The ten years of the Global Action Plan for Influenza Vaccines
Report to the Director-General from the GAP Advisory Group

The Global Action Plan for Influenza Vaccines (GAP) was launched in 2006 to address the expected serious shortfall in the global vaccine supply in the event of a pandemic. Recognizing that pandemic vaccines will be produced in existing influenza vaccine production facilities, the programme adopted three major approaches: (1) increase evidence-based use of seasonal vaccines; (2) increase vaccine production capacity, together with the necessary corresponding regulatory capacity in producing countries and in non-producing countries where influenza vaccine is used; and (3) promote research and development of improved vaccines and vaccine production technologies. With its focus on building both seasonal and pandemic vaccine production capacity, GAP has also supported the Pandemic Influenza Preparedness (PIP) Framework goal of improving the access of developing countries to pandemic vaccines.

GAP is also linked to the WHO public health research agenda for influenza, in particular to the stream dedicated to influenza vaccination.¹ This research agenda was established in 2009 and is currently being updated.

From the outset, GAP was envisioned as a 10-year initiative to provide specific focus on the anticipated future pandemic vaccine shortfall. In November 2016, WHO convened a final consultation to review the progress made and assess continuing needs. The conclusions of the consultation are summarized below.

1. Increasing evidence-based use of seasonal vaccines

This approach supported the implementation of World Health Assembly resolution WHA56.19, which urged Member States to establish and implement strategies to increase influenza vaccination coverage of all people at high risk. The resolution also requested the Director-General to provide support to developing countries in assessing the disease burden and economic impact of influenza, and in framing and implementing appropriate national policies for influenza prevention.

To support an evidence-based increase in seasonal vaccine use, GAP aimed to generate evidence on the disease burden in developing countries, as well as on vaccine effectiveness in different population groups. Studies conducted over the past ten years have contributed significantly to allowing more countries to put in place a national influenza immunization policy. A recent analysis of data from the WHO/UNICEF Joint Reporting Form on Immunization found that 115 countries now have such a policy, compared with 74 countries and territories in 2006.

It is, however, of concern that, despite the generation of data in support of broader use of seasonal influenza vaccine, 79 Member States still do not have a policy in place. Even in countries where a policy is in place, the implementation is frequently weak. There is a need to better understand and

¹ http://www.who.int/influenza/resources/research/en/.
address the reasons for this. This will not only help reduce the burden of seasonal influenza, but will also help build the infrastructure that will be needed during a pandemic. Countries without policies and vaccination programmes for seasonal influenza are unlikely to have the experience and infrastructure needed to rapidly deploy influenza vaccines in response to a pandemic. Since such vaccines are likely to be in short supply at the start of the pandemic, there may be a reluctance to distribute vaccines to countries that have not demonstrated that they can use them effectively.

In addition, despite the existence of national policies, data on vaccine use are still sporadic and unreliable; in recent years, dose distribution has been used as a proxy. Figures provided by the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA) for 2004–13 show an increase of 87% in doses of seasonal influenza vaccine distributed, from 262 million to 489 million. There are, however, considerable variations among regions, with some regions showing little progress. The recent downward trend in Europe is of particular concern and a better understanding of the drivers of this trend is needed.

2. Vaccine production capacity

When GAP was established in 2006, the best estimate of potential annual global production capacity of pandemic vaccine was 1.5 billion doses; all of this capacity was based in a few industrialized countries.

Now, after a concerted global effort to diversify the production base, the best estimate of potential production capacity\(^2\) has more than quadrupled to 6.4 billion doses. This is still short of the expected need (about 10 billion doses), but would allow all countries to vaccinate a significant proportion of their population. Through GAP’s technology transfer initiative, 14 vaccine manufacturers in developing countries and the respective governments have received funding and technical support to establish or expand influenza vaccine production capacity. In the past 10 years, six of these countries have licensed locally produced influenza vaccines, of which three are now prequalified; other countries are making progress towards this goal. Provided that it can be maintained, this increased capacity in developing countries will ensure that the regions concerned will not be entirely dependent on industrialized countries for vaccine in the event of a pandemic.

However, maintaining this capacity requires a thriving market in which seasonal influenza vaccines can be sold and used. Without sufficient demand, production will decrease and the potential supply will not be achievable. This demand will only be realized with appropriate national policies and well implemented programmes to control seasonal influenza.

Vaccine production requires effective regulatory oversight, and there has been a concerted effort to strengthen expertise in the national regulatory authorities (NRAs) of the 14 countries that

\(^2\) Certain assumptions are made in estimating potential capacity, including: all facilities are put on full-scale production, sufficient eggs are available, 15 µg of antigen is enough, dose-sparing technology (adjuvants) is factored in when available.
received support to increase production capacity. In 2006, only four of these countries had a functional NRA; this number was increased to ten by GAP, providing the potential for prequalification of the vaccines. This progress also highlights the synergy between PIP and GAP, since NRA capacity strengthening is a one focus of investment under PIP.

3. Research and development of improved vaccines and vaccine production technologies

The GAP initiative focused on the short-term goal of increasing pandemic vaccine production capacity. It also monitored progress in research and development of better influenza vaccines and vaccine production platforms. Over the ten-year period, there have been numerous advances, including: adjuvanted pandemic vaccines that permit dose-sparing; live attenuated influenza vaccines with improved production efficiency and significant programme advantages; tetravalent vaccines with broader strain coverage; and tissue-culture and recombinant vaccines that avoid the need for eggs in the production process and, especially for recombinant vaccines, can be produced more quickly. These advances have contributed to improved pandemic preparedness. However, the long-term aim is to have a universal vaccine that does not need to be adapted each year to the circulating seasonal strains or to the pandemic strain, and that could be stockpiled and made available in a timely manner in the event of a pandemic. There are numerous challenges to the development of a universal vaccine, including scientific, regulatory and financial constraints. A coordinated approach to supporting product development is required. WHO’s Initiative for Vaccine Research is currently developing preferred product characteristics for the next generation of influenza vaccines.

The path forward

The world is still at risk of an influenza pandemic. Despite the progress achieved, global vaccine production capacity is still insufficient, the time between identification of a pandemic strain and availability of a vaccine is still several months, and use of seasonal vaccine remains low in most parts of the world and is declining in some industrialized countries. Low use of seasonal vaccine could lead manufacturers to reduce their capacity or even stop production. At the same time, even as there are troubling signs of an emerging H7N9 virus in China, there seems to be what has been called “global influenza fatigue” — less interest among policy-makers, reduced funding for influenza-related activities, and increased vaccination hesitancy among key groups, such as health care workers. Yet, it is certain that there will be an influenza pandemic. We do not know when it will occur or how serious it will be, but it will happen.

The GAP Advisory Group identified the following issues as requiring global coordination and WHO’s leadership. These are proposed to the Director-General as priority issues.

- Manufacturers in developing countries still require technical assistance to bring their fledgling capacity on-line and business acumen to ensure that their technical efforts are sustainable and will be in place when the next pandemic occurs. Beyond that, sustainability
also requires various factors to be in place, especially those elements that can help to ensure sustainability -- including a functional national regulatory authority, a sustainable business plan (including the potential need for outside funding in the short term), strong political will, availability of funding and a health care system that serves the whole population and is trusted to have a vaccination infrastructure of good quality.

- Research and development of improved influenza vaccines and vaccination strategies need to be coordinated, to ensure that products meet public health needs and to facilitate development and licensing.
- The root causes of influenza vaccine hesitancy need to be identified and addressed in all countries, as they undermine vaccine uptake and threaten the sustainability of current production levels.
- More evidence is needed on vaccine effectiveness in specific risk groups. Studies need to take into account recent suggestions that yearly vaccination may not be optimal.
- An expert review of the assumptions that led to the definition of the three GAP approaches would be useful, to identify innovative ways of addressing global preparedness for pandemic influenza and point the way forward.

Finally, it should be recognized that GAP served an important coordinating role, bringing together the different groups working on influenza within WHO, including PIP, the Global Influenza Programme, Essential Medicines and Health Products, and Immunization, Vaccines and Biologicals, as well as the Health Systems and Innovation technology transfer initiative. The GAP Advisory Group therefore recommends that WHO should maintain such an influenza vaccine coordination role or mechanism to ensure that the Organization can continue to provide technical assistance, oversight and engagement with stakeholders, both across WHO and in Member States, industry, and civil society. And, at the risk of appearing self-serving, the Advisory Group considered that it had itself helped the Organization pull together the many strands, in order to take full advantage of resources and to ensure that the vast experience and expertise available were used to their full potential. The establishment of a group with similar function may not only be of assistance to the Organization but may provide additional reassurance to Member states that this important activity is not being overlooked.