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Vaccines in a hurry

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ABSTRACT

Preparing populations for health threats, including threats from new or re-emerging infectious diseases is recognised as an important public health priority. The development, production and application of emergency vaccinations are the important measures against such threats. Vaccines are cost-effective tools to prevent disease, and emergency vaccines may be the only means to prevent a true disaster for global society in the event of a new pandemic with potential to cause morbidity and mortality comparable to the Spanish flu, the polio epidemics in the 1950s, or the SARS outbreak in 2003 if its spread had not been contained in time. Given the early recognition of a new threat, and given the advances of biotechnology, vaccinology and information systems, it is not an unrealistic goal to have promising prototype vaccine candidates available in a short time span following the identification of a new infectious agent; this is based on the assumption that the emerging infection is followed by natural immunity. However, major bottlenecks for the deployment of emergency vaccine are lack of established systems for fast-track regulatory approval of such candidates and limited international vaccine production capacity. In the present discussion paper, we propose mechanisms to facilitate development of emergency vaccines in Europe by focusing on public–private scientific partnerships, fast-track approval of emergency vaccine by regulatory agencies and proposing incentives for emergency vaccine production in private vaccine companies.

1. Introduction

Although progress in medical science has eradicated one infectious disease (smallpox) and threats from other infections such as polio have been reduced by widespread vaccination, new infectious diseases emerge at historically surprisingly high rates—more than one disease per year. There are several explanations. Globalisation with its correspondingly increased transport of persons, products and animals can rapidly spread new infectious diseases around the world. Furthermore, the condensing of populations with worldwide urbanization and encroachment of humans into new habitats, facilitating close contact with wild animals creates new hazards for transmission of zoonotic infectious agents from animals to man and possibly in the reverse direction, transmitting human pathogens to animals [1,2]. It has been suggested that more than 50% (868/1461) of all new human pathogens in the last century originated from an animal reservoir [3].

There is an international recognition of the importance of emerging infectious disease in an age of changes, as recently underlined by the World Health Organisation: "It would be extremely naïve and complacent to assume that there will not be another disease like AIDS, another Ebola or SARS, sooner or later" [4]. The recent experience with emergence of Chikungunya virus in Italy 2007 underlines these issues. The spread of Chikungunya exemplifies how easily a well-known virus from a subtropical region in Africa is able to shift vector from one mosquito vector (*Aedes aegypti*) to another (*Aedes albopictus*), disseminate to other climatic zones – including Europe – and cause disease in a susceptible population [5]. The adaptation to a new vector can probably be ascribed to a point mutation in the virus, whereas international travel served as the means of introduction of the virus to the competent vector. *A. albopictus* have recently become prominent around the Mediterranean basin from Greece to Spain and other arboviral diseases including Dengue and West Nile virus may use the same vector—possibly causing the next outbreak in Europe. Climate change may boost this development further by expanding the range of vectors and their capacity to spread disease, together with other activities that transfer potential vectors to new areas. *A. albopictus* has extended its distribution to Europe and the Americas as its larvae can be transported in used automobile tyres [6].

Emerging infections have impact not only on the health but also on the economics of the afflicted region. The SARS epidemic was

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estimated to have a direct cost of 80 billion US$ in Asia, and the international community was on the verge of a true disaster of even larger dimensions. This blow could have disrupted health care services, and affected societies and economies for years. It was a fortunate coincidence that SARS was not transmissible before the onset of the patient's signs and symptoms of disease. Hence, the epidemic was contained by traditional measures of disease control such as early case finding, isolation and quarantine. If this had not been the case, the rapid development and use of an emergency vaccine might have been the only feasible measure to prevent further spread.

Over the last century, vaccines have been shown to be one of the most cost-effective ways to prevent and control diseases. In some situations, such as the re-emergence of smallpox or a new influenza pandemic with a severity comparable to the Spanish flu, emergency vaccinations may be the only way to prevent a true disaster for Europe and the global society.

Following the early recognition of a new threat, the current advances in biotechnology, vaccinology (including reverse genetics) and information systems offer us the possibility of developing promising vaccine candidate shortly after the identification of a new infectious agent, under the assumption that this emerging infection is followed by natural immunity. However, additional major bottlenecks for the deployment of emergency vaccines include the lack of established systems for fast-track regulatory approval of such candidates and limited international vaccine production capacity. In the present discussion paper, we address mechanisms to facilitate development of emergency vaccines in Europe by focusing on regulatory aspects and proposing incentives for emergency vaccine production in private vaccine companies.

2. Past experience shows it is possible to develop "vaccines in a hurry"

The control of poliomyelitis by rapid development of a vaccine shows that it can be done. It exemplifies what is possible with a strong governmental commitment, public demand and dedication. It also underlines the importance of government institutions taking the lead and responsibility in vaccine development.

Within only one year – from 1954 to 1955 – double blinded placebo controlled studies were conducted involving 419,000 vaccines and 330,000 controls receiving placebo. These trials proved safety and efficacy, leading to licensing of the vaccine shortly after [7]. The fruit of basic immunology and vaccinology research led to the success of the vaccine and can be condensed into four major discoveries. Firstly, characterization of the poliovirus and the definition of three serotypes leading to a trivalent vaccine [8]. Secondly, pathogenicity: the discovery that poliovirus causes paralysis [9]. Thirdly, proof of principle: confirmation that neutralizing antibodies protect against disease [10] and finally, that virus could be grown in cell cultures for mass vaccine production [11]. The vaccine campaign was a huge success, and was accepted very well by the population, leading to a steep decrease in polio cases in the years immediately following the vaccine's deployment in Europe and USA. Today, polio is eradicated in most parts of the world and remains present only in a few of the poorest countries.

On the other hand, diseases selected for mass vaccination have to be chosen carefully. The attempt to prevent the spread of swine influenza by vaccination, in USA 1976, is a good example of why to think twice before initiating mass vaccination. Influenza specialists were worried that an influenza strain isolated from swine might cross the species barrier and cause a repeat of the Spanish flu pandemic from 1918. Although no human cases were detected, the decision to start mass vaccination was made and more than 45 million people were vaccinated within a few months. However, suspicion that vaccination was increasing the risk of Guillain–Barré Syndrome as a side effect soon stopped the vaccination campaign [12].

Thus, with a strong public commitment and vital basic knowledge about the pathogen, a successful vaccine can be developed within a short timeframe. However, the decision whether to implement a new vaccine needs to be based on solid risk assessment. Potential and unknown hazards associated with the early mass deployment of a new vaccine must be weighed against the risk and nature of the disease.

3. Who and how to develop emergency vaccines in Europe today?

Vaccine development – in particular for emergency vaccines – needs a different business plan than the market-driven approach that underlies the pharmaceutical industry [13]. Private vaccine companies cannot be expected to use resources on improving existing vaccines or developing new vaccine candidates for emerging infectious diseases when there is no current market or if the market is too small or diffuse to be economically feasible. Hence, it is important that governments find mechanisms and funding to ensure the fundamentals for the success of a vaccine, namely basic and applied research in public health institutions and academia.

Furthermore, clear communication is necessary between governments and the vaccine industry on which vaccines need to be developed from a public health perspective. The challenge is to find incentives for the vaccine industry to take part in the development of products that currently do not have a clear market. One solution might be public support to public–private research and development of vaccine candidates in their early preclinical/clinical phases or advance assurances of confirmed purchases of certain volumes of vaccines if they make it to licensure. The European Union has promoted the concept of public–private partnerships, but this concept has not resulted in important changes so far [14]. It is important to find new ways to achieve these aims: it will be too late by the time we suddenly need new vaccines against an emerging epidemic. Public–private partnerships in particular are necessary to secure vaccine production from laboratory bench through pilot plant to mass scale industrial production. Specific contracts between governments and vaccine companies must be in place to secure that private production capacity is available for emergency vaccination production if needed.

4. The need for correlates of immunity and safety

As mentioned, modern biotechnology has opened novel approaches for the development of new vaccines allowing production to be carried out in only a few months under the best circumstances (see Table 1). But obtaining data on clinical efficacy for licensure and regulatory approval will be a major bottleneck for making use of the current technology.

Without some indication of the immune response required for protection, basic efficacy studies will be difficult. Without an animal model, they will be all but impossible. That leaves only the possibility of going to human studies without an indication that the vaccine is effective—a step that is highly unlikely, even in a dire situation. This leads us back to the responsibility of governments and international agencies – including the European Union – for laying the groundwork. The first vaccines for SARS were developed this way, leveraging preclinical work that had already been done on other coronaviruses [15]. Seasonal influenza vaccines are also made this way; working on the assumption that what has proved efficacious in the past against a related virus will prove efficacious in the future

Table 1
A toolbox for the rapid development, production and deployment of an emergency vaccine.

Early recognition of an emerging microbial threat
Identification and characterization of the causative agent
Rapid understanding of natural history, pathogenesis, molecular biology and epidemiology; building on work in related pathogens as well as ongoing clinical, laboratory and epidemiological studies
Identification of potential vaccine candidates
Identification of potential delivery systems and suitable adjuvant to improve immunogenicity and sparing of antigen and dosages
Production at pilot plant level
Development and acceptance of correlates of immunity
Development and acceptance of correlates of safety
Limited trials in animals and humans based on these correlates as outcome measures
Fast-track approval of the vaccines
Enhancing production capacity by public–private partnerships
Based on risk assessment and defined objectives: implementation of emergency vaccination
Post-licensure follow-up of emergency vaccination with data accessible in real-time to medicine- and public health agencies as a surrogate for phase III trials

and ensuring development with advance purchase agreements to establish a market.

Testing novel vaccine candidates also becomes a bottleneck: just any combination of antigen and delivery system may not be effective. Toxicity testing – which is designed to catch only acute problems with a vaccine – can be generally applied to most vaccines. In theory, it may be possible to produce basic safety data even before a complete product is available by testing "mock-up vaccines" in which a placeholder antigen or antigens are used [16]. This would provide information on the safety of the delivery system including adjuvant, which is generally the most reactogenic part of a vaccine. Safety testing of a specific product would still be required, but the reactogenicity of the generic components would already be defined and be one less variable to consider in designing the vaccine. However, efficacy studies require animal models of the infection or the disease and this is both time- and money-intensive. In the absence of a defined animal model, the obvious choice is non-human primates, as the closest match to humans, but even if this is possible (i.e. the pathogen will infect primates and produce disease) it may not be practical. Both primate and non-primate animal research facilities are in short supply. Support of animal facilities is likely to pay dividends when a need arises for rapid assessment of new vaccines. This should be relatively easily put into place, by making it an explicit goal, since it is really only an expansion of existing activities by research supporting agencies. Certainly, in the United States, the biodefense initiative has led to a significant expansion in capacity. But it cannot be put into place on an *ad hoc* basis, nor is it likely that the private sector will become involved—the return on investment in possible emerging diseases is highly uncertain. Such facilities take years to establish and their benefits are primarily in research and public health: therefore bodies involved in research and public health will need to take the initiative.

5. Risks and benefits of clinical trials

Once a potential vaccine has been produced and some evidence for efficacy and safety produced in animals through accepted correlates, the same data needs to be reproduced in humans. The current procedures were designed with safety as the foremost consideration and rapidity is not a characteristic of the process: it can take 8–10 years (occasionally longer) for a new vaccine to pass through clinical trials. Under normal conditions, this is a sensible application of risk/benefit analysis with the emphasis on "First, do no harm". By definition, emerging diseases are not a major health risk—until a significant outbreak occurs. Thus, clinical assessment is built around gradual steps—first screening for major risks (phase I, trials generally conducted in very small groups) then subsequently screening for less frequent risks (phase II, in larger, but still small groups). It is not until phase III studies, which are often large (thousands to tens of thousands), that efficacy data are expected to be produced. And while phase III studies are large, they still occasionally fail to uncover rare risks, which only emerge after hundreds of thousands of people have been vaccinated, for example, intussusception of the bowel after administration of Rotashield, a vaccine to prevent diarrhoea caused by rotavirus infection [17]. Such events are only uncovered during post-licensure pharmacovigilance.

In an epidemic situation, however, the risk/benefit balance changes: if morbidity and mortality due to the pathogen is high, then even a vaccine with significant side effects becomes much more acceptable. It is therefore important to develop procedures for alternative pathways of approval. This should be done in close collaboration with regulatory agencies, and be based on accepted correlates of immunity and safety plus [probably] limited human data.

6. Fast-track approval and licensure of emergency vaccine

6.1. Redesigning the clinical trial process for "fast-track/emergency" application

While it will ultimately be up to governments with WHO guidance under International Health Regulations to decide what constitutes an "emergency" in which it could be invoked, the bare bones of a "fast-track approval" system for new treatments already exists (influenza mock-up vaccines EMEA)[18], and this procedure could be expanded to accelerate vaccine-testing in clinical trials during a public health emergency. In most cases, the greatest amount of time in a clinical trial is devoted to paperwork, to ensure that the trial complies with regulations designed to minimize risk to participants, ensure transparency and provide a paper trail as a shield against future litigation, should things go awry. In diseases with a poor survival chance – aggressive cancers, for example, or anti-retroviral therapy in the early days of the HIV epidemic – regulatory agencies tended to be more forgiving. In such a situation, while safety remains a major issue (particularly for preventive vaccines administered to healthy individuals), testing for efficacy assumes greater importance.The demands for faster processing of vaccines can be addressed by the following steps:

1. An already-defined regulatory framework within which fast-track clinical trials can be conducted. This should contain rules for priority review and approval, some (limited) protection against liability to open the process to commercial entities (as they are best equipped for large scale production and distribution) and rules for invoking such a process. They may not (perhaps should not) lead to open-ended approval of a product, being instead intended to allow limited release.
2. Rapid access for vaccine developers to the appropriate regulatory authorities within the EMEA and authorization for regulators to draw on necessary expertise (perhaps in the form of expert panels) to enable assessments to be made quickly. Regulations on relaxing approval (perhaps in the form of approval for a limited time) for import of vaccines not currently approved for use in Europe.
3. A process whereby approval can be granted under the understanding that the complete necessary paperwork can be submitted retrospectively—enabling a rapid progress of efficacy trials, as soon as initial data suggests a vaccine is safe, without

waiting for collation, submission and approval before progressing to the paperwork for the next step.

4. A broader acceptance of surrogate data, e.g., correlates of protection and safety, in the early steps. If (for example) animal toxicity studies raise no concerns, it may be possible to proceed directly to combine phase I/II studies. This would provide human safety data, but at the cost of placing slightly more participants at risk. The payoff would be earlier access to data indicating whether the vaccine is immunogenic and stimulates the desired type of immune response, plus a more rapid assessment of vaccine safety. Acceptance of immunogenicity data as a surrogate for efficacy, based on animal models (and it is here that expert panels will be crucial) might allow rapid release of a product from phase III trials, subject to the study continuing to collect efficacy data. Such an approach could shorten vaccine-testing time by months to years.
5. Finally, while it is possible to enter phase I trials with an experimental product, phase II has stricter requirements and the product tested needs to be closer to, if not identical with, that which will be taken into phase III trials—which itself will be the final product. Some flexibility on vaccine composition would allow a more rapid progress to phase III.

6.2. Phase III trial design issues

Phase III trials are intended to demonstrate that a product is efficacious. This is never an easy task and for emerging diseases is complicated by the fact that such diseases are, by definition, not endemic. That means that without reliable surrogate markers, efficacy studies can only be done in endemic countries or selected high-risk populations. It can be expected that even in countries where the disease is endemic, people will be reluctant to accept testing of a vaccine for which safety data and approval has been fast-tracked: some form of compensation mechanism is almost certain to be required to encourage manufacturers and the public to participate in a clinical trial. This passes out of the remit of organizations such as EMEA and into that of international cooperation, which needs to be arranged at the governmental level.

The risks of rapidly proceeding into phase III can be ameliorated by compromising (to some extent) impartiality. To avoid bias, such large studies are normally blinded and results assessed at the end of the study. However, in a situation where large numbers of people are being vaccinated with a "fast-tracked" vaccine safety concerns will be higher than normal. By putting enhanced surveillance into place and assessing data from cohorts within the main phase III study, data on adverse events possibly associated with vaccination and efficacy of the vaccine could be collected much faster. Objectivity could be maintained by maintaining blinding with regard to the study monitors. This approach essentially expands the role of the Data Safety Management Board, whose role is normally to oversee the safety of the study and who do review results on an ongoing basis, to cover decision-making on vaccine efficacy. In such a case, they would need to involve the study designers, which may raise issues of conflict of interest. This can be addressed by again involving expert review panels, but that will almost certainly face resistance from commercial developers who would face exposure of their operating procedures. But where there is an overwhelming public interest in rapid assessment of vaccine efficacy, the conventional rules may need to be relaxed and increased transparency is the safest counter to decreased regulatory oversight.

In conclusion, new infectious diseases are emerging at a historically high rate. To secure both public health and economic stability in the future effective countermeasures have to be instituted in advance at governmental levels. Implementing fast-track approval systems for emergency vaccines by the regulatory agencies, and underpinning public private partnerships to enable production in the absence of a market would be an important step in order to be prepared for a new pandemic. Finally, innovative research towards the understanding of vaccine safety and efficacy and leading to shorter development times should be promoted.

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