Overview

The Workshop on Business Modelling for Sustainable Influenza Vaccine Manufacturing was one in a series of jointly organized workshops by the U.S. Department of Health and Human Services (HHS) and the World Health Organization (WHO) to address the challenges to sustainable influenza vaccine production in low and middle income countries (LMICs)\(^1\).

The estimated global capacity to produce enough influenza vaccines in the event of a pandemic is well below the projected needs. In addition, production is largely concentrated in developed and industrialized countries. In the event of a pandemic, LMICs without local vaccine production or contractual supply agreements in place with producers of medical countermeasures, will have to rely on internationally coordinated pandemic influenza vaccine deployment to have access to such vaccines. The development of sustainable local manufacturing capacity is one way to address the risk of inequitable and delayed availability of vaccines.

Sustainability of production is however a major challenge faced by influenza vaccine manufacturers particularly in LMICs. The decision to produce influenza vaccines was often taken primarily in response to pandemic threats: sound business modelling is essential to make it sustainable.

The Workshop was organized to highlight the need for influenza vaccine manufacturers to develop appropriate business models to ensure sustainability, and to identify an array of options for manufacturers and governments that would enable the creation of environments conducive to sustainable vaccine manufacturing and pandemic preparedness. It took place in the WHO Regional Office for the Americas/Pan American Health Organization in Washington, DC, and was attended by more than 120 participants from 30 different countries, representing the full range of stakeholders: national governments, developed and developing country vaccine manufacturers, academic business institutions and development partners.

Influenza vaccines present unique manufacturing and sustainability challenges that are not present for other vaccines: the production is seasonal, so for many manufacturers the facility is idle for half the year; the vaccine needs to be administered yearly, to match the circulating strains, so the cost of maintaining the population protected is high, and the timing and severity of influenza epidemics and pandemics is unpredictable. Establishing influenza vaccine manufacturing capacity represents for

LMICs a strategic measure to mitigate the effect of influenza pandemics for their populations. However, to retain this response capacity, manufacturers need to maintain sustainable seasonal influenza vaccine capacity which in turn is linked to the size of the market for seasonal vaccine, that in many countries is limited.

The range of factors affecting sustainability, both from the public health perspective and the business perspective, requires a combination of government political commitment, policy and financial investments, private investment, research and development partnerships and stimulation of evidence-based demand and vaccine uptake. This mix of government interventions and market forces is unique to the context where the production takes place, and the appropriate combination needs to be determined in each context by manufacturers and governments.

**Factors of Complexity in Influenza Vaccine Manufacturing**

- Wide variety of stakeholders
- Balance of public and private interests
- Interaction between national, regional and global investment and initiatives
- Relative importance of ensuring national security
- Competing public health priorities and limited national budgets
- Regulatory challenges and processes inherent to vaccine production
- Sensitivity linked to marketing and communications for a health product
- Research and development costs of new technologies
- Communication of the risks and benefits of vaccination

*Government considerations for sustainability of local production*

There are a series of considerations to be made when developing policies around influenza vaccination:

1. Domestic influenza vaccine manufacturing capacity represents a national resource: (a) it contributes to national security by ensuring timely access to pandemic vaccines for the local population; (b) it generates economic and industrial value by ensuring revenues, creating job opportunities and creating demand for correlated sectors (raw and semi-finished materials, related services etc.). These factors must be weighed against the possibility, in some cases, of importing seasonal vaccines at a lower direct cost, and considered in a wider economic perspective.

2. The intersectoral nature of local influenza vaccine manufacturing comes with many ramifications. Governments should therefore engage all relevant national agencies to achieve influenza vaccine manufacturing sustainability, beyond the responsibility of the ministry of health, focusing on the national value generated by a sustainable influenza vaccine manufacturing system that extends to areas such as:
3. Governments have a role in interpreting and communicating evidence about the risks of influenza and benefits of vaccination. Analysis of data and information such as burden of disease and other evidence-based studies, should inform government policies. In many cases, existing mechanisms already collect key data which can be easily accessed and used for policy development. If nation-specific health data is not available or sufficient, regional data can be helpful to provide insight into influenza disease severity and burden.

4. Ministries of Health have a lead role in communicating the value of vaccination to health care workers and the public. A strong and efficient national communication system may help dispel the perception that influenza is a mild disease, and encourage uptake of annual influenza vaccination.

5. If the Government recognizes the value of local influenza vaccine production for preparedness and national security, and beyond as shown above, it may consider subsidizing local production through various measures such as: tax breaks; industrial incentives; subsidies for improvement of working conditions; and other fiscal advantages.

6. A functional national regulatory authority, a timely and reliable surveillance system and coherent industrial, trade and public health policies are government responsibilities and key determinants for influenza vaccine manufacturing sustainability.

7. The Government can facilitate the engagement with international partners to maximize the use of the resources and create synergies among relevant programmes. Regional and global industrial organizations, such as African Vaccine Manufacturing Initiative, Developing Country Vaccine Manufacturing Network, Developing Country Vaccine Regulatory Network, Association of South-East Asian Nations and the International Federation of Pharmaceutical Manufacturers and Associations, can provide resources and expertise to help work through challenges.

Manufacturers considerations to improve sustainability

From the manufacturer’s perspective there are a series of considerations to be made when developing a business model:

1. Develop a realistic step-wise middle- to long-term business plan: start-up costs and costs to maintain vaccine manufacturing capacity shouldn’t be underestimated when deciding to invest in new influenza vaccine technology or facilities. Potential demand, cost per dose of the vaccine and overall return on investment are parameters that need to be weighed in the
decision. It is critically important to use a thorough, realistic and in-depth market analysis to inform the business model with clear estimation of the potential demand and an adapted production capacity.

2. Define the price of the final product: this can be used to shape the market, and tier pricing together with insurance coverage are push mechanisms that can contribute to sustainability of production through predictable and sustainable demand.

3. Engage pro-actively with the government to contribute to the generation of evidence and the estimation of the needs in terms of quantity of vaccines in the short and long run. When developing the business plan, manufacturers should take into consideration national and international multilateral and bilateral agreements affecting commercialization, import and export of products.

4. Consider possible other products that could be produced in the facility/plant: diversification of products manufactured at the same facility and economies of scale play an important role, since they contribute to the reduction of the infrastructural costs per dose produced, and therefore, the price of the final product. Moreover, it can contribute to addressing the influenza seasonality issue and mitigate business risks.

5. Strategically approach regional markets or other markets in neighboring countries: local production does not necessarily mean cheaper products, and manufacturers should maximize their added-value within the local context to overcome market challenges developing niche-specific products (i.e. non-injectable and heat resistant vaccines) or targeting recommended high-risk groups (i.e. pregnant women, elderly, and healthcare workers) also beyond their national borders.

6. Strengthen partnerships between stakeholders, in particular, with other vaccine manufacturers, academic institutions and key government agencies, such as Ministry of Health and Ministry of Science and Technology. Stakeholders need to communicate their expectations of each other, and define some roles and responsibilities (and capabilities) to move the influenza vaccination agenda forward.

7. Engage in manufacturers’ networks to find concrete areas to work together to advance the pandemic preparedness agenda. Potential common interests to advocate for can be, but are not limited to:
   - Workforce skill development
   - Research and product development
   - Technology development
   - Vaccine use
   - Raising pandemic preparedness and influenza vaccines to local, regional and international priority
   - Entering products in new markets.

8. Engage into political outreach outside the health sector, stimulating discussion forums with also unusual partners (for example, other industrial sectors).
Conclusion

Influenza vaccine manufacturers in LMICs may face serious challenges if they try to compete on the international market on a pure cost-of-vaccine basis, particularly if their facilities are of a small-medium size where economies of scale are not realized. The fact that in many developing countries the current market for seasonal vaccines is limited, is a major barrier to establishing and maintaining a large manufacturing capacity which would be competitive. Manufacturers could address this challenge by identifying a niche where competition can be reduced and the manufacturer strengths can be leveraged, focusing on comparative advantages deriving from the specific national and regional context. Manufacturers should try to expand their partnership network to create new markets, work to optimize existing markets, and explore options of innovative financing.

Gathering burden of disease and cost effectiveness data is critical, not only to inform and develop policy, but also to communicate the value of vaccination to health care workers and the public. It is important to measure influenza burden and vaccination benefits, and illustrate how these benefits exceed the cost that government and society would incur if influenza is not adequately prevented. The government can bolster existing surveillance systems to gather burden of disease data and take an active role in promoting vaccination uptake, by recommending influenza vaccination for high-risk or other population groups and including it in State-provided health programmes.

Sustainability of production is difficult to ensure. Merely having a policy that includes influenza vaccination among the health priorities is not enough to achieve sustainability: industrial, international trade and other economic policies are needed to foster a conducive environment to support sustainable influenza vaccine manufacturing, minimizing the risks and leveraging the potential of the local context. If governments decide not to provide direct or indirect financial support, they can promote national influenza vaccine production through a series of actions that support vaccination policies, harmonization of the production process across the supply chain, strengthening of their vaccine regulatory capacities, coordination of the work of the different ministries and government agencies in developing a conducive environment to sustainability and engaging with regional stakeholders to leverage national capacities. National governments should recognize the value of the vaccine manufacturing investments made in their country, for the benefit of the health of their populations and for pandemic preparedness.