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

Modern technology: The preferred biosecurity strategy?

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During the past decade we have experienced disease outbreaks caused by many emerging viruses, including a variety of influenza viruses with pandemic potential, SARS Coronavirus (CoV), MERS, EBOLA, and most recently the ZIKA virus, to name a few. Our current approach to an effective biosecurity response is clearly inadequate to address the challenge posed by these rapidly emerging infectious agents. Every time a new virus poses a threat, we tend to re-invent the wheel instead of building on proven technology. It is time for a critical "pause" and an evaluation of how we can best deploy available tools to protect ourselves against emerging disease threats.

Vaccines are essential tools for stopping or reducing the impact of a disease or an infection. They are intended to protect healthy populations, but proving they are safe and effective often requires very large human clinical studies. Furthermore, the infecting agent needs to be in active circulation and, depending on its attack rate, the number of subjects required to provide regulatory authorities with convincing evidence of vaccine efficacy can be substantial. For example, if the attack rate for an infectious agent is 5%, 20 times as many subjects would be required for a clinical trial than if the entire population were infected. For this and other reasons, vaccine development is challenging, and it often takes decades to generate the required data using a traditional vaccine development approach. This obviously conflicts with the need for speed, which is essential when dealing with an acute biosecurity threat. Thus we need to rethink our overall strategy for developing vaccines to counter emerging virus diseases. The development of Protein Science's recombinant hemagglutinin (rHA) influenza vaccine (Flublok®) to combat a possible influenza pandemic provides some important lessons for successful vaccine development: speed, safety and scaleability.

Speed: The greatest challenge to manufacturing seasonal influenza vaccines results from the need to adjust their composition each year. The time available to make these adjustments is extremely short, usually no more than a few months. Only a versatile and robust manufacturing process can result in timely delivery of new vaccine antigens.

Safety: Recombinant vaccines do not contain the pathogen or their genetic material and therefore cannot escape from a manufacturing facility and cause disease. Recombinant protein-based vaccines have been safely produced for decades. Their safety when administered to human populations is well established.

Scaleability: Recombinant vaccines do not require the cultivation of (pathogenic) viruses, and thus offer the potential for surge production capacity by utilizing flexible multipurpose manufacturing facilities. Cell culture processes to produce proteins have been scaled to 20,000L and beyond.

The baculovirus-insect cell expression technology (BEST) is an established platform for producing complex proteins. This production platform has been extensively studied for producing viral and parasitic antigens [1]. More recently, it has demonstrated its suitability as a commercial manufacturing technology [2]. Its major advantage is that it is a "Plug and Play" system that uses the same cells and baculovirus backbone into which a protective antigen of interest can be inserted [3]. The BEST production platform does not require the amplification and subsequent inactivation of large quantities of infectious virus, and therefore does not require a high-level biocontainment manufacturing environment. This has a number of clear advantages: manufacturing personnel are not exposed to infectious agents and the escape of live viruses during production is impossible. Moreover, the manufacturing process can be readily introduced into any country with an existing bioreactor capacity, which should enable rapid expansion and availability of locally produced vaccine. For example, in Japan, UNIGEN Inc. built 2 × 21,000-L bioreactor capacity, enough to supply millions of doses of vaccine in a relatively short time. This facility could produce sufficient monovalent bulk rHA protein to manufacture approximately one million doses of a 15 μg rHA-containing influenza vaccine within a 5-day production cycle. For global pandemic vaccine production, 425 million doses of a vaccine containing 10 μg rHA/dose could be produced within one month if 25% of the global bioreactor capacity (or 500,000 L) could be allocated to rHA vaccine production [4]. Furthermore, use of this technology might avoid serious political obstacles for exporting vaccine from manufacturing to non-manufacturing countries as occurred in 1976 when the U.S. prohibited pandemic vaccine export in anticipation of a potential swine flu outbreak. BEST-based manufacturing of an rHA pandemic vaccine might permit the export of large quantities to other countries.

The first evidence for the use of BEST platform for a biosecurity emergency was provided in the late 1990s when an H5N1 influenza virus outbreak in Hong Kong claimed the lives of six out of

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eighteen people infected [5]. This outbreak was especially alarming because the usual egg-based influenza vaccine manufacturing process was incapable of producing an H5N1 vaccine: the highly pathogenic H5N1 virus killed the chick embryos used for ordinary vaccine production. However, the cDNA encoding the hemagglutinin gene of the avian H5N1 virus was used to produce an H5 rHA vaccine. Within a period of six weeks, an H5 rHA antigen was produced and first tested in chickens. Animal tests subsequently confirmed the immunogenicity of this product and, more importantly, showed that it protected chickens from a lethal viral challenge [6]. Unfortunately, following this initial success, it took another 15 years of development and approximately USD 250 million to obtain a FDA license for a seasonal influenza rHA vaccine (Flublok).

Protein Sciences encountered several technical, regulatory and financial challenges on the way to Flublok licensure. Technical challenges were largely due to the need to annually adjust of the vaccine's HA antigen within the limited time available and the fact that BEST manufacturing platform had yet to be accepted for any vaccine destined for human use. Regulatory challenges and the complexity of product licensure increased exponentially with the number of novel elements included in the process. The mechanism of action of the Flublok vaccine is similar to that of the licensed inactivated influenza vaccines; i.e., the induction of antibodies against hemagglutinin. Flublok is also standardized to contain a certain amount of HA using the same potency method that is used for egg-based inactivated influenza vaccines (IIVs). However, as a novel vaccine, Flublok contained three times more hemagglutinin antigen (45 μg instead of 15 μg HA) and was produced using a novel cell substrate The regulatory challenge would have been easier if Protein Sciences had first developed an rHA vaccine with the same antigen content as regularly licensed influenza vaccines and later developed another vaccine with a higher antigen content as an improved variant to serve more vulnerable populations such as the elderly. Finally, Flublok development nearly failed because of difficulty in securing adequate funding. Support from the U.S. Department of Health and Human Services (Biomedical Advanced Research and Development Authority) was essential in providing the funding necessary to complete Flublok's development and obtain FDA approval for use in adults 18 years of age and older.

The development of this rHA vaccine teaches us three important lessons: (1) using a proven platform technology may lead to new ideas and new and potentially better products, but its inherent uncertainty risks delaying product availability; (2) the regulatory process should focus on vaccine safety and evidence of protection in animals, while confirmatory evidence of vaccine effectiveness can be gathered after its introduction into clinical use; and (3) adequate funding must be available for all stages of vaccine development.

A successful strategy for biosecurity should focus on two or three platform technologies that are already used for manufacturing at least one licensed product and that support the simultaneous development of pre-clinical evidence for vaccines against several infectious agents. Furthermore, regulatory review for emergency use should be limited to assessing the safety and efficacy of new protective antigens in defined pre-clinical studies. Adequate funding for vaccine development must be available to support the generation of data to establish vaccine effectiveness during its actual deployment. Finally, it is important to identify an existing infrastructure that can be used for deployment of the vaccine as for example described for seasonal influenza vaccination and pandemic preparedness [7].

The BEST platform serves this purpose because its safety and versatility in both humans and animals have already been demonstrated. We have demonstrated for influenza that it is possible to develop a recombinant seasonal vaccine and the manufacturing process has been scaled to the 21,000 L scale ensuring adequate production capacity for biosecurity purposes. For many of the emerging virus diseases, the protective antigen is already known or can be readily identified through animal studies. Production of a recombinant baculovirus can be completed within 25 days. With limited adjustment to the purification process, it should be feasible to produce within three to four months (instead of decades) a vaccine for an emerging virus disease that could be available for testing and clinical use.

The recent development of a ZIKA vaccine using the BEST platform showed that it is important to secure commitments for a proposed biosecurity strategy from all parties involved. Protein Sciences manufactured a candidate ZIKA vaccine for human use within four months, but its development suffered delays because of a lack of funding and regulatory requirements such as completion of a toxicology study in animals prior to initiating human testing. The Ebola outbreak provided yet another example. Protein Sciences was again able to produce a GP protein vaccine within twelve weeks because some preliminary work had been performed prior to the outbreak. However, in the absence of funding, the promise of this vaccine could not be realized in time to make a difference.

Modern technology can be the preferred biosecurity strategy. The BEST platform used for the manufacturing of a FDA licensed recombinant influenza vaccine meets the essential requirements to be successful as not only development and regulatory risk is reduced for new vaccine candidates but also required production and distribution capacity is in place.

Conflict of interest

Manon Cox is an employee and shareholder of Protein Sciences Corporation, the maker of Flublok.

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