EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 2
34-37
Year: 2021

THE ANTICIPATED COVID-19 VACCINE WILL KEEP THE WORLD PHARMACOVIGILANCE SYSTEMS VERY BUSY

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Article Received on 02/12/2020 **Article Revised on 22/12/2020** **Article Accepted on 12/01/2021**

ABSTRACT
Coronavirus Disease 2019 (COVID-19) pandemic demands the development of a suitable vaccine accordingly; pharmaceutical companies ubiquitously spare no effort to achieve the hopeful vaccine in the near future. The novel vaccine may possess risks of adverse drug reactions (ADRs) which may be over looked during the crushed time of development and testing. Therefore, this article discusses the problems which the partakers particularly, pediatric populations may suffer from the expected vaccine. This in turn puts a lot of pressure on the pharmacovigilance systems everywhere. Moreover, Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) is regarded as one of the RNA viruses that exhibit high extent of genetic mutations so that the anticipated vaccine may not keep its effectiveness along with theses mutations and it may need revaccination every year. Furthermore, future COVID-19 vaccine may confront general challenges like any new vaccine under progress such as the cost of the final product and its ability to provide appropriate protection. Therefore, continuous post-marketing surveillance globally should ensure the efficacy, safety and stability of any forthcoming vaccines.

KEYWORDS: COVID-19, vaccine, ADRs, Pharmacovigilance.

KEYPOINTS: The imminent COVID-19 vaccine could carry risks for humans and cause negative consequences. Pharmacovigilance systems worldwide duties to guarantee the safety and efficacy of the projected vaccine.

1 INTRODUCTION
On 30 January 2020, the World Health Organization (WHO) announced an outbreak of a novel coronavirus not previously seen in humans. This plaque was accompanied by a pandemic declaration on 11 March 2020. SARS-CoV-2 is the responsible virus for COVID-19.[1] This virus is swiftly spreading over more than 210 nations all over the world.[2] Globally, it has infected 17 millions of patients and killed about 700,000 as of July 2020.[3] Currently, SARS-CoV-2 infection is generally managed by medications that have shown antiviral activity in earlier clinical studies like Arbidol, Chloroquine, Favipiravir, Lopinavir/Ritonavir, Remdesivir and Ribavirin. However, these medications require additional researches to confirm their safety and effectiveness. A thoughtful approval of these medications without more investigations should be practiced.[4] Numerous pharmaceutical industries agencies in association with several academic institutes and governmental organizations have begun studying novel treatments and repurposing official medications in order to get fast and reasonably priced treatments for this infection. The World Health Organization (WHO) would support clinical studies for repurposing some medications that require further investigations for the evaluation of their safety and effectiveness against SARS-CoV-2 infection, particularly, in reducing death rate and hospital stay.[5] Extensive horror, disturbances and complications due to the COVID-19 necessitate the development of a vaccine for this contagious infectious disease.[3] Pharmaceutical companies all over the world have great efforts to develop a hopeful vaccine against SARS-CoV-2 like; CanSino Biologics, Moderna Therapeutics, Inovio, Arcturus Therapeutics, BioNTech, Pfizer, GlaxoSmithKline (GSK), Sanofi, Curevac and Johnson & Johnson.[5] This apparent necessity for a vaccine puts great pressure to skip steps or accept certain compromises through the process of vaccine development.[3,6] These novel vaccines against COVID-19 may entail risks for humans consequently; pharmacovigilance systems everywhere should make every effort to ensure the safety, efficacy and all aspects of rational use of these expected vaccines. This current opinion communication discusses the reasons why new COVID-19 vaccines carry a lot of risks to humans in ours points of view. It sheds light on the expected great role of pharmacovigilance systems universally.

2 The length of vaccines development

The development of an innovative vaccine is a result of great efforts which involves several steps. Through all developmental steps, the main concern is the safety of this novel product, which could be used in human including young children. The primary researches take from one year to about few years then they are followed by pre-clinical and clinical studies, which can extend to about twenty years before the product approval. The objective of the clinical studies is to determine vaccine safety, efficacy and immunogenicity. Before marketing, new vaccines are assessed clinically through three phases. Phase 1 studies are planned to evaluate vaccines safety and immunogenicity. These studies involve from twenty to eighty adult volunteers. Phase 2 studies may involve from one hundred to three hundreds contributors. From the outcomes of these studies additional data about safety and immunogenicity as well as information on the doses and schedule that will be used in the large scale phase 3 studies. These studies evaluate the efficacy and provide further judgment of safety. Phase 3 studies include thousands of participants and occasionally tens of thousands when they are aimed to assess uncommon adverse reactions.[7] For instances, the studies to innovate rational vaccines like hepatitis B, rotavirus, human papillomavirus (HPV) vaccines have taken several years[6,8-10]. Furthermore, the safety of the vaccine should be considered for identifying ADRs as febrile seizures and anaphylaxis that were associated with the measles, mumps, rubella, varicella.[11,12] and rabies vaccines[13] as well as HPV vaccine is linked to headache, lightheadedness, and syncope.[11] Besides Bacillus Calmette–Guerin (BCG) vaccine rare ADRs that could be presented in 1-10% of people receiving the vaccine. These reactions are frequently seen as mild local reactions such as abscesses, ulceration, injection site reactions and lymphadenitis. Severe rare ADRs could also happen, generally in immunocompromised patients.[14] *Based on that, the expended time for developing the recent COVID-19 vaccines may not be long enough to ensure both the safety and efficacy of the innovated vaccines.*

3 Pediatric patient safety is of utmost importance

Pediatric population are vulnerable and at high risk for ADRs[15]. Such as the neurological ADRs associated with the whole-cell pertussis (wP) vaccine that led to vaccine suspension in several countries all over the world in the period from 1970s to 1980s.[16] As well as, intussusception as an ADR that caused the withdrawal of the first rotavirus vaccine to be approved in the US. (Rotashield®).[17] *Therefore, the pediatric patients' safety is regarded as a great challenge for the upcoming COVID-19 vaccine.*

4 SARS-CoV-2 genetic mutations

4.1 The difficulty of the anticipated vaccines in keeping their efficacy

RNA viruses exhibit obvious high degree of mutations that form genetically diverse populations due to the absence of proofreading property of RNA polymerases. The lack of these enzymes activities leads to mistaking or error-prone replication. As well as RNA viral mutations make these viruses extremely adaptive to changes in the surrounding environment and provide a great apparent viral evolution over a short period of time.[18-21] For example, the known RNA virus, human immunodeficiency virus (HIV) shows pronounced mutations equivocate the immune system, resist various antiviral strategies and hinder vaccine development.[21,22] In addition, influenza, RNA virus, mutations develop various genetic mutants that generate antiviral resistance and necessitate the annual update of influenza vaccines.[18]

Therefore, it is not a surprise to observe the genomic variations and mutations all over the world of the RNA virus, SARS-CoV-2.[23,24] *Thus, it is a great challenge for antiviral agents and vaccines to keep its effectiveness along with SARS-Co-V-2 genomic mutations. Consequently, any upcoming vaccine effectiveness (VE) should be investigated regularly.*

4.2 The need for annual revaccination

Regarding Tetanus and Diphtheria vaccination, some researches showed that long-lasting levels of protective antitoxin immunity commonly present in the vaccine. This immunity may last for more than 10 years.[25] On the other hand, the seasonal-RNA influenza virus vaccine requires annual revaccination so, annual researches for ensuring (VE) are conducted.[26] *Consequently, any forthcoming SARS-CoV-2 vaccine may face this obstacle and need a yearly revaccination.*

5 Challenges facing the expected SARS-CoV-2 vaccines

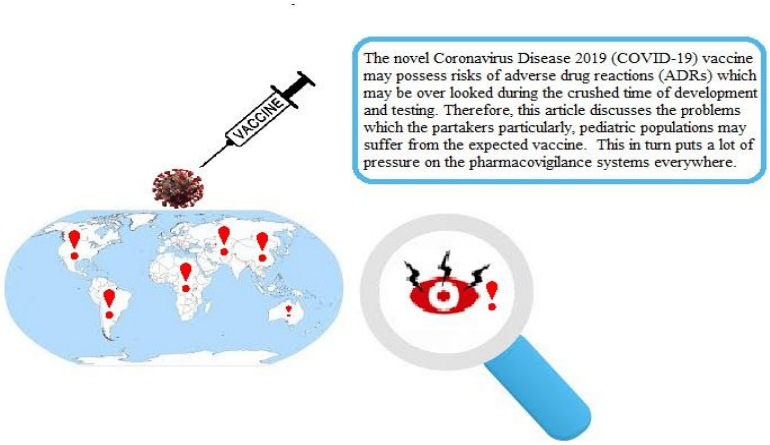
The challenges confronted during vaccines developments include the cost of the final product and the ability of the new vaccines to reproduce suitably intrinsic antigens (Ags). Theses Ags should be adequate in strength and quality to enhance the immune system response for proficient protection.[27,28] The initial cost of the development of the vaccine should be kept in mind since it will affect the price of the final product. For example, the original cost of the recombinant hepatitis B vaccine was approximately $150 of its three-dose series for adults, which was expensive to public.[29] Moreover, a poor response of the immune system to vaccines is not a rare condition such as the low response to influenza vaccine seen in elderly population.[30] *Accordingly, COVID-19 vaccine is expected to face pronounced challenges of high cost and low response in elderly.*

6 The roles of pharmacovigilance systems

SARS-CoV-2 vaccines are being rushed to be developed. However, vaccines development take generally about more than 10 years with the exception of the mumps vaccine innovation that extended for 4 years.[6] Consequently, the role of pharmacovigilance is to ensure the safety and efficacy through post-marketing

researches that are able to detect uncommon ADRs, evaluate the extent of vaccine-induced immunity and guarantee novel vaccine effectiveness.[6,7]

Furthermore, through this continuous surveillance, the vaccine as a new product will be investigated well for its stability.[7] In the meantime, developing countries, where the proper tools for pharmacovigilance may not exist, should act with the well developed countries to ensure the rational use of the novel vaccines.[6] Subsequently, pharmacovigilance systems should identify as possible every ADR and/or event that relates to novel vaccines. *These surveillance systems should detect these negative effects early for ensuring precise evaluations of risks and suitable responses to new vaccines problems.*



7 CONCLUSION

SARS-CoV-2 is hastily spreading all over the world, leading to millions of infections and thousands of deaths. This necessitates the development of a vaccine against this plaque. Big pharmaceutical industries all over the globe are making their best to get the COVID-19 vaccine in a short timeline for saving lives of susceptible populations to SARS-CoV-2 infection. This noble work however, in rushing the development ng the hopeful vaccine quickly could carry excessive risks. The fast development phases could not guarantee the satisfactory safety and effectiveness as generally vaccine development takes about several years. The safety is an essential concern particularly in pediatric population who are at risk of ADRs that may trigger an early vaccine withdrawal from the market. Moreover, the new vaccine may require annual revaccination as well as the VE possibly will need continuous testing due to the unceasing genomic mutations of SARS-CoV-2 that regarded as one of RNA viruses. Besides, this vaccine could face the general challenges for any vaccine after development such as the cost of the product and its ability to warrant appropriate protection. Consequently, a heavy burden will be on pharmacovigilance systems universally in order to monitor the vaccines safety, efficacy and product stability through continuous post-marketing surveillance.

8 Declarations

8.1 Funding

The authors received no financial support for this research, authorship, and/or publication of this article.

8.2 Conflicts of interest/Competing interests

The authors declare that they have no conflict of interest with this work.

8.3 Ethics approval

Not applicable

8.4 Consent to participate

Not applicable

8.5 Consent for publication

Not applicable

8.6 Availability of data and material

The authors confirm that all relevant data are included in the article.

8.7 Authors' contributions

The two authors participate in drafting the article then the article revised critically twice by Mohammed G. Maslub for the first time then by Mahasen A. Radwan for the second time

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