The Path to a More Effective Influenza Vaccine

Vaccines are one of the most cost-effective means to combat infectious diseases, and while most approved vaccines are effective, several existing vaccines, such as influenza vaccines, are in need of innovation to meet the challenges of the world's population

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Today, it is estimated that vaccines save more than 2.5 million lives each year (1). Given the tremendous success of vaccines, it may seem strange that we are facing a controversy regarding their role in modern society. Vaccines are similarly experiencing a decline in the commercial sector with some companies exiting the space and innovation lagging behind. Innovation is critical to realise the full potential of vaccines, but the current system of discovery and development may not be fostering it as well as it could.

Need for Vaccine Innovation

Influenza vaccines provide protection against infection, and importantly, decrease the associated morbidity and mortality. Nevertheless, despite protecting against 7 million illnesses in the 2017-2018 flu season alone, the average effectiveness of influenza vaccines between 2004 and 2017 was only 41%, and in some years the effectiveness dropped to as low as 10% (2-3). Moreover, the vaccine must be taken annually as it is continually updated to keep pace with the constant evolution of the influenza virus. Significant innovation in influenza vaccines has been largely absent despite the FDA approval of three new types of influenza vaccines in the last seven years – one using a recombinant antigen, another based on a mammalian cell culture manufacturing process instead of the traditional egg-based process, and a third that includes an adjuvant to boost the immune response to the vaccine (4-6). Improving the overall effectiveness of influenza vaccines is important for their yearly use as a seasonal vaccine, not only to provide better protection to the population, but also to increase influenza vaccine coverage, which was only 45% for adults during the 2018-2019 flu season in the US (7). Critically, improved influenza vaccines are also needed in response to an influenza pandemic. During an influenza pandemic, the population has little baseline immunity to the circulating influenza virus, and it is expected that two doses of the current vaccine types would be required for adequate protection. The development of more effective influenza vaccines that provide pandemic protection after a single dose could dramatically slow the spread of the infection through the population.

Barriers to Innovation

There are a variety of factors that have stifled innovation in the influenza vaccine space. Currently, the influenza vaccine market in the US and Europe is dominated by four manufacturers with a long history of vaccine production and the global infrastructure to adequately manufacture and distribute the vaccines. This oligopoly makes it difficult for smaller companies to enter the market in the absence of a deal with the established companies. These deals typically require products to be de-risked and in late-stage clinical testing before partnering or acquisition. Additionally, vaccine development is complicated and can command high manufacturing costs (8). As innovation typically occurs in small biotechnology companies where the cost of capital is high, the industry is hesitant to invest in influenza vaccines when the real or perceived return on investment is low. One of the biggest disincentives for innovation in this space is that influenza vaccines are currently sold as a commodity with low and relatively consistent pricing, with little differentiation between the various vaccine products.

Aside from the economic disincentives to influenza vaccine innovation outlined above, the scientific challenge of creating a substantially improved vaccine is formidable. The fundamental problem is overcoming the diversity of

the influenza virus types and subtypes, and the ability of the virus to continually mutate and evade the immune system. Current influenza vaccines are actually a mixture of three or four vaccines, each designed to protect against one type or subtype of the currently circulating influenza viruses. In Europe and the US, a prediction is made between February and March each year as to which influenza strains will predominate during the upcoming flu season, and the components of the influenza vaccine are changed in an attempt to best match the composition of the new vaccine to the anticipated circulating influenza strains. Given the limited cross-reactivity of the current influenza vaccines and the educated guesses that are made each year about which strains will circulate, it should not be surprising that the overall effectiveness of the current influenza vaccines is low. If one also considers the short duration of protection afforded by the currently approved vaccines, which may not last through the entire flu season, the magnitude of the challenge is drawn into focus (9).

A Different Approach

Arguably, there is no shortage in creative approaches towards an improved influenza vaccine that provides better and longer protection, one that either obviates yearly updating or at least minimises the need for it. There are a number of definitions for a universal influenza vaccine, but most include protection against a wide variety of strains over several flu seasons. Most of the work towards a universal vaccine is occurring in a small number of biotech companies and research institutions and some of these new technologies are now just reaching the clinical evaluation stage. While the promise of a universal influenza vaccine is tantalising, the pace of progress has been slow in translating concepts and encouraging preclinical data to clinical results. More importantly, companies and institutions are working more or less in isolation with standalone technologies that ultimately may slow advancement or end in failure. In order to meet the challenge of quickly developing a fundamentally improved influenza vaccine, the traditional pharmaceutical approach of independent product development should be replaced by an international collaborative consortium. This should serve as an honest broker to bring stakeholders and promising technologies together for standardised evaluation under a single, well-organised, and well-funded effort.

Improved and Universal Influenza Vaccines

Influenza viruses come in several related but distinct forms, such that immunity to one form does not confer immunity to the others. To overcome this problem, influenza vaccines are made up of three or four components to cover this diversity. One central problem is that current vaccines must be closely matched to the strains of the various influenza types, and subtle changes in the makeup of a strain often lead to loss of protection. One of the goals of influenza vaccine innovation is to make each component of the vaccine effective against a broader range of strains. An improved influenza vaccine would provide protection against mismatched strains for a year or more. A universal influenza vaccine would guard against all influenza viruses, regardless of type or strain, obviating the need to update the vaccine components each season. With sufficient durability, a universal influenza vaccine could last multiple seasons, or even a lifetime.

Key to this approach would be a consortium that can combine technologies to optimise the attributes of a candidate vaccine. Here, a promising antigen from one company could be delivered using another company's delivery vehicle in a formulation developed by a third company. The success of such a coordinated approach will be dependent on the ability of the consortium to broker the difficult issues of funding, intellectual property rights, territorial rights, and compensation for a successful vaccine. However, without such a key intermediary it will be difficult to recruit the talent and technologies necessary for success. A number of initiatives have already been established or are proposed to address the influenza vaccine problem, including the Bill and Melinda Gates Foundation, the Coalition for Epidemic Preparedness Innovations, the National Institute of Allergy and Infectious Diseases, the Biomedical Advanced Research and Development Authority, and, recently, the Global Funders Consortium for Universal Influenza Vaccine Development and the Collaborative Influenza Vaccine Innovation Center – to name a few.

The growing number of organisations involved in the development of better influenza vaccines is welcome and acknowledges the importance of the problem, but the overall approaches and funding mechanisms remain focused on individual entities and technologies. Significant portions of the funding currently directed to these entity- and technology-specific proposals should be redirected towards a collaborative consortium to support the efforts of that group. Other entities, not typically associated with funding or promoting drug development, could also be solicited for involvement in the collaborative consortium. For example, health insurance companies are keenly aware of the risk that an influenza pandemic represents to their bottom line. The direct costs of influenza-associated illness in the US, including hospitalisations and visits to doctors' offices, were estimated to be $10.4 billion in 2003 and $3.2 billion in 2015. In the 2017-2018 season, one of the worst in over a decade, 15% of the US population got the flu and 79,000 people died of influenza-related illness despite a vaccine effectiveness of 38%, close to the average effectiveness (10). In an influenza pandemic, where the influenza virus suddenly and dramatically changes its coat to something not previously experienced, seasonal vaccine effectiveness is expected to be very low with a commensurately high level of hospitalisations and death. The financial impact on insurance companies could be catastrophic.

Equally important in addressing the issue of better influenza vaccines is providing the necessary incentives to attract the best players and technologies to the fight. Here, there are important roles for governments and non-governmental organisations (NGOs) in addressing the current economics of the influenza vaccine market. While most of the current innovation occurring in the area of influenza vaccines is being fully or partially funded at the governmental or NGO level, the funding initiatives resemble equity investments that place educated guesses on which technologies are likely to succeed, instead of investments in a consortium-driven process to find or create the best vaccine. Governments and NGOs can also play a critical role in promoting innovation by creating new types of rewards for a company's involvement in achieving a breakthrough vaccine. The type of reward would be best tailoredto the interests of the stakeholder and could include manufacturing rights, priority review vouchers, extensions on intellectual property rights, regulatory exclusivity, or support of non-influenza development programmes. There is a successful track record of governments effectively incentivising the industry towards the development of products to meet a specific national need. In the US, the Generating Antibiotic Incentives Now Act of 2012 extends the exclusivity for qualified products by five years over existing exclusivity periods, and by most accounts, the programme has been successful with the number of new antibiotic approvals per year – more than doubling from an average of 0.8 between 2000-2012, compared to 1.8 between 2013-2018 (11). While this programme did not attempt to bring stakeholders and technologies together for a common solution, as proposed here for influenza vaccines, it does demonstrate the ability of governments to incentivise innovation towards a recognised goal.

Another important role governments can play in influenza vaccine innovation is in regulatory science. For a variety of reasons, including an insufficient degree of scientific knowledge, the current regulatory requirements for improved influenza vaccines are not clear, creating a situation where significant investment of resources is required without a clear understanding of exactly what improvements are being sought, how they are to be measured, or how those requirements may change from one regulatory jurisdiction to another. In particular, many of the new vaccine technologies currently being developed do not elicit the same type of immune response on which traditional influenza vaccines are based, creating regulatory uncertainty regarding which measures of immunity are correlated with protection. A better understanding of what data are required to obtain product labelling that differentiates an improved influenza vaccine from those currently approved is also needed so that vaccine developers know how to design their pivotal clinical trials. Lastly, influenza challenge studies, in which volunteers are vaccinated with an influenza vaccine under development and then intentionally infected to gauge the efficacy of the vaccine under controlled conditions, are being used increasingly, and clarity on the role these studies will play in the approval process can also spur innovation.

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