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EDITORIAL

SARS-CoV-2, from its current highly contagious spreading toward the global development of an effective and safe vaccine: challenges and uncertainties

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1. Introduction

The development of vaccines has come along far since the key contributions involving antiviral therapies and the development of vaccines against various infectious diseases made by Alexandre Mikhailovich Besredka (1870–1940). Besredka was a French biologist and immunologist working at the Pasteur Institute who became famous for the discovery of the 'Besredka's method', a type of vaccination for avoiding anaphylactic shock [1,2].

Today, we are worryingly witnessing the fast and global spreading of a new and highly contagious SARS-CoV-2. Since the first officially reported and confirmed case of infection in China on 8 December 2019, some other reports state that the first case may have occurred on 17 November [3], the virus has so far caused over 6,441,152 million positive cases and contributed to over 380,265 deaths worldwide during the covid-19 pandemic [4].

Inevitably and rationally, the solution to neutralize the virus seems to lead toward the development of a new, effective, long-lasting vaccine, which must also be safe globally and in all ages. Right at this point in time, in my medical opinion there is a fundamental question needed to be addressed: 'Which steps must be followed to produce an effective and safe vaccine? Despite the restrictive measures indicated by the World Health Organization (WHO) and variably adopted by the governments, we remain in the middle of this covid-19 pandemic with some countries still to pass the acute/peak phase and, more importantly, far away in neutralizing this highly life-threatening virus.

The Editorial carefully revisits the major uncertainties and challenges for the common understanding on what it takes for the clinical development of a global, long-lasting, effective and safe vaccine.

2. Focus on challenges and uncertainties to develop a long lasting, effective and safe SARS-CoV-2 vaccine

The conceptual approach of producing a new vaccine is based on the inactivation of the infectious charge of the virus, but by maintaining its antigenic properties. A new vaccine requires a good knowledge of the virus, its mechanism of action, the capacity and power to replicate in human cells. It is scientifically relevant to emphasize that up to now, the knowledge of the new SARS-CoV-2 is continuously unfolding, alongside its ability to mutate in multiple strains as they were recently identified [5].

As covid-19 became pandemic, certainly it is key to remember the need to develop and produce an effective and safe vaccine on a global scale.

The development of a long-lasting, effective and safe vaccine has always been a complex. We must recall that there are still today viral infections (i.e. HIV) where the vaccine hasn't been developed yet. Firstly, it has always been a challenge to achieve full immune protection with a vaccine. The development of current available vaccines has been mostly empirical with poor understanding on how they are able to stimulate the immune system. Effective vaccines induce production of antigen specific antibodies. These antibodies should guarantee an early immune protection. But, the effectiveness of a vaccine is very much linked to the quality of such antibodies (e.g., their avidity, specificity, or neutralizing capacity of the virus). These are identified as determining factors of the efficacy of any vaccine [6]. Effective vaccines need also to provide long-term immune protection. In this regard, persistence of vaccine generated antibodies above the 'protective threshold' is necessary. This should be achieved via induction and maintenance of those 'immune-defined memory cells' capable to promptly and effectively reactivate after any subsequent microbial exposure [7]. It is still unknown whether the SARS-CoV-2 infection will provide lasting immunity or will reoccur at any time [8]. Another critical challenge links to the maintenance of effectiveness of the new vaccine against new sequential waves of the virus in view of multiple mutations and viral strains. The risk of viral escape through mutations still remains to be determined. This is a significant challenge, which merits close attention through continuous monitoring of all new developing mutations.

Critically, the most worrisome and clinically relevant challenge pertains to the safety of the vaccine. This will have to be thoroughly and robustly demonstrated in the short, medium and long run. Any vaccination that is currently being developed for neutralizing this SARS-CoV-2, must be safe for the elderly, for the younger generation, for all the working population and for those who are more vulnerable, including people at risk who have already developed a compromised immune system condition [9].

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The development of a new vaccine has already started globally by several public and private research pharmaceutical and biotechnology organizations. There is an increasingly and worryingly disseminated information that the vaccine might be developed expeditely [10]. Hopefully, biotechnologies can play a crucial role in accelerating the process of developing a new vaccine. We must emphasize that this result can only be achieved through a global, harmonized and coordinated effort from all involved stakeholders and is based on a comprehensive clinical development plan. The plan also includes the identification and use of vaccine adjuvants to enhance the speed and strength of the immune responses to vaccination. The overall strategy management plan must account for global manufacturing capabilities to make sure the pandemic vaccine can be finally provided to everyone.

Historically, this path includes some basic preclinical research followed by a well-controlled, randomized clinical trials program (phase 1, 2 and 3) and then by a post-approval observational safety surveillance phase. The whole process often lasts 10–15 years [11]. Due to the gravity and speed of spreading of covid-19, understandably, the clinical development of a new vaccine should be expedited, but hopefully without missing any of the crucial steps of preclinical research and human clinical development [12]. Potential vaccines should be tested in animals first to rule out disease enhancement, before trials move on to humans. The clinical development of an effective and safe vaccine begins with healthy volunteer subjects (phase 1). This is firstly carried out in adults; then the development gradually steps down to younger subjects to assess the pharmacological targets. Phase 1 is crucial to understand from start the safety of the candidate vaccine and to determine the type and extent of the immune response that the vaccine may provoke. After phase 1, a dose-response clinical study follows in few hundreds subjects (phase 2). Sequentially, a confirmatory and global clinical investigation comes into place on a larger population (phase 3). Finally, if the vaccine is approved, the clinical development will enter a surveillance period, which allows to keep a close effectiveness/safety monitoring of the vaccine on a wider and global scale.

The illusion of fully developing an effective and safe vaccine in a very short timeframe, is a dangerous message to disseminate. This creates false expectations in people, future uncertainties and, more importantly, will carry inevitable risks due to limited information available at the time of approval. The whole process must take its necessary time, as for any other clinical development plan conducted with other vaccines and antibiotics in the past. Since the SARS-CoV-2 outburst, multiple worldwide phase 1, 2 and 3 clinical studies for covid-19 vaccines have been so far identified. These studies are currently running, some are recruiting, whilst others are not recruiting yet (Table 1) [13].

Table 1. (*https://clinicaltrials.gov/ct2/results/details?term=covid+19+vaccines*). 101 studies found for: '**covid 19 vaccines**'. Accessed on 27 May 2020.

Terms and Synonyms searched	Search Results*	Entire Database**
covid 19 vaccines:	3 studies	3 studies
covid 19:	**101 studies**	1,808 studies
SARS-CoV-2	72 studies	904 studies
severe acute respiratory syndrome coronavirus 2	6 studies	141 studies
2019-nCoV	4 studies	74 studies
2019 novel coronavirus	2 studies	38 studies
Wuhan coronavirus	–	4 studies
Vaccines:	**101 studies**	9,232 studies
Vaccination	37 studies	5,638 studies
Immunization	14 studies	1,959 studies
VACCIN	1 study	36 studies
inoculations	–	228 studies
Covid:	**101 studies**	1,814 studies
SARS-CoV-2	72 studies	904 studies
severe acute respiratory syndrome coronavirus 2	6 studies	141 studies
2019-nCoV	4 studies	74 studies
2019 novel coronavirus	2 studies	38 studies
Wuhan coronavirus	–	4 studies

–No studies found
*Number of studies in the search results containing the term or synonym
**Number of studies in the entire database containing the term or synonym

3. Expert opinion

So far, several global vaccines have been successfully developed. But over time, their development did also generate controversies, mostly of ethical nature [14]. It takes years to develop and to license a new long-lasting effective and safe vaccine. The whole process requires the accomplishment of rigorous clinical assessments and regulatory standards. It involves many scientific public and private parties and disciplines, including governments and political stakeholders, all with different priorities and economic interest.

The most responsible clinical advice to give is to make sure this SARS-CoV-2 vaccine is/remains effective and safe for the global population and will not harm by causing serious medical complications ten/+ years or earlier down the line. The message to deliver is the need to take the adequate time, not to rush in the development of the vaccine, which, if not investigated comprehensively and progressively (preclinical-phase1-phase2-phase3, post-approval safety surveillance phase), could end up in harming more people than the virus itself in the years to come. The SARS-CoV-2 vaccine/s will have to be part of a continuous monitoring plan with clear understanding, ongoing calibration and continuous risk assessment of its overall risk/benefit profile. It is reassuring to point out that WHO works closely with national authorities to ensure that global standards are developed and made readily available to assess the quality, safety and immunogenicity of biological products including vaccines [15].

Vaccine development is a well-designed and structured process, which involves combined public and private collaborative efforts and research. This should not be conceived as a business profit activity, but needs to be designed and managed through a fully comprehensive development plan, which encompasses the thorough investigation of the efficacy and safety of the vaccine globally. Unless we adhere to the safety rules of the standardized and harmonized guidelines and procedures of conducting and monitoring clinical studies, an accelerated and worryingly incomplete clinical development plan will ultimately create in years to come more suffering for people and a heavier burden on the NHS globally than the damage caused by this SARS-CoV-2 itself. The challenges and uncertainties related to this vaccine, inevitably remind all clinical developers of the primary focus on vaccine safety and highlight the importance in the 21st century of designing robustly scientific studies to make adequate conclusions on the

safety of the vaccine at global level [16]. This includes the pre and post-licensing safety assessments and the generation of surveillance data from multiple sources and epidemiological settings [17,18].

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Reviewer disclosures

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