July 2015

State of PCV Use and Impact Evaluations

PCV Technical Coordination Project

A strategic gap analysis of the amount of evidence generated from published and ongoing PCV impact studies in the context of routine immunizations globally. Compiled for the July 31, 2015 deliverables of the PCV Technical Coordination Project and the Reduced Dose Policy Analysis funded by the Bill & Melinda Gates Foundation.

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Executive Summary

SCOPE of ANALYSIS: This report describes the state of PCV10 and PCV13 impact evidence in the context of PCV introductions globally as of July 2015. This was undertaken for the PCV Technical Coordination Project and PCV Reduced Dose Policy Analysis, both funded by the Bill & Melinda Gates Foundation. Specifically, this report describes the ***amount of evidence*** that is published or actively being collected/analyzed on PCV10 and PCV13 impact and identifies key gaps. The strategic analysis of the technical findings from these studies is ongoing and will help inform countries, donors, and key global and regional partners about areas of uncertainty, risk, and emerging technical or programmatic issues.

ANALYSIS FINDINGS:

OVERALL: There are 44 countries with PCV10 or PCV13 impact studies in the context of introduction of the vaccine into routine programs, published or ongoing as of July 2015, reporting on various outcomes of interest for various recommended dosing schedules. Of the countries that have introduced PCV10 or PCV13, 35% have a published or ongoing impact study; at least one study is ongoing in every WHO region.

PRODUCT: Seventy-three percent of countries using PCV are using PCV13; this does not vary by Gavi/non-Gavi status. Among the countries that have introduced PCV, the fraction with an impact evaluation is similar by vaccine type (34% of PCV13 vs. 38% of PCV10 using countries have an impact evaluation).

SCHEDULE: Seventy-six percent of countries are using a 3-dose schedule (i.e., 2p+1 or 3p+0). All Gavi countries, except for Nepal and Moldova (using 2p+1), are using a 3p+0 schedule. More countries (n=18) and a greater fraction of countries (45%) using a 2p+1 schedule have an impact evaluation than countries using 3p+0 schedules (n=15, 27%) or 3p+1 schedules (n=11, 37%).

OUTCOME: Pneumonia and IPD are the most commonly measured PCV impact outcomes across all countries. NP carriage is also being monitored in many studies. Impact on mortality and economic outcomes are measured least by countries with PCV studies.

PCV Impact Studies

PCV impact studies are essential for monitoring the health impact resulting from the rapid, widespread PCV rollout that has occurred over the past 5 years in Gavi countries and over the past 15 years globally. The pace of PCV introduction and progress toward universal vaccine coverage has been more rapid than for any vaccine in the past with the exception of the regional use of MenAfriVac. With this massive population level change in immunity, it is important to monitor changes in the epidemiology of disease post-introduction of PCV into routine immunization programs, especially because the currently licensed PCV products target some, but not all, serotypes of the *Streptococcus pneumoniae* organism. These studies generate the ***evidence*** that will inform program optimization and will drive the strategy on new and modified pneumococcal vaccines, treatment regimens, and other pneumococcal disease control strategies. These PCV impact results influence policy for PCV introductions in countries that have not yet made a decision on introduction, program optimization in countries already using PCV, and for financing sustained use in countries that will move toward self-financing (i.e., graduate from Gavi support).

This report aims to describe and evaluate the ***availability*** of evidence on PCV10 and PCV13 impact by reporting the number of impact studies per country and key information on PCV products, schedules, and outcomes assessed in the evaluations. This analysis can be used to identify potential gaps within the objectives of the PCV Technical Coordination Project and the Reduced Dose Policy Analysis funded by the Bill & Melinda Gates Foundation. The evidence included in this analysis is described in **Table 1**.

Table 1. Inclusion and exclusion criteria for PCV impact studies described in this report, by product and country income group

	High-income countries	Low- and middle-income countries

PCV10 or PCV13	**Included**:
	Impact studies from HICs with routine PCV use
	• Published: extensive search (2009- June 2015)
	• Unpublished:
	  ○ Opportunistically identified and included
	  ○ Published PCV7 surveillance, ongoing for PCV10/13
		Included:
		Impact studies from LMICs with routine PCV use
		• Published: extensive search (2009- June 2015)
		• Unpublished: systematically identified through[1]
		  ○ Gavi-funded studies list
		  ○ BMGF-funded studies list
		  ○ CDC collaborations list
		  ○ GREEN (Latin America Collaboration)
		  ○ Communications with other partners

	Excluded: Research studies outside context of routine use	**Excluded**: Research studies outside context of routine use
PCV7 or unlicensed products	**Excluded all PCV7-only information from this impact gap analysis** • PCV7 information was systematically abstracted for the Dosing Landscape Project (papers published (1990-2010)[2] for IPD, pneumonia, NP, mortality, indirect effects; it is available, as needed for any strategic questions/issues. from the Dosing Landscape Project **Included PCV7 studies if the study also evaluated PCV10 or PCV13**	

[1] Ongoing studies in EMR, SEAR, and AFR were included to a high a degree of certainty. Ongoing studies in the PAHO region are included, but verification of the data from these studies is ongoing through collaboration between the PCV Technical Coordination Project and the study teams in the region.

[2] Systematic review conducted by IVAC/CDC for Dosing Landscape Project (2010) was leveraged.

The most recent WHO Vaccine Preventable Diseases Surveillance Bulletin reports that there are 128 sites in 56 countries reporting IPD surveillance data to the WHO program; 57 sites in 41 countries meet the following criteria for consistent performance:

(1) Enrolled cases in all 12 months of the year AND

(2) (a) enrolled ≥100 meningitis cases or ≥500 cases with suspected pneumococcal disease (meningitis, sepsis or pneumonia),

OR

(b) enrolled ≥50 meningitis cases or ≥250 cases with suspected pneumococcal disease (meningitis, sepsis or pneumonia), AND collected blood or cerebrospinal fluid (CSF) specimens on >90% of enrolled cases.

Of these 57 consistently performing sites, 45 are in Gavi-eligible countries that are currently receiving financial support from WHO. These data may in the future be used to measure impact of PCV in those countries that have introduced. This analysis only includes data from WHO Invasive Bacterial Surveillance Sites if they have published them as evidence of PCV impact in a peer-reviewed journal.

We have included a summary table from the WHO Bulletin (**Table 2**) on the amount of data that is available from this surveillance system; further details can be found on the WHO surveillance website.[3] *We will create a table of individual countries with WHO IBD surveillance sites for the PCV impact study gap analysis; if the list is compiled prior to the next deliverable date, it will be submitted to the Foundation as supplemental supporting material.*

Table 2: Number of reporting countries and sites that met criteria for consistent surveillance performance and number of children <5 years of age hospitalized for the treatment of suspected meningitis, pneumonia, or sepsis in consistently performing and targeted sites, WHO Invasive Bacterial Vaccine Preventable Disease Network, July 2013-July 2014.

Region	Number of Member States with at least one site meeting criteria	Number of sites meeting criteria	Number of sites receiving targeted* support from WHO meeting criteria for consistent performance	Of sites receiving WHO targeted support and meeting criteria for consistent performance		
				Number of children <5 years of age enrolled with suspect meningitis (% of total global cases)	Number of children <5 years of age enrolled with suspect pneumonia or sepsis (% of total global cases)	Total number of suspected meningitis, pneumonia or sepsis cases enrolled
AFR	20	26	22	6964 (38)	11 (<1)	6975
AMR	7	9	3	1499 (8)	4073 (32)	1499
EMR	4	8	8	3547 (20)	810 (6)	4357
EUR	4	5	4	427 (2)	N/A	427
SEAR*	3	5	5	5127 (28)	5857 (46)	10,984
WPR	3	4	3	625 (3)	1891 (15)	2516
Total	**41**	**57**	**45**	**18,189 (100)**	**12,642 (100)**	**26,758**

**Targeted defined as a consistently performing site in a Gavi-eligible country that receives financial support from WHO.*
Source: Vaccine Preventable Diseases Surveillance, Global Invasive Bacterial and Rotavirus Surveillance Bulletin. Volume 11: Data Period 2013-2014. July 2015.

[3] http://www.who.int/immunization/monitoring_surveillance/burden/VPDs/en/

I. PCV Impact Studies

Key Messages

- Availability of PCV impact data in routine use is dependent on dates of introduction, therefore evidence from the countries using PCV in the Africa region, where introduction started earlier, is more mature than that from the Asia region.

- 35% (44 of 126) of countries using PCV10 or PCV13 have a published or ongoing impact study.
    - 10 (29%) in the WHO African region (AFR)
    - 13 (52%) in the Americas Region (AMR)
    - 1 (8%) in the Eastern Mediterranean Region (EMR)
    - 12 (32%) in the European Region (EUR)
    - 2 (100%) in the South-East Asia Region (SEAR)
    - 6 (40%) in the Western Pacific Region (WPR)

- **Product**: More impact evaluations in PCV13 using countries (n=31) than in PCV10 using countries (n=13). While the fraction of PCV using countries with an impact evaluation is similar for the two products globally, among Gavi countries a greater fraction of PCV10 using countries have impact evaluations (although there are more total impact studies of PCV13 in Gavi countries).

    - 38% (13 of 34) countries using PCV10 have ongoing or published impact studies.
        - 46% (6 of 13) Gavi countries using PCV10 have an impact evaluation established.

    - 34% (31 of 92) countries using PCV13 have ongoing or published impact studies.
        - 25% (9 of 36) Gavi countries using PCV13 have an impact evaluation established.

- **Schedules**: There are impact evaluations of all recommended schedules: n=18 2p+1, n=15 3p+0, and n=11 3p+1. A greater fraction of countries using 2p+1 (45%) have an impact evaluation than either 3p+0 (27%) or 3p+1 (37%). Impact studies in Gavi countries are dominated by 3p+0 schedules (14 of 15 studies).

    - 45% (18 of 40) of countries using a 2p+1 schedule for their PCV program have ongoing or published impact studies.
        - 1 of the 2 Gavi countries using a 2p+1 is evaluating impact.

    - 27% (15 of 56) of countries using a 3p+0 schedule for their PCV program have ongoing or published impact studies.
        - 30% (14 of 47) of Gavi countries using 3p+0 are evaluating impact.

- 37% (11 of 30) countries using a 3p+1 schedule for their PCV program have ongoing or published impact studies.
    - No Gavi country is using or evaluating this dosing schedule.

- Two countries, Nepal and Bangladesh, are currently evaluating PCV schedules that are modifications of the standard EPI 6, 10, 14 week schedule; this change was motivated by wanting to avoid giving 3 injections at the 14-week visit. Nepal's schedule (6w, 10w, 9m) is not in accordance with the recommended minimum 8-week interval between the two primary doses in a 2p+1 schedule. Bangladesh's schedule (6w, 10w, 18w) is aligned with the WHO recommendation for a minimum 4 week interval between doses in a 3p+0 schedule.

- **Disease Outcomes**: IPD and pneumonia are evaluated most commonly across all PCV impact studies (each at 56% of studies). Herd effects and NP carriage are measured in many studies (45% and 33%, respectively). However, mortality and economic outcomes are each being measured in only 14 (17%) of the 82 studies that are evaluating PCV impact.

    - IPD, pneumonia and NP carriage are measured in at least one study in every WHO region.

    - 57% of countries with at least one PCV impact study are measuring indirect effects of the vaccine.
        - At least 1 impact study measuring this outcome exists in every region, except for EMR.

    - Data on PCV impact on mortality are being collected in ongoing/published 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 three regions: AMR (Brazil, Chile, Nicaragua, and the United States), EUR (Denmark), and WPR (New Zealand).

    - Other outcomes being measured by PCV impact studies include urine antigen detection validation, immunogenicity, and safety.

    - Sites measuring multiple outcomes allow for triangulation of impact and an assessment of relationships between changes in NP colonization and the disease impacts, and analysis of such sites is a part of ongoing work. Currently, there are 8 known studies (mostly unpublished) in 7 countries (Chile, Gambia, Malawi, Mozambique, Pakistan, Papua New Guinea, and Togo) that are evaluating NP colonization along with one or more disease outcome.

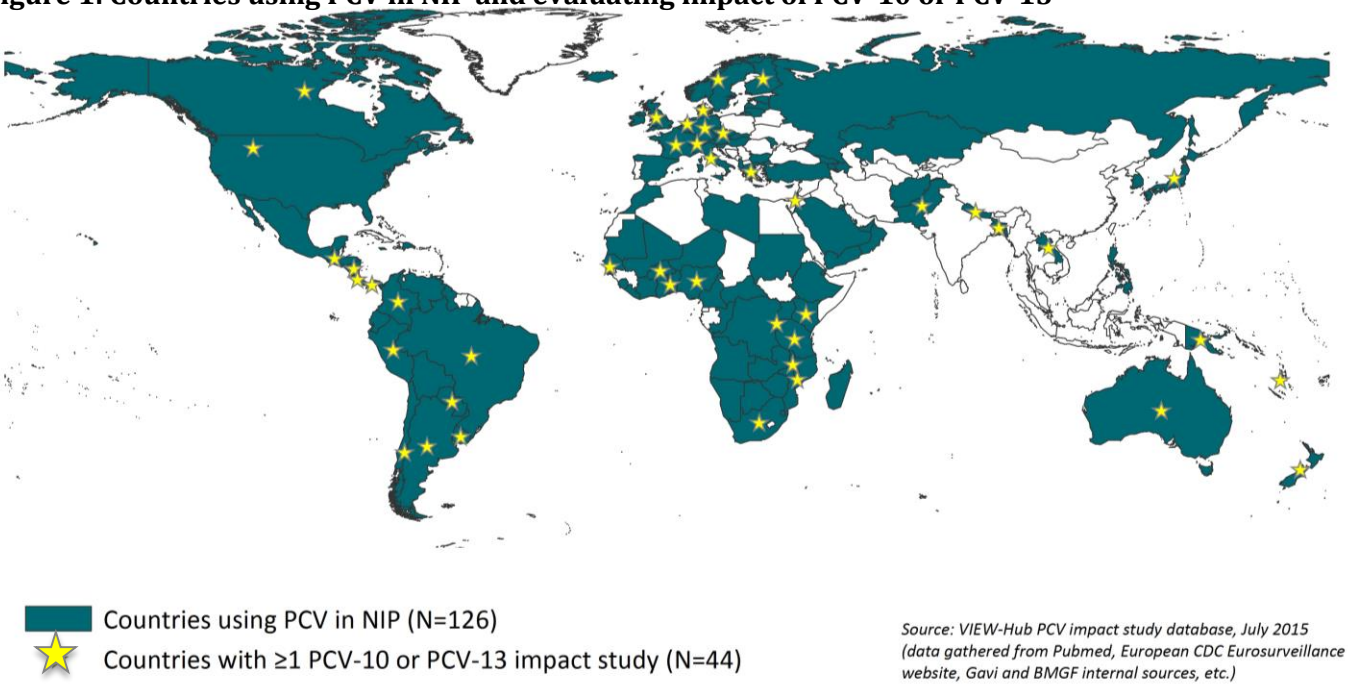
Introduction

Monitoring the impact of a vaccine in a routine use program is considered a core element of vaccine program management and disease control monitoring. However, the capacity to undertake that monitoring is absent in some countries and insufficient to monitor impact in others. This section of the report evaluates the PCV10 and PCV13 impact study availability. Subsequent sections provide the context for this impact study section.

Findings

- Although 126 countries have introduced PCV10 or PCV13, only roughly one-third are actively monitoring PCV impact on colonization or disease (**Figure 1**).

Figure 1: Countries using PCV in NIP and evaluating impact of PCV-10 or PCV-13

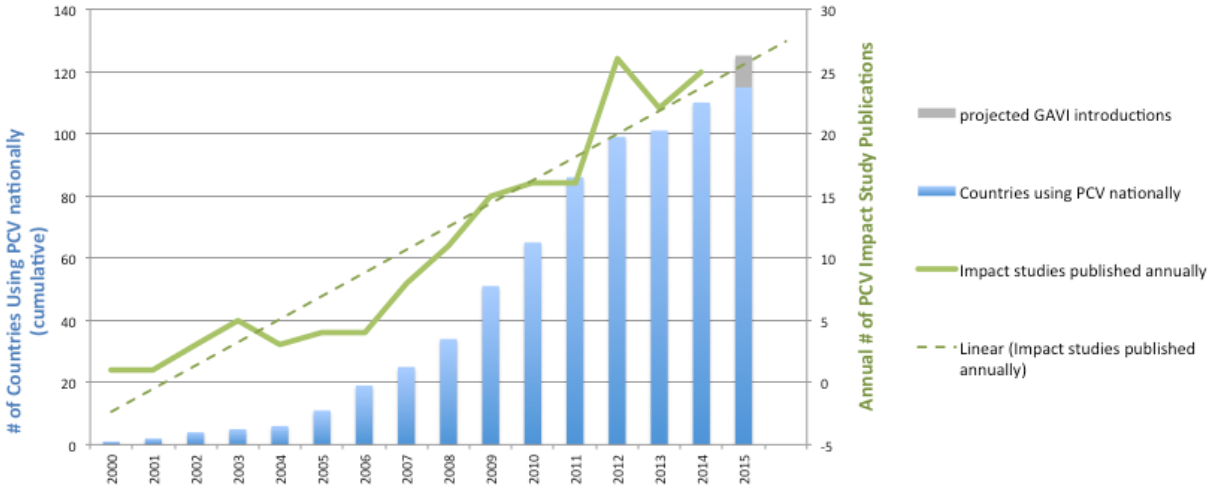


- From a global or regional perspective, not every country needs to have an impact study in order for the technical community to have credible insights into the impact of PCV on communities and populations. However, there need to be studies in countries representing the different epidemiological and geographic settings in order to inform global and regional policies and that countries with similar epidemiological settings can use in the absence of local 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 these evaluations.

- Nevertheless, availability of PCV impact studies in the published literature has increased and is expected to increase more rapidly as more countries will soon have sufficient number of years of post-PCV introduction observation to begin the analysis of impact. In an analysis of PubMed, from 2013-2015, an average of 25 PCV

impact studies were published per year, compared to an average of 16 studies per year from 2010-2012 (**Figure 2**).

Figure 2: Number of countries using PCV nationally & annual number of PCV impact study publications



Source: Analysis conducted by IVAC, 2015

- As results from studies on PCV10 and PCV13 become available, summary analyses can be conducted to assess many of the technical questions about quantitative impact observed (rather than gaps in availability of PCV impact data).

PCV Impact Study Gaps by Region

- All WHO regions have at least one country that is undertaking a PCV impact study, but the number and proportion of regional countries with such evaluations vary substantially (**Table 3**).

Table 3: Availability of PCV10 or PCV13 impact studies, by region

WHO Region (Total # Countries)	# Countries (%) in Region with PCV Routine Use	# Countries (%) with PCV Routine Use with ≥1 PCV10 or PCV13 Impact Study	# PCV10 or PCV13 Impact Studies
AFR (47)	34 (72%)	10 (29%)	17
AMR (35)	25 (97%)	13 (52%)	33
EMR (21)	13 (62%)	1 (8%)	1
EUR (53)	37 (70%)	12 (32%)	20
SEAR (11)	2 (18%)	2 (100%)	4
WPR (27)	15 (56%)	6 (47%)	7
Total (194)	126 (65%)	44 (35%)	82

- The regions with the least data are the Eastern Mediterranean Region, where we are aware of only one country that has an impact evaluation (Pakistan) among the 13 countries using PCV, and the South East Asia Region, where only two countries have introduced PCV, but they both have ongoing evaluations (Nepal and Bangladesh). There appears to be a paucity of studies in Eastern Europe and the Middle East.

    - *It is worth noting that we have not yet vetted this information with the WHO Regional Offices. It is possible that additional impact evaluations are ongoing.*

- Although 12 EUR countries have at least 1 PCV impact study, these are largely concentrated in Western Europe. There appears to be a gap in evaluations from the Eastern European countries within this region.

- Availability of data on impact of PCV in routine use is dependent on the amount of data collected pre- and post-introduction, which allow for secular trends in disease to be accounted for. In general, introductions occurred first in high-income countries primarily in the European and North American regions, followed by Gavi-supported countries in the Africa region. Low- and middle-income countries (both Gavi and non-Gavi) in the Asia region began introducing later; therefore, a lag in the availability of PCV impact evidence from this area is expected.

- *Ongoing work includes further stratification of countries with impact studies by income strata and Gavi status. Due to Gavi support for both introduction of PCV and impact evaluations of the vaccine(s) and vaccine programs, it is likely that a higher proportion of these countries have ongoing or published PCV impact studies than non-Gavi middle-income countries. High-income countries have the capacity and resources to fund and measure impact of PCV through surveillance systems and other research efforts, and thus we expect a greater proportion of them evaluating PCV impact among those that have introduced than unsupported middle-income countries. In particular, the middle-income countries outside of the PAHO region are predicted to have few PCV introductions as well as PCV impact studies compared to other income strata countries. This analysis will be presented in a future impact study gap analysis.*

- PCV impact studies from low- and middle-income countries, especially those with high pneumococcal disease burden will improve the evidence base for sustaining PCV immunization in the highest disease burden settings.

- Importantly, the WHO regions, by which countries were stratified in this gap analysis, are often epidemiologically heterogeneous. Further scrutiny of such differences in disease burden is important to strategically assess epidemiologic gaps in PCV impact studies.

- *We will conduct an analysis for the next report that evaluates 2015 pneumococcal disease burden estimates in relation to PCV use and location of the impact studies. The 2015 disease burden estimates from the MCEE project will be available in Q4/2015.*

PCV Impact Study Gaps by Product

- Analysis of PCV impact studies by the product (i.e., PCV10 or PCV13) and dosing schedule (i.e., 2p+1, 3p+0, or 3p+1) used in routine immunization programs may

influence future global and regional policy recommendations and decisions for future use of the vaccine by countries, or for the generation of further evidence surrounding PCV impact by funders.

- **Table 4** describes countries that have at least one impact study, by the vaccine product (PCV10 or PCV13) currently used in their national immunization program (NIP), with Gavi countries highlighted in gold. The year of introduction is included in the table; this can provide perspective on the amount of post-PCV introduction data that could be available from the country, but not necessarily the amount of data in the PCV impact studies that are ongoing or published.

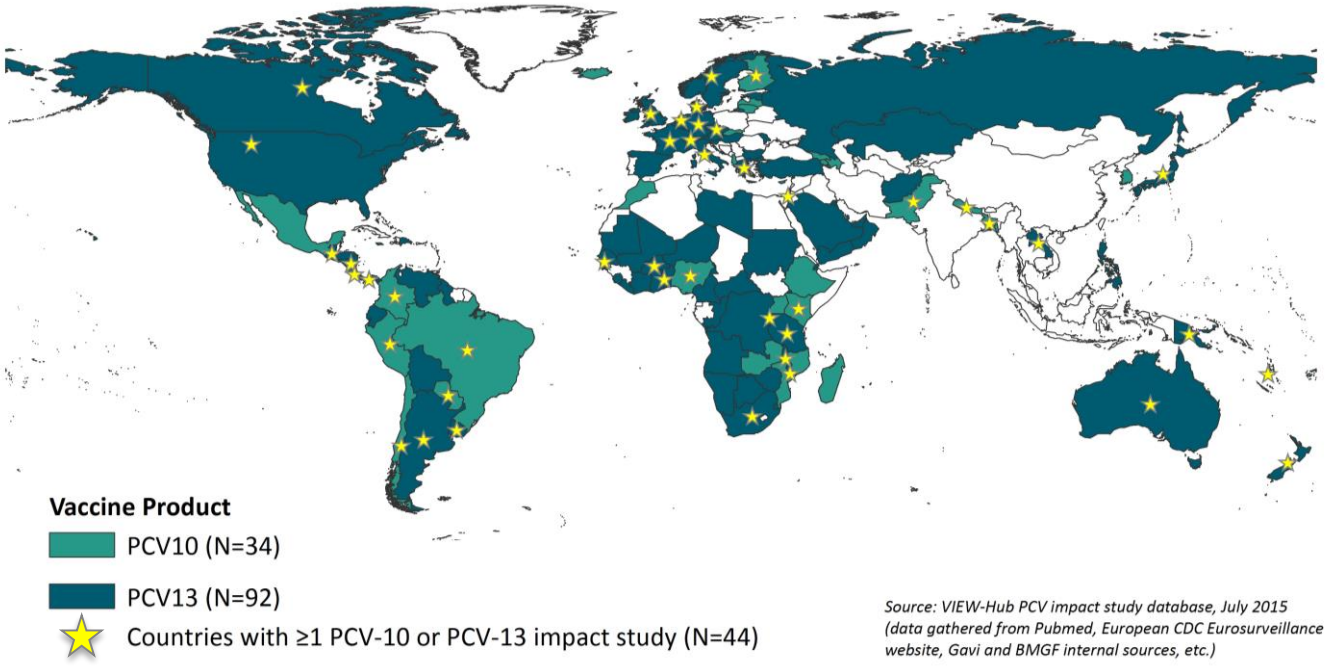
Table 4: Countries with at least 1 PCV10 or PCV13 impact study, by product introduced into National Immunization Program (NIP)

WHO Region	Country	Introduction Year of First PCV Product	PCV10 Introduced	PCV13 Introduced
AFR	Burkina Faso	2013		✓
	Gambia	2009		✓
	Kenya	2011	✓	
	Malawi	2011		✓
	Mozambique	2013	✓	
	Nigeria	2014	✓	
	Rwanda	2009		✓
	South Africa	2009		✓
	Tanzania	2012		✓
	Togo	2014		✓
AMR	Argentina	2012		✓
	Brazil	2010	✓	
	Canada	2002		✓
	Chile	2011	✓	
	Colombia	2011	✓	
	Costa Rica	2008		✓
	Guatemala	2012		✓
	Nicaragua	2010		✓
	Panama	2010		✓
	Paraguay	2012	✓	
	Peru	2009	✓	
	United States	2000		✓
	Uruguay	2008		✓
EMR	Pakistan	2012	✓	
EUR	Czech Republic*	2010	✓	✓
	Denmark	2007		✓
	Finland	2010	✓	
	France	2006		✓
	Germany	2006		✓
	Greece	2006		✓
	Israel	2009		✓
	Italy	2005		✓
	Netherlands	2006	✓	
	Norway	2006		✓
	Portugal*	2001		✓
	Switzerland	2006		✓
	United Kingdom	2006		✓
SEARO	Bangladesh	2015	✓	
	Nepal	2015	✓	
WPRO	Australia	2005		✓
	Fiji	2012		✓
	Japan	2011		✓
	Lao, PDR	2013		✓
	New Zealand**	2008	✓	✓
	Papua New Guinea	2013		✓

Note: Gavi countries are highlighted in gold.
*Czech Republic introduced PCV10 in 2009, then PCV13 in 2010, when their national PCV program officially started.
**New Zealand introduced PCV10 in 2011 and then replaced it with PCV13 in 2014.
Portugal has a PCV impact study, but has not introduced PCV into its NIP (private market use only); therefore, it is not included here.

- **Figure 3** maps the countries with impact studies, according to the product in their NIP, illustrating that both products are used in every region of the globe; however, both products are not being evaluated in every region.

Figure 3: Countries with a PCV-10 or PCV-13 impact study, by product used in NIP



- SEAR has 2 ongoing impact studies (Bangladesh and Nepal), both evaluating PCV10. EMR has only 1 ongoing impact study (Pakistan), evaluating PCV10. WPR has 6 countries with impact studies, evaluating PCV10 and PCV13. AFR, AMR, and EUR have at least one impact study evaluating each product independently (i.e. not a head-to-head evaluation of the impact of both products, but simultaneous and separate studies).

- 34 (27%) of the 126 countries that have introduced PCV are using PCV10, and 15 of those (44%) have ongoing or published impact studies on PCV10. Six of 13 (46%) Gavi countries using PCV10 are evaluating impact.

- 92 (73%) of the 126 countries that have introduced PCV are using PCV13 and 27 of these (29%) have ongoing or published impact studies on PCV13. Nine of the 36 (25%) Gavi countries using PCV13 are evaluating impact.

- There are no PCV13 impact studies ongoing in SEAR or EMR.

PCV Impact Study Gaps by Dosing Schedule

- **Table 5** and **Figure 4** provide information on countries with PCV impact studies by dosing schedule used in routine programs. The analysis that follows was done in the context of previous work conducted by IVAC including the Reduced Dose Policy Analyses in February 2015.

- *In a future report we will be assessing the use of catch-up schedules in the various countries.*

Table 5: Countries with at least one PCV-10 or PCV-13 impact study, by dosing schedule

WHO Region	Dosing Schedule					
	2p+1 (product)		3p+0 (product)		3p+1 (product)	
AFR	PCV-13 South Africa		PCV-10 Kenya Mozambique Nigeria	PCV-13 Burkina Faso Gambia Malawi Rwanda Tanzania Togo		
AMR	PCV-10 Chile Colombia Paraguay Peru	PCV-13 Argentina Costa Rica Guatemala Uruguay	PCV-13 Nicaragua		PCV-10 Brazil	PCV-13 Canada Panama United States
EMR			PCV-10 Pakistan			
EUR	PCV-10 Finland	PCV-13 Denmark France Israel Italy Norway Switzerland UK			PCV-10 Netherlands	PCV-13 Czech Republic Greece
SEAR	PCV-10 Nepal		PCV-10 Bangladesh			
WPR			PCV-13 Laos Papua New Guinea Fiji		PCV-13 Australia Japan New Zealand	

Note: Gavi countries are highlighted in gold.

- Forty countries (32%) are using a 2p+1 dosing schedule, 56 (44%) are using a 3p+0 schedule, and 30 (24%) are using a 3p+1 schedule for PCV in their national programs.

- Eighteen of the 40 (45%) countries using a 2p+1 schedule for their PCV program have ongoing or published impact studies. Among these, 1 of the 2 (50%) Gavi countries using a 2p+1 schedule are evaluating PCV impact.

- Fifteen of the 56 (27%) countries using a 3p+0 schedule for their PCV program have ongoing or published impact studies. Among these, 14 of the 47 (30%) Gavi countries using a 3p+0 are evaluating impact of PCV.

- Eleven of the 30 (37%) countries using a 3p+1 schedule for their PCV program have ongoing or published impact studies. No Gavi countries are using or evaluating this dosing schedule for PCV.

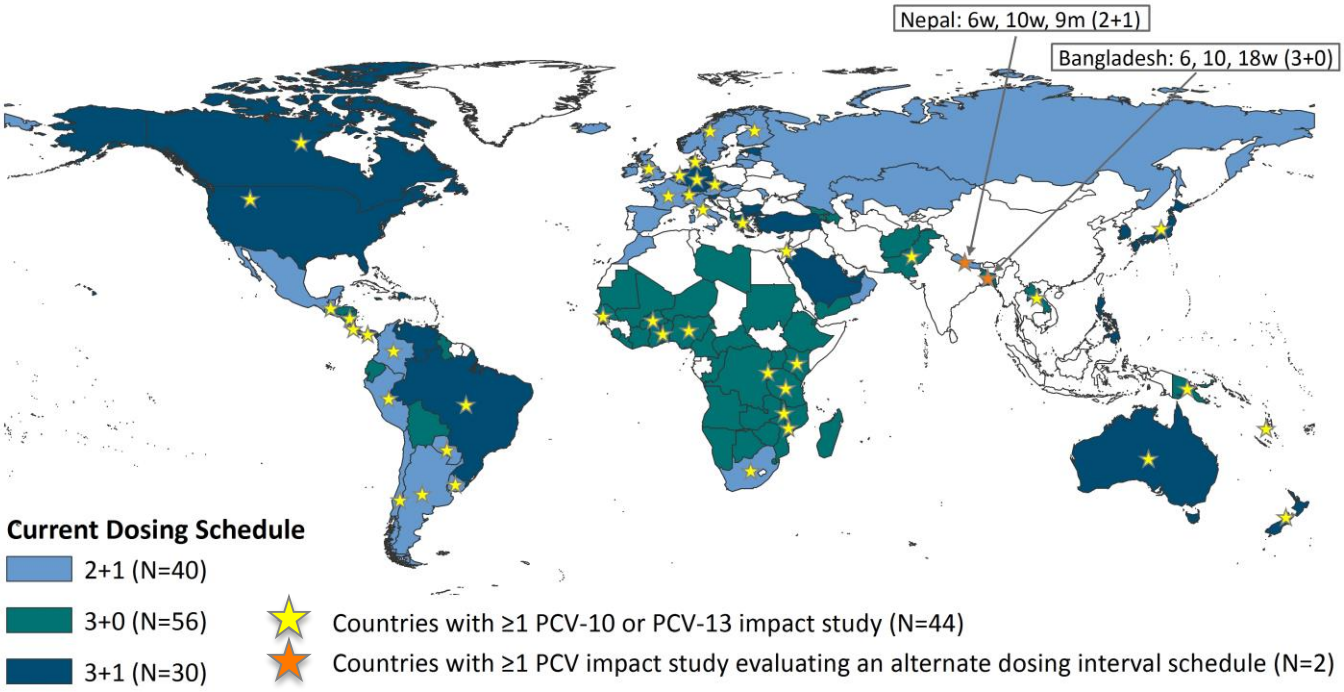
- Of particular interest are countries evaluating alternate interval dosing schedules due to logistics or programmatic issues that interfere with the recommended dosing timing of 3p+1, 3p+0, or 2p+1 schedules.

    - Both Nepal and Bangladesh are evaluating unique schedules, which change the timing of a PCV dose because of concerns for giving 3 injections at the 14-week routine immunization visit (i.e., IPV is being introduced at 14 weeks).

    - Bangladesh is evaluating a 6w, 10w, 18w schedule (3p+0), lengthening the window between the 2nd and 3rd doses of PCV.

    - Nepal is evaluating a 6w, 10w, 9m schedule (2p+1), shortening the recommended window between the 2 primary doses from 8 to 4 weeks. The results of such evaluations could have implications for the dosing schedule used in national programs for PCV in other countries (i.e., if shown to be non-inferior).

Figure 4: Countries with a PCV-10 or PCV-13 impact study, by dosing schedule used in NIP



Source: VIEW-Hub PCV impact study database, July 2015 (data gathered from Pubmed, European CDC Eurosurveillance website, Gavi and BMGF internal sources, etc.)

Impact Study Gaps: By Outcome Measured

- **Table 6** below describes the information and data available in countries from published and/or ongoing PCV10 or PCV13 impact studies by outcome assessed. The details for what evidence was included in this table can be found in the notes sections prior to and at the end of Table 6. Table 6 (and corresponding gap analysis) does not evaluate the quality or quantity of data from each country for each outcome; availability of data does not exactly correlate with the ability to determine PCV impact from such data; some studies may be underpowered to provide robust analyses for one or another outcome.

- The amount of available evidence on PCV10 and PCV13 impact varies by outcome across the globe. The greatest number of evaluations assess PCV impact on IPD and pneumonia.

- **Pneumonia** outcomes are commonly being assessed. *We will be disaggregating these further by study outcome to assess those using administrative data (e.g., patient records and ICD codes) or special studies, as well as those that include chest radiographs, NP carriage, or urinary antigen testing to further improve the specificity of reporting on outcome measurements.*

- **NP carriage** studies are also very common**.** *Future analyses will assess whether these are in targeted or non-targeted age group, cross-sectional or cohort, year round or selected months.*

- **Mortality** is being assessed in 13 countries; most of these data are unpublished because the analysis or data collection is still ongoing. It is unclear how many of these studies will have a sufficient amount of data for a valid assessment of this outcome.

- **Health Economic** data are being collected in 13 countries. *It is likely that the methods and outcomes are not well harmonized across these studies. In future analyses, we will be assessing the specific outcomes evaluated across these studies and their generalizability and collective contribution in addressing the substantial data gaps on the health economic impact of PCV.*

- *Future analyses will also assess how many sites have multiple outcomes being assessed in the same study site. These types of studies/evaluations are some of the most informative because they allow for triangulation of impact and assessment of the relationships between changes in NP colonization and disease outcomes.*

- We have characterized the amount of evidence by outcome, and compared the availability of evidence across the various outcomes of interest. **Figures 5-9** show the global availability of evidence by outcome.

Table 6: PCV10 or PCV13 impact studies

(Published studies are included for all income strata countries. Ongoing studies are included comprehensively for low- and middle-income countries; ongoing studies in high-income countries have been included based on a non-systematic, expert input approach.

WHO Region	Country (# Studies)	Outcomes measured by PCV10 or PCV13 impact studies						
		IPD*	Pneumonia	NP carriage	Herd effect	Mortality	Economic	Other ❖
AFR (10)	Burkina Faso (1)	✓	✓	✓	✓	✓	✓	✓
	Gambia (2)	✓	✓	✓	✓	✓	✓	
	Kenya (3)	✓	✓	✓	✓	✓	✓	✓
	Malawi (4)	✓	✓	✓	✓	✓		
	Mozambique (1)	✓	✓	✓				
	Nigeria (1)	✓	✓					✓
	Rwanda (1)	✓	✓					
	South Africa (2)	✓	✓	✓	✓	✓		✓
	Tanzania (1)			✓				
	Togo (1)	✓	✓	✓	✓			
AMRO (13)	Argentina (4)	✓	✓				✓	✓
	Brazil (4)	✓	✓	✓	✓	✓		✓
	Canada (4)	✓	✓	✓	✓		✓	✓
	Chile (2)	✓	✓	✓		✓		✓
	Colombia (1)	✓	✓					✓
	Costa Rica (1)	✓	✓					
	Guatemala (1)		✓					
	Nicaragua (1)		✓		✓	✓		
	Panama (2)		✓	✓				✓
	Paraguay (1)			✓				
	Peru (2)	✓	✓	✓			✓	✓
	United States (7)	✓	✓	✓	✓	✓	✓	✓
	Uruguay (3)	✓	✓	✓	✓			
EMRO (1)	Pakistan (1)	✓	✓	✓				
EURO (12)	Czech Republic (1)	✓	✓	✓	✓			
	Denmark (2)	✓	✓	✓	✓	✓		
	Finland (1)	✓	✓	✓	✓			
	France (2)	✓	✓	✓				✓
	Germany (1)	✓	✓	✓	✓		✓	
	Greece (4)	✓	✓		✓		✓	
	Israel (1)	✓	✓	✓	✓			✓
	Italy (1)			✓				
	Netherlands (2)	✓	✓	✓	✓		✓	
	Norway (1)	✓	✓	✓	✓			

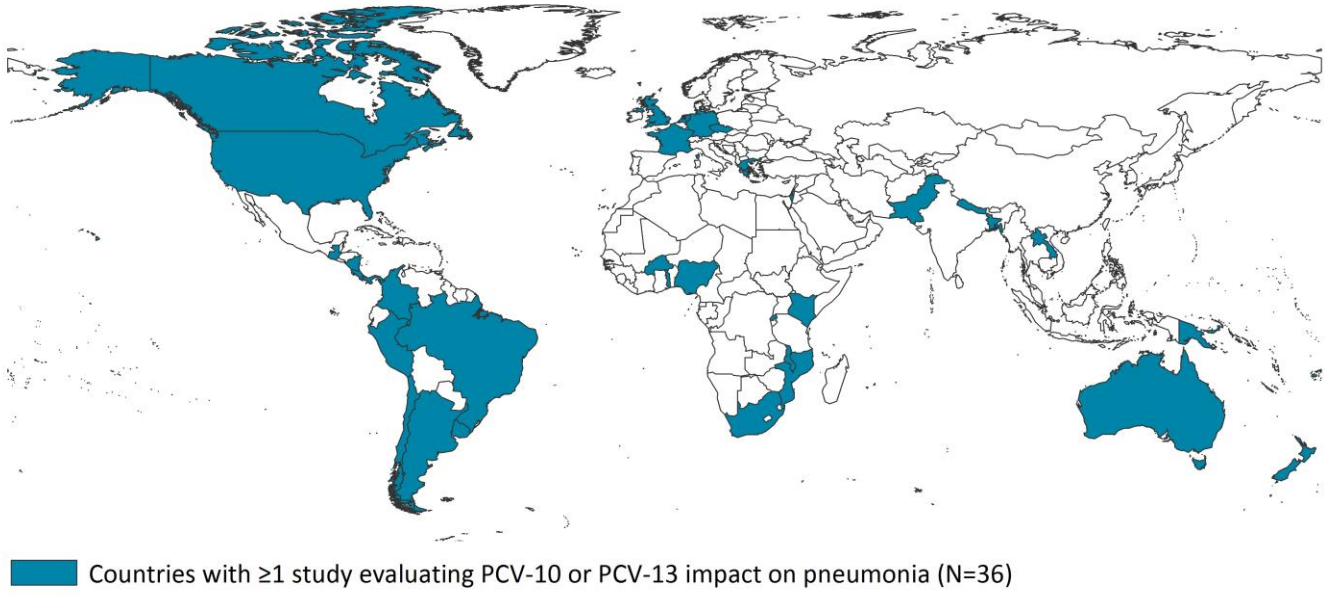
	Switzerland (1)	✓	✓	✓	✓			
	United Kingdom (3)	✓	✓	✓	✓		✓	
SEARO (2)	Bangladesh (3)	✓	✓	✓	✓	✓	✓	✓
	Nepal (1)	✓	✓	✓			✓	✓
WPRO (6)	Australia (1)	✓	✓	✓	✓			
	Fiji (1)	✓	✓	✓	✓			
	Japan (1)							✓
	Lao PDR (1)	✓	✓	✓	✓			
	New Zealand (1)	✓	✓	✓	✓			
	Papua New Guinea (2)	✓	✓	✓				

*In future analyses, we will assess which of these IPD studies evaluated meningitis as a sub-outcome.
❖UAD validation, acute otitis media (AOM), immunogenicity, safety, or other outcomes measured but not specifically listed here.
✓Based on expert(s) and lead staff knowledge of ongoing studies or that the outcome was published for PCV7 impact, but has not yet been reported for PCV10 or PCV13 impact. These data will be verified for the future gap analyses and reports.
Note: Portugal has a PCV impact study, but has not introduced PCV into its NIP (PCV is used in the private market only). Therefore, it is not included and reported as a country with PCV impact evaluation in the context of routine use in the national immunization schedule.

Measuring PCV Impact on Pneumonia

- N=36 (82%) of the 44 countries with PCV impact studies are measuring pneumonia. Along with IPD, pneumonia is the most commonly measured outcome among all PCV impact studies and is evaluated in 9 (90%) of AFR countries, 12 (92%) of AMR countries, 1 (100%) of EMR countries, 7 (54%) of EUR countries, 2 (100%) of SEAR countries and 5 (83%) of WPR countries with ongoing or published studies.

Figure 5: Map of countries with at least 1 PCV-10 or -13 impact study measuring pneumonia

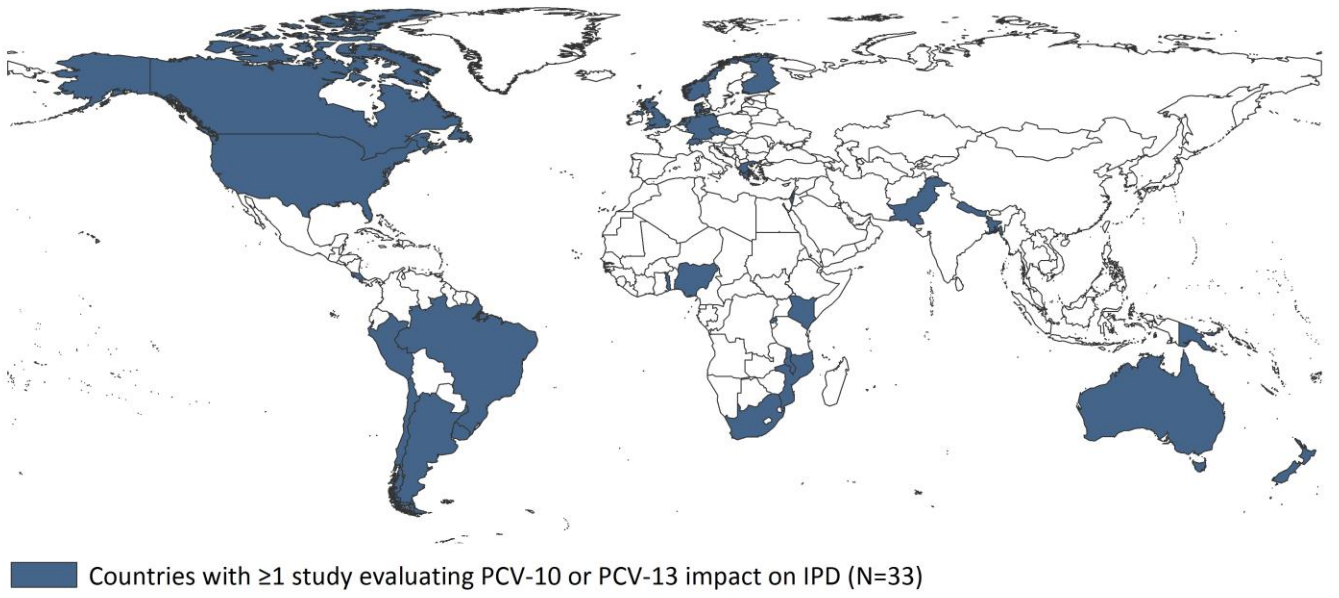


Source: VIEW-Hub PCV impact study database, July 2015 (data gathered from Pubmed, European CDC Eurosurveillance website, Gavi and BMGF internal sources, etc.)

Measuring PCV Impact on IPD

- N=33 (75%) of the 44 countries with PCV impact studies are measuring impact on IPD. This includes 8 (80%) of AFR countries, 8 (62%) of AMR countries, 1 (100%) of EMR countries, 11 (85%) of EUR countries, 2 (100%) of SEAR countries and 4 (67%) of WPR countries with ongoing or published studies.

Figure 6: Map of countries with at least 1 PCV-10 or -13 impact study measuring IPD

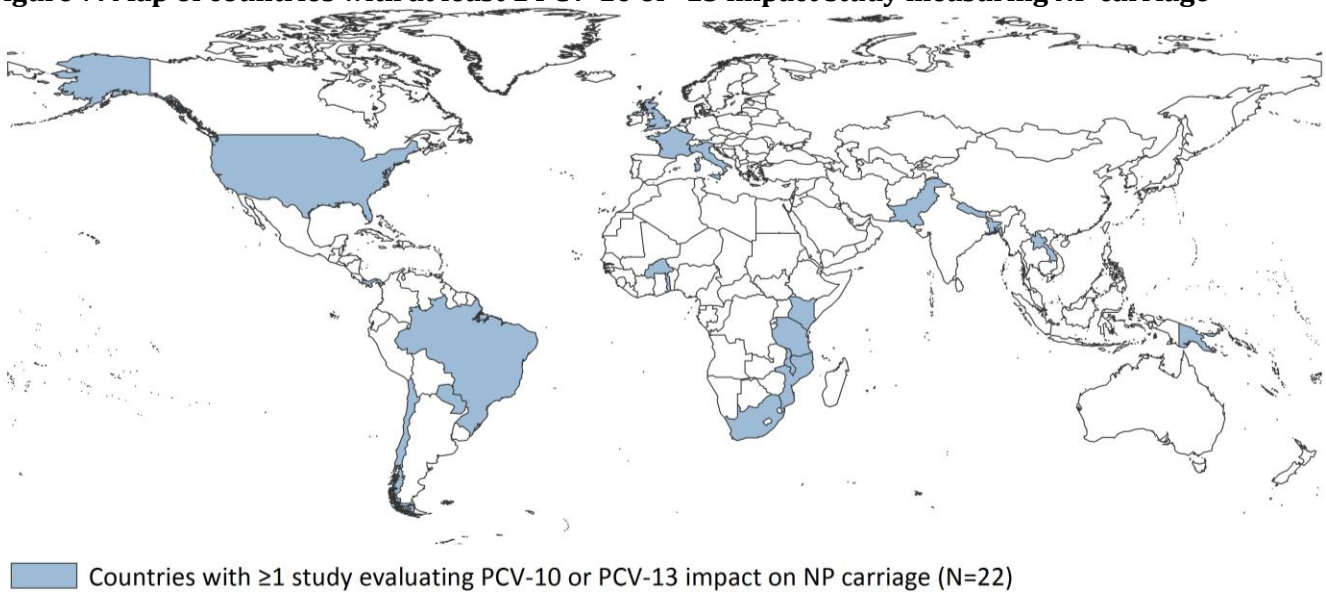


Source: VIEW-Hub PCV impact study database, July 2015 (data gathered from Pubmed, European CDC Eurosurveillance website, Gavi and BMGF internal sources, etc.)

Measuring PCV Impact on Nasopharyngeal Carriage

- N=22 (50%) of the 44 countries with PCV impact studies are measuring pneumococcal nasopharyngeal (NP) carriage. This includes 8 (80%) of AFR countries, 5 (38%) of AMR countries, 1 (100%) of EMR countries, 3 (23%) of EUR countries, 2 (100%) of SEAR countries and 3 (50%) of WPR countries with ongoing or published studies. Of particular interest are studies that measure NP carriage and a disease outcome since these improve our understanding of the relationship between carriage and disease, as well as the impact of vaccination on this relationship.
- *Such studies will be identified in future gap analyses and reports.*

Figure 7: Map of countries with at least 1 PCV-10 or -13 impact study measuring NP carriage

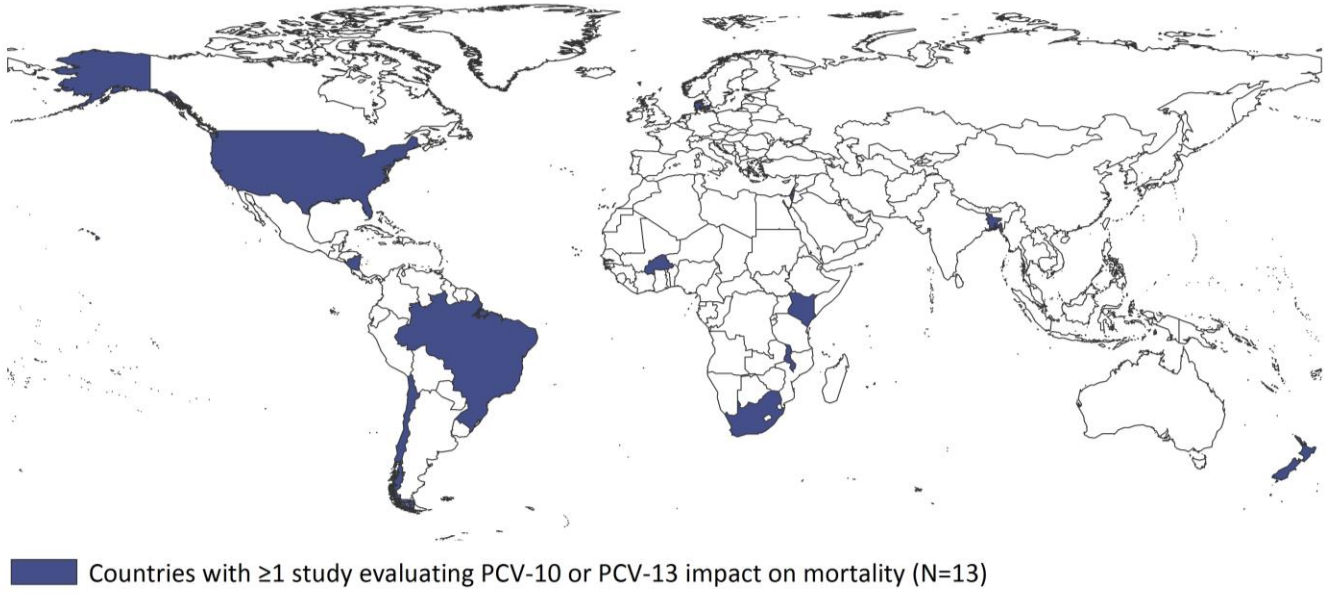


Source: VIEW-Hub PCV impact study database, July 2015 (data gathered from Pubmed, European CDC Eurosurveillance website, Gavi and BMGF internal sources, etc.)

Measuring PCV Impact on Mortality

- N=13 (30%) of the 44 countries with PCV impact studies measure mortality as an outcome; only N=7 have published data on this outcome: Brazil, Chile, Denmark, Israel, Nicaragua, New Zealand, and the United States.[4] This includes 5 (50%) of AFR countries, 4 (31%) of AMR countries, 0 of the EMR countries, 2 (15%) of EUR countries, 1 (50%) of SEAR countries and 1 (20%) of the WPR countries with ongoing or published studies.

Figure 8: Map of countries with at least 1 PCV-10 or -13 impact study measuring mortality



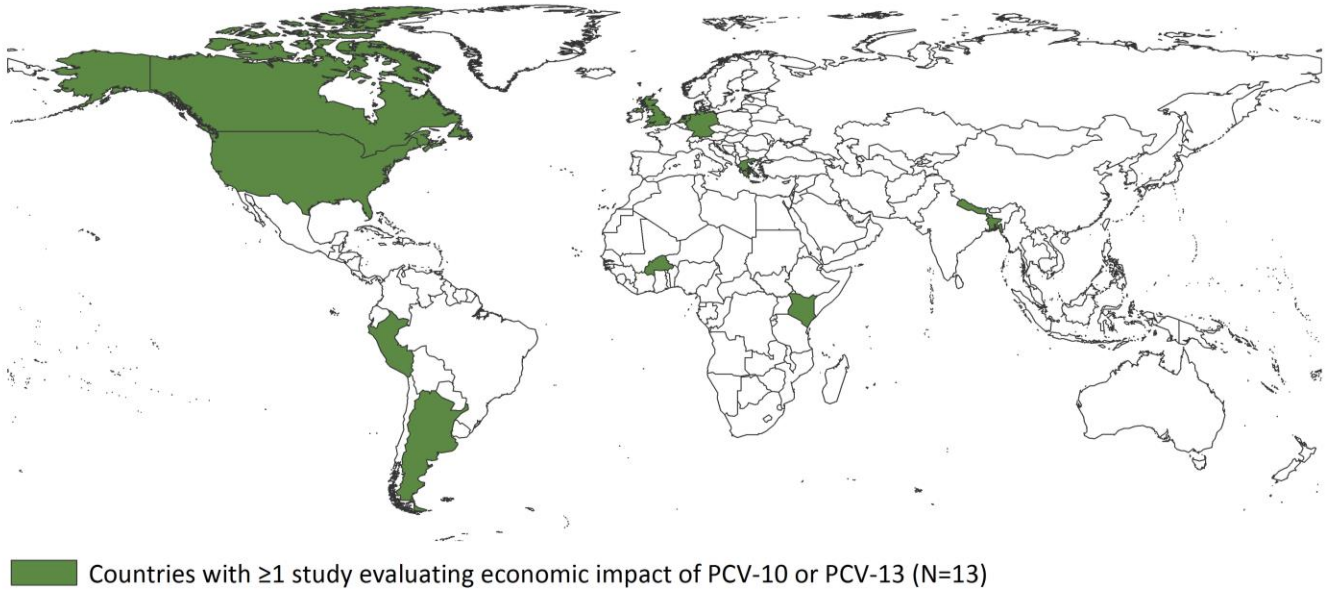
Source: VIEW-Hub PCV impact study database, July 2015 (data gathered from Pubmed, European CDC Eurosurveillance website, Gavi and BMGF internal sources, etc.)

[4] Note: Data on impact of PCV-9 on mortality in Gambia was published, however this study did not meet our criteria for inclusion in this analysis (i.e., results reported from impact of an unlicensed product).

Measuring Economic Impact

- N=13 (30%) of the 44 countries with PCV impact studies assess economic outcomes, and the majority of these are from ongoing (rather than published) studies. Thus, the availability of data on the economic impact of PCV use is limited.

Figure 9: Map of countries with at least 1 PCV-10 or -13 impact study measuring economic impact



Source: VIEW-Hub PCV impact study database, July 2015 (data gathered from Pubmed, European CDC Eurosurveillance website, Gavi and BMGF internal sources, etc.)

Measuring other outcomes

In addition to the outcomes mapped above, 25 (57%) of the 44 countries with PCV impact studies measure indirect effects of PCV (i.e. herd immunity to the unvaccinated portion of the population). This includes 6 (60%) of AFR countries, 4 (31%) of AMR countries, 0 of the EMR countries, 10 (77%) of EUR countries, 1 (50%) of SEAR countries and 4 (67%) of WPR countries with ongoing or published studies.

N=21 (48%) of the 44 countries with PCV impact studies are measuring other outcomes not listed here, such as AOM, urine antigen detection validation, immunogenicity, safety, etc.

Conclusions

Overall, among 126 countries using PCV10 or PCV13, 44 countries have a published or ongoing study to collectively document the impact of both PCV10 and PCV13 using different vaccination schedules.

While there are published or ongoing studies in all WHO regions, there are a few important gaps. We did not identify studies in EMR countries, other than in Pakistan. The other countries in this region have child mortality levels that are quite different from Pakistan;

hence, the Pakistan PCV impact data are unlikely to be seen as regionally representative. In addition, many of these countries are using PCV13, as opposed to PCV10 in Pakistan.

There is also the potential for gaps in information from Eastern Europe. While not many central Asian countries have introduced the vaccine, the capacity to conduct impact studies may be limited in these countries and may need to be strengthened. Some of these countries belong to the WHO sentinel site surveillance network and this surveillance may require strengthening to allow the use of these surveillance platforms to conduct impact studies.

The impact on the most important disease outcomes are being measured most commonly across all PCV impact studies, namely pneumonia and IPD. In addition, NP carriage is being monitored in several studies. The studies that monitor both disease and carriage may provide further insights on whether and how NP carriage may be used as a surrogate for disease outcomes.

Contact Information & Corresponding Authors for PCV Impact Studies

A 'general pneumococcal point person' as well as the available contact information for corresponding author(s) of publications included in the VIEW-Hub database and gap analysis to date are included in **Table 7**. The 'general point person(s)' for each country is not necessarily a study-specific PI, but rather an initial point of contact for ongoing PCV impact work in the particular country. Ongoing work for the PCV Technical Coordination Secretariat includes communication with these individuals to identify specific-study PIs and improve our list of contacts for future gap analyses and related PCV projects.

Table 7: General country contact & corresponding author information for PCV10 and PCV13 impact studies

WHO Region	Country	General Pneumococcal Point Person For Country	Corresponding Author Information (Abstracted from PubMed)	PubMed Abstract Links *Note: Not a Systematically Inclusive List; Consists of First Deep Dive Into the Literature
AFRO	Burkina Faso	Bradford Gessner <bgessner@aamp.org> Jennifer Moisi <jmoisi@aamp.org>		
	Gambia	Grant Mackenzie <gmackenzie@mrc.gm>	- E Usuf <effuau@gmail.com>	1. http://www.ncbi.nlm.nih.gov/pubmed/24503271
	Kenya	Laura Hammitt <lhammitt@jhu.edu> Anthony Scott < ascott@kemri-wellcome.org>	- Anthony Scott <ascott@kemri-wellcome.org> - Philip Ayieko <payieko@nairobi.kemi-wellcome.org> - Laura Hammitt <lhammitt@jhu.edu>	1. http://www.kemri-wellcome.org/index.php/en/studies_inner/75 2. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3691111/ 3. http://www.ncbi.nlm.nih.gov/pubmed/25103393 4. http://www.sciencedirect.com/science/article/pii/S2214109X14702244 5. http://www.ncbi.nlm.nih.gov/pubmed/24465570 6. http://www.ncbi.nlm.nih.gov/pubmed/22403235
	Malawi	Neil French <N.French@liverpool.ac.uk> Malcolm Molyneux <mmolyneux999@gmail.com>		
	Mozambique	Betuel Sigauque <Betuel.Sigauque@manhica.net> Cyndy Whitney <cgw@cdc.gov>		
	Nigeria	Stephen Obaro <Stephen.obaro@unmc.edu>		
	Rwanda	Bradford Gessner <bgessner@aamp.org> Jennifer Moisi <jmoisi@aamp.org>		
	South Africa	Shabir Madhi <shabirm@nicd.ac.za>	- Shabir Madhi <shabirm@nicd.ac.za>	1. http://www.ncbi.nlm.nih.gov/pubmed/25784729 2. http://thorax.bmj.com/content/early/2015/06/19/thoraxjnl-2014-206593.short?rss=1
	Tanzania	Robert Booy <RobertB2@chw.edu.au>		

	Togo	Bradford Gessner <bgessner@aamp.org> Jennifer Moisi <jmoisi@aamp.org>		
	Zambia	Don Thea < dthea@bu.edu > ***(Note: no ongoing evaluations of PCV in Zambia)***		
AMRO	Argentina	Maria Luisa Avila <avilaaguero@gmail.com> Lucia Helena de Oliviera <oliveiral@who.int>	- Tregnaghi MW (CEDEPAP, Córdoba, Argentina) - A. Urueña <anauru@yahoo.com>	1. http://www.ncbi.nlm.nih.gov/pubmed/24892763 2. http://www.ncbi.nlm.nih.gov/pubmed/21621575
	Brazil	Carla Domingues <carla.domingues@saude.gov.br> Maria Luisa Avila <avilaaguero@gmail.com> Lucia Helena de Oliviera <oliveiral@who.int>	- Carla Domingues <Carla.domingues@saude.gov.br> - Ana Lucia Andrade <ana@iptsp.ufg.br> - G. Vespa (Escola Paulista de Medicina, Universidade Federal de São Paulo)	1. http://www.ncbi.nlm.nih.gov/pubmed/24726406 2. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3647414/ 3. http://www.ncbi.nlm.nih.gov/pubmed/24892409 4. http://www.ncbi.nlm.nih.gov/pubmed/25760162 5. http://www.ncbi.nlm.nih.gov/pubmed/20107706
	Canada	Jim Kellner <jim.kellner@calgaryhealthregion.ca>	- Philippe De Wals <Philippe.De.Wals@ssss.gouv.qc.ca> - Gillian Lim <Gillian.lim@oahpp.ca> - Stephanie Earnshaw <searnshaw@rti.org>	1. http://www.ncbi.nlm.nih.gov/pubmed/18845982 2. http://www.ncbi.nlm.nih.gov/pubmed/20125062 3. http://www.ncbi.nlm.nih.gov/pubmed/22921290 4. http://www.ncbi.nlm.nih.gov/pubmed/24486346 5. http://www.ncbi.nlm.nih.gov/pubmed/25887086 6. http://www.ncbi.nlm.nih.gov/pubmed/24313450 7. http://www.ncbi.nlm.nih.gov/pubmed/23597716 8. http://www.ncbi.nlm.nih.gov/pubmed/22530841
	Chile	Rosana Lagos <rosanna.lagos@adsl.tie.cl> Maria Luisa Avila <avilaaguero@gmail.com> Lucia Helena de Oliviera <oliveiral@who.int>	- Rosana Lagos < rosanna.lagos@adsl.tie.cl>	1. http://www.ncbi.nlm.nih.gov/pubmed/18959497 2. http://www.ncbi.nlm.nih.gov/pubmed/25679919
	Colombia	Maria Luisa Avila <avilaaguero@gmail.com> Lucia Helena de Oliviera <oliveiral@who.int>	- MW Tregnaghi - GSK Vaccines (Panama City & Bueños Aires Teams)	1. http://www.ncbi.nlm.nih.gov/pubmed/24892763
	Costa Rica	Maria Luisa Avila <avilaaguero@gmail.com> Lucia Helena de Oliviera <oliveiral@who.int>	- A. Arguedas <aarguedas@iped.net>	1. http://www.ncbi.nlm.nih.gov/pubmed/22300725
	Guatemala	Maria Luisa Avila <avilaaguero@gmail.com> Lucia Helena de Oliviera <oliveiral@who.int>		
	Nicaragua	Maria Luisa Avila <avilaaguero@gmail.com> Lucia Helena de Oliviera <oliveiral@who.int>	- S. Becker-Dreps <sbd@unc.edu>	1. http://www.ncbi.nlm.nih.gov/pubmed/24445827 2. http://www.ncbi.nlm.nih.gov/pubmed/25444795
	Panama	Maria Luisa Avila <avilaaguero@gmail.com> Lucia Helena de Oliviera <oliveiral@who.int>	- M.W. Tregnaghi	1. http://www.ncbi.nlm.nih.gov/pubmed/24892763
	Paraguay	Maria Luisa Avila <avilaaguero@gmail.com> Lucia Helena de Oliviera <oliveiral@who.int>		
	Peru	Maria Luisa Avila <avilaaguero@gmail.com> Lucia Helena de Oliviera <oliveiral@who.int>	- M.W. Tregnaghi	1. http://www.ncbi.nlm.nih.gov/pubmed/24171921
	United States	Cyndy Whitney <cgw3@cdc.gov> Farrar, Jennifer Loo <ihi4@cdc.gov>	- Sandra Richter (Cleveland Clinic) - R. Singleton <Ris2@cdc.gov> - P.P. Gounder (CDC) - L. Simonson <lone@gwu.edu> - Matt Moore <matt.moore@cdc.hhs.gov> - C. Stoecker <cfstoecker@tulane.edu> - Jaime Rubin <jaime.rubin@i3innovus.com>	1. http://wwwnc.cdc.gov/eid/article/19/7/12-1830_article 2. http://www.ncbi.nlm.nih.gov/pubmed/23001026 3. http://www.ncbi.nlm.nih.gov/pubmed/24273178 4. http://www.ncbi.nlm.nih.gov/pubmed/21264063 5. http://www.ncbi.nlm.nih.gov/pubmed/24815804 6. http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(14)71081-3/fulltext?rss=yes 7. http://www.ncbi.nlm.nih.gov/pubmed/23821695

				8. http://www.ncbi.nlm.nih.gov/pubmed/20883739
	Uruguay	Maria Luisa Avila <avilaaguero@gmail.com> Lucia Helena de Oliviera <oliveiral@who.int>	- García Gabarrot G: Departamento de Laboratorios, Ministerio de Salud Pública, Montevideo, Uruguay. - Maria Hortal: <marujahortal@gmail.com> - Maria Pirez <mcpirez@yahoo.com> - Teresa Camou <tcamou@msp.gub.uy>	1. http://www.ncbi.nlm.nih.gov/pubmed/25375647 2. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4048159/ 3. http://www.ncbi.nlm.nih.gov/pubmed/22664222 4. http://www.ncbi.nlm.nih.gov/pubmed/24492286 5. http://www.ncbi.nlm.nih.gov/pubmed/25375647
EMRO	Pakistan	Cyndy Whitney <cgw3@cdc.gov> Anita Zaidi (AKU) <anita.zaid@aku.edu>		
EURO	Czech Republic	Roman Prymula <prymula@seznam.cz. >	- R, Prymula (University Hospital, Hradec Králové, Czech Republic) <prymula@fnhk.cz> - N. Stock, (The National Institute of Public Health, Prague, Czech Republic; European Program for Public Health Microbiology (EUPHEM), ECDC, Stockholm, Sweden) <nkstock2015@gmail.com> - H. Zemlickova (National Institute of Public Health, Prague, Czech Republic)	1. http://www.ncbi.nlm.nih.gov/pubmed/23391599 2. http://www.ncbi.nlm.nih.gov/pubmed/26125583 3. http://www.ncbi.nlm.nih.gov/pubmed/20113561
	Denmark	Ziita Harboe <ZIT@ssi.dk>	- Helene Ingels (Statens Serum Institut) <HIG@ssi.dk>, <helene ingels@yahoo.dk>	1. http://www.ncbi.nlm.nih.gov/pubmed/22504662 2. http://www.ncbi.nlm.nih.gov/pubmed/25034421
	Finland	Jukka Jokinen <jukka.jokinen@thl.fi>	- Arto Palmu <arto.palmu@thl.fi> - Jukka Jokinen <jukka.jokinen@thl.fi>	1. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4364013/ 2. http://www.ncbi.nlm.nih.gov/pubmed/23158882
	France	Robert Cohen < robert.cohen@wanadoo.fr>	- Robert Cohen <robert.cohen@wanadoo.fr> - F. Angoulvant (Groupe de Pathologie Infectieuse Pédiatrique, Société Francaise de Pédiatrie) - C. Alexandre (Department of Paediatrics, Paediatric Emergency Unit and Infectious Diseases, Université Lille Nord-de-France, Lille, France)	1. http://www.ncbi.nlm.nih.gov/pubmed/22330166 2. http://www.ncbi.nlm.nih.gov/pubmed/24532543 3. http://www.ncbi.nlm.nih.gov/pubmed/20626365
	Greece (Crete)	Maria Tsolia <matsolia@ath.forthnet.gr	- O. Tsachouridou <olgat_med@hotmail.com> - G.A. Syrogiannopoulos <syrogian@otenet.gr> - David Strutton <david.strutton@pfizer.com>	1. http://www.ncbi.nlm.nih.gov/pubmed/26192868 2. http://www.ncbi.nlm.nih.gov/pubmed/25252194 3. http://www.ncbi.nlm.nih.gov/pubmed/22085813
	Israel	Ron Dagan <rdagan@bgu.ac.il>	- G. Regev <gregev@hsph.harvard.edu> - S. Ben-Shimol (University of Negev)	1. http://www.ncbi.nlm.nih.gov/pubmed/23518404 2. http://www.ncbi.nlm.nih.gov/pubmed/24516649 3. http://www.ncbi.nlm.nih.gov/pubmed/25159581 4. http://www.ncbi.nlm.nih.gov/pubmed/25764098
	Italy	F. D'Ancona V. Alfonsi M. Caporali	- R. Camilli (Dipartimento di Malattie Infettive, Parassitarie ed Immunomediate, Istituto Superiore di Sanità)	1. http://www.ncbi.nlm.nih.gov/pubmed/24124543
	Netherlands	Lieke Sanders <L.Sanders@umcutrecht.nl>	- Marie-Josée J <m.j.j.mangen@umcutrecht.n> - Gerwin Rodenburg <g.d.rodenburg@umcutrecht.nl>	1. http://erj.ersjournals.com/content/early/2015/07/09/13993003.00325-2015.full 2. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2953990/
	Norway	Pekka Nuorti <Pekka.Nuorti@uta.fi>		
	Portugal	Raquel Sa-Leao <rsaleao@itqb.unl.pt>		

	Switzerland	Claire-Ann Siegrist <Claire-Anne.Siegrist@unige.ch>		
	United Kingdom	Elizabeth (Liz) Miller < liz.miller@hpa.org.uk>	- C. Rodrigo <chamira@doctors.org.uk> - Liz Miller < liz.miller@hpa.org.uk> - David Goldblatt <d.goldblatt@ucl.ac.uk> - Albert Jan van Hoek <albertjan.vanhoek@phe.gov.uk>	1. http://www.ncbi.nlm.nih.gov/pubmed/25792633 2. http://www.ncbi.nlm.nih.gov/pubmed/21983361 3. http://www.thelancet.com/journals/laninf/article/PIIS1473-3099(14)70822-9/abstract 4. http://www.ncbi.nlm.nih.gov/pubmed/24657717
SEARO	Bangladesh	Abdullah Brooks <wbrooks3@jhu.edu> Samir Saha <samirk.sks@gmail.com> Abdullah Baqui (JHU) <abaqui@jhu.edu>	- R. Heinzen <rheinzen@jhsph.edu>	1. http://www.ncbi.nlm.nih.gov/pubmed/18828944
	Nepal	Andrew J. Pollard <andrew.pollard@paediatrics.ox.ac.uk>		
WPRO	Australia	Peter McIntyre <PeterM@chw.edu.au>		
	Fiji	Kim Mulholland <Kim.Mulholland@lshtm.ac.uk>	- Paul Licciardi <paul.licciardi@mcri.edu.au> - FM Russel <fmruss@unimelb.edu.au>	
	Japan		- N. Ihiwada, <ishiwada@faculty.chiba-u.jp> - Hideki Akeda (Okinawa Prefectural Nanbu Medical Center & Children's Medical Center, Okinawa, Japan) - T. Togashi (Sapporo City University, Hokkaido, Japan)	1. http://www.ncbi.nlm.nih.gov/pubmed/25131741 2. http://www.scirp.org/Journal/PaperInformation.aspx?PaperID=55746#.VZqVzPlViko 3. http://www.ncbi.nlm.nih.gov/pubmed/26121200
	Lao PDR	Kim Mulholland <Kim.Mulholland@lshtm.ac.uk>		
	New Zealand	David Goldblatt <d.goldblatt@ucl.ac.uk>	- E. Lim, H. Heffernan - Adrian Trenholme <Adrian.Trenholme@middlemore.co.nz>	1. https://surv.esr.cri.nz/PDF_surveillance/IPD/2012/2012AnnualIPDRpt.pdf 2. http://www-ncbi-nlm-nih-gov.ezp.welch.jhmi.edu/pubmed/24045313
	Papua New Guinea	Kim Mulholland <Kim.Mulholland@lshtm.ac.uk>		

Note: Table excludes publications reporting ONLY on PCV7 and those reporting on any experimental PCV product that did not move forward for licensure (e.g. PCV-9).
*Table has not systematically included publications after 2010 (date of Landscape Dosing review); publications from 2010-2015 have been included based on extensive literature reviews of PubMed and other databases, but should not be considered 100% comprehensive. An update of the systematic review to identify and include all publications in future gap analyses is ongoing.

Context for PCV Impact Assessment: PCV Introductions & Use

Key Messages

- 126 (65%) of 194 countries have introduced PCV into routine immunization programs.
- 49 (67%) of the 73 Gavi-eligible countries have introduced PCV and 8 more are approved for Gavi financial support of PCV introduction.
- 53% (70 million) of the world's infants are not likely to receive PCV this year because their country has not yet introduced the vaccine.
- An additional 6% (9 million) of the world's infants are not likely to be fully immunized with PCV this year because they are not being reached by routine immunizations (indicated by DTP3 coverage) even though the country they live in provides PCV in the national immunization program.
- Introduction of PCV in low- and middle-income countries has advanced more quickly in the Africa region than in the Asia region; PCV was introduced in 34 (72%) of the 47 AFR countries, compared to 17 (45%) of the 38 WPR & SEAR countries.

II. PCV Introductions: The Global Picture

The introduction of PCVs into routine immunization programs started in 2000, though the uptake accelerated only in 2004 (in upper-income countries) and in 2008-2010 (in middle- and lower-income countries) (**Figure 10**). **Figure 11** and **Table 8** display and summarize the 126 countries that have introduced PCV. Introduction of PCVs in low- and middle-income countries occurred primarily in the African region: 35 of the 47 AFR countries (74%) have introduced. In the Asian region introduction has occurred in 2 of the 11 SEAR countries (18%), and 15 of the 27 WPR countries (56%).

Gavi PCV support began in 2010, and the number of Gavi countries introducing PCV has increased approximately 12% per year over a five-year period. In high-income countries (HIC), the increase in introductions was approximately 9% per year in a similar five-year period (**Figure 10**). Thus, the rate of introductions in Gavi-supported countries has exceeded that of HICs, albeit the first year of introductions differs (2010 vs. 2000)

Figure 10: Percentage of countries introducing PCV over time

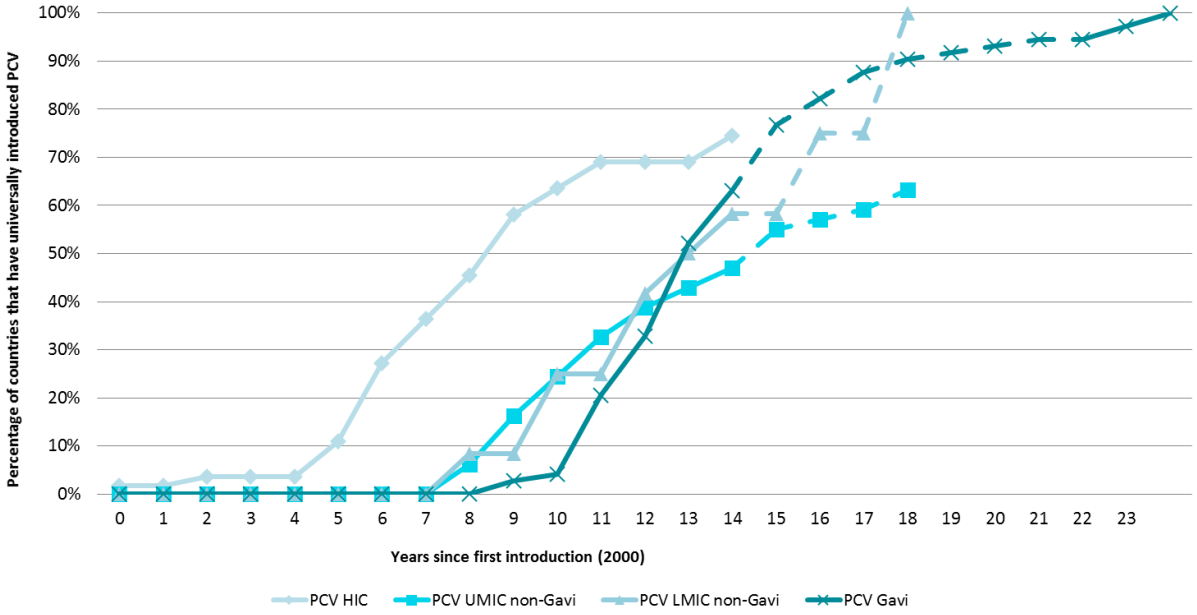


Table 8: Number of countries that have introduced PCV

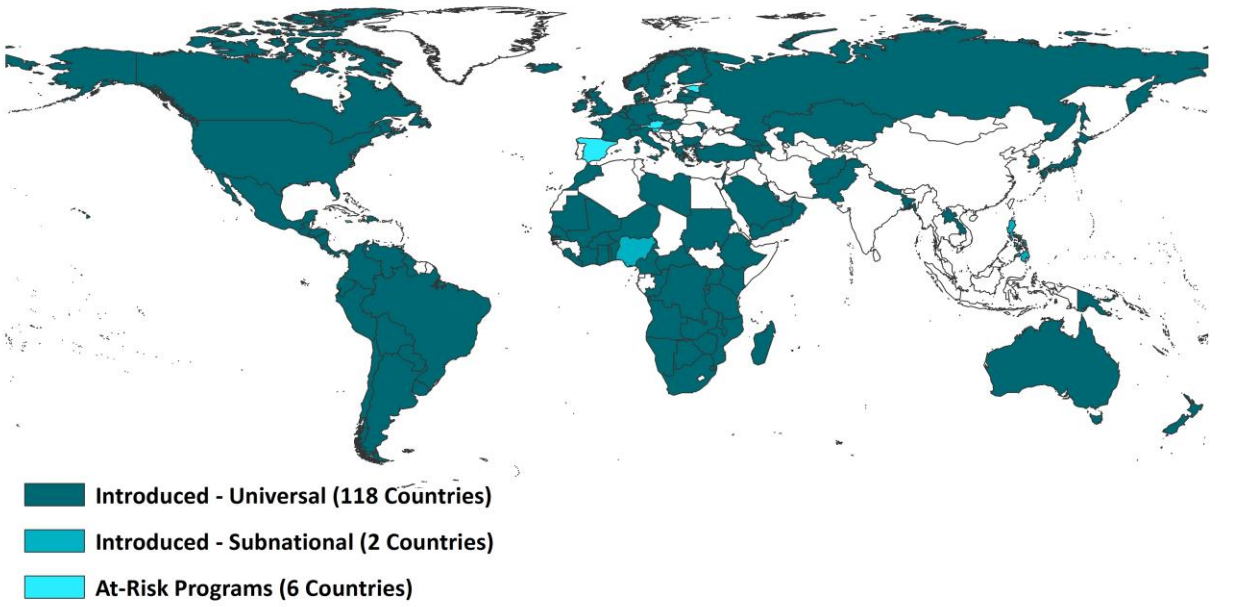
Vaccine	Global Introductions (194 Countries)			Gavi Introductions (73 Countries)	Total
	Universal	Risk	Subnational		
PCV	118	6	2	49	126

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

Fifty-three percent of the world's infants currently live in countries that have not yet introduced PCV into their National Immunization Programs (NIPs), and therefore do not have access to the vaccine. Although rapid progress has been made, a total of 59% of the world's birth cohort (79 million infants) is unlikely to receive PCV this year, either because their country has not yet introduced the vaccine or they are not receiving routine immunizations (as measured by DTP3 coverage).

Twenty-six countries have announced plans to introduce PCV into their NIPs in the coming years, 16 of these 26 are Gavi countries. Forty-one countries have not yet made a decision about the vaccine, including 8 Gavi countries.

Figure 11: Global introductions of PCV

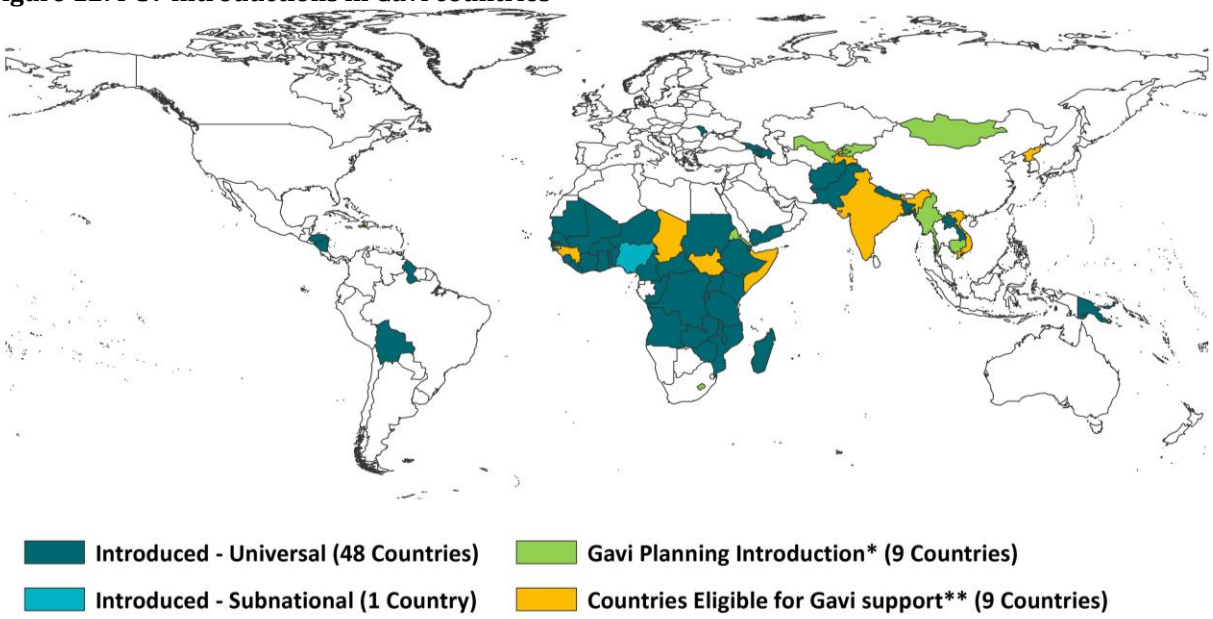


Source: IVAC VIEW-Hub, July 2015.

Zooming In: Gavi-Eligible Countries

Countries are Gavi-eligible if their average gross national income (GNI) over the past three years is equal to or below the threshold amount ($1,580 in 2014 USD). Such countries are eligible to apply for New Vaccine Support (NVS) and/or Health Systems Strengthening (HSS) support. Forty-nine (67%) of the 73 Gavi countries have introduced PCV (**Figure 12**). Nine additional Gavi countries are planning to introduce PCV, eight countries have been approved/approved with clarification, and one country has been conditionally approved for Gavi support of PCV introduction.

Figure 12: PCV introductions in Gavi countries



*Includes Gavi approved/approved with clarification and conditional approval

**Angola, Armenia, Azerbaijan, Bhutan, Bolivia, Congo, Cuba, Georgia, Guyana, Honduras, Indonesia, Kiribati, Moldova, Mongolia, Nicaragua, Papua New Guinea, Sri Lanka, Timor Leste, Ukraine, and Uzbekistan are graduating countries that are no longer eligible to apply for new vaccine support (NVS). Ghana, Nigeria, Solomon Islands, and Vietnam also became graduating countries in 2015, but are still eligible to apply for NVS from Gavi in 2015.

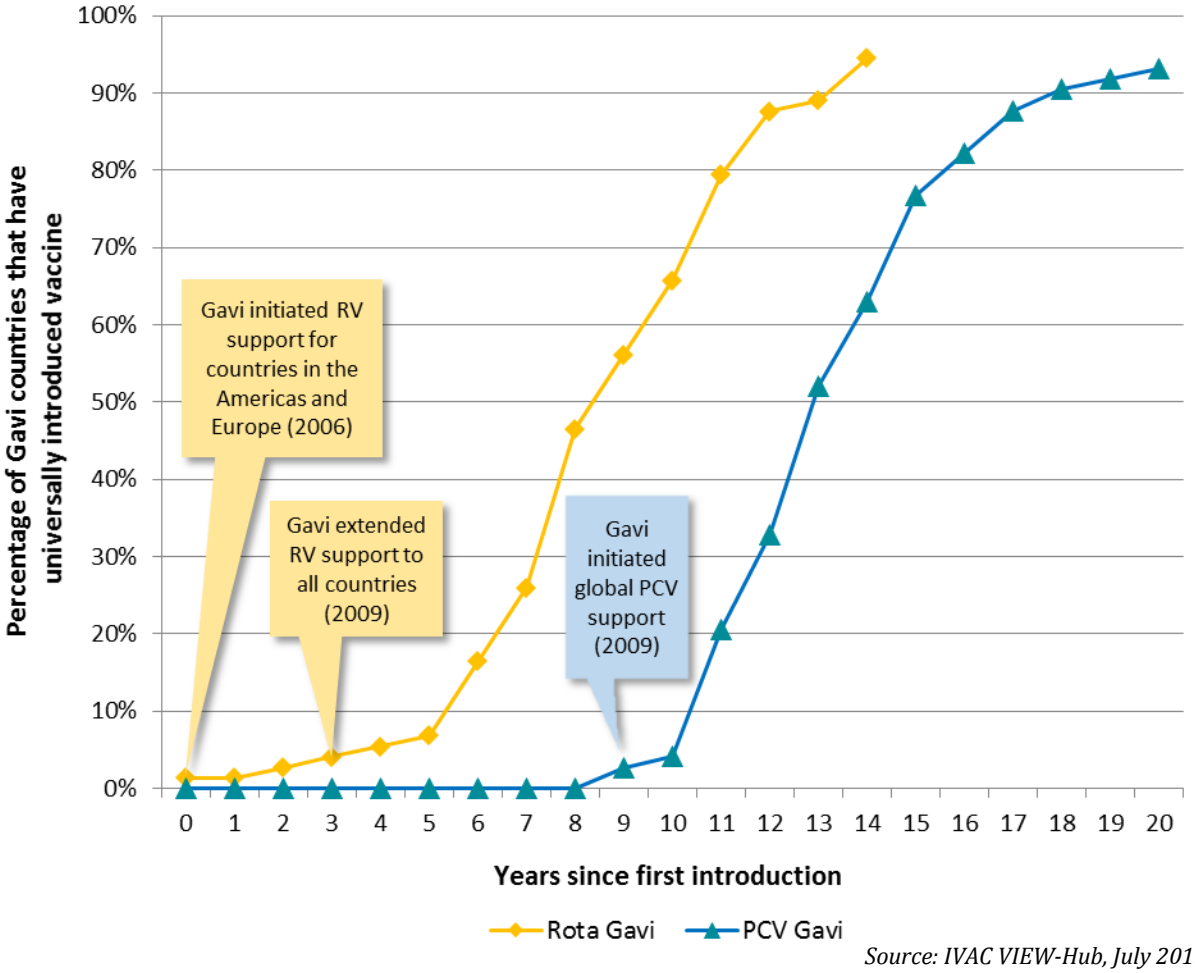
Source: IVAC VIEW-Hub, July 2015.

- Fifty-four percent (41 million) of the surviving Gavi birth cohort live in the 24 (33%) Gavi countries that have not introduced PCV and therefore lack access to the vaccine. Many of these countries have large birth cohorts (e.g., India, Indonesia) and contribute substantially to the total number of infants targeted for vaccination. Some of these countries, such as India and Indonesia, have local manufacturers that are currently developing pneumococcal vaccines (either PCV or others). In such cases, preference for nationally-manufactured vaccines may influence the timing of introduction in those countries.

- Another 9% of the Gavi-birth cohort are unlikely to receive PCV, due to low coverage of routine immunizations (based on national DTP3 coverage data).

- PCV introduction has progressed at a more rapid pace than any other vaccines intended for global use, especially in low-income country (LIC) settings. **Figure 13** displays a comparison of the Gavi rates of introduction for rotavirus and PCV, two new vaccines introduced in the same era.

Figure 13: Percentage of countries introducing PCV and Rotavirus vaccines over time



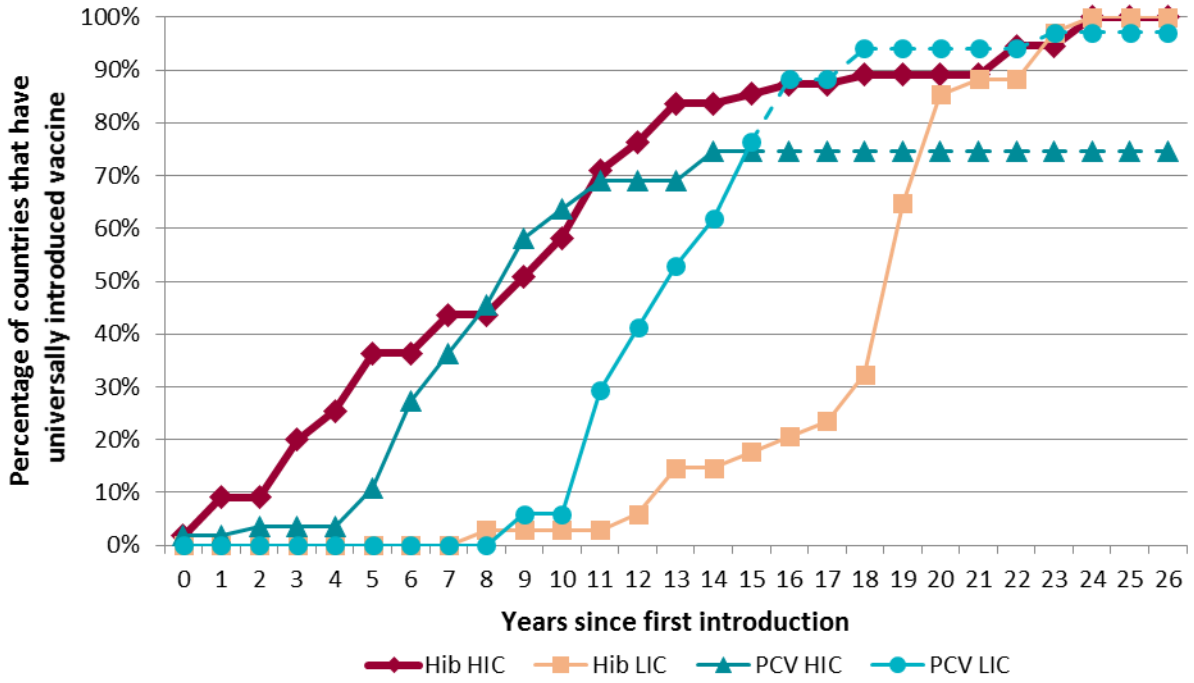
Source: IVAC VIEW-Hub, July 2015.

- PCV was first introduced in 2000 globally and Gavi support initiated in 2009. In comparison, rotavirus vaccine was first introduced in 2006 and Gavi support initiated that same year for eligible countries in the Americas and Europe and was later expanded to all countries in 2009. Since the availability of Gavi funds to support new vaccine introductions, rotavirus vaccine introductions have been slow compared to that of PCV. Three years after Gavi support was made available to all countries, PCV introductions reached 33% of Gavi countries, compared to 16% for rotavirus vaccine.

- **Figure 14** illustrates this trend with comparison to Hib vaccine; the year of first introduction for Hib vaccine was 1989. It took 20 years for Hib vaccine to reach 70 percent of LICs. PCV is projected to reach 70 percent of LICs five years faster. This

time differential was similar for both vaccines to reach 50% of LICs (i.e., PCV reached 50% approximately 5-6 years faster).

Figure 14: Percentage of countries introducing PCV and Hib vaccines over time



Source: IVAC Vaccine Information Management System (VIMS) Global Vaccine Introduction Report, May 2015.
HIC = High Income County; LIC = Low Income Country
Graph indicates years since first introduction of PCV in any country: 2000

- The speed of introduction of PCV in LICs has been driven by Gavi support in AFR, with 34 (72%) of the 47 AFR countries now using PCV in their NIPs.

III. Product & Schedules in Use Globally

Key Messages

- Globally, the distribution of PCV products is unequal; 73% (92 countries) are using PCV13 and 27% (34 countries) are using PCV10.

- The same ratio pertains to Gavi countries: 36 (73%) of Gavi countries that have introduced PCV are using PCV13.

- Product-specific supply constraints in past years have influenced country product choice and product allocation by Gavi.

- 96 (76%) of the 126 of countries using PCV are using 3-dose schedules (either 2p+1 or 3p+0), including all Gavi countries that have introduced PCV.

- All Gavi countries are using a 3p+0 schedule for PCV, with the exception of Nepal and Moldova (which use a 2p+1 schedule).

- With the introduction of IPV, alternate interval PCV dosing schedules are being used and evaluated in order to limit the number of injections per visit.

Countries are responsible for choosing the PCV product and dosing schedule they will use in routine immunization programs. However, methods for decision making and guidance on product choice for countries are not well defined, and assumptions of effectiveness, budget, and/or supply constraints may influence such decisions. Schedule choice is usually made to best fit the routine immunization context of a country and optimize the visits already made for infants.

PCV Use by Product

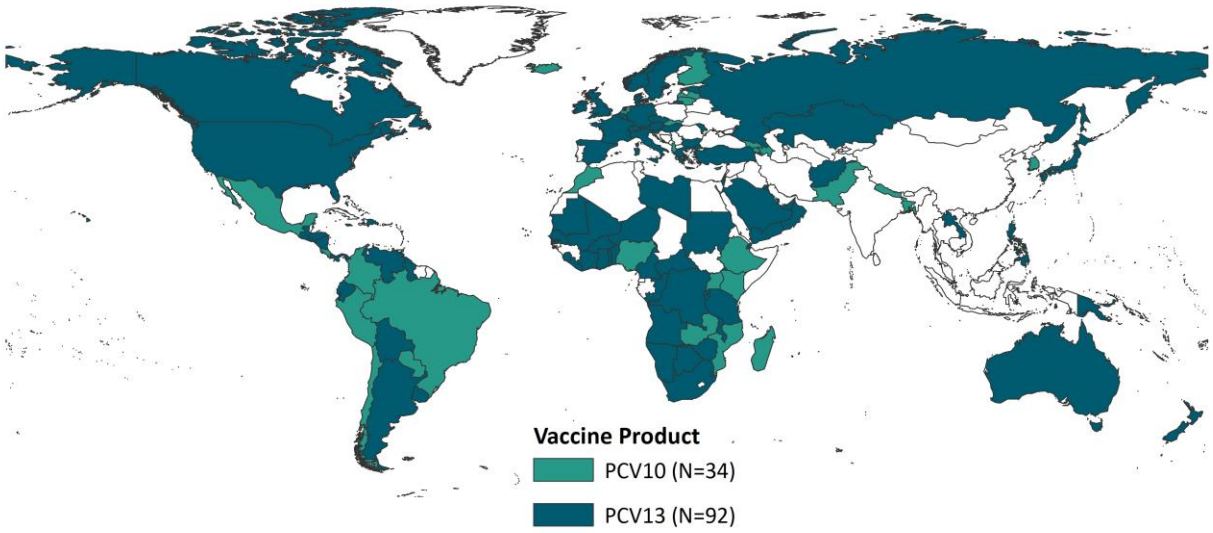
Two PCV products are currently licensed for use, 10-valent and 13-valent PCV. **Figure 15** indicates the serotypes included in each formulation. A global map of the distribution of products is displayed in **Figure 16.**

Figure 15: Serotypes included in PCV10 and PCV13 product formulations

Serotype / Formulation	1	3	4	5	6A	6B	7F	9V	14	18C	19A	19F	23F
PCV10	■		■	■		■	■	■	■	■		■	■
PCV13	■	■	■	■	■	■	■	■	■	■	■	■	■

■ Serotype included in the vaccine

Figure 16: Countries using PCV-10 or PCV-13, by product introduced into NIP

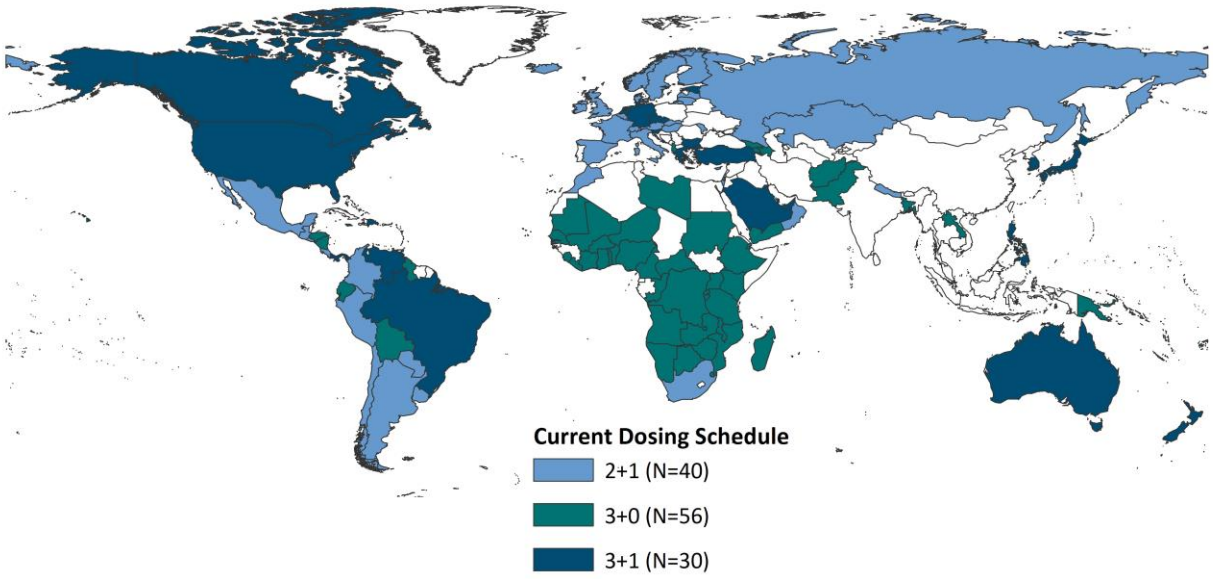


Source: IVAC VIEW-Hub, July 2015.

PCV Use by Schedule

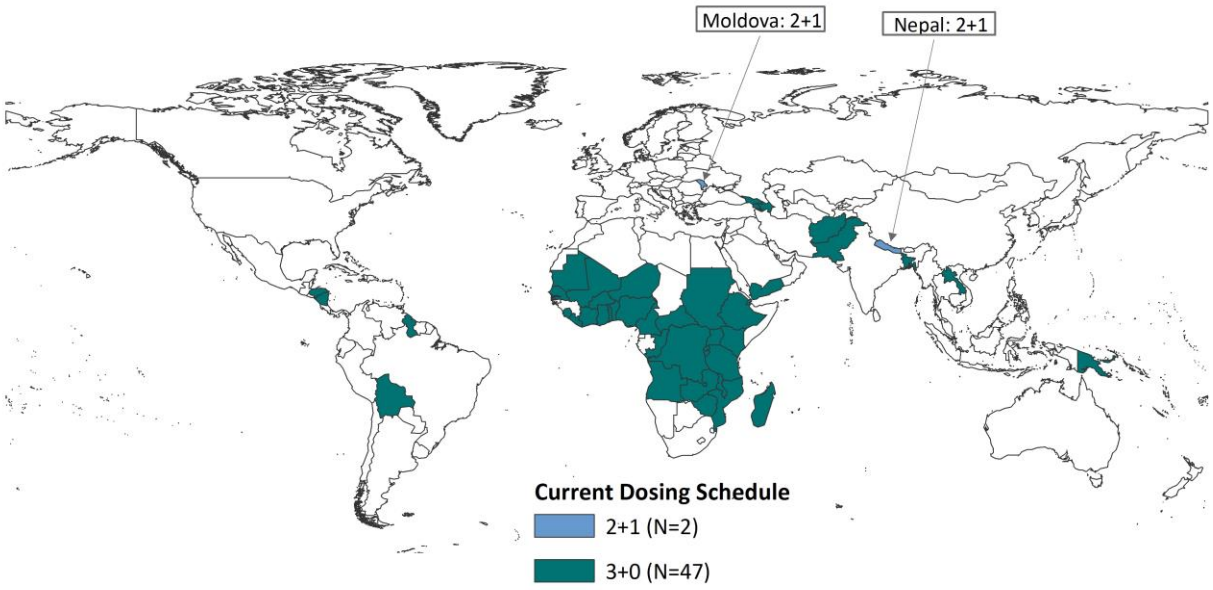
WHO/SAGE recommendations for PCV use include three dosing schedules options: 3p+1, 3p+0 or 2p+1 (for either product).

Figure 17: Countries using PCV-10 or PCV-13, by dosing schedule



Source: IVAC VIEW-Hub, July 2015.

Figure 18: The 49 Gavi countries that have introduced PCV-10 or PCV-13, by dosing schedule



Source: IVAC VIEW-Hub, July 2015

Table 9: Countries using PCV10 or PCV13 in NIP, by dosing schedule

WHO Region	Dosing Schedule		
	2p+1	3p+0	3p+1
AFR	South Africa	Angola	
		Benin	
		Botswana	
		Burkina Faso	
		Burundi	
		Cameroon	
		Central African Rep.	
		Congo	
		Congo, DR	
		Cote D'Ivoire	
		Ethiopia	
		Gambia	
		Ghana	
		Kenya	
		Liberia	
		Madagascar	
		Malawi	
		Mali	
		Mauritania	
		Mozambique	
		Namibia	
		Niger	
		Nigeria	
		Rwanda	
		Sao Tome and Principe	
		Senegal	

WHO Region	Dosing Schedule		
	2p+1	3p+0	3p+1
AFR (cont.)		Sierra Leone	
		Swaziland	
		Tanzania	
		Togo	
		Uganda	
		Zimbabwe	
AMR	Argentina	Barbados	Bahamas
	Chile	Bolivia	Brazil
	Colombia	Ecuador	Canada
	Costa Rica	Guyana	Jamaica
	El Salvador	Honduras	Panama
	Guatemala	Nicaragua	United States
	Mexico	Trinidad and Tobago	
	Paraguay		
	Peru		
	Uruguay		
EMR	Morocco	Afghanistan	Bahrain
	Oman	Djibouti	Kuwait
		Libya	Qatar
		Pakistan	Saudi Arabia
		Sudan	United Arab Emirates
		Yemen	
EUR	Andorra	Albania	Bulgaria
	Austria	Armenia	Czech Republic
	Belgium	Azerbaijan	Estonia
	Cyprus	Georgia	Germany
	Denmark		Greece
	Finland		Netherlands
	France		Slovenia
	Hungary		Turkey
	Iceland		
	Ireland		
	Israel		
	Italy		
	Kazakhstan		
	Latvia		
	Lithuania		
	Luxembourg		
	Moldova, Rep. of		
	Monaco		
	Norway		
	Russian Federation		
	Slovakia		
	Spain		
	Sweden		
	Switzerland		
	United Kingdom		
SEAR	Nepal	Bangladesh	
WPR	Singapore	Solomon Islands	Australia
		Lao PDR	Japan
		Papua New Guinea	Korea, Rep. of
			Marshall Islands
			Micronesia, Fed. States of

WHO Region	Dosing Schedule		
	2p+1	3p+0	3p+1
WPR (cont.)			New Zealand
			Niue
			Palau
			Philippines

Note: Gavi countries are highlighted in gold.

Table 10: Globally recommended PCV dosing schedules and number of countries using each

TOTAL DOSES	3+1	3+0	2+1
Licensed Schedule*	✓	✓	✓
WHO/SAGE Recommendation	✓	✓	✓
COUNTRY SCHEDULE	30	56	40
Non-GAVI	30	9	38
GAVI	0	47	2**

*For routine immunization; does not include catch-up schedules (updated 7 Jul 2015)
**Moldova and Nepal

With the exception of Nepal and Moldova (using 2p+1), all Gavi countries that have introduced PCV are using a 3p+0 schedule for PCV.

Nine non-Gavi countries are currently using a 3p+0 schedule (Albania, Barbados, Botswana, Ecuador, Fiji, Libya, Namibia, Swaziland, and Trinidad and Tobago), while the remaining non-Gavi countries maintain a 2p+1 or 3p+1 schedule.

The 2p+1 schedule was first used at the provincial level by Quebec, Canada in 2004 (de Wals, 2014).[5] The schedule was first used nationally by the UK in 2006 following an immunogenicity study of various schedules, motivated by the reduction in the number of injections to allow room in the schedule for other vaccines and reduction in PCV program costs without compromising impact. Careful post-introduction studies have shown the schedule to be highly effective. Many non-Gavi countries have likewise introduced this schedule.

[5] Canada is shown on maps as 3p+1 schedule country because only some provinces use the 2p+1 schedule.

IV. Next Steps

This gap analysis of PCV impact studies aims to describe the ***availability of evidence*** that has been or is being collected globally, with focus on product, schedule, and outcomes by country, as of July 2015. This analysis provides the first view of potential gaps within the objectives of the PCV Technical Coordination Project and the Reduced Dose Policy Analysis funded by the Bill & Melinda Gates Foundation.

Ongoing work includes systematically identifying and evaluating evidence from published and ongoing work to review and summarize the impact of each vaccine by outcome, schedule, and setting. Topics of interest for such ongoing activities are listed below. *(Note: the topics listed here are in no particular order, and may be edited and reordered based on Foundation priorities, relevance to WHO and NITAGs, or other considerations.)*

Topics of interest

1. Assess the availability of PCV impact evaluations across the WHO regions by Gavi-status and income strata of countries.
    - Due to Gavi support for introduction and impact evaluation for PCV, it is likely that a higher proportion of Gavi countries have ongoing or published PCV impact studies than non-Gavi middle-income countries. In particular, the middle-income countries outside of the PAHO region are predicted to have a fewer PCV introductions and PCV impact studies compared to other income strata countries.

2. The use of catch-up schedules in various countries.

3. Further disaggregate this analysis of PCV impact studies by outcome to assess those using different approaches to measure pneumonia impact (e.g., use of administrative data, chest radiographs, NP carriage, and urine antigen testing), which can inform future assessments.

4. Include an assessment of age group evaluated in NP carriage studies to determine the direct and indirect effects of PCV on this outcome, and assessment of the methods used in such studies (e.g., cross-sectional or cohort) to evaluate the relative merits of each approach.

5. Assess the 2015 pneumococcal disease burden estimates in relation to PCV use, by region. Compare the regional disease burden estimates and location of PCV impact studies for future MCEE estimates and updating of assumptions used in models. (The 2015 disease burden estimates from the MCEE project will be available in Q4/2015).
    - To assess the validity of, and revise if required, the assumptions used in the model for the MCEE disease burden estimates based on the available results of PCV impact studies.

6. Assess the generalizability or collective contribution to address the substantial data gaps on the health economic impact of PCV since it is likely that the methods and outcomes are not well harmonized across these studies.

7. Data from studies with multiple outcomes will be analyzed and triangulated to assess the relationships between the impact on different outcomes and whether the results indicate the possibility of conducting less resource intensive assessments (e.g., using NP carriage studies alone in countries with limited resources).

8. Compare the serotype-specific effects of PCV10 and PCV13 (direct and indirect), particularly in terms of serotypes 3, 19A, 1, and 5 that are present in PCV13, but not in PCV10.

9. Replacement serotypes: specifically an evaluation of the trends in 19A incidence in countries using PCV10

10. Evaluation of vaccine effectiveness from sites evaluating alternate dosing schedules (such as Nepal and Bangladesh with off-label studies, or reduced-dose schedules)

Various topics have become of particular interest to the PCV Partners and others in the pneumococcal field, and this limited list may be necessary to provide some immediate updates on:

- Data becoming available from Mozambique and Kenya on the impact of PCV10

- Data becoming available from Finland on the impact of PCV10

- GSK applying for a serotype 19A label within their PCV10 product label

- Data and coordination among Latin Americas sites regarding evidence on the use and impact of PCVs in the region (through the GREEN research group)

Strategic gap analyses are to be conducted on the amount of evidence and the technical content of such evidence to address arising issues surrounding PCV use via systematic and comprehensive evaluations. Such analyses may help strategically inform allocation of resources and collection of data to measure suspected or unknown effects of PCV in national immunization programs or to better inform country-level decision makers on the potential impact of PCV use in their own national immunization programs.

Acknowledgements and Notes

This report was prepared for the July 31, 2015 deliverable associated with the PCV Technical Coordination Project and Reduced Dose Policy Analysis, both funded by the Bill & Melinda Gates Foundation.

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

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

For any inquiries, comments, or feedback on this report or future gap analyses conducted by IVAC or WHO staff in compliance with this scope of work, please contact Olivia Cohen at ocohen3@jhu.edu or coheno@who.int. For inquiries specifically related to VIEW-Hub (regarding global vaccine use or PCV impact studies), please contact Linh Nguyen at linh.nguyen@jhu.edu.

Appendix A. Global PCV Introductions, by Region

WHO Region	Country		
AFR	Angola	Ghana	Sao Tome and Principe
	Benin	Kenya	Senegal
	Botswana	Liberia	Sierra Leone
	Burkina Faso	Madagascar	South Africa
	Burundi	Malawi	Swaziland
	Cameroon	Mali	Tanzania
	Central African Republic	Mauritania	Togo
	Congo	Mozambique	Uganda
	Congo, DR	Namibia	Zambia
	Côte D'Ivoire	Niger	Zimbabwe
	Ethiopia	Nigeria (subnational)	
	Gambia	Rwanda	
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	Morocco	Sudan
	Bahrain	Oman	United Arab Emirates
	Djibouti	Pakistan	Yemen
	Kuwait	Qatar	
	Libyan Arab Jamahiriya	Saudi Arabia	

WHO Region	Country		
EUR	Albania	Georgia	Monaco
	Andorra	Germany	Netherlands
	Armenia	Greece	Norway
	Austria	Hungary	Russian Federation
	Azerbaijan	Iceland	Slovakia
	Belgium	Ireland	Slovenia
	Bulgaria	Israel	Spain
	Cyprus	Italy	Sweden
	Czech Republic	Kazakhstan	Switzerland
	Denmark	Latvia	Turkey
	Estonia	Lithuania	United Kingdom
	Finland	Luxembourg	
	France	Moldova, Republic Of	
SEAR	Bangladesh	Nepal	Palau
WPR	Australia	Lao PDR	Papua New Guinea
	Fiji	Marshall Islands	Philippines (subnational)
	Japan	Micronesia, Federated States of	Singapore
	Kiribati	New Zealand	Solomon Islands
	Korea, Republic of	Niue	