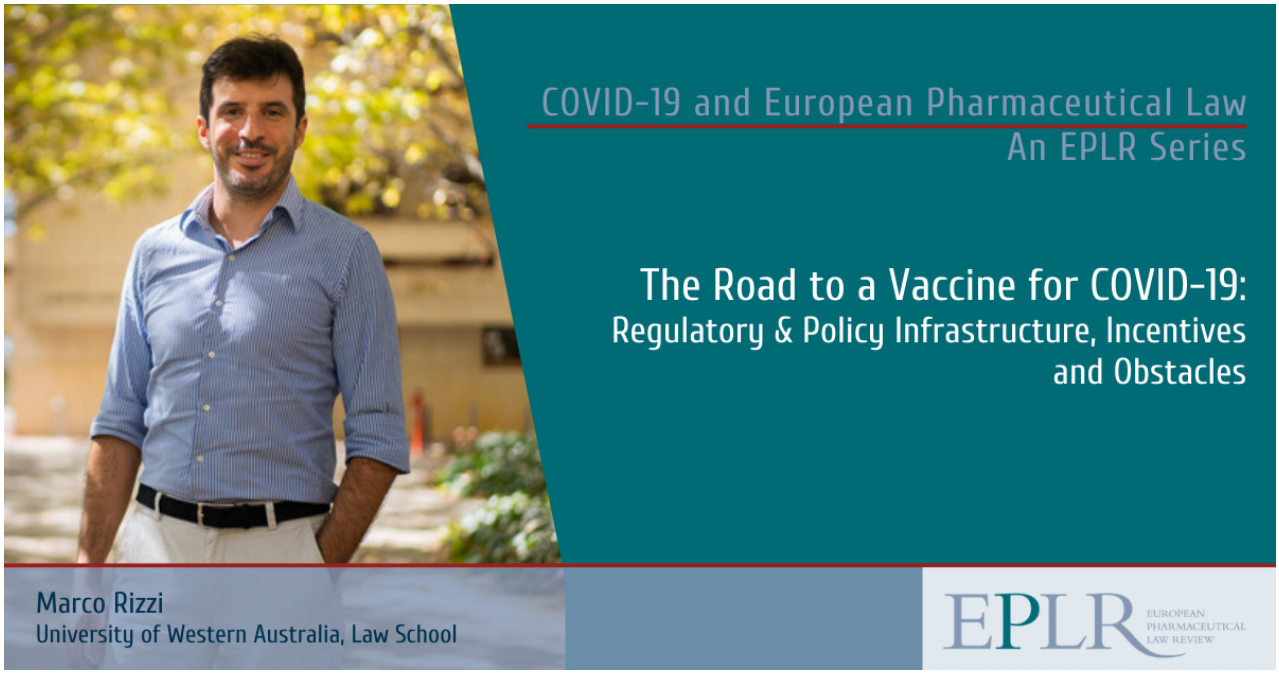


The Road to a Vaccine for COVID-19: Regulatory & Policy Infrastructure, Incentives and Obstacles

Introduction

As the COVID-19 pandemic keeps spreading, authorities across the world are adopting unprecedented containment measures. These are having a severe impact on the economic and social order of our democracies, raising serious and compelling questions about the hold of fundamental rule of law tenets. The inability to gather and socialise is inevitably taking a significant toll on our daily lives and that of countries the regular functioning of which relies on human aggregation. Yet, for the moment, strict social distancing remains the only effective strategy to contain the spread of the virus. One aspect that is becoming increasingly clear is that no version of 'normality' is realistically going to be possible in the absence of a vaccine. As eloquently put by Sheila Jasanoff, 'science will not come on a white horse with a solution' in the absence of adequate understanding of (and preparation for) the social consequences of the disease. That said, alternative measures including the use of contact tracing apps are only a surrogate for and not an alternative to vaccination. It is therefore essential to confront the complexity of rolling out a vaccine, once developed, into societies. How will sufficient doses be procured by governments? What priority criteria will be laid out and by whom? Will vaccination be made mandatory? These are some of the many pressing questions that will animate future debates. The starting point, however, remains the availability of a vaccine as a *condition sine qua non* to move past social distancing.

Information about the state of play in the rush to a COVID-19 vaccine is varied, but a level of consensus is emerging around the fact that it will take at least between 12 and 18 months for any vaccine to become available for rollout in the general population. It is important to understand that, if this were to happen, it would be unprecedented. Under normal circumstances, it takes between 10 and 15 *years* for a new vaccine to be developed from scratch. The timeframe is largely dictated by the levels of unavoidable uncertainty that characterise any scientific enterprise of this sort and the need for transnational data on safety and efficacy, as well as regulatory fragmentation. So why is a 12 to 18 months timeframe even thinkable in the circumstances? Essentially because of the unprecedented amounts of political will and resources that are being thrown behind the race to this particular vaccine.

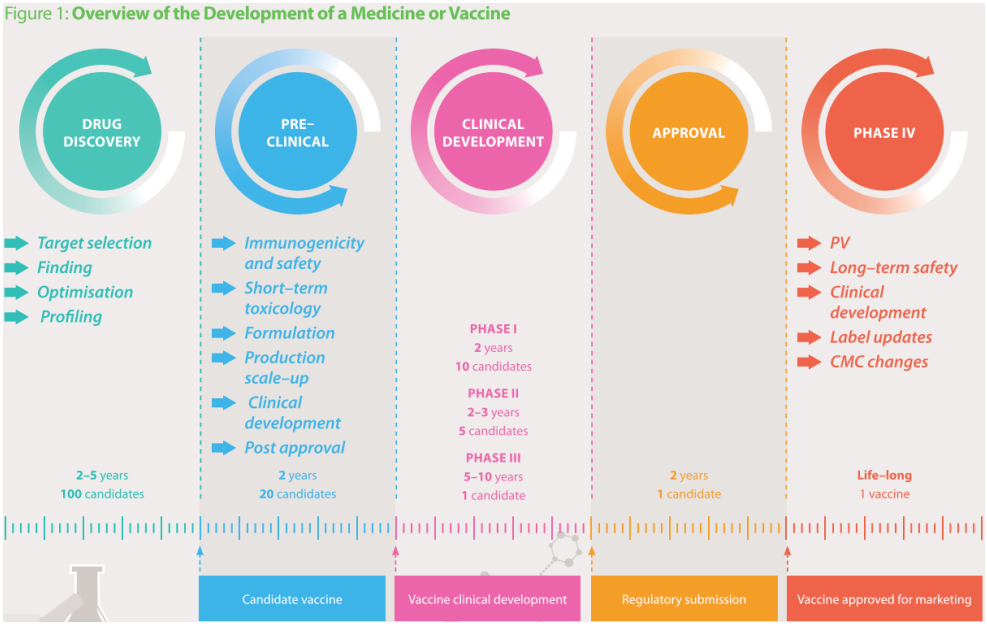
This observation leads to a set of important questions: what is the role of the regulatory framework governing the research, development and approval of new vaccines in shaping the timeframe leading up to availability to the general population? What are the policies underpinning these regulations and what type of incentives do they provide? What can we learn from this experience that might assist us in future crises?

This contribution seeks to stimulate a debate on these important questions. It briefly sketches the characteristics of vaccine research, development and approval under 'normal circumstances' and confronts it with the pandemic scenario. It looks into the practice of 'disease-specific' regulatory streams and provides a comparative case analysis between the road to a vaccine during the A-N1H1 pandemic and the Ebola epidemic. It concludes with a reflection on possible future designs of regulatory and policy infrastructure.

Setting the Scene: Research, Development and Approval of a Vaccine in 'Normal Times'

Developing a new vaccine is an arduous task. As with any other pharmaceutical product, a candidate has to undergo a series of tests, from preclinical to clinical, and strict ongoing pharmacovigilance once the product hits the market. But the development of a vaccine can be even more challenging than that of a therapy for a number of reasons. These include the fact that therapies are targeted to sick people suffering from a certain condition, whereas vaccines aim to prevent infection and are administered to healthy people across all age ranges, which requires extremely large safety and efficacy datasets. A summary view of the typical timeline for vaccine development is laid out in this 2019 infographic by the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA):

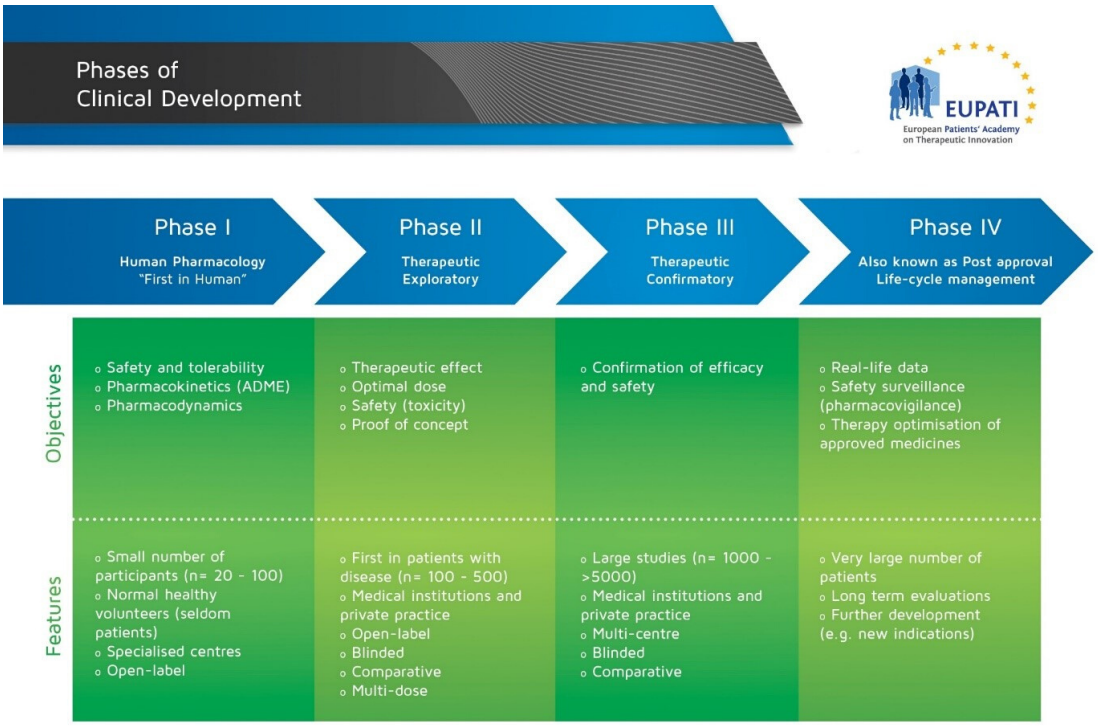
Figure 1: **Overview of the Development of a Medicine or Vaccine**



Source: IFPMA, *The Complex Journey of a Vaccine – Part III* (July 2019), p. 4

From a regulatory perspective, this structure translates into a series of hoops that candidate vaccines have to jump through, which accounts for the decreasing number of viable candidates from about 100 to 1 between discovery and the conclusion of clinical trials. The stages from discovery to clinical trials have been progressively harmonised by a combination of public international guidelines and transnational regulatory standard setting. A leading role in the latter is played by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH is a transnational regulatory network that brings together regulators and representatives of the industry from all regions of the world. In particular, the clinical stage of the development process, where vaccine candidates are tested on human subjects,

has to be done in accordance with the ICH Good Clinical Practice guidelines, and it is the most time consuming, costly and labour demanding. As well captured in the graphic below, phase III of clinical development requires the candidate to be tested on thousands to tens of thousands of people.



Source: EUPATI, Phases of Clinical Development (November 2018)

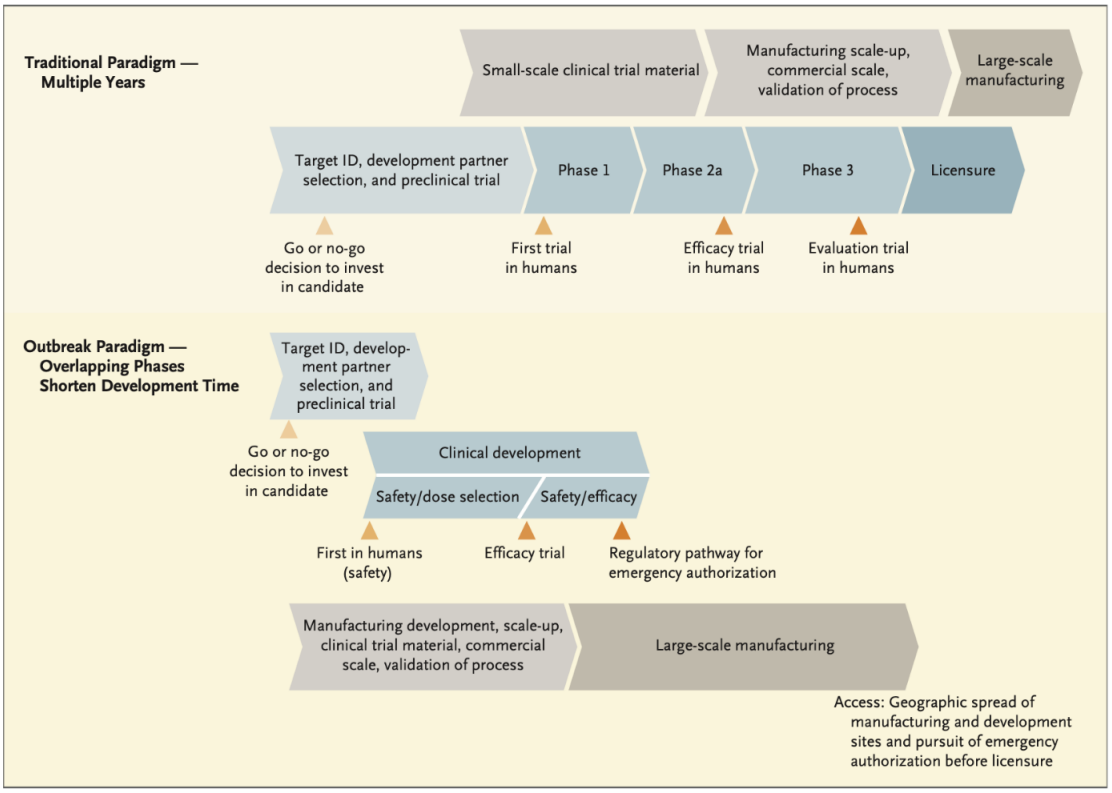
Once the data is collected, the approval process is guided by an independent regulatory agency that reviews and approves or rejects the application. In the European Union, where there is no special regulatory pathway for vaccines (under 'normal circumstances'), the process is the same followed for any application for the marketing approval of pharmaceutical products through the European Medicines Agency (EMA). This usually takes 18 to 24 months. In the United States, despite the existence of a specialised Center for Biologics Evaluation and Research within the Food and Drug Administration (FDA), the timeline is comparable and vaccines undergo largely the same process as other medicines.

In Europe, the lack of a specialised regulatory pathway for vaccines has been criticised as being at the core of recent shortages of vaccines for preventable diseases (the stockpiling problem), as well as the decrease in development of new vaccines. The process is allegedly too long and cumbersome to be profitable, and as a result vaccine manufacturing capacity is decreasing. In 2018, the US Centers for Disease Control and Prevention (CDC) made a similar point with regard to American manufacturers leaving the vaccine market. That notwithstanding, in 2019 a report by Vaccines Europe, which includes leading global vaccine producers such as GSK, Sanofi Pasteur, Pfizer and MSD, indicates that 76% of its members' vaccine production still takes place in Europe and 13% in North America, where other main players such as Merck also have their production hubs. It is therefore not unreasonable to expect that Europe and the US will have major roles to play in the development of a vaccine for the COVID-19 virus.

Vaccines for Pandemic and Epidemic Diseases: Changing Paradigm in Emergency Scenarios

The pandemic (or epidemic) scenario adds a significant layer of complexity to the business of regulating new vaccines' access to market because of the urgency of the need and immediacy of the threat to global or regional public health. The image on the next page, published in a recent contribution to the *New England Journal of Medicine*, captures the need for different

paradigms of vaccine development in a pandemic as opposed to under normal circumstances:



Source: Nicole Lurie et al., 'Developing Covid-19 Vaccines at Pandemic Speed', *NEJM* (30 March 2020)

The key differences are (a) the speed of development and safety & efficacy trials, and (b) the timing of large-scale manufacturing, which is to take place alongside the development and testing phases. The highlighted box in the image refers to 'regulatory pathway for emergency authorisation' as the key for access to market. But what exactly is this pathway? Both the FDA and the EMA have special provisions for fast-tracking the approval of medicines, including vaccines, during emergencies, although the two follow a different philosophy.

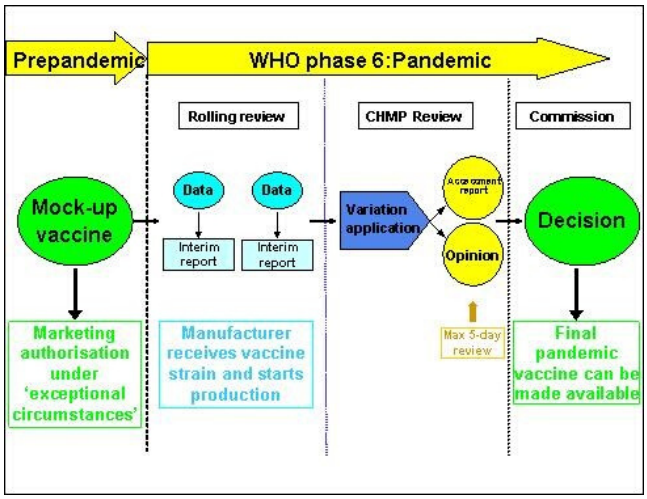
In the US, under the Public Readiness and Emergency Preparedness Act (PREP), the FDA can issue wide immunities from liability to defined entities engaging in 'Recommended Activities', or countermeasures, including 'the manufacture, testing, development, distribution, administration, or use' of effective pandemic countermeasures. PREP empowers the FDA to vary substantially the levels of safety and efficacy required for approval in order to accelerate the process. A similar logic underpins the WHO Emergency Use Assessment and Licensing Procedure (EUAL), developed in the aftermath of the Ebola epidemic of 2014. This is 'a special procedure for vaccines in the case of a public health emergency when the community may be more willing to tolerate less certainty about the efficacy and safety of products, given the morbidity and/or mortality of the disease and the shortfall of treatment and/or prevention options.' EUAL therefore provides a blueprint for fast-tracking approval of vaccines by affected WHO member states.

In the EU, regulatory changes to fast-track approvals only allow a reduction in the bureaucratic burdens involved in submitting marketing authorisation applications and clinical trial reporting, without any substantive variation to the general requirements of safety and efficacy established under Directive 2001/83/EC. The EMA is offering free scientific advice to sponsors developing COVID-19 therapies or vaccines, it has issued guidance on the implications of COVID-19 for ongoing clinical trials, and it is involved in numerous regional and international COVID-19 related initiatives. Yet the main document outlining European preparedness policy, the Health Threats Decision 2013, does not focus on therapeutic countermeasures

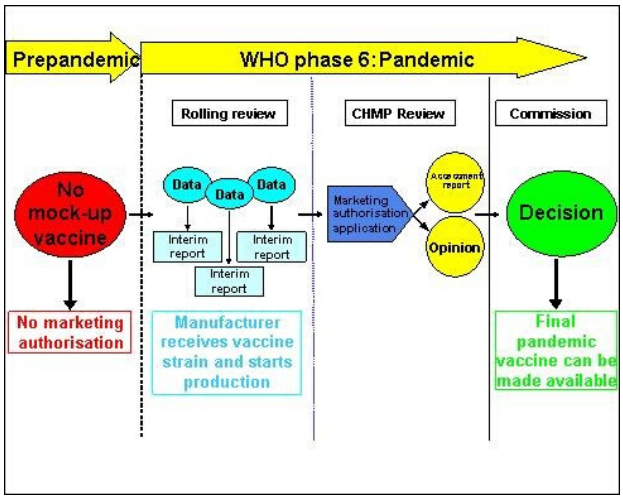
(including vaccination), and prioritises other public health strategies such as coordination of risk communication and early warning mechanisms. This is consistent with the public international level, where the WHO International Health Regulations 2005 (IHR) follow a similar logic, with immunisation strategies largely absent from the core of the pandemic or epidemic response strategy, and confined to more sectoral or ad hoc voluntary instruments such as the EUAL. Indeed, at WHO level, both the Global Action Plan for Influenza (GAP) and the general Global Vaccine Action Plan (GVAP) are more squarely focused on accessibility issues (e.g. combating stockpile shortages or ensuring equitable access) rather than promoting R&D of new vaccines.

The notable exception in the EU is the fast-tracking of vaccines for influenza pandemics or epidemics, for which the EMA has in place two special authorisation procedures. These allow for exceptional and/or conditional approvals of influenza vaccines, either ahead of a pandemic on the basis of strains that may cause violent outbreaks (the 'mock-up' procedure) or in the course of the pandemic, speeding up the pre-approval clinical testing phase (emergency procedure). The two procedures are outlined in the images below:

The 'mock-up procedure'



The 'emergency procedure'

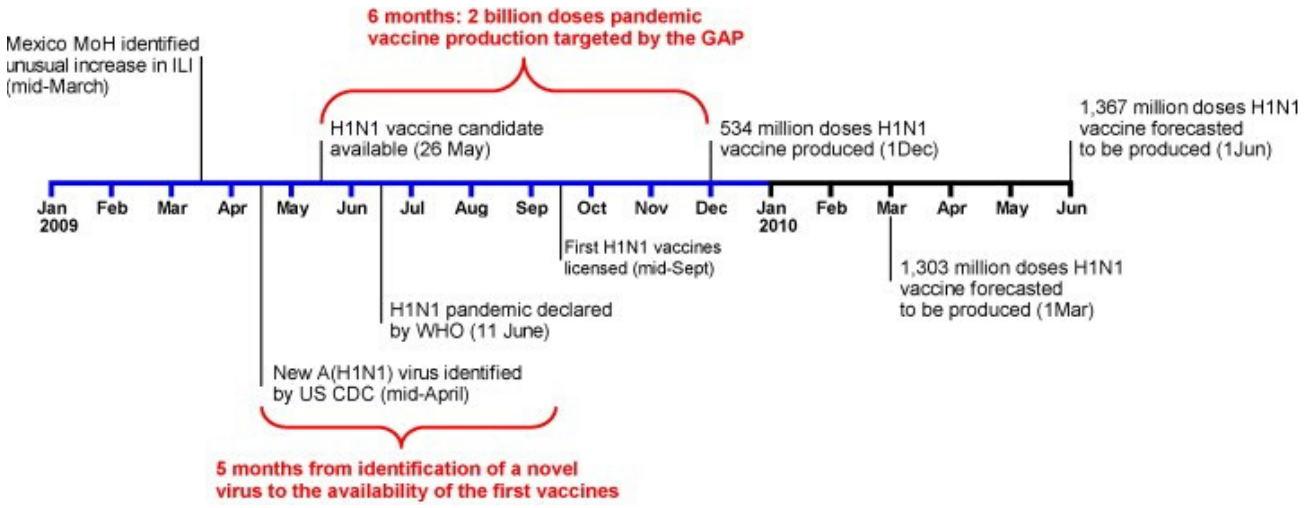


Source: EMA, Authorisation Procedures (accessed May 2020)

Comparing Vaccine R&D Across Outbreaks: A-H1N1 vs Ebola

It is interesting to compare vaccine R&D experiences across the two most significant pandemic or epidemic outbreaks of the past ten years: the A-H1N1 influenza of 2009-2010, and the Ebola outbreak of 2014-2016. This exercise prompts some useful reflections on the future of the regulatory landscape for vaccine R&D, and its incentives and policies.

In the summer of 2009, the WHO declared a state of global pandemic following the outbreak of a new strain of A-N1H1 influenza virus, which became known as 'Swine Flu' due to the fact that it was the result of separate bird and human flu viruses 'recombining' in pigs, then passed on to humans. The outbreak started in Central America, in the State of Veracruz in Mexico, and spread globally. Within months, both the FDA and the EMA had approved a number of monovalent (strain-specific) vaccines for the disease, which were swiftly made available to states for roll-out into the general population. In that context, the approval and rapid distribution of a vaccine constituted the primary public health response. To account for the inherent risks of deploying a fast-tracked vaccine, European Member States included exemption from liability clauses in their procurement contracts with vaccine manufacturers, while the FDA guaranteed immunity under PREP. The image on the next page provides a useful timeline:



Source: J. Partridge et al: Global production of seasonal and pandemic (H1N1) influenza vaccines in 2009–2010 and comparison with previous estimates and global action plan targets (2010) 28(30) Vaccine.

The story of the Ebola outbreak of 2014 was radically different. The first patient was reported in December 2013 in rural Guinea. By July 2014 the disease had spread to the capital cities of Guinea, Liberia and Sierra Leone. In August, the WHO declared the situation in West Africa a Public Health Emergency of International Concern (PHEIC). Most recently, the Democratic Republic of Congo (DRC) declared local Ebola outbreaks, which continue in 2020. The Ebola virus has been known since 1976, when it first caused outbreaks in human populations in Sudan and the DRC. Yet a vaccine received approval from the European Commission only in November 2019, almost six years after patient one was reported in Guinea. A similar pattern is emerging with the Zika virus, which gained global attention in 2015-2016 when an outbreak that started in Brazil spread to several other countries in South and North America. Zika was declared a PHEIC by WHO in February 2016. The virus had been known since as early as 1947, and first identified in humans in Uganda in 1952, but to this day a vaccine is still to be developed.

The stark contrast between the vaccine R&D experience for influenza viruses as opposed to other viruses that cause highly infectious and deadly diseases is due to two fundamental factors. First, the scientific community has been dedicating significant effort to the fight against influenza viruses for over a century, since the 'Spanish Flu' of 1918. This level of accumulated expertise allows for fast reactions to emerging threats such as the 2009 Swine Flu. Other diseases simply have not had the same impact, recurrence and diffusion as influenza. This influences the second factor, which is the market-based nature of pharmaceutical R&D. The scale of the Ebola or Zika threats never reached the critical mass required to prompt R&D investment, even after the 2014 and 2015 outbreaks occurred. There is a structural lack of incentives to invest in potentially pandemic viruses, which is further exacerbated by the absence of dedicated regulatory pathways – the endeavour is simply not worthwhile.

The COVID-19 pandemic could (and arguably should) change this deeply entrenched state of affairs. While the road to a vaccine for this pandemic disease remains uncertain, vaccine R&D for future outbreaks may benefit from a number of lessons that are becoming apparent.

An Opportunity to Rethink the Approach: Public Health over Market-based Model

Three interrelated aspects of vaccine R&D for pandemic and epidemic diseases are manifestly in need of reform.

- The market-based and efficiency-oriented model that underpins vaccine research and manufacturing. The global spread of COVID-19 is a severe indictment to a model that relies heavily on private investments to develop and test new vaccines. COVID-19 is the third outbreak of a coronavirus in a relatively short period of time, following the SARS outbreak of 2002-2003 and the MERS outbreak of 2012. In both cases, the relatively low death tally and the fact that the epidemic died out autonomously prompted vaccine developers to interrupt R&D and relocate funding towards other initiatives. This was, in hindsight, a very poor decision, as a fully developed vaccine for a coronavirus might have proved decisive in accelerating the development of a vaccine for this one. What needs to change is the strategic thinking that underpins vaccine R&D. Short-term profitability of the final product and immediacy of the threat cannot constitute the (sole) drivers for R&D investment. Public health preparedness needs to extend its reach beyond the current health threat management logic to include immunisation. The recent summit hosted by the EU pledging €7.4bn to research on COVID-19 vaccine is encouraging but public investment in immunization preparedness should become structural.

- With sufficient resources dedicated to R&D, regulatory frameworks need to cater for potential pandemic viruses by developing dedicated pathways for vaccine approval. In this sense, it could be fruitful to explore models based on the blueprint of the 'mock-up procedure' designed by the EMA, which is currently limited to potential pandemic influenza strains.

- Finally, as recently observed in *Nature*, currently 'scores of coronavirus vaccines are in competition'. Given the disastrous impact COVID-19 is having on global public health, the world economy and societies, it is worth considering whether, in the face of a global pandemic, a radically alternative model based on cooperation would be more appropriate for the magnitude and urgency of the task at hand.

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