Strengthening national decision-making on immunization by building capacity for economic
evaluation: implementing ProVac in Europe

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1. Background and regional context

New vaccines, such as rotavirus and pneumococcal vaccines, have the potential to prevent deaths and reduce disease burden. However, the national decisions to introduce new vaccines need to be strongly justified because the vaccines are expensive and often lead to a substantial increase in the cost of immunization programs. The ministries of health should carefully consider the financial aspects of such introductions, including evidence on cost-effectiveness of the new interventions. Therefore, many low- and middle-income countries have expressed a need for support in obtaining local evidence on cost-effectiveness of new vaccines as well as building capacity in interpreting and communicating this type of evidence to national decisionmakers.

To respond to these needs in the Americas, the Pan American Health Organization's (PAHO) ProVac Initiative was created in 2004 to strengthen national technical capacity to make evidence-based immunization policy. The ProVac Initiative produced models for cost-effectiveness analysis (CEA), conducted regional training workshops, and provided direct technical support to individual nations. This approach and the experience in the Americas have been described elsewhere [1].

Due to the success of the ProVac Initiative in the Americas, countries from other world regions requested help in building capacity in economic evaluation in order to strengthen their national decision-making processes for immunization. In response, the Bill & Melinda Gates Foundation funded a two-year pilot project called the ProVac International Working Group (IWG). This effort, which took place in 2012 and 2013, was coordinated by PAHO and carried out in collaboration with international partners that included the Agence de Médecine Préventive (AMP), London School of Hygiene & Tropical Medicine (LSHTM), Program for Appropriate Technology in Health (PATH), Sabin Vaccine Institute, United States Centers for Disease Control and Prevention (CDC), and World Health Organization (WHO). The mandate of this group was to implement ProVac tools and methods in countries in the WHO African, Eastern Mediterranean, and European regions.

AMP, in collaboration with WHO regional offices, implemented the ProVac tools and methodology in six countries, four in the WHO European Region and two in the WHO Eastern Mediterranean Region. Joint WHO and AMP workshops were conducted in both of these regions to raise countries' awareness of the need to use evidence to support decision-

making and of the availability of the ProVac IWG support as well as to briefly train the countries on health economic evaluation.

This article focuses on the experience of implementing ProVac in the WHO European Region. The experience and lessons learned from the Eastern Mediterranean Region with AMP and from the African Region with PATH can be found in an article by Jauregui et al. [2].

2. Methods

2.1. *The use of the ProVac Initiative methodology and tools*

AMP and WHO benefited from the successful development and use of ProVac tools and methodologies in the Americas, and applied them in the WHO European Region. AMP, in collaboration with WHO, trained the country teams on two levels. First, the general ProVac approach was explained to the teams, insisting on the importance of transferring the skills and the knowledge to the teams, to enable country capacity-building and ownership of the project results. Second, the tools themselves were presented.

The main tool used was the TRIVAC model. TRIVAC is a decision-support model developed by the LSHTM, and it had been used by the ProVac Initiative in Latin America for many years [1]. It is built in Excel and can be used by countries to conduct CEAs of vaccines that prevent disease caused by three pathogens: rotavirus, pneumococcus, and *Haemophilus influenzae* type b.

The TRIVAC model has three particular characteristics that facilitate training in countries. First, it is a transparent model that shows data inputs, calculations, and results, thus allowing analysts to understand the steps that lead to the results. Second, a range of results are displayed that can be used as evidence for decision-making. These results include the number of cases, hospitalizations, and deaths averted; number of fully vaccinated children; cost of the immunization program; and cost of health services avoided. Third, the Excel software is globally available (as part of the ProVac support package) and user-friendly. With TRIVAC, people from many countries and backgrounds, independent of their knowledge of models and software, can conduct an economic evaluation with the appropriate data [3].

2.2. *A regional training workshop*

In October 2012, AMP and the WHO Regional Office for Europe held a regional training workshop, in the city of Dubrovnik, Croatia, on the cost-effectiveness of the pneumococcal conjugate vaccine (PCV). The aim of the workshop was to train health professionals, increase the countries' knowledge on the use of economic evaluation to inform new-vaccine introduction policy, improve countries' capacity to conduct country-owned CEAs, and assess regional demand for economic studies. Thirty-one participants from four countries (Albania, Croatia, Estonia, and Georgia) attended. The PCV component of the TRIVAC model was used as a basis for workshop exercises.

After the workshop, three of the four countries that had participated (Albania, Croatia, and Georgia) submitted official letters to the WHO Regional Office for Europe, asking to be included in the ProVac IWG. Estonia did not present a request because data on cost-effectiveness of new vaccines became available from studies conducted by that country's University of Tartu. However, the ProVac IWG did also support a national study in Azerbaijan, which made a request to WHO in 2012.

2.3. *A multidisciplinary national working group*

A common priority for AMP and the WHO Regional Office for Europe was to use CEAs to strengthen decision-making in immunization policy and to ensure the sustainability of vaccine introduction. Therefore, emphasis was given to maximizing the commitment and support of existing advisory bodies in the country (e.g., National Immunization Technical Advisory Group (NITAG) or interagency coordination committee (ICC)) as well as other stakeholders involved in decision-making (e.g., ministry of health, ministry of finance, WHO country office, and United Nations Children's Fund).

At the national level, AMP and the WHO Regional Office for Europe utilized the ProVac approach in helping each country create a national team of experts from diverse organizations and with multiples areas of expertise, such as epidemiology, infectious disease, finance, pediatrics, and economics. This multidisciplinary team of experts was responsible for collecting the appropriate data for the CEA. The team included staff from such institutions as the respective ministry of health (MoH), the institute of public health, the main university hospital, and the NITAG. The coordinator and leader of this team was a national focal point, previously designated officially by the MoH. AMP and the WHO Regional Office for Europe

encouraged the inclusion of candidates who could devote at least half of their time to the ProVac IWG, since they would be in charge of conducting the studies. AMP and WHO strongly advised the selection of a focal point already in position with a relevant immunization policy-making organization, in order to ensure that the capacities learned would endure in the country. If the national focal point was already an employee of the national immunization program, this would help guarantee country ownership of the study and thus sustainability of the process.

2.4. *A six-month country-led study process*

AMP, the WHO Regional Office for Europe, and the other ProVac IWG partners worked with countries for an average of six months. This included two or three in-country visits lasting two or three days each. The first visit aimed to raise awareness on the project and to ensure commitment from authorities and to train the focal point and the multidisciplinary team on economic evaluation and the TRIVAC model. The second visit focused on assessing data collected to populate the model. The third visit consisted of validating final data, interpreting results, undertaking scenario analysis, and assisting the team in preparing a presentation for national stakeholders. This three-visit approach allowed a close follow-up with the national team by international experts who could provide needed assistance.

With this approach, many national authorities were brought into the CEA process. In Albania, for example, the study results were presented to the NITAG, ICC, MoH, institute of public health, Red Cross Albania, health insurance institute, national drug control center, and UNICEF. National teams were also encouraged to publish an article on their study in a peer-reviewed journal.

2.5. *Support from the ProVac International Working Group*

The ProVac IWG brought together different actors, different institutions, and different areas of expertise to jointly work on the undertaking. AMP was in constant communication with the other partners to share and gain from their experiences and expertise. For example, the partners suggested improvements in the TRIVAC model and the ProVac methodologies. The needs and level of development of the non-PAHO countries were different from those of the PAHO nations. AMP provided feedback to the LSHTM and PAHO on making the tools more useful and tailored to the countries' circumstances. CDC experts helped the countries

validate the data used for their study models and provided the best available evidence on the efficacy of vaccines and the burden of disease at both the regional and international level.

3. Results

With the 53 Member States in the WHO European Region, the ProVac IWG effort was aimed at middle-income countries, which have to bear the full cost related to introducing new vaccines. Some of these countries have been able to receive support from Gavi, the Vaccine Alliance (Gavi)¹, but they have had to co-finance an increasing proportion of the price of new vaccines, starting at 20% and ending with the full price within four years.

Even with initial support from Gavi, the introduction of vaccines doubles or triples the cost of immunization programs in middle-income countries and requires either increasing the overall MoH budget or redistributing funds from other programs within the MoH. The resources available for public health programs in these countries are limited, and ministries of health face a number of competing priorities. Therefore, economic evidence to help decide if introducing new vaccines should be ranked along with other public health programs has been particularly important for middle-income countries. Additionally, the CEA results, along with other evidence, could help policy and decisionmakers to advocate to the ministries of finance for allocation of additional funds. Further, in Croatia, the CEA conducted with ProVac IWG support was the country's first economic evaluation in the area of infectious disease prevention and control; this effort has helped build economic evidence into the nation's decision-making process.

In all four countries, the CEA studies provided an opportunity to use national surveillance statistics and global estimates to review the data on the burden of the diseases preventable by the new vaccines. For example, the CEA team in Albania estimated the burden of rotavirus gastroenteritis using data from rotavirus sentinel surveillance and national mortality statistics. The Croatian team conducted analysis of data from their national infectious disease notification system and reviewed publications related to the distribution of pneumococcal serotypes in their country. The teams in Azerbaijan and Georgia critically reviewed data from

¹ The Global Alliance on Vaccines and Immunization (GAVI) was established by the Bill & Melinda Gates Foundation in late 1999. (Recently, the organization changed its name to Gavi, the Vaccine Alliance (Gavi)). Gavi's mission is "saving children's lives and protecting people's health by increasing access to immunization in poor countries." More information is available at: www.gavialliance.org

population-based passive pneumonia and meningitis surveillance. The ProVac IWG helped these teams to better understand the potential biases in these estimates and provided alternative WHO estimates to use in scenario analysis.

The work also improved the understanding of the financial implications that these diseases hold for public health systems. The CEA teams in all the countries estimated a frequency of hospitalizations and outpatient visits due to diseases that could be prevented by the new vaccines, along with the potential resulting cost savings in the health care and treatment provided by governments.

3.1. *Two Gavi graduating countries: Azerbaijan and Georgia*

In 2010, Azerbaijan and Georgia applied for Gavi support to introduce PCV. The applications were submitted in order to use the last opportunity to receive Gavi support because both countries were due to lose their Gavi eligibility status in 2011. However, those two countries' decisions to introduce new vaccines were still at a preliminary stage. In 2010, due to global constraints in new-vaccine supplies, it was not known when pneumococcal vaccines would become available for these countries. Therefore, the MoH decisions and corresponding financial commitments needed to be reconsidered and confirmed at a later stage. In addition, in Azerbaijan, in accordance with local regulations, prior to the introduction of the new vaccine, the MoH had to obtain approval of its decision from the Cabinet of Ministers.

In both of the countries, the national advisory bodies provided scientific recommendations to support final decisions on introducing PCV based on evidence related to the burden of pneumococcal diseases, efficacy and safety of PCV, programmatic feasibility of introduction, and acceptance of the new vaccine by medical workers and the population. However, policymakers needed additional economic evidence to make sure that the vaccine introductions should be prioritized among other public health interventions, confirm their preliminary decision to introduce pneumococcal vaccine, and warrant the allocation of additional funds.

The MoHs were also going to use the CEA results to advocate with the Ministry of Finance for additional funds to ensure timely provision of increasing co-financing payments as well as sustainable financing of PCV vaccination after the end of the Gavi support. The

lack of local expertise in health economics and economic evaluation prompted the MoHs to request support from the WHO Regional Office for Europe, which in turn requested support from the ProVac IWG.

In Azerbaijan, the CEA results indicated that introducing PCV10 would be highly cost-effective (Table 1) [4]. The results helped the MoH of Azerbaijan to confirm its decision to introduce pneumococcal vaccine. The results were also included in the request submitted to the Cabinet of Ministers, contributing to their final approval and to introduction of PCV in December 2013. The MoH has expressed an interest in further studies using the TRIVAC model and methodology, including for a comparative analysis of the 13-valent PCV and for a CEA of the HPV vaccine.

In Georgia, the results of the study indicated that introducing PCV would be highly cost-effective (Table 1) [5]. The MoH confirmed its preliminary decision to introduce pneumococcal vaccines and made corresponding financial commitments. The pneumococcal vaccine was introduced into the national immunization schedule in November 2014.

3.2. *Two middle-income countries: Albania and Croatia*

In the middle-income nations of Albania and Croatia, the national advisory bodies recommended introducing new vaccines into the routine immunization schedule. However, the MoHs requested additional economic evidence to make a final decision to introduce new vaccines and to ensure that allocating additional funds would be justified.

In Albania, the national immunization program and the ICC discussed introducing the rotavirus vaccine. They concluded that introduction was justified, given the burden of disease, vaccine characteristics, and public health considerations. However, final recommendations to the MoH were dependent on additional evidence indicating that introducing rotavirus vaccination would be cost-effective. Therefore, the MoH asked the WHO Regional Office for Europe and AMP for support in conducting an economic evaluation.

The ProVac IWG CEA results indicated that introducing vaccination against rotavirus in Albania was either cost-effective or highly cost-effective², depending on the vaccine (RV1 or RV5) and on the perspective chosen (governmental or societal) (Table 1) [6]. Based on these results and other relevant evidence (such as safety, efficacy, burden of disease, and acceptance), the ICC (which served as a national advisory body) recommended the MoH introduce the vaccine into the country's immunization schedule. The MoH accepted the ICC recommendation. However, the introduction of rotavirus vaccine in Albania has been scheduled for 2015 because in 2014 the country planned to introduce IPV as part of implementing the Polio Eradication and Endgame Strategic Plan. The ProVac IWG economic evaluation helped to better the understanding of how vaccine price influences cost-effectiveness. The analysis also prompted the MoH to request that the UNICEF procurement division include Albania in its initiative to support middle-income countries in accelerated introduction of rotavirus vaccines.

Croatia was a middle-income country when it was selected to participate in the ProVac IWG. In July 2012, Croatia became a high-income country, in accordance with the World Bank classification³. Similar to Albania, the NITAG in Croatia discussed recommendations on PCV introduction, but final recommendations were pending additional economic evidence that could help to prioritize the introduction of PCV among other public health interventions. Support to conduct a CEA came from the WHO Regional Office for Europe and the ProVac IWG. One objective of the CEA was to assess if introducing PCV vaccine would be cost-effective, taking into account the high vaccine price set by the manufacturers. The Croatian government had data from pharmaceutical company studies but wanted to have an independent source of information.

The CEA results indicated that introducing pneumococcal vaccine into the routine immunization program in Croatia would not be cost-effective, based on the costs and benefits to children aged <5yrs (Table 1) [7]. This was true for both PCV13 and PCV10. The major parameters affecting the incremental cost-effectiveness ratio (ICER) were the high price of

² Based on the threshold of >1 GDP per capita to >3 GDPs per capita established by the WHO's Commission on Macroeconomics and Health. For more information please, see: http://www.who.int/choice/costs/CER_thresholds/en/.

³ For additional information, visit the World Bank website, at: <http://www.worldbank.org/en/country/croatia>.

the vaccine and the relatively low mortality due to pneumococcal diseases. The MoH decided to postpone PCV introduction until the vaccine's price is reduced.

This CEA work was one of the first MoH-led cost-effectiveness studies in Croatia. It was also the first time in the country that a decision on introducing a new immunization intervention took into account economic evidence. The evaluation stimulated interest in improving existing analyses (such as on incorporating health benefits for older age groups) and in generating similar economic evidence each time a new vaccine is considered. The multidisciplinary team has recommended that the MoH make routine use of economic evaluations to support decisions and prioritization of public health interventions.

4. Discussion

The ProVac IWG enabled advisory bodies (NITAGs or ICCs) in four countries to develop evidence-based recommendations to the ministries of health on making or confirming preliminary decisions on introduction of rotavirus and pneumococcal vaccines. The CEAs provided the ministries with additional economic evidence that helped them to prioritize the introduction of the new vaccines among other public health programs.

In Albania, for example, following the CEA, introduction of rotavirus vaccine was recommended by the ICC. The MoH accepted the ICC recommendation, and introduction is planned for 2015. In Georgia and Azerbaijan, preliminary decisions made 2010 (in order to not lose an opportunity to receive Gavi support) were confirmed by the ministries of health, and relevant financial commitments were made. PCV was introduced in Azerbaijan in December 2013 and in Georgia in November 2014. In Croatia, the MoH made a decision not to introduce PCV until the vaccine price decreases to a level where the introduction becomes cost-effective.

Overall, the transparency of the TRIVAC model developed by LSHTM allowed the process of producing evidence and its value to be demonstrated and understood by a variety of national experts and national authorities. Importantly, all four ProVac IWG country teams recommended that economic evaluations become a routine approach in making decisions and prioritizing public health interventions.

A second notable effect was capacity-building. The national focal points were trained on economic evaluation and on the TRIVAC model, using a learning-by-doing approach. The focal points were active workers in the field and in institutions surrounding vaccination decision-making processes. In Albania, the focal point worked at the Institute of Public Health; in Azerbaijan, he was head of the MoH department for immunization; in Croatia, he was the EPI manager; and in Georgia, the focal point worked at the Department of Communicable Disease Surveillance. This choice of focal points encouraged sustainability because the skills gained through the ProVac IWG process remained in those institutions, rather than being lost as when an external consultant leaves.

AMP and the IWG partners also trained the multidisciplinary teams on the TRIVAC model and on the process of economic evaluation in general. In addition, the members of national advisory committees were trained to better understand the methodology of economic evaluations and to properly interpret the results of CEAs. They learned how to use the economic evidence to develop recommendations on new vaccines and how to communicate the results of CEAs to policymakers and decisionmakers.

A third benefit was that the CEAs helped the countries to conduct thorough analyses and better estimate the burden of disease by combining locally available data and the results of global estimates. The ProVac IWG helped the national teams to better understand the limitations of and properly interpret their national surveillance and statistics data. The studies provided estimates that helped the ministries of health to better understand the financial burdens that diseases preventable by new vaccines impose on the health care system. The countries were also able to define the price that would make introducing the new vaccines cost-effective.

A fourth noteworthy outcome came at the regional level. AMP and the WHO Regional Office for Europe applied the ProVac IWG methodology in a standardized way in all four countries in order to provide consistent support, but also to enable the nations to help each other through peer-to-peer exchanges and to build long-lasting regional collaborations. Indeed, the focal point from Georgia attended the final country visit of the AMP team to Azerbaijan, to see the work to be done there and to observe the work of its national team in action.

In June 2014 the WHO Regional Office for Europe conducted a regional meeting where the methodology and results of the CEAs conducted with ProVac IWG support were shared

with other middle-income countries. The participants achieved common agreement on the important role of economic evidence in justifying the introduction of expensive new vaccines. They also discussed using CEA results to prioritize introducing new vaccines and to advocate for additional funding to cover the cost. Many of the countries expressed their interest in obtaining WHO Regional Office for Europe support in conducting similar economic evaluations. The Regional Office is going to extend the peer-to-peer exchange implemented within ProVac IWG by having trained specialists from Azerbaijan, Georgia, or Croatia participate in evaluations planned for the Republic of Moldova and Uzbekistan.

While the ProVac IWG effort has had a clear impact on the individual countries and the WHO European Region overall, some ongoing challenges must be mentioned. A major constraint for the countries involved was the lack of available national data on disease burden and cost of treatment of diseases preventable by new vaccines. This was especially true for the nations that do not implement laboratory-based invasive bacterial diseases surveillance or countries that have recently been through substantial health system reforms. This limitation affected the results of the CEAs since the countries sometimes had to rely on global estimates, international data, or expert opinions. For example, Georgia went through a change in the financing of its health care system, so it was difficult to obtain cost data. Of course, these approximations were assessed as much as possible in the scenario analyses that were done as part of the CEAs.

Table 1 briefly summarizes the data and results across the four nations, and more detailed information and results are available in a set of country-specific articles [4-7] and in table 2 of the ProVac IWG overview piece [2].

It is difficult to make comparisons among the four country studies described in this paper. Three of the studies focused on PCV, and one dealt with RV. Two of the nations are Gavi graduating countries; one is a middle-income nation, and one is a middle income nation which became a high-income nation during the study (Croatia). In addition, assumptions, perspectives, and scenarios were customized to each country context to ensure the results were meaningful for national decisionmakers.

All of these factors make it hard to compare results across the countries. In particular, the source of evidence varied depending on the parameter considered. For example, the source of health care cost estimates ranged from expert opinion in one country to a carefully conducted costing study in another. The PCV studies also presented a range of results. In Croatia, PCV

was not found to be cost-effective in the base case or in most alternative scenarios, but the analysis did not include the additional, indirect benefit that herd immunity would have for older individuals. Neither Georgia nor Azerbaijan considered this factor, but the case for vaccination was still clear in those two countries. The difference in Croatia is that it has a much higher GDP per capita and a much lower mortality rate in children. Thus, the case for vaccination is less clear, and the next step will be to assess the potential importance of the benefits for older individuals.

5. Conclusion

The ProVac experience gained by PAHO in the Americas was shared with AMP and the WHO Regional Office for Europe and its partners, and then applied to the WHO European Region. This type of cooperation should be scaled up. The strong collaborations among the ProVac IWG partners and the countries in the WHO European Region have been very fruitful, and they should be continued. In addition, many other countries in the WHO European Region have expressed interest in receiving assistance from the ProVac IWG. The way forward is to make sure that all those countries receive the support they need to implement economic evaluations and promote evidence-based decision-making for vaccines and other health interventions.

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Table 1
Summary of data and results of the cost-effectiveness analysis for each country.

Country	Albania		Azerbaijan	Georgia	Croatia	
Vaccine(s)	RV1	RV5	PCV10	PCV10	PCV13	PCV10
Estimated price of vaccine (per dose)	\$8.5	\$8.5	\$3.5	\$3.5	\$35	\$30
GDP/capita	\$3707	\$3707	\$7490.5	\$3508	\$13227	\$13227
Base case ICER from governmental perspective ^a	\$1935/DALY	\$4954/DALY	\$66/DALY	\$1599/DALY	\$87,053/DALY	\$73,642/DALY
Result	Highly cost-effective	Cost-effective	Highly cost-effective	Cost-effective	Not cost-effective	Not cost-effective

Abstract:

Background: For many years, low- and middle-income countries have made efforts to strengthen national decision-making on immunization. The Pan American Health Organization (PAHO) ProVac Initiative was established to help expedite the use of evidence-based decision-making around new vaccine introduction. This initiative provides training in user-friendly cost-effectiveness models and supports the development of country-led economic evaluations. Due to the success of the ProVac Initiative in the Americas, and following requests from countries from outside the Americas, the Bill & Melinda Gates Foundation funded a two-year pilot effort to expand the initiative to other world regions. Called the ProVac International Working Group (IWG), this endeavor took place in 2012 and 2013. It was coordinated by PAHO and carried out in collaboration with several international partners, including the Agence de Médecine Préventive (AMP), London School of Hygiene & Tropical Medicine (LSHTM), Program for Appropriate Technology in Health, Sabin Vaccine Institute, United States Centers for Disease Control and Prevention, and the World Health Organization (WHO). In the WHO European Region, technical support was provided by AMP, in close collaboration with the WHO Regional Office for Europe and other ProVac IWG partners.

Methods: In 2012, AMP, the WHO Regional Office for Europe, and other partners held a training workshop in Dubrovnik, Croatia, for 31 participants from four countries of the WHO European Region. The aim was to train health professionals in standard methods of economic evaluation and to assess regional demand for economic studies to support decision-making on immunization. AMP and the other organizations also supported four national cost-effectiveness studies in the WHO European Region. The assistance included country visits and continuing support over a period of six months, the establishment of multidisciplinary

teams of experts, ongoing training on the TRIVAC decision-support model for new-vaccine economic analysis, review of local evidence, recommending key data inputs, and support in presenting results to national decision makers.

Results: National cost-effectiveness studies were conducted in four countries: Albania (rotavirus vaccine (RV)), Azerbaijan (pneumococcal conjugate vaccine (PCV)), Croatia (PCV), and Georgia (PCV)). All four countries improved their estimates of the burden of disease preventable by the new vaccines. National advisory bodies and ministries of health obtained economic evidence that helped Albania and Croatia to make decisions on introducing the new vaccines. Azerbaijan and Georgia used economic evidence to confirm previously made preliminary decisions to introduce PCV and make corresponding financial commitments. The study helped Albania to obtain access to affordable prices for rotavirus vaccines through participation in the UNICEF procurement mechanism for middle-income countries. Croatia was able to define the PCV price that would make its introduction cost-effective, and can use this figure as a basis for price negotiations.

Discussion: Despite some challenges due to competing national priorities, tight budgets for immunization, and lack of available national data, the ProVac IWG helped to build capacity of national health professionals, support decision-making for the introduction of new vaccines, and promote utilization of economic evidence for making decisions on immunization. This type of strong collaboration among international partners and countries should be scaled up, given that many other countries in the WHO European Region have expressed interest in receiving assistance from the ProVac IWG.