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.

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Commentary

The influenza vaccines roadmap – A better future through improved influenza vaccines

Peter Hart *, Jeremy Farrar

The Wellcome Trust, 215 Euston Road, London NW1 2BE, United Kingdom

Events of the last eighteen months reminded us yet again of the power of emerging infectious diseases to disrupt every aspect of our lives. SARS-CoV2 is the archetypical Disease-X, a zoonotic RNA virus that likely crossed the species barrier into humans, with efficient human-to-human transmission including when people are asymptomatic. Illness ranges from very mild through to very severe and at the onset of the pandemic, humanity had little or no immunity. We also had no diagnostic tests, no treatments and no vaccines, highlighting just how unprepared the world was for such an event caused by a hitherto unknown virus. The emergence of novel, infectious, viruses poses a threat to which the world remains highly vulnerable.

Yet the virus most likely to cause a global catastrophe is one we have known since antiquity, one which we live with despite its high annual burden and pandemic risk, and for which frighteningly, we still only have mediocre diagnostic tests, treatments and vaccines. Influenza was first described over 2500 years ago and has caused devastating pandemics intermittently ever since. Between pandemics, and even with modern vaccines, influenza claims between 290,000 and 645,000 lives globally each year [1]. The burden of influenza disproportionately falls on low-to-middle-income countries (LMICs), where hospitalisations, death rates and economic consequences are substantially higher than in high-income countries [1–4]. With its potential for antigenic drift and shift, an extensive animal reservoir and failure to induce robust and durable immunity, humanity has always been vulnerable to both seasonal and pandemic influenza. With changes in ecology, animal-human interactions, urbanization and travel, humanity is arguably more at risk in the 21st century than at any other moment in history.

Current influenza vaccines – Good is not enough

Humanity simply cannot continue to live under the very real threat of a devastating influenza pandemic with the current tools we have available. Our way out of the Covid19 pandemic has been via the rapid development and deployment of highly effective virally-vectored or nucleic acid vaccines. Though estimates vary by vaccine, variant and population being studied, the best vaccines offer >80% protection against hospitalisation and death in real-world settings [5–7]. Contrast this with influenza, where we are dependent on slow-to-produce, egg-based vaccines of moderate effectiveness against hospitalisation (20–60% [8] and the pandemic risk from influenza is clear. We must have better interventions that can prevent and mitigate inevitable future pandemics and, having developed these tools, we must ensure they are available equitably and affordably to everyone who needs them. That starts with acknowledging the risk and then committing to do what it takes to reduce that risk. The only way to reduce that risk is to bring the research and development (R&D) of new medical countermeasures for influenza, such as vaccines, into the 21stCentury.

Current influenza vaccine R&D and production systems are outdated and traditional which presents challenges to the development and use of better influenza vaccines. At the basic research level, poor models and incomplete understanding of influenza immunology and virology lead to the creation of poorly, or moderately, effective vaccines which do not induce durable immune responses. Waning immunity necessitates costly annual vaccination programmes which bring a new suite of challenges – vaccine virus strain selection is not an exact science, strain mismatching occurs, and a reliance on eggs for production not only reduces the effective of vaccines due to egg adaptation, but introduces supply chain risk. Once vaccines are available, their suboptimal effectiveness can undermine vaccine confidence and exacerbate demand on healthcare systems as was observed in the severe influenza season of 2017–2018 when overall vaccine effectiveness was low. More broadly, the existence of moderately effective, licensed influenza vaccines may create the perception that the challenge of influenza has "been met" and make the development of new or improved influenza vaccines less desirable. Coupled with existing barriers to entry, such as the high cost of demonstrating superiority of new candidates, and markets have failed to generate any recent major advances in influenza vaccines. An inability to quickly manufacture, deploy and distribute vaccines, particularly in LMICs, is another chink in our pandemic preparedness armor – when the H1N1 pandemic of 2009 occurred, it would have taken the world 2–3 years to produce sufficient doses for global coverage. While production capacity has increased since, current best case scenarios still predict a shortfall in doses and long lead time for first supplies [9].

Broadly speaking, global cooperation on influenza is a success, and provides a working model for efforts on other diseases, with much to be celebrated and leveraged. The inclusive World Health

* Corresponding author.
E-mail address: p.hart@wellcome.org (P. Hart).

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Organization Global Influenza Surveillance and Response System has stood the test of time for almost seventy years, functioning through tense geopolitical times to ensure the (mostly) reasonable sharing of viruses and effective vaccine production pathways which reduce the burden of seasonal disease. Recent modernization in production methods has lessened our dependency on egg-based vaccines, but there remains much to be done to modernize influenza vaccines and support the adoption of new technologies. At the time of writing, both Sanofi and Moderna had initiated Phase 1 clinical trials of candidate mRNA influenza vaccines. The staggering scientific and manufacturing progress over the last year with SARS-CoV2 vaccines now offers us an opportunity to disrupt the established approach to influenza vaccine R&D.

The Influenza Vaccines Roadmap

Prior to the Covid19 pandemic, global health funders and the public health community were acutely aware of the pandemic threat from influenza and the shortfalls of current influenza vaccines. Recent years saw a number of influenza R&D related strategies or tools published, such as the WHO Global Influenza Strategy 2019–2030, the Sabin Influenzer Initiative and the US Government's National Influenza Vaccine Modernization Strategy 2020–2030. In 2017, the Global Funders Consortium for Universal Influenza Vaccine Development (GFC) was convened with the purpose of overcoming the multidimensional challenges specifically facing influenza vaccine R&D and effecting change by enhancing coordination and broadening protection to LMICs and vulnerable populations. The Consortium called for the development of an Influenza Vaccines R&D Roadmap (IVR), based on innovation and shared responsibility among stakeholders in academia, industry, government, philanthropies, and multilateral organizations. Importantly, the roadmap was informed by, and builds upon the existing strategic, or research prioritisation, tools in a number of ways: its globality, having been developed through global consultation and intended for global use; its granularity, having influenza vaccine-specific research gaps and milestones identified, which audiences can use to guide their work; and its end-to-end nature, with consideration given to both basic research and also vaccine development, production and use. As we exit the Covid19 pandemic, there will never be a better time to catalyze change in influenza vaccine R&D, which is why, following two years of extensive and global expert consultation, we are now launching the IVR.

The IVR, funded by Wellcome and developed by Center for Infectious Disease Research and Policy (CIDRAP) at the University of Minnesota working in partnership with the World Health Organization, Wellcome, Sabin Vaccine Institute, Bill & Melinda Gates Foundation, and the Task Force for Global Health is a strategic, disruptive and ambitious tool for influenza vaccine research prioritisation. Importantly, the roadmap recognizes the tensions, sensitivities and trade-offs in influenza vaccine R&D and it aims to align improved effectiveness and production of strain-specific seasonal influenza vaccines with the development of broadly protective or universal influenza vaccines.

The IVR is a global public good. It is a tool for the research community, funders, industry, policymakers and others engaged in influenza vaccine R&D. It highlights key research barriers and knowledge gaps; identifies strategic goals with aligned milestones to address them; encourages synergistic and innovative strategies to accelerate R&D; and is intended to stimulate informed investment on influenza vaccines, particularly with regard to vaccines that are suitable and affordable in LMICs. Over a 10-year framework, the IVR prioritizes a wide range of critical R&D activities and establishes a basis for a mission-driven effort aimed at producing improved influenza vaccines for global use. The roadmap makes clear what is needed for the global health and research communities to move from dependency on current vaccines, to a world which is better protected against influenza with next generation, or even universal influenza vaccines.

We are calling on the global public health community, particularly funders and researchers, to use the IVR to inform their decision-making around influenza vaccine R&D. The roadmap ought to reduce the need for in-house research prioritisation exercises, guide institutional strategy and lead to high priority, non-duplicative and impactful decision-making for influenza vaccine R&D. As a commitment to this effort, Wellcome plans to support a multi-year program of work to implement the roadmap which will see key stakeholders brought together to encourage crosstalk among vaccine researchers and developers and progress against roadmap milestones assessed. The roadmap developers and associated partners will strive to create new networks of collaboration, particularly around coordination of funding through groups such as the GFC. With broad buy-in, and its use to guide influenza vaccine R&D decision making, we believe that the IVR will improve research coordination and catalyse development of new or improved influenza vaccines.

By aligning enhanced global pathogen surveillance with the roadmap, and combining improved influenza vaccines with the ability to rapidly pivot R&D, manufacturing and distribution for vaccines against Disease-X, we can create sustainable, predictable, capacity for equitable access to these critical tools. We need to drive home the advances of the last year and make sure they provide utility all of the time, to all people, not just for the rarer black swan events of a Disease-X. Coupled with initiatives such as the Partnership for Influenza Vaccine Introduction (PIVI) and Ready2-Respond, we can use improved influenza vaccines to provide better access to influenza vaccination programs in LMICs and broaden coverage to vulnerable populations. Widespread influenza vaccination will also reduce antibiotic consumption and contribute to tackling the antimicrobial resistance crisis [10]. Equitable access to enhanced influenza vaccines will save lives from influenza, it will also reinforce the critical sustainable infrastructure the world needs ahead of the next pandemic.

The tragedy of the COVID-19 pandemic is an opportunity to change the influenza vaccine paradigm. Research funding is not the issue – influenza research scores highly in terms of overall funding on specific pathogens, coming 4th to HIV, TB and Malaria [11,12]. Yet, in the absence of global coordination or prioritisation specifically for vaccine development, an abundance of funding has failed to yield next generation influenza vaccines, and the dream of a universal flu vaccine remains a distant hope. The lack of any sizeable shift in influenza vaccine R&D over the last 60 years begs the question - are we serious about changing the influenza vaccine ecosystem? The Covid19 pandemic has provided a reminder of the threat posed by a novel transmissible respiratory virus with its severe impact on families, health care systems, schools, businesses, and economies. The still unfolding tragedy has also shown us what is possible - COVID-19 vaccine development carried out under emergency conditions, along with innovation in regulation, policy, partnerships and financing, has succeeded in record time and pushed the boundaries of vaccine science and technology. We must now ask ourselves how we can learn from this tragedy and change our approach to influenza? The IVR marks a first step in beginning this process.

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Peter Hart is a senior research adviser for Wellcome. Wellcome supports a range of research funding activities including

awards made to the development of the Influenza Vaccines Roadmap and to Ready2Respond. Jeremy Farrar contributes to SAGE for UK Government, is chair of the WHO R&D Blueprint Science Advisory Group and a CEPI board member. JF has authored a book on the pandemic (all payments/royalties to charity).

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