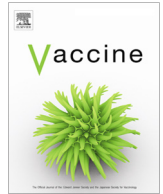




Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



## Editorial

## Preparing for the unpredictable: The continuing need for pandemic influenza preparedness



Ebola, Zika, Middle East respiratory syndrome (MERS), Chikungunya, Severe Acute Respiratory Syndrome (SARS). The cadence of emerging infectious diseases that travel, transmit and stand ready to spark a public health emergency of international concern seems to be accelerating. These infectious diseases cause significant human suffering, can overwhelm unprepared health care systems, and significantly disrupt societies and economies. It is estimated that a severe pandemic similar to the 1918 “Spanish flu” could nowadays cost as much as 5% of global gross domestic product; the global cost of even a moderately severe pandemic could be as much as US\$ 570 billion, or 0.7% of global income [1].

Given the health, social and economic impact of infectious diseases with pandemic potential, there has been much attention to these microbial threats and, not surprisingly, the first question is always, “Is there a vaccine?” But too often we find that the vaccines we need most are not available when we need them most. A number of efforts are focused on better anticipating the vaccines that we may need [2–6] and a global emergency fund has been proposed to support accelerated vaccine development [7].

### The ever present threat of influenza

The current headlines about Zika virus have replaced last year’s headlines about Ebola...and next year’s headlines will undoubtedly feature something new. Imperfect crystal balls fail to guide us with certainty. But looming in the background is the ever present threat of influenza, the only microbe that causes regular widespread epidemics around the world. Not so exotic and all too familiar – casually referred to as the “flu” – influenza is the virologist’s Trojan horse, as it readily and rapidly mutates (drift), has the ability to swap genetic elements from influenza viruses with origins in other species (shift) and, as an RNA virus lacks repair and self-correcting mechanisms that are the basis of its genetic instability and makes it both dangerous and unpredictable. A reassortment leading to an extremely virulent and readily transmissible pandemic virus is inevitable.

Of the many things that need to be in place to prepare for and respond to the next influenza pandemic, vaccines – together with the capacity to mount a timely global vaccination effort – are paramount. A pandemic can only be brought under control through a shift in the population from susceptibility to immunity. But as we learned in the 2009 influenza pandemic, although our response time has improved, a significant shift in approach is needed if an effective vaccine is to be in place before the next pandemic emerges. With that goal in mind, the science of influenza and of vaccine development needs to be looked at with fresh eyes [8].

The Holy Grail is an influenza vaccine that provides a broader and more durable immune response than the natural infection and that can provide population immunity to pandemic influenza viruses before they emerge. A number of efforts are now focused on developing such a “universal” influenza vaccine; however, the scientific challenges involved are enormous [9,10]. Until such a universal influenza vaccine becomes available, global influenza vaccine production capacity needs to be ready to respond when the next pandemic emerges.

Vaccines obviously need to be safe and effective, but they must also be available and affordable. While vaccine supply is clearly essential for a large-scale vaccination programme, the logistics and supporting policies needed to conduct effective and efficient vaccination campaigns in a range of community settings also need to be addressed and the needs of high-risk and vulnerable populations and of low- and middle-income countries accommodated. Ultimately, the success of a vaccination programme will hinge not only on the technical aspects of its implementation, but on the demand for it among the population; this underscores the need to understand the factors that promote vaccine acceptance [11,12].

### Mind the GAP

Within this broad framework, and with a focus on the role of vaccines in mitigating the impact of both seasonal and pandemic influenza, WHO established in 2006 the Global Action Plan for Influenza Vaccines (GAP) as “a comprehensive strategy to reduce the present global shortage of influenza vaccines for seasonal epidemics and pandemic influenza in all countries of the world” [13].

The papers in this Special Issue of *Vaccine*, provide a foretaste of the in-depth review to come in November 2016, when WHO will host the third and final consultation on GAP as the programme, as it exists today, comes to close. The background papers prepared for this consultation are available on the WHO website ([http://www.who.int/influenza\\_vaccines\\_plan/news/gap3\\_Nov16/en/](http://www.who.int/influenza_vaccines_plan/news/gap3_Nov16/en/)). While this event is advertised as a programme review, in reality as an examination of the progress achieved during the decade, it should also serve to direct the global community on the path forward for the work that remains to achieve global pandemic influenza vaccine and vaccination preparedness.

This review, combined with the current rethinking of global preparedness for emerging threats, the review of the Pandemic Influenza Preparedness (PIP) Framework [14], and WHO’s restructuring of its approach to global health emergencies [15], allows a timely reassessment not only of the impact of this programme

but of global pandemic influenza vaccine and vaccination preparedness overall.

The Global Action Plan for Influenza Vaccines was structured around three broad objectives that underpin pandemic influenza vaccine and vaccination preparedness:

- evidence-based increase in seasonal influenza vaccine use;
- increase in influenza vaccine production capacity and regulatory capacity;
- research and development for improved influenza vaccines.

The articles contained in this issue not only relate to the GAP objectives but also reflect the principles and goals of PIP and highlight the synergy of these two efforts. PIP's pandemic preparedness goal of increasing the access to vaccines and other pandemic-related supplies by developing countries (and the critical importance of improving the sharing of influenza viruses with human pandemic potential toward that end), will ultimately depend on influenza vaccine production capacity in place when the next pandemic occurs.

These articles present a variety of perspectives on the system that will develop, produce, regulate, distribute and evaluate pandemic vaccines and mass vaccination programmes. They have been selected to represent some of the many elements of the system that will be necessary for a pandemic vaccine response – including clinical trials of new vaccines, new vaccine production platforms, national regulatory systems, implementation of policy recommendations for vaccine use, and assessment of the sustainability of the global influenza vaccine manufacturing capacity that GAP has supported.

Progress has already been significant and measurable. One clear example is that global production of seasonal influenza vaccine increased from less than 500 million doses in 2006 to nearly 1.5 billion doses in 2015 [16,17]. Yet, there is a pressing need for additional burden of influenza illness studies to provide the essential data that will be looked to by policymakers to assess the role of vaccines in national influenza control strategies. It is the implementation of these policies that will determine demand. Without a concomitant increase in global demand for seasonal influenza vaccine, the capacity that will produce the world's pandemic vaccines that GAP has stimulated cannot be sustained [18].

At the end of the day there is the expectation that the efforts and investments made to prepare for a pandemic will result in the timely and equitable availability of a vaccine that is safe and effective, and that can be used in vaccination campaigns before the majority of the global population is exposed to the virus. However, a continuing dedicated effort is needed to ensure that all the elements of the system that will allow this to happen are in place before we need them. Because we don't know when that day is, the global community must continue with speed and focus. And, as WHO develops a new structure to respond for the call to be prepared for all hazards, in its complex organizational chart pandemic influenza preparedness must remain front and center.

## References

- [1] Fan VY, Jamison DT, Summers LH. The inclusive cost of pandemic influenza risk (working paper 22137). Cambridge, MA: National Bureau of Economic Research; 2016. <<http://www.nber.org/papers/w22137>>.
- [2] An R&D blueprint for action to prevent epidemics. Accelerating R&D and saving lives. Geneva: World Health Organization. <[http://www.who.int/csr/research-and-development/r\\_d\\_blueprint\\_brochure2015.pdf?ua=1](http://www.who.int/csr/research-and-development/r_d_blueprint_brochure2015.pdf?ua=1)>.
- [3] Giersing BK, Modjarrad K, Kaslow DC, Moorthya VS. Report from the World Health Organization's Product Development for Vaccines Advisory Committee (PDVAC) meeting, Geneva, 7–9 September 2015. *Vaccine* 2016;34:2865–9.
- [4] Antibiotic resistance threats in the United States, 2013. Atlanta, GA: Centers for Disease Control and Prevention; 2013. <<http://www.cdc.gov/drugresistance/threat-report-2013/index.html>>.
- [5] US Federal Select Agents and Toxins List. <<http://www.selectagents.gov/SelectAgentsandToxinsList.html>>.
- [6] The Coalition for Epidemic Preparedness Innovations (CEPI). <<http://cepi.net/>>.
- [7] Plotkin SA, Mahmoud AAF, Farrar J. Establishing a global vaccine-development fund (perspective). *N Engl J Med* 2015;373:297–300.
- [8] Osterholm MT, Kelley N, Manske JM, Ballering KS, Leighton TR, Moore KA. The compelling need for game-changing influenza vaccines. Minnesota: Center for Infectious Disease Research and Policy. <<http://www.cidrap.umn.edu/compelling-need-game-changing-influenza-vaccines>>.
- [9] Krammer F, Palese P. Advances in the development of influenza virus vaccines. *Nat Rev Drug Discovery* 2015;14:167–82.
- [10] Nabel GJ, Fauci AS. Induction of unnatural immunity: prospects for a broadly protective universal influenza vaccine (commentary). *Nat Med* 2010;16:1389–91.
- [11] Global Vaccine Action Plan 2011–2020. Geneva: World Health Organization. <[http://www.who.int/immunization/global\\_vaccine\\_action\\_plan/GVAP\\_doc\\_2011\\_2020/en/](http://www.who.int/immunization/global_vaccine_action_plan/GVAP_doc_2011_2020/en/)>.
- [12] Eskola J, Duclos P, Schuster M, MacDonald NE. SAGE Working Group on Vaccine Hesitancy. How to deal with vaccine hesitancy? *Vaccine* 2015;33(34):4215–7.
- [13] Global Action Plan for Influenza Vaccines. Geneva: World Health Organization. <[http://www.who.int/influenza\\_vaccines\\_plan/objectives/en/](http://www.who.int/influenza_vaccines_plan/objectives/en/)>.
- [14] Pandemic Influenza Preparedness (PIP) Framework. Geneva: World Health Organization. <<http://www.who.int/influenza/pip/en/>>; <<http://www.who.int/influenza/pip/2016-review/en/>>.
- [15] <<http://www.who.int/mediacentre/news/releases/2016/wha69-25-may-2016/en/>>.
- [16] WHO Global Influenza Surveillance and Response System (GISRS). Melbourne: Peter Doherty Institute for Infection and Immunity. <[http://www.influenzacentre.org/centre\\_GISRS.htm](http://www.influenzacentre.org/centre_GISRS.htm)>.
- [17] Global Action Plan for Influenza Vaccines. Global progress report, January 2006–September 2013. Geneva: World Health Organization. <[http://apps.who.int/iris/bitstream/10665/112307/1/9789241507011\\_eng.pdf?ua=1](http://apps.who.int/iris/bitstream/10665/112307/1/9789241507011_eng.pdf?ua=1)>.
- [18] Silva ML, Perrier L, Cohen JM, Paget WJ, Mosnier A, Späth HM. A literature review to identify factors that determine policies for influenza vaccination. *Health Policy* 2015;119:697–708.

Bruce G. Gellin\*

National Vaccine Program Office, Department of Health and Human Services, Washington, DC, United States

\* Corresponding author at: National Vaccine Program Office, Department of Health and Human Services, 200 Independence Avenue, Washington, DC, 20201, United States.  
E-mail address: [bruce.gellin@hhs.gov](mailto:bruce.gellin@hhs.gov)

Firdausi Qadri  
Infectious Diseases Division, ICDDR,B – International Centre for Diarrhoeal Disease Research, Dhaka, Bangladesh

Available online 24 September 2016