-to-pay analysis (WTP) is used to provide direct estimates of a population's preference for an intervention and ability to pay for the intervention; or, to identify the true demand for affordable and acceptable services. Choosing a suitable method depends on the task underlying the estimation of WTP and is influenced by conceptual considerations (e.g. if individual estimates are required or not) and practical restrictions (time and budget availability). Results of WTP studies assist in evaluations and decision-making on vaccine use and immunization programs.

Costing studies, while not a type of economic evaluation per se, are important components of the comprehensive economic assessment of disease. A common approach is the **cost of illness** (COI) or cost burden that estimates the total costs attributable to a particular disease rather than a particular intervention. COI studies aim to inform choices regarding health care resource allocation. COI identifies those elements of cost that might be reduced by prevention or by a more effective treatment, and can identify the illnesses that consume the most health care resources. There are two distinct approaches to undertaking a COI study: the prevalence approach and the incidence approach. These approaches refer to the manner in which costs are attributed to a particular illness. A simpler approach to costing is to value and measure costs per case reported.

Types of PCV economic impact studies

Most economic studies identified were CEA or CUA (75%) in both Gavi and non-Gavi countries (**Figure 13, 14**). Such studies assess the potential economic impact of a specific vaccine intervention by providing average estimates for averted disease treatment costs, and compare them to the costs of the vaccine. A cost-effectiveness study's external validity is difficult to assess, as the estimates it provides are only valid for the specified comparison and in the chosen setting and time. The remaining studies included cost analyses (9%), COI (7%), BIA (6%) and WTP (3%) analyses. Overall, the lack of BIA and WTP evidence indicates a gap in knowledge that could better inform country-level policies and optimize programs and budgets.

Figure 13: Study types evaluating PCV economic impact

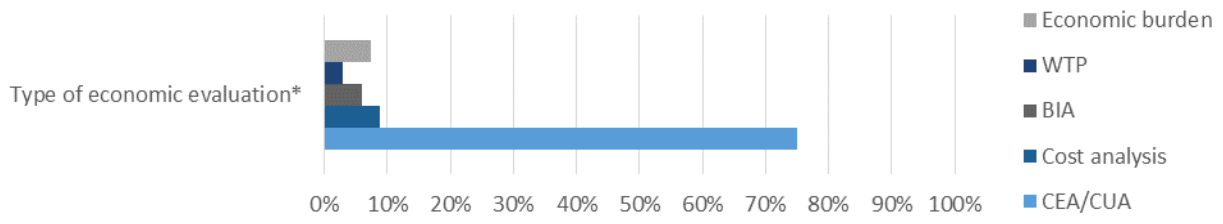
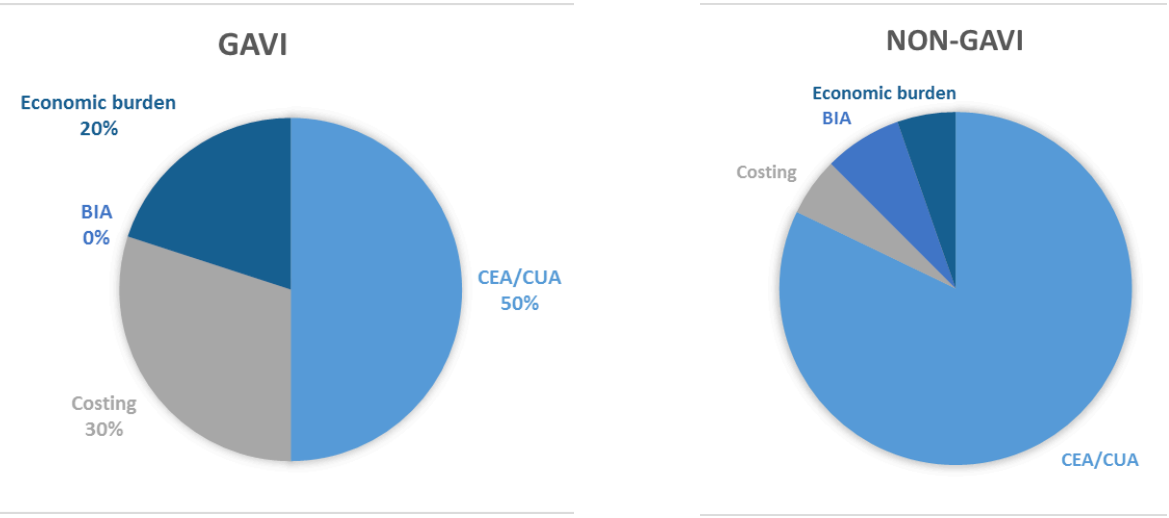


Figure 14: Study types evaluating PCV economic impact by Gavi status



The breakdown of types of economic impact analyses performed was similarly skewed towards CEA/CUA studies (**Table 14**). No single country had every category of economic impact analysis, and the vast majority of countries (26, or 79%) had *only* CEA/CUA studies. Only three countries (the U.S., Nepal and the Philippines) had evidence that used more than one type of analyses.

Although the majority of countries have not evaluated economic impact of PCV, a significant number of Gavi countries using PCV have entered or will soon enter the transition phases from Gavi support. During transition, the country's share of financing for PCV will substantially increase until the country must fully self-finance the full cost of the program (see countries shaded in green in **Table 15**). In these situations, decision-makers considering the financial aspects of sustainability may need information on the expected costs and economic benefits of PCV in order to make well-informed decisions.

Of the two Gavi countries already fully self-financing (Honduras and Mongolia), neither has an economic impact study indicating that availability of economic information may vary substantially by country. Of the 32 countries in the Preparatory Transition and the Accelerated Transition phases, only 5 have economic impact studies to inform future sustainability financing decisions (Bangladesh, Georgia, India, Kenya, Pakistan). Although data from other countries in similar regions may be available to Gavi-transitioning countries, each country's health and economic system is unique (i.e. some are public, some are private, currencies differ, etc.) and regional use of country-specific data is unlikely to be informative for economic studies.

Unlike health impact studies, which require several years of preparation as well as several years of data collection to observe significant impact, economic evaluations usually require less preparation and data collection time (and often fewer resources), but can still provide important evidence for decision-makers. Thus, for countries in Preparatory or Accelerated Transition, there may be opportunity for economic evaluations to inform decision-making on sustained PCV use.

Table 14: Countries with studies evaluating PCV economic impact, by type of analysis

WHO Region (# Countries with PCV economic impact evaluation)	Gavi Status (# Countries with PCV economic impact evaluation)	Country	CEA/CUA	COI	BIA	WTP	Economic Burden
Global Total (Number of Countries)			29	6	3	2	2
AFR (4)	Gavi (4)	Ethiopia	✓				
		Kenya	✓				
		Malawi		✓			
		Mozambique		✓			
		Total	2	2			
AMR (9)	Non-Gavi (9)	Argentina	✓	✓			
		Brazil	✓				
		Canada	✓	✓			
		Chile	✓				
		Colombia	✓				
		Mexico	✓				
		Paraguay	✓				
		Peru	✓				
		United States	✓	✓	✓		
		Total	9	3	1		
EMR (2)	Gavi (2)	Pakistan					✓
		Somalia	✓				
		Total	1				1
EUR (14)	Gavi (1)	Georgia	✓				
	Non-Gavi (13)	Belgium	✓				
		Croatia	✓				
		Estonia	✓				
		France			✓		
		Germany	✓				
		Greece	✓				
		Netherlands	✓				
		Romania	✓				
		Russian Federation	✓				
		Spain	✓				
		Sweden	✓				
		Switzerland	✓				
		United Kingdom	✓				
		Total	13		1		
SEAR (3)	Gavi (3)	Bangladesh				✓	
		India				✓	
		Nepal		✓			✓
		Total		1		2	1
WPR (6)	Non-Gavi (6)	Australia	✓				
		China	✓				
		Japan	✓				
		Malaysia	✓				
		New Zealand	✓				
		Philippines	✓		✓		
		Total	6		1		

Table 15: Countries with studies evaluating economic impact, by type current Gavi transition status
(Countries shaded green indicate available PCV economic evaluation)

WHO Region	Introduction Status	Non-Gavi Countries	Gavi Countries, by 2016 Gavi transition status			
			Initial Self Financing could reach fully self-financing within **7 years** at earliest	**Preparatory Transition** *could* reach fully self-financing within **6 years** at earliest	**Accelerated Transition** *must* reach fully self-financing within **5 years**	**Fully self-financing**
AFR (18/38)	Introduced PCV into NIP	BOTSWANA MAURITIUS NAMIBIA SWAZILAND SOUTH AFRICA	BENIN BURKINA FASO DR CONGO ETHIOPIA GAMBIA MALAWI MOZAMBIQUE NIGER RWANDA TOGO BURUNDI CAR ERITREA GUINEA-BISSAU LIBERIA MADAGASCAR MALI SIERRA LEONE TANZANIA UGANDA ZIMBABWE	CAMEROON CÔTE D'IVOIRE GHANA KENYA NIGERIA SENEGAL LESOTHO MAURITANIA SAO TOME AND PRINCIPE ZAMBIA	CONGO ANGOLA	
AMR (16/25)	Introduced PCV into NIP	ARGENTINA BRAZIL CANADA CHILE COLOMBIA COSTA RICA DOMINICAN EL SALVADOR GUATEMALA MEXICO PARAGUAY PERU UNITED STATES URUGUAY VENEZUELA BAHAMAS BARBADOS ECUADOR JAMAICA PANAMA TRINIDAD AND			NICARAGUA BOLIVIA GUYANA	HONDURAS
EMR (4/14)	Introduced PCV into NIP	KUWAIT QATAR SAUDI ARABIA BAHRAIN LEBANON LIBYA MOROCCO OMAN UNITED ARAB	AFGHANISTAN	PAKISTAN DJIBOUTI SUDAN YEMEN		
	Not introduced		SOMALIA			

EUR (24/42)	Introduced PCV into NIP	BELGIUM CZECH REPUBLIC DENMARK FINLAND FRANCE GERMANY GREECE HUNGARY ICELAND IRELAND ISRAEL ITALY KAZAKHSTAN NETHERLANDS NORWAY POLAND PORTUGAL RUSSIA SLOVAKIA SPAIN SWEDEN SWITZERLAND TURKEY UNITED ALBANIA ANDORRA AUSTRIA BELARUS BULGARIA CYPRUS ESTONIA LATVIA LITHUANIA LUXEMBOURG MONACO SLOVENIA		KYRGYZSTAN	ARMENIA AZERBAIJAN GEORGIA MOLDOVA UZBEKISTAN	
	Not introduced	CROATIA ROMANIA				
SEAR (2/3)	Introduced PCV into NIP		NEPAL	BANGLADESH MYANMAR		
	Not introduced			INDIA		
WPR (8/16)	Introduced into NIP	AUSTRALIA JAPAN NEW ZEALAND MARSHALL MICRONESIA NIUE PALAU PHILIPPINES	CAMBODIA	LAO PDR SOLOMON ISLANDS	PNG KIRIBATI	MONGOLIA
	Not introduced	CHINA MALAYSIA				

8. Acknowledgements

This report was written by Olivia Cohen, Kirthini Muralidharan, Katrin Gorham, Kate O'Brien, and Maria Deloria Knoll. Section 6 of the report (on the economic evidence) was written by Gatien de Broucker and Dagna Constenla.

The VIEW-Hub and development of this technical analysis output was supported by the Bill & Melinda Gates Foundation (BMGF) and Gavi, the Vaccine Alliance, as part of the PCV Technical Coordination Project and the Targeted Assessment Study Coordination (TASC), respectively

Vaccine introduction dates and proposed impact studies do not imply an obligation by any funding organization or country. Information reported here reflects documentation or communication that we have received from our partners (including Gavi, the Bill & Melinda Gates Foundation, the US Centers for Disease Control & Prevention, the World Health Organization), Pfizer, and GSK, as well as others).

The report leverages the VIEW-hub introductions and impact databases (www.VIEW-hub.org), which is supported by multiple institutions including Gavi and BMGF. Various data sources and information were used to generate the VIEW-Hub platform, 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.

For any inquiries or feedback on this gap analysis report please contact Olivia Cohen at ocohen3@jhu.edu, and on VIEW-Hub please contact Kirthini Muralidharan at kmurali2@jhu.edu

Appendix B. Global PCV Introductions, by Region

WHO Region	Country		
AFR	ANGOLA	GHANA	NIGERIA
	BENIN	GUINEA-BISSAU	RWANDA
	BOTSWANA	KENYA	SAO TOME AND PRINCIPE
	BURKINA FASO	LESOTHO	SENEGAL
	BURUNDI	LIBERIA	SIERRA LEONE
	CAMEROON	MADAGASCAR	SOUTH AFRICA
	CENTRAL AFRICAN REPUBLIC	MALAWI	SWAZILAND
	CONGO	MALI	TANZANIA
	CONGO, DR	MAURITANIA	TOGO
	CÔTE D'IVOIRE	MAURITIUS	UGANDA
	ERITREA	MOZAMBIQUE	ZAMBIA
	ETHIOPIA	NAMIBIA	ZIMBABWE
	GAMBIA	NIGER	
AMR	ARGENTINA	DOMINICAN REPUBLIC	PANAMA
	BAHAMAS	ECUADOR	PARAGUAY
	BARBADOS	EL SALVADOR	PERU
	BOLIVIA	GUATEMALA	TRINIDAD AND TOBAGO
	BRAZIL	GUYANA	UNITED STATES
	CANADA	HONDURAS	URUGUAY
	CHILE	JAMAICA	VENEZUELA
	COLOMBIA	MEXICO	
	COSTA RICA	NICARAGUA	
EMR	AFGHANISTAN	LIBYAN ARAB JAMAHIRIYA	SAUDI ARABIA
	BAHRAIN	MOROCCO	SUDAN
	DJIBOUTI	OMAN	UNITED ARAB EMIRATES
	KUWAIT	PAKISTAN	YEMEN
	LEBANON	QATAR	

EUR	ALBANIA	GEORGIA	MONACO
	ANDORRA	GERMANY	NETHERLANDS
	ARMENIA	GREECE	NORWAY
	AUSTRIA	HUNGARY	POLAND
	AZERBAIJAN	ICELAND	PORTUGAL
	BELARUS	IRELAND	RUSSIAN FEDERATION
	BELGIUM	ISRAEL	SLOVAKIA
	BULGARIA	ITALY	SLOVENIA
	CYPRUS	KAZAKHSTAN	SPAIN
	CZECH REPUBLIC	KYRGYZSTAN	SWEDEN
	DENMARK	LATVIA	SWITZERLAND
	ESTONIA	LITHUANIA	TURKEY
	FINLAND	LUXEMBOURG	UNITED KINGDOM
	FRANCE	MOLDOVA, REPUBLIC OF	UZBEKISTAN
SEAR	BANGLADESH	MYANMAR	NEPAL
WPR	AUSTRALIA	LAO PEOPLE'S DEMOCRATIC REPUBLIC	PALAU
	CAMBODIA	MARSHALL ISLANDS	PAPUA NEW GUINEA
	FIJI	MICRONESIA, FEDERATED STATES OF	PHILIPPINES
	JAPAN	MONGOLIA	SINGAPORE
	KIRIBATI	NEW ZEALAND	SOLOMON ISLANDS
	KOREA, REPUBLIC OF	NIUE	

Gavi countries are highlighted in gold.