

Key elements of sustainability for influenza vaccine manufacturing in low and middle income countries

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This publication contains the report of the informal consultations with Indonesian agencies of the Ministry of Health on Key elements of sustainability for local production of influenza vaccines, and does not necessarily represent the decisions or policies of the World Health Organization.

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Introduction

The World Health Organization Global Action Plan for Influenza Vaccines (GAP) was initiated in 2006 to address challenges to sustainable influenza vaccine production and uptake in developing countries through three critical avenues to increase equitable access to pandemic vaccines and contributing to international pandemic preparedness efforts:

- Increase of evidence-based seasonal influenza vaccine use,
- Increase of global pandemic vaccine production capacity and strengthening of corresponding national regulatory competency
- Development of new influenza vaccines that have higher-yielding, faster to produce, broader in protection and with a longer duration.

The GAP proposes a link between seasonal influenza vaccination and pandemic preparedness, as the first contributes to the development of a solid influenza prevention system that can be scaled up to activate the response to a pandemic.

WHO, through its Technology Transfer Initiative, directly supports 14 developing countries to establish or expand influenza vaccine manufacturing within the framework of GAP. The ability to meet the vaccination needs during an influenza pandemic, or “vaccine readiness,” can be achieved through the establishment and maintenance of a regionally-based seasonal influenza vaccine manufacturing capacity.

The Technology Transfer Initiative exists as part of a larger WHO mandate born within the mandate and scope of the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property (GSPA-PHI)¹, approved in 2008 by Member states, that encourages an holistic approach to increase innovation for and access to medical products and technologies for diseases disproportionately affecting developing countries.

The case for local production of influenza vaccine

Within the GSPA-PHI, a prominent role is occupied by transfer of technology as a means to promoting local production in developing countries and improving access to medicines, vaccines and diagnostics. The report *Local Production for Access to Medical Products*², developed under the scope of the GSPA-PHI, defines transfer of technology “as the transfer of technical information, tacit know-how and performance skills, technical materials or equipment, jointly or as individual elements, with the intent of enabling the technological or manufacturing capacity of the recipients... in a mutually beneficial manner, while promoting public health objectives.”

Various studies³ have demonstrated that coordination of industrial and health policies with the goal of encouraging local production can lead to improvements in access to medical products, given certain conditions, such as a coherent policy environment, reliable government procurement, product quality assurance, and market certainty.

When established, local production has a large number of potential benefits:

- It can result in potential cost savings due to less expensive, locally produced medical products, if the production scale is sufficiently big.

¹ *Global strategy and plan of action on public health, innovation and intellectual property*. Geneva, World Health Organization, 2011 (http://www.who.int/phi/publications/Global_Strategy_Plan_Action.pdf?ua=1, accessed 22 July 2014).

² *Local Production for Access to Medical Products: Developing a Framework to Improve Public Health*. Geneva, World Health Organization, 2011 (http://www.who.int/phi/publications/Local_Production_Policy_Framework.pdf, accessed 22 July 2014).

³ *Local production and access to medicines in low- and middle-income countries*. Geneva, World Health Organization, 2011 (http://www.who.int/phi/publications/Local_Production_Literature_Review.pdf, accessed 22 July 2014).

- The supply of medical products can also be more reliable.
- The products can be of higher quality than certain imports, due to suitability to local culture and conditions.
- It can stimulate local increased innovation capacity and greater development of human capital.
- Some manufactures are able to develop export capacity for their products, improving the national balance of payments.
- Finally, there is potential for employment generation and spill-over effects in other sectors of the economy⁴.

However, in order to achieve these benefits, countries must have policy coherence with regards to local production, ensuring a policy environment that secures increasing financial returns to local enterprises over time. There are strong economic and political drivers to establish and enhance national capacity to manufacture medical products, in addition to the public health objectives, and countries should be aware of these drivers and purposefully work to maintain the sustainability of local production to accomplish public health objectives.

In the particular case of influenza vaccines, a report from the Centre for Global Health Policy at the University of Sussex⁵ encouraged the development of sustainable business models for medicines, vaccines, and diagnostics. The report encouraged the promotion of “enhanced regulatory certainty, particularly for manufacturers... of pandemic influenza vaccines,” “strengthening intergovernmental collaboration through global joint programming and greater harmonization of policy priorities, markets and regulation,” and “greater efforts to combine emergency and commercial use applications of products.” Market certainty and reliable government procurement strategies are two important incentives for engaging industry with partnerships for health security.

Local production contributes to health security by maintaining an uninterrupted supply of essential medical products: the long lead times for offshore producers of medical products can cause interruptions in supply. Furthermore, local producers with their potentially more efficient local supply chains can prevent greater disruptions in rural and poor areas.

Disentangling influenza complexitie

The WHO and the United States Department of Health and Human Services (HHS), together with many other stakeholders, are addressing identified technological, political, financial, and logistical issues that affect sustainability of influenza vaccine manufacture in developing countries⁶ and that are linked to complexities and challenges that result from the multi-sectorial nature of influenza vaccine manufacturing. A “sustainability checklist” has been developed to support policy-makers and influenza vaccine manufacturers to identify their specific issues. To allow for the many stakeholders within the government agencies involved in various influenza aspects to properly understand the “influenza world” and its interconnected activities, the check-list addresses the following areas: policy environment and healthcare system; surveillance system and influenza specific evidence; product development and manufacturing; product approval and regulations; and communication to support influenza vaccination.

⁴ Gehl -Sampath P. *Reconfiguring global health innovation*. London, Routledge, 2010.

⁵ Elbe E, Roemer-Mahler A. Summary Report: Pharmaceuticals and Security Strengthening industry Engagement. *Centre for Global Health Policy, University of Sussex*, 7 February 2014.

⁶ http://www.who.int/influenza_vaccines_plan/resources/vaccine_workshops/en/index6.html

The framework proposed in the *Local Production for Access to Medical Products*⁷ report provides a reference model for Member States to use the “sustainability check-list,” as it describes the importance of policy coherence (especially between industrial and health policy) in local production and the necessity of such coherence in accomplishing public health objectives.

Sustainability requires a coherent and coordinated approach to industrial, economic and public health policies, brought forward through transparent and joint actions of all stakeholders (government agencies, manufacturers, international multilateral institutions, donor communities, etc.). There are variables that cannot be influenced by the government or by the manufacturer that need to be factored in during the planning stage. Among these are the population size and the influenza burden in the country: these two variables determine the scale of the vaccine need and influence therefore the vaccination policy that the government can put in place. The Gross Domestic Product (GDP or Gross National Product – GNP) represents another variable that influences public health and industrial policy development, but the government has the capacity to address the economic growth of the country using its economic and fiscal powers. For this reason, government and manufacturers should put in place measures and models for a multi-variable analysis that allows sound decisions that influence the scale of the policies, the manufacturing capacity, and the budget implication.

The checklist has been used in several of the developing countries participating to the Technology Transfer Initiative and has grown in depth and breadth thanks to these country experiences, offering an opportunity to define options and possible solutions to face the challenges linked to policy making and vaccine manufacturing for influenza. It is important to bear in mind that the specific manufacturing context and products fabricated play a key role in the identification of a successful mix of policies and actions to achieve sustainability. Also, WHO decided to test an adapted version of the checklist in a non-influenza-vaccine-producing country to understand the needs to ensure sustainable preparedness efforts from the perspective of a country that relies on procurement for its preparedness and response activities. The final version of the check-list, presented in annex 1, incorporates procurement among the 5 areas assessed replacing the product development and manufacturing one.

The sustainability checklist

The full check list is presented in annex 1. Below, a description of its areas is provided.

Policy environment and healthcare system

Policies have a central role in strengthening sustainability for any influenza program. International expert bodies, such as the Strategic Advisory Group of Experts (SAGE) on Immunization, GAVI alliance, WHO, etc. all contribute to the international body of health evidence and vaccination recommendations. These recommendations are important to inform national governments and regional priorities. Beyond using the international recommendations and body of evidence, it is encouraged that national governments collect their own disease burden data to make evidence-based adjustments to national policies. By utilizing the evidence collected and using proxies of influenza impact, policy makers may create opportunities to better combat the seasonal influenza burden, as well as prepare the country for an influenza pandemic. By developing multi-purposed health policies, influenza prevention can be incorporated within other health strategies to have greater cumulative

⁷ See footnote 2.

impact on the health of populations. By including influenza preventive measures when developing national health policies, for example in prevention and treatment of non-communicable or chronic diseases, countries may achieve cost savings in their health systems.

Health System and Policies

- **Ensuring political will** and buy-in is critical in establishing influenza as a national and/or regional priority. The most successful examples of this have been achieved by a local champion who prioritizes influenza prevention and continually keeps influenza on the health agenda.
- **Use international and national influenza recommendations**, such as the SAGE, National advisory committees on immunization, and regional technical advisory group recommendations to support local policy development. Seasonal vaccination policies should be based on the local burden of disease, the vaccine effectiveness among at-risk groups and vaccination cost-effectiveness studies to ensure context-specific issues are considered.
- Develop **coherence among relevant national health policies and programs** that would otherwise function independently. An example of this would be to review influenza-specific policies and programs, alongside existing policies and programs for health-care workers, maternal and childhood immunization, non-communicable diseases and the chronically ill. There may be existing low cost opportunities to leverage access to the country's identified high-risk target populations.
- It is important for all stakeholders to understand that seasonal influenza vaccine sustainability directly strengthens **national security and pandemic preparedness**. The value generated by seasonal influenza vaccination goes beyond a healthier population and cover also these two fundamental aspects . A solid and regularly updated pandemic influenza preparedness policy and plan should be published and appropriately disseminated to all relevant agencies.
- **Health system infrastructure and human resources with respect to vaccination (vaccine delivery infrastructure)** should be examined comprehensively to identify gaps and opportunities. It is important for government stakeholders and manufacturers to understand the capacity of the cold chain, the availability of health care workers to administer vaccine, the regularly available stock of vaccine in healthcare centers and other distributions sites, and the surge capacity available for a pandemic response. Awareness of the limitations of the existing system can help for planning purposes and possible re-prioritizing of investment into the health system to provide the greatest benefit.
- **Health system financing for influenza vaccine** plays a key role in encouraging population to get vaccinated. The inclusion of seasonal influenza vaccination in health insurance schemes or directly provided by the public health sector is considered an incentive for seasonal vaccination uptake.⁸

⁸ N Hehme, T Colegate, B Palache, L Hessel, *Influenza vaccine supply : Building long-term sustainability*, Vaccine 26S (2008) D23-D26

Policies other than health-specific

- Some manufacturers have encountered issues that created bureaucratic obstacles that impasse their progress in establishing influenza vaccine production. Manufacturers find themselves navigating the complex of Ministries of Health, Science and Technology, Human Services, Education, Trade, Regulatory, Industry, Finance, Development etc., the policies of which may overlap and not have coherence. It is important that **governments consider the multi-sectoral space** in which influenza vaccine manufacturing operate to create a fully supportive environment for sustainability. Industrial policies to support the development of a strong bio-pharmacological sector require interagency coordination and strategic vision for economic development.
- Examine the relevant **national and regional procurement and distribution policies** and look for opportunities and incentives to promote in-country production and sourcing of materials. As WHO pre-qualification becomes more widespread as an indicator of vaccine safety and efficacy, manufacturers may also consider using this mechanism to widen the markets available for their products (see “pre-qualification” under product approval and regulatory section).
- Existing **multilateral and bilateral agreements affecting commercialization and the import and export of products** can have an impact on the business model, markets and sourcing of technologies and materials available to the manufacturers, and therefore on the sustainability of the local influenza vaccine environment. The government should consider the consequences that these trade agreements have on the economic and public health situation of the country and the manufacturers should be aware of their existence and implication when developing their business strategy.
- Sustainable vaccine manufacturing requires maintaining **a skilled local workforce**, which is challenging in many areas of the world. Governmental incentives and education policies to prevent brain-drain, or partnerships between manufacturers and academia can help strengthen a vaccine manufacturing workforce.
- Establishing **policies to influence the development and size of the GMP bio-manufacturing environment**. These policies should touch upon the scientific/academic institutions of the country, the infrastructure to support laboratory research and biologicals manufacturing, the stimulation of up-stream and down-stream research on biologicals etc.
- **Establishing a constant dialogue and strong cross sectorial collaboration between veterinary public health institutions and public health sector.**⁹ Animal health could have an impact on human infections and animal to human transmission causes sporadic cases of influenza outbreaks each years. A good coordination would contain the propagation in case of seasonal epidemic or in the event of a pandemic. During the elaboration of the policies stakeholders need to understand how human environment and animal infections interfere with the influenza immunization programs. Therefore, surveillance systems and response protocols need to be jointly developed.

⁹ The FAO- OIE-WHO Collaboration, a tripartite concept note
http://www.who.int/influenza/resources/documents/tripartite_concept_note_hanoi_042011_en.pdf?ua=1

Influenza specific evidence

An accurate surveillance system is a key requirement for the early detection of disease insurgence, spread and trend to enable a timely response. The absence of strong data on influenza burden, transmission landscape and antiviral resistance and economic impacts of influenza is an obstacle to establishing evidence-based policies to reduce the impact of influenza nationally and worldwide. In many countries the public perception is that seasonal influenza is a mild illness, with a low to negligible impact on health and economies; however, proxies (such as childhood pneumonia) in the country and morbidity and mortality data from neighboring areas help to understand that seasonal influenza can have a much greater impact. Moreover, rising burdens of non-communicable diseases and growing elderly populations increase the importance of considering seasonal influenza impact on these high risk groups.

The policy maker's information needs and priorities should be taken into consideration when framing disease burden and cost-effectiveness data from influenza studies. Traditional cost-effectiveness studies take into consideration the typical parameters familiar to public health officials, i.e. health benefits (in terms of DALY and QALY) and averted health costs. In addition, framing evidence for the Minister of Finance or Trade can be powerful by highlighting cost-savings and other economic advantages of supporting influenza vaccination and influenza vaccine manufacturing.

- Governments should **establish or utilize an existing surveillance system** based on available resources. Sentinel sites, population-based studies, insurance data, hospital and out-patient clinic and regional data are examples of types of surveillance systems typically employed. It is important for countries to establish regular burden of disease data collection that:
 - Provides diagnostic testing for respiratory viruses, allowing collection of data from in- and out- patient facilities;
 - Integrates virological and clinical data with molecular test verification;
 - Provides information on seroprevalence studies, and
 - Provides timely and accessible reporting to detected trends and inform policy decisions.
- Determine what kind of data should be collected, the current informatics systems available and analyze **data accurately and appropriately**. Once data is collected, it is helpful to report findings to regional/international databases to strengthen regional and international estimates of influenza disease burden. An extensive use should be made of the collected data for example for burden of disease analysis, identification of the required doses to be purchased by the MoH, definition of risk groups etc., and all the results of the analysis should be fully disseminated and made public.
- Invest in local **burden of disease and cost-effectiveness studies to build evidence for influenza vaccination policies**. Cost-effectiveness analyses are generally prepared using data from many different sources, to create a layered analysis of the burdens and costs, along with cost-savings of particular interventions. Limited specific data can be supplemented with information from other countries, proxy measurements and estimates. WHO can provide general recommendations about disease burden standards and models to inform data collection and study design.
- Consider the priorities, motivations, values and perspectives of the specific decision maker who will review the data analysis, and **frame the evidence to be most relevant**,

“translating” it to highlight the elements that resonate most strongly with the decision makers.

Product development and manufacturing

The development of a solid business plan is essential for the sustainability of the vaccine manufacturing. Through the use of this tool, manufacturer will be guided to analyse the production environment and the marketplace where the product will be sold and used. Aside from the technical and business details of the manufacturing process, the manufacturer should be aware of the international, regional and national context in which it operates. This includes understanding the many rules and restrictions on commercialization, taking advantage of existing associations and networks operating in the influenza vaccine field, and having a proactive role with all the government agencies supporting the production process.

- Undertake **an in-depth analysis of production costs and price of product**, considering scale of production, other products produced in the facility, running costs (including labor, utilities, materials), infrastructure costs, etc.
- Ensure a reliable and stable supplies of utilities (water, electricity), developing mechanisms to allow self-sufficiency.
- Secure supply chain for all components, taking into account their costs, their foreseeable substitution and their maintenance. Consider possible challenges to importation and supply chain challenges in the event of a pandemic.
- Identify a technology for which you have freedom to operate (own a license, non-proprietary) and there is a regulatory pathway to approval. Examine the technology used, scale of production and products produced. The **technology selected affects the initial investment, the time to market and approval of the product and also the running costs**. If the production scale is smaller, the cost of the product will be higher and the positioning on the market will be affected. The identification of market niches specific to the context in which the manufacturer operates could help overcoming the constraints due to the price of the product. Consider also that the chosen technologies affect the time for responding in the event of a pandemic and the ramp up capacity.
- Because of its seasonality, influenza vaccine presents risks of underutilization of human resources and infrastructure, with the consequence of higher production costs. It may be strategic to **complement the products manufactured in the facility**, and distribute the human resource and infrastructural costs among multiple products to mitigate the business risks.
- Workforce availability is key for a successful manufacturing and commercialization of the product. **Skilled workforce needs to be available**, which requires planning ahead to face the turnover and ensuring motivating career paths for workforce retention. Strong links and continuous dialogue with academic institutions support the availability of skills necessary to perform appropriately every step of the production process and ensure high managerial competencies.
- Business and marketing strategies are important to **identifying desirable and realistic return on investment**, based on potential size of the national, regional and international markets. Manufacturers may have an advantage if they focus their initial strategy on globally targeted high-

risk populations (like pregnant women, elderly, HCW and the chronically ill) and encourage vaccination policy development at government level whether not already there.

- Control of biological products nearly always involves biological techniques that have a greater variability than physicochemical determinants. In-process controls take on a great importance in the manufacturing of biological products because certain deficiencies may not be revealed by testing the finished product. In the manufacture of biological products **full adherence to Good Manufacturing Practice (GMP)** is necessary for all production steps, beginning with those from which the active ingredients are produced. Good manufacturing practices and quality control procedures require stringent adherence to standards and international guidelines covering personnel, premises, equipments, animal quarters, production processes, labelling, lot processing and distribution records. Investing adequate resources and dedicating highly skilled personnel to this aspect of manufacturing guarantees a smoother production process and ensures the quality of the final product, reducing the risk of costs linked to substandard quality steps or by-products.
- **Clinical trials and vaccine effectiveness studies** represent one of the highest costs and require expertise for their design and conduction. A careful planning and a strategic approach to the identification of relevant partners for clinical trial conduction can avoid inefficient and ineffective use of resources. The identification of the target populations and the design of the clinical studies to evaluate effectiveness and safety in those populations help to define the reference market for the product. This also helps to create competitive advantages with the other manufacturers.
- There are many options that can be used to overcome potential challenges in the various phases of the production process. For example, **Public Private Partnerships or Product Development Partnership** allow the manufacturer to contractually engage with partners that handle specific areas of operation, according to their expertise, to share the risks of development and manufacturing. There are many contractual agreements that can be developed and the manufacturer should explore the available talents and opportunities to address potential challenges in the business model.
- There is a **role for advocacy/category associations/networks** to sustain influenza vaccine manufacturing in developing countries. Many forums exist to discuss economic/industrial activities in developing and emerging economies, and influenza manufacturers can benefit from engaging directly in these fora. There are areas of opportunities for manufacturers to work together, for example workforce skill development and raising seasonal and pandemic influenza awareness as a local, regional and international priority.

Influenza vaccine procurement

For non-producing countries, the following area should be considered in substitution of the area above (product development and manufacturing). If a country relies on import of influenza vaccines for its seasonal vaccination and to respond to a pandemic, the procurement system should be strong and a network of suppliers should be in place. Potentially, in a multi-year standing contract with an influenza vaccine manufacturer, a specific clause should be included in the contract with the manufacturer to ensure supply of vaccines in the event of a pandemic.

- All countries should have **advanced purchase agreement (APA)** with at least one manufacturer to secure their procurement in case of an epidemic or a pandemic.¹⁰ APAs are agreements between a state and a manufacturer that are broad enough to reserve doses of vaccines that do not exist yet. In a case of a pandemic, that would facilitate approval as well as delivery of pandemic vaccines.
- **Pool procurement** is an opportunity to lower the price per dose.¹¹ When many countries gather to purchase the same product, this increases the number of ordered doses and consequently creates economy of scale and procure to countries a better negotiation leverage. An external structure with specific agreed term of references could be established to look at the procurement criteria and negotiation with manufacturers. The structure would also bring together necessary competences that might not be available locally to define such contract.
- Relying on procurement of vaccines, countries should ensure their stock and cold chain capacities serve the entire national territory and are reliable in case of scale up of operations during an emergency.
- The procurement agency utilizes an up to date list of pre-qualified manufacturers to drive its procurement activity and is aware of all relevant information regarding possible changes impacting their capacity to acquire all the relevant products needed in the event of a pandemic.
- Vaccine procurement procedures are entrenched under national laws and enforced. The rules for local or international procurement tendering are clear and ensure a transparent allocation of contracts.
- Batch release' rules are well understood by the custom staff and concur to a permanent and timely release of vaccines doses. In the event of a pandemic, the custom staff is trained to react actively to shorten and accelerate batch release and distribution while respecting high standards of monitoring and safety.

Product approval and regulations

The assessment, licensure, control, and surveillance of biological medicinal products are major challenges for national regulatory authorities confronted by a steadily increasing number of novel products, complex quality concerns, and new technical issues arising from rapid scientific advances. With the emerging global market, the volume of biological medicinal products crossing national borders continues to rise, and it has become critical that regulatory knowledge and experience can be shared, and approaches to their control are harmonized to the greatest extent possible.

- All countries should have at least a **minimally functional national regulatory authority (NRA)**, and countries producing vaccines need an NRA with more robust abilities to exercise six critical control functions. NRAs need to exercise these control functions in a competent and independent manner, backed up with enforcement power. These six functions are:

¹⁰ STRENGTHENING RESPONSE TO PANDEMICS AND OTHER PUBLIC-HEALTH EMERGENCIES, WHO, 2011

¹¹ http://www.who.int/immunization/programmes_systems/financing/analyses/Brief_12_Pooled_Procurement.pdf

- License of manufacturers and product regulation (a published set of requirements for licensing);
- Surveillance of vaccine field performance (post marketing surveillance)
- System of lot release;
- Laboratory access (use of laboratory when needed);
- Regular inspections for GMP;
- Clinical trial approval (evaluation of clinical performance).

From the government perspective, having a functional NRA ensures the **quality, safety and effectiveness of the products** circulating within its borders. A strong and efficient NRA ensures manufacturers that the dossiers presented are analysed in a timely and accurate manner, reducing the time for the product to reach the people in need.

- **Regional harmonization and integration of regulatory approvals** are critical for increasing the market size and sustainability of seasonal influenza vaccines. Efforts to strengthen capacity for national regulation of vaccines and harmonization of rules and regulations at regional level can play a key role to facilitate and improve the accuracy of regulatory work and international capacity building efforts.
- The purpose of the **United Nations prequalification assessment** is to provide assurance that candidate vaccines: (a) meet WHO recommendations on quality, safety and efficacy, including compliance with WHO's recommended standards for GMP and good clinical practice (GCP); and (b) meet the operational packaging and presentation specifications of the relevant United Nations agency. The aim is to ensure that vaccines provided through the United Nations for use in national immunization services in different countries are safe, effective and suitable for the target populations at the recommended immunization schedules and with appropriate concomitant products. The prequalification procedure established by WHO for vaccines has been effective in promoting confidence in the quality of the vaccines shipped to countries through United Nations purchasing agencies. The procedure is based on the following principles:
 - reliance on the national regulatory authority (NRA) of the country of manufacture, which is required to be "functional", i.e. meeting the published WHO NRA indicators for prequalification purposes;
 - general understanding of the product and presentations offered, the production process, quality control methods, quality system in place, and available clinical data that are relevant to the target population;
 - assurance of production consistency through compliance with GMP requirements and monitoring of continued compliance with specifications through testing of final product characteristics.

Communication for influenza vaccination

Due to the complexities of vaccine manufacture and distribution along with the need for widespread uptake of influenza vaccine, it is critical to have a comprehensive communication plan and well developed infrastructure to assure a maximally effective system of influenza prevention and pandemic preparedness. In essence, a communication plan and its attending infrastructure is about designing, understanding, assessing, and improving all of the linkages in a given human process. Changes in manufacturing processes, government standards, vaccine administration, vaccine schedule etc. affecting the perception that the population and healthcare workers have of the product and the policy need to be linked to timely and

effective communication to ensure information is disseminated and decisions understood to prevent negative reactions.

Each governmental, NGO, and private sector unit or organization that is involved in influenza vaccination should be connected in ways that assure timely, meaningful, and appropriate communication takes place to guarantee the best use of resources and the most effective practices.

Risk communication and public campaigns during outbreaks should be developed, conducted, and monitored in the context of local and regional needs, in concert with manufacturers and HCW, to both create the best response and to evaluate for future action.

For a national communication system to be effective, the following functions are required¹²:

- **Communication policy, planning and strategy:** An explicit influenza vaccination policy can achieve several things: it defines a commonly agreed goal; it outlines vaccination priorities and the expected roles of different groups; it reduces vaccine hesitancy and it ultimately builds consensus and informs people. Clear policy guidance based on evidence and data with specific recommendations for seasonal influenza and pandemic influenza is therefore important. Such evidence and policies can advocate for resources and investments and build political will. Communication supports the development and implementation of these policies as well as translating them into a language which will resonate with policy makers, partners and the public.
- **Communication research, monitoring and evaluation:** Just like any other public health intervention, it is essential to develop meaningful and measurable metrics for communication to evaluate progress and results against communication strategy objectives and against agreed public health goals and objectives. Monitoring and evaluating progress and achievements in communication are fundamental to knowing how well communication is doing to contribute to public health outcomes. It is essential to continuously monitor (listen to) behaviors and “conversations” using various tools (social networks analysis, surveys, interviews, observations, etc.). The on-going “listening” and evaluation results should feed directly into a mechanism to adjust the outreach and decision-making processes at the political, programmatic and technical levels.
- **Partnerships, stakeholders, and public engagement:** Partners are essential to support all aspects of influenza programmes from strategy design to implementation to evaluation. Developing effective partnerships are much easier when there are well-formulated policies leading to clearly defined public health goals, objectives and strategies. An on-going and transparent process for information sharing is vital to build and maintain trustful relationships with the media. The media is one of the many ways to convey information and media engagement strategies need to be part of an integrated communication strategy. Public engagement requires an intimate understanding of influenza vaccinations from the perspective of those who will benefit. How health messages and information are

¹² Report of the International Workshop on Enhancing Communication around Influenza Vaccination, Centers for Disease Control and Prevention, Atlanta, USA, 11-13 June 2013 - http://www.who.int/influenza_vaccines_plan/resources/vaccine_workshops/en/

interpreted cannot be controlled because it is filtered through individual, family and community experiences and interpretations.

- **Communication capacity building and training:** Building and strengthening communication capacities of different actors and stakeholders who contribute to influenza programmes to meet their goals is key and can be done through targeted and joint partner training. Different professional groups, job functions, individuals, teams and organizations will need different kinds of skills, competencies, tools etc.: Groups targeted for training could be: communication staff; communication focal points; health-care providers; policy makers; administrators; and reporters and media. Resources, tools and scientific expertise need to be made available to all stakeholders, and health officials should make themselves available to help build the understanding of stakeholders and especially the public and the media. Strengthening the link between communication scientists and communication practitioners is to make sure that the discipline informs good practice and good practice in turns shapes the further development of theory and models. Investments in professional development are also essential especially in non-emergency situations before a crisis occurs.
- **Knowledge translation and Information Communication Technologies (ICT):** Bridging the knowledge practice gap and integrating ICTs to support the four core building blocks of a communication system are key to ensuring that the system is efficient and effective and is in line with the developments and application of tools and technologies outside of the health sector. ICT skills and knowledge are particularly essential for health staff to work in a 21st century information society.

Country experiences in using the check list

Using the checklist to assess the national environment for pandemic influenza preparedness through local production of influenza vaccines the government will be able to address this topic with a holistic, multi-sectoral and multi-stakeholders approach that will lead to the identification of, and agreement on, possible policy recommendations to improve the system.

Methodology for assessments

The preparation of the assessment is done with the strong collaboration of the Country Office. A locally based consultant works on the adaptation of the checklist to the specific context and develops a list of relevant stakeholders to be interviewed. The Country Office offers its support in the identification of the list of interviewees and for the access to relevant documentation.

1. *Literature, policy and legislation review*

A systematic analysis is conducted to identify and evaluate:

- The way the healthcare system is organized (coverage, source of funds, availability of human resources and infrastructures, etc.),
- The environment for the manufacturing sector including its international relations (free trade agreements, business plan, vaccine manufacturing price, return on investment, supply chain, availability of skilled local workforce, etc.),
- The public health policies regarding seasonal influenza vaccination (at risk groups covered by the policy, responsibility for the payment of the vaccine, provider of the service, annual availability of vaccines, etc.)

- The pandemic preparedness plans (governance mechanism, vaccine deployment plans, communication strategy, containment measures at borders, surge capacity for healthcare providers, etc.),
- The surveillance system and data on the burden of disease for influenza and other related illnesses in the country (influenza-like illness - ILI, severe acute respiratory illness - SARI),
- The regulatory framework for new vaccines in the country (the capacity in terms of personnel of the national regulatory authority (NRA), its level of functionality, its impartiality and independence, etc.) and
- Other relevant information.

The evaluation is conducted based on several WHO guidelines and reference guidance documents, such as the WHO guidelines for NRA¹³ assessments, the WHO guidelines for preparation of pandemic preparedness plans¹⁴, the WHO reference guidance on seasonal influenza¹⁵, etc.

The consultant evaluates, in collaboration with the Country Office, the existence and the quality of these policies, legislations, plans and strategies.

2. Key informants' interviews

The key informants are selected considering their work on influenza vaccines: personnel working in institutions involved in influenza vaccines production, and/or on the development of regulation and policies regarding influenza, and/or on the collection of surveillance data, or on the formulation/implementation of communication strategy for vaccination.

After the identification, a questionnaire is developed following the five areas of the checklist. Informants are asked whether the policy exists, is in development or doesn't exist and if this represents a challenge for their context. They will also be allowed to comment on each of their answers.

3. Tools and data analysis

The qualitative analysis based on information collected by the interviewer, and interpretation of the comments, help to identify whether a missing policy or a not yet approved policy is causing a problem in terms of coherence for the overall system.

Similarly, in reviewing the literature and reading the policy documents, an evaluation will be made on whether a particular aspect is a strength or a weakness. This binary assessment approach permits the quick identification of the gaps and facilitate the formulation of recommendations.

Both the findings from the literature review and responses to the questions need to be categorized to address specific themes of the checklist such as the policy and regulatory environment, the production and approval processes, the feasibility of influenza vaccine production, the communication issues etc.

¹³ (http://www.who.int/biologicals/publications/trs/areas/biological_therapeutics/WHO_TRS_822_A2.pdf?ua=1)

¹⁴ (<http://www.who.int/influenza/resources/documents/FluCheck6web.pdf>)

¹⁵ (<http://www.who.int/mediacentre/factsheets/fs211/en/>)

4. *Discussion of findings – identification of policy recommendations*

Workshops are organized to discuss the findings, get buy-in from the government policy makers and identify the policy recommendations for sustainability. All interviewees are invited together with subject matter experts from WHO to provide expert opinion and guidance in the formulation of policy recommendations. The aim of the workshop is to reach consensus on the policy options/recommendations to improve sustainability of the investment in local production of influenza vaccines.

Findings

From the use of the checklist similarities and differences emerged from one country to another. Although on the countries are different in terms of demographic and socio-economic status (summarized in Annex 2), common points can be identified from the assessments (annex 2). Several critical lessons and common findings have emerged that can be useful for other countries pursuing sustainable production and long-term availability of influenza vaccines. In particular, political awareness, financial accessibility of vaccination for targeted populations, and a strong NRA have been shown to provide a solid foundation for a coherent political and administrative environment.

- As stated before in this report, a **strong political support** and government investment make a significant difference in helping the development of a local product. This support can take several forms: the development and updating of a pandemic influenza preparedness plan that links seasonal influenza vaccination to pandemic preparedness and vaccine availability during a pandemic, financial commitment, and long-term commitment for the supply of the vaccine.
- High rates of vaccination occur when there is public or third-party reimbursement of vaccinations through government run healthcare centers or insurance schemes¹⁶, therefore, direct or indirect **financial supports** need to be foreseen by governments. An example of financial support is when vaccination is free of charge and accessible to target population, substantially contributing to the increase of coverage rates.
- A **strong NRA**, operating in accordance with international and WHO standards, offers strong support to the manufacturer during product development and testing. Moreover, a strong regulatory presence helps build confidence among the population that the vaccine is safe, effective and of high quality and provides assurance that the product will reach the population under reliable supply conditions.
- Investment in **communication and training** especially for healthcare workers are paramount to ensure high levels of vaccination among at-risk populations.
- Manufacturers that develop a **solid business plan** that considers return on investment on product development have more sustainable operations. This ensures that price is not a barrier to vaccine procurement and that the manufacturer is better prepared and responsive to future changes, challenges or opportunities.
- **Using evidence based policies to address influenza.** Countries with well-developed surveillance systems in place are able to make informed decisions about the scale-up of influenza vaccine use. Prioritizing evidence in policy making is the most effective way to

¹⁶ See footnote 8

mitigate the economic and disease burden of seasonal and pandemic influenza. There are several ways to collect data and incorporate it into policies. Probe studies, even if very costly, are one of those underutilized methods that could help estimate the vaccine preventable disease incidence and establish causality of the disease.

Annex 1: Checklist

Sustainability Element	Lead Agency or Org	Status			Does this represent a challenge in your specific context?		Comment
		Currently Exists	In Progress	Does not Exist	Yes	No	
Policy environment and Health Care System (government representatives are expected to have the information required below)							
Health System and Policies							
Political will for in-country influenza vaccine manufacture							
Political will for pandemic influenza preparedness							
International influenza recommendations to shape national policies							
Coherence among relevant national health policies and programs							
Seasonal vaccination policies are based on the local burden of disease, the vaccine effectiveness among at-risk groups and vaccination cost-effectiveness studies							
Seasonal Influenza vaccination and control policies are developed also as means to sustain pandemic preparedness and national security							
The price of the vaccine is not a barrier for the government to provide it for free to the target groups							
Seasonal influenza vaccination is included in health insurance schemes or directly provided by the public health sector							
Vaccine delivery infrastructure is in place and maintained							
The vaccine distribution system is in place and efficient							

There is availability of the vaccine at the hospital, healthcare centers and pharmacies level							
Target groups for pandemic influenza immunization have been established and are part of the pandemic preparedness plan							
The pandemic influenza preparedness plan takes into consideration the seasonal influenza vaccination policy and the local manufactured product							
The pandemic influenza preparedness policy and plan is regularly updated, published and appropriately disseminated to all relevant agencies							
<u>Policies other than health-specific</u>							
Efforts are made to overcome possible bureaucratic obstacles to establish and sustain vaccine manufacturing							
National and regional procurement and distribution policies to promote in-country production and sourcing of materials are developed							
Policies are created to generate skilled local workforce for local vaccine production, also through facilitation of exchanges at national and international level and government grants to further education							
Interactions between academic institutions and local manufacturers are encouraged and facilitated for the development of useful curricula for the vaccine manufacturing sector and for exchange and on the job trainings							
Policies are created to influence the development and size of the GMP bio-manufacturing environment							
Understanding of how the multilateral and bilateral agreements affect commercialization and import and export of products							

Sustainability Element	Lead Agency or Org	Status			Does this represent a challenge in your specific context?		Comment
		Currently Exists	In Progress	Does not Exist	Yes	No	
Influenza-Specific Evidence (government representatives are expected to have the information required below)							
Surveillance system for virological surveillance in place (sentinel cites, technology and human resources)							
There are clear and well-functioning procedures for communication of alerts from sentinel sites to central level (information transmission chain tested and updated)							
Accurate and timely surveillance reporting							
Design of data collection driven by surveillance objectives.							
Annual surveillance reports with risk factor data produced							
Data aggregated and reported on international data sharing platforms							
The burden of influenza is known in the country							
Cost-effectiveness of seasonal influenza vaccine in target groups is known							
Data on impact of influenza is expressed in a way that resonates with priorities of policies makers							

Sustainability Element	Lead Agency or Org	Status			Does this represent a challenge in your specific context?		Comment
		Currently Exists	In Progress	Does not Exist	Yes	No	
Product development and Manufacturing (this section is answered by local manufacturers)							
Business plan based on analysis of production costs, price of product and return on investment							
Reliable and stable supply of utilities							
A proportion of the revenues is planned to be re-invested in R&D							
Reliable supply chain for all components							
Technologies selected based on cost-benefit analysis of initial investment, operating costs, time to market and product approval							
More than one product manufactured in the vaccine manufacturing facility							
Access to and retention of skilled workforce							
Complies with and is certified for Good Manufacturing Practice (GMP)							
In-house skills to design and administer clinical trials for vaccine product							
A system is in place at the manufacturing or governmental level to monitor adverse events after product commercialization							
Animal facility for the conduction of preclinical studies is available and under GLP							
Partnerships with public or private entities to acquire know how and technology, conduct clinical trials, conduct post marketing surveillance, distribute the product, etc.							

Participation in manufacturers' networks or associations to do advocacy, exchange experiences, training etc.							
Sustainability Element	Lead Agency or Org	Status			Does this represent a challenge in your specific context?		Comment
		Currently Exists	In Progress	Does not Exist	Yes	No	
Product Approval and Regulations (this section is answered by representatives of the national regulatory authority)							
National Regulatory Authority (NRA) "functional" in WHO – Pre-Qualification terms							
NRA staff trained and re-trained continuously							
Effective working relation between manufacturers and NRA							
Effective exchanges among NRA staff and other governments and international organization							
Manufacturer's full awareness of regulatory requirements for the product in the country							
Manufacturer's full awareness of the requirements to submit a dossier for WHO Prequalification (PQ)							
Regional regulatory approvals harmonized and integrated							

Sustainability Element	Lead Agency or Org	Status			Does this represent a challenge in your specific context?		Comment
		Currently Exists	In Progress	Does not Exist	Yes	No	
Communication for influenza vaccination (government representatives are expected to have the information required below)							
key functions established and strong relationships among stakeholders with a public communication role							
Well-trained and skilled communication staff							
Operational research and metrics for influenza communication outcomes							
Mechanisms for ongoing listening/feedback to update communication strategies and tactics							
Integrated communication strategy with other policies (with clear behavioral objectives for priority groups)							
Routine use of sound communication methodologies, tools and scientific expertise							
Regular evaluation of public campaigns and feedback to stakeholders							
There is awareness among the public and the healthcare workers of the benefits of seasonal influenza vaccination							

Annex 2 – Socio-economic characteristics of assessed countries

<http://apps.who.int/gho/data/node.imr>

In 2013	Population in thousands total	population median age	GNI per capita	Per capita total expenditure on health (PP int.\$)	Per capita government expenditure on health (PP int.\$)	Preparedness ¹⁷ (%)
Brazil	20,425.9	30.3	14,750	1,334.10	601.90	90
Mexico	1,263.6	27	16,110	1,070.12	553.65	90
Viet Nam	91,378.8	29.8	5,030	372.44	197.32	90
Indonesia	25,1268	27.8	9,260	292.45	115.31	100
X	33,452.7	27	7,000	428.80	141.44	100
Y	53,416.6	26	12,240	1,123.63	538.62	83

¹⁷ The proportion/percentage of attribute (a set of specific elements or functions which reflect the level of performance or achievement of Core Capacity 5: Preparedness) that have been attained.

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http://www.who.int/influenza_vaccines_plan/news/gap3_Nov16/en/