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Adverse Events Following Immunization with SARS-CoV-2 Vaccines and its Reporting in India: A Growing Concern

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Abstract

The COVID-19 pandemic has led to many drug delivery systems and vaccine developments globally. Implementation of immunization programs has been done through emergency approvals and has also raised concerns regarding side effects and adverse events following immunization. The side effects are fever, injection site pain, arthralgia, redness, swelling, induration, pruritus, myalgia, induration, chills, headache, vomiting, and fatigue. The adverse events are anaphylaxis, thrombotic thrombocytopenic purpura, intracranial venous sinus thrombosis, Guillain–Barre syndrome, seizures, Steven–Johnson Syndrome, pulmonary embolism, acute myocardial infarction, myocarditis, and pericarditis associated with different vaccines. The factsheet of many vaccines does not convey sufficient details to alert the beneficiaries. These need to be updated timely and beneficiaries need to be made aware of the same. In some countries, authorized portals have captured these data on a real time basis. Similar portals need to be in place in India also so that data generated can be used for further timely recognition, reporting, and management of AEFI. The reporting of the same should be made mandatory for all and guidance should be provided regarding levels of management, home based, or hospital based.

Keywords: Adverse events, COVID-19, Humans, Immunization, Side effect, vaccines

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Introduction

COVID-19 caused by the novel coronavirus, SARS-COV-2, has created havoc and captured the attention of entire communities globally.[1] It was first reported in Wuhan, China, in December 2019. The World Health Organization gave an official declaration of a pandemic in the succeeding New Year and India too, ushered in the first case in the same timeline. Till October 26, 2021, 243,857,028 persons have been confirmed to be suffering from COVID-19 and 4,953,246 deaths have taken place, in spite of administration of 6,697,607,393 vaccine doses. This is in sharp contrast to May 2021 figures in which 168,599,045 persons were confirmed cases of and 3,507,477 died of the aforesaid disease.[2]

With an incubation period of 2 weeks, most of the patients start presenting with symptoms at the 11th day. In more than 50% of the affected persons, the presenting symptoms are headache, fever, dry cough, and fatigue. Less common symptoms present in less than 50% of infected persons and these are ageusia, anosmia, stuffy nose, Madras eye, and raw throat. Dyspnea, anorexia, lack of clarity, continuous discomfort in the chest, and fever are present as severity of the disease increases. Symptoms which are infrequent are feeling of agitation, disorientation, panic, despondency, and insomnolence. Neurological sequelae can occur sometimes, such as cerebrovascular accident, encephalitis, and neuropathy.

Two rare syndromes associated with COVID-19 infection have also been reported, that is, multisystem inflammatory syndrome – children and multisystem inflammatory syndrome – adults.[3]

The SARS-CoV-2 RNA is present in the upper and lower respiratory tract from where samples are collected for diagnosis by RT-PCR. Presence and mere detection are not an indication of viral transmission. The virus can be transmitted 3 days before and maximum 10 days after symptoms appear, in a person whose immune system is robust.

The treatment modalities include supportive measures such as oxygenation and fluid management and therapeutic interventions. The latter has been subject to dynamic changes till date, including convalescent plasma therapy, remdesivir, hydroxychloroquine with or without azithromycin, lopinavir, ritonavir and other antiviral agents, thromboprophylaxis and fibrinolysis, antifibrotic therapy, interleukin-6 receptor antagonists and complement antagonists, monoclonal antibodies, nonsteroidal anti-inflammatory drugs, systemic corticosteroids, bronchodilators/vasodilators, and mechanical ventilation/high nasal flow/extracorporeal membrane oxygenation.[4] All of the above therapeutic modalities are based on clinical trials and provide symptomatic relief and none have been proved to cure the disease. Hence, the need for developing immunity against coronavirus was realized, which led to the fast track process of vaccine development across the globe.

Different strategies have been used to develop vaccines against SARS-CoV-2 such as m-RNA-based vaccines, DNA based, protein based, inactive or live-attenuated virus, virus like particles, or viral vectors.[5] Of these, seven vaccines have been approved for use in India, the non-replicating viral vector Oxford/AstraZeneca AZD1222, Gamaleya SPUTNIK V, Serum Institute of India's COVISHIELD, DNA vaccine Zydus Cadila ZyCoV-D, RNA vaccine Moderna mRNA-1273, non-replicating viral vector Janssen, Ad26.

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COV2.S, and Bharat Biotech's COVAXIN having the inactivated virus.[6] As of June 1, 2021, around 213,723,425 vaccine doses have been administered in India.

There have been several side effects and adverse events following administration of SARS-CoV-2 vaccines. This article aims to review AEFI with SARS-CoV-2 vaccines and suggests ways to address this issue.

Virology

Morphology

An RNA virus, SARS-CoV-2 belongs to the genus *Coronavirus* and family *Coronaviridae*. It has 16 non-structural proteins (nsps), many accessory and structural proteins of which four prominent ones are spike surface glycoprotein (S), membrane (M), nucleocapsid protein (N), and envelope (E). The S protein is required for attaching to the ACE 2 receptor present on the cell and facilitating entry of the virus into the cell. Morphogenesis of the virus is carried out by M and E proteins.[7]

Pathogenesis

Virus-induced cytopathic effects are seen in patients infected with SARS-CoV-2 with signs of acute respiratory distress syndrome in lung cells such as prominent desquamation of pneumocytes and formation of hyaline membrane, cellular fibromyxoid exudates, interstitial mononuclear patchy inflammatory infiltrates dominated by lymphocytes, significant reduction of CD4 and CD8 T-cell counts, and multinucleated syncytial cells with atypical enlarged pneumocytes in intra-alveolar spaces.[7]

Mutation in SARS-CoV-2

In the course of the pandemic, mutations have occurred in the SARS-CoV-2 virus leading to genetic variations in the population of circulating viral strains. Such mutations have resulted in the virus escaping the host's immune response, altering its infectivity and severity of disease. The amino acid substitution, D 614G, within the receptor-binding motif (RBM) in SARS-CoV-2, resulted in emergence of N439K in Scotland in March 2020. This was designated B.1.141 in the Pango nomenclature system.

SARS-CoV-2 variants with S protein D 614G mutations enter ACE 2 expressing cells more efficiently and increase infectivity by assembling more functional S protein into the virion. Furthermore, during its movement from bats to humans, the virus got a furin cleavage site and managed to cleave into the host cells.[8]

SARS-CoV-2 Vaccines: Types

Vaccines for SARS-CoV-2 have been developed using different technologies. Viral vaccines use the virus itself in a weakened or inactivated form. Viral vector vaccines are developed using genetically engineered viruses in a weakened form to produce coronavirus proteins in the body. Both replicating and non-replicating viral vectors have been used to develop SARS-CoV-2 vaccines. Nucleic acid vaccines, DNA and RNA based, when inserted into the host, produce an immune response by developing copies of viral protein. Protein-based vaccines use viral protein fragments or protein shells to develop immune response.[9]

SARS-CoV-2 Vaccines: Implementation

Russia gave regulatory approval to Sputnik V on August 12, 2020, becoming the first country in the world to register a COVID-19 vaccine for use. However, it raised international concerns as Phase III trials were yet to be completed.[10] The Comirnaty COVID-19 mRNA vaccine was given emergency approval for use on December 31, 2020, making Pfizer/BioNTech vaccine the first to receive emergency validation. The Strategic Advisory Group of Experts on Immunization (SAGE) formulated vaccine-related policies and recommendations for use of Astrazeneca-SKBio, Serum Institute of India, AstraZeneca EU, Janssen, Moderna, and Sinopharm vaccines worldwide.[11] COVAXIN has been included in the emergency use list (EUL) of the WHO on November 3, 2021. It can now be used in all the age groups above 18 years and shall be recognized by other countries without any requisite for quarantine.[12]

Multiple layers of vaccine implementation were prioritizing populations, allocation, distribution, administration, safety, effectiveness, uptake, and second dose.[13,14]

Operational guidelines for the administration of the vaccine in India were established by the Ministry of Health and Family Welfare on December 28, 2020. A digital platform, COVID-19 vaccine intelligence network (Co-WIN), was established in January 2021 to track enlisted beneficiaries for vaccination and COVID-19 vaccines on a real-time basis. With the concerted efforts and deliberations of National Expert Group on Vaccine Administration for COVID (NEGVAC), Drug Controller General of India (DCGI), and various manufacturing companies, India began its vaccination program on January 16, 2021, with 3006 vaccination centers. In the first phase, health-care personnel and frontline workers were administered the vaccine. In the second phase, the prioritized population were adults above 60 years of age and between 45 and 60 years of age with comorbidities. On April 1, 2021, vaccination was available to all individuals above 45 years of age. On April 12, 2021, the DCGI approved Russia's Sputnik V vaccine for emergency use in India. On April 19, 2021, announcement for the next phase of the vaccine program was given as May 1, 2021, extending the eligibility to all residents over the age of eighteen.[15]

SARS-CoV-2 Immunization

Immunization is the process of administering a vaccine to a person to provide protection from certain diseases.[16] Antibodies are formed in response to the vaccine which helps in developing immunity.[17] This pandemic has been challenging and has usurped the world's health and economy. Scientists and doctors across the globe realized vaccination as the need of the hour, as the virus spread rapidly through aerosols, causing severe damage to the lungs and going on further to cause a multisystem damage. The Delta variant strain in India has been associated with severe morbidity and mortality in the second wave in India in April 2021. To prevent this from happening again in the near future, at least 69.6–90% herd immunity has to be achieved through immunization.[18,19] With the advent of the third wave in many countries such as Spain, France, and Germany, it was most likely expected to be in India in November–December 2021.[19,20] The core competencies of any vaccine, that is, efficacy and safety need to be in place. Although all vaccines are approved for use only after completing clinical trials in which it is established to be safe and effective, no vaccine is completely risk free and adverse events occur occasionally after immunization.

Advantages of Immunization

SARS-CoV-2 vaccines provide immunity to the person receiving it and also help in building herd immunity. There are chances of breakthrough infection in vaccinated people also. The severity depends on the humoral response mounted by the person. Getting vaccinated reduces the chance of hospitalization as well as the requirement of supplemental oxygen, with more chances of recovery at home. This, in turn, reduces the chances of health care-associated infections.

AEFI

Immunization can be followed by any untoward medical event known as an AEFI. This may not be associated directly with the vaccine. It may present in the form of a symptom or test parameter. These can be due to vaccine product, quality defect related, immunization error, anxiety-related reactions, or coincidental events.[21]

1. AEFI of mRNA vaccines: The mRNA vaccines have more side effects such as fever, pain, arthralgia, petechiae, itching, ache in the muscles, induration, chills, headache, puking, and tiredness compared to other types of vaccines. These have been captured by the Adverse Event Reporting System of the Centre for Disease Control and Food and Drug Administration, USA. In m-RNA-based vaccines such as Pfizer and Moderna, excipients such as egg protein, formaldehyde, gelatin, neomycin, thimerosal, polyethylene glycol (PEG), Polysorbate, and PEG-related products have been known to cause adverse reactions.[22]. Some cases of myocarditis and pericarditis have been observed in young adults following the administration of mRNA vaccines such as the Pfizer and Moderna vaccine.[23] Anaphylaxis associated with Pfizer COVID-19 mRNA vaccine is 10 times higher than other vaccines.[24]
2. AEFI of viral vectored vaccines: Adenovirus vectored vaccines such as Johnson and Johnson are associated with higher rates of diarrhea and arthralgia.[25]
3. AEFI of vaccines with or without adjuvants: Based on adjuvants in COVID-19 vaccines, those with alum adjuvant had lower systemic side effects than other adjuvants or vaccines without adjuvant.[25] There are two main potential allergenic/immunogenic excipients in COVID 19 vaccines.
    i. Polyethylene glycol (PEG): Also known as macrogol, is a component of various laxatives and injectable formulations such as Depo steroids.
    ii. Polysorbate 80: This is a component of many medical products, cream, ointments, lotions, and tablets.[26]

Following immunization, if an AEFI leads to death, in-patient hospitalization, prolongs existing hospitalization, leads to persistent or significant disability, or results in congenital anomaly/birth defect, then it is to be considered as a serious event. The regulatory reporting portals should report these serious events, as these indicate patient/event outcome or action criteria.

4. AEFI of inactivated viral vaccines: Thrombotic thrombocytopenic purpura and intracranial venous sinus thrombosis have been reported following the administration of Oxford AstraZeneca vaccine, known as COVISHIELD in India.[27] Eleven cases of Guillain–Barre syndrome have been reported following the administration of Oxford's AstraZeneca vaccine out of which four cases have been reported in the United Kingdom and seven cases in Kerala.[28] Out of 3656 cases of health-care personnel in Kerala, 20 developed seizures after administration of the first dose of COVISHIELD.[29] A rare case of Steven–Johnson syndrome due to cell-mediated hypersensitivity has been reported as recently as in July 2021, at AIIMS, New Delhi, 3 days after the first dose of COVID-19 vaccination.[30] Few unusual cardiovascular events such as pulmonary embolism and acute myocardial infarction have been reported following SARS-CoV-2 vaccine.[31] Inactivated vaccines have much lower AEFI incidence than viral vector vaccines and mRNA vaccines. The mechanism of allergic reaction associated with mRNA vaccine is still unclear.[32]
5. AEFI of plant-derived virus-like particle (VLP) vaccine: CoVLP NCT04450004 is in its early phase of clinical trial, being administered alone or with AS03 or CpG1018 adjuvants. Adverse events have been noted even after two doses of vaccine-like pain at the injection site, headache, and fatigue. Hypersensitivity to plant material is a theoretical risk.[33] Data regarding AEFI of some vaccines are not yet available as some of them still await approval for use.

SARS-CoV-2 Vaccines: Contraindications

Pregnant and lactating women are not contraindicated for taking the COVID-19 vaccine as also anyone above 12 years of age. It is advisable that persons with previous episode of allergic or untoward event after vaccination should defer from taking the next dose. Furthermore, those with a history of any type of allergy to vaccines, medicines, and eatables should defer from the vaccination at present.[34] It is advisable that they follow COVID – appropriate behavior and adhere to a nutritious diet and a lifestyle that include yoga, meditation, and exercises.[35]

Discussion

COVID-19 vaccines have been recognized to be the most effective public health interventions to control the pandemic. However, there have been adverse effects following immunization. Most of them are caused by the protective immune responses initiated by vaccines. Most are not serious but some can be life threatening. These can be due to response to the excipients in the vaccine. mRNA vaccines, viral vectored vaccines, and inactivated vaccines are known to cause AEFI. The VLPs have not been known to cause AEFI as they are still in Phase-2 clinical trials. It is important that the population at large should understand these events better and have their concerns addressed by health experts. This will help to alleviate any fear and loss of confidence regarding safety issues about the COVID-19 vaccines.

A laudable effort was made by the Government of India, by launching a user-friendly digital platform, COVID-19 Vaccine Intelligence Network (Co-WIN) which has efficiently tracked those who were registered. However, AEFI data of COVISHIELD and COVAXIN are not being reported nor actively tracked whereas, data regarding mRNA vaccine AEFI are captured by the by Adverse Event Reporting System of the Centre for Disease Control and Food and Drug Administration, USA.[22]

It is suggested that our government portal should include a format for reporting AEFI and the public health departments should educate and motivate people through local languages, the significance of reporting the same. In this context, the State of Kerala, India, has been very proactive in that it already had a monitoring network for AEFI and pointed out that certain adverse events happened, which were not mentioned in the COVISHIELD

factsheet. The factsheets of vaccines should be put up as large posters in local language in vaccination centers so that the public can make an informed decision. The NEGVAC should also now concentrate on AEFI's especially those which are quality defect related, error or anxiety related, or coincidental events.

Hospitals should have a digital portal of all the COVID-19 patients with a history of vaccination, type of vaccine and dates of vaccination, and symptoms after vaccination. Since recall bias can hamper the collection of true facts, especially regarding the timeline of appearance of symptoms, history taking should be taken with a lot of patience.

It might not be practically possible in situations of high patient overload, as was the case during the second wave in April–May 2021 in India, therefore, a minimum information regarding whether the patient was vaccinated or not should be made mandatory in all the office records.

In areas where there are still network issues, or inability to access the internet, capacity building measures have to be implemented by the local health authorities. People also need to be made aware of the AEFI through print media, audio–visuals, and social media platforms so that morbidity and mortality can be prevented. Awareness should be spread among people with associated illness such as diabetes, chronic lung disease, high blood pressure, kidney ailments, and cancers that they might also suffer from any sudden health issues such as heart attack. However, linking all such issues to the vaccine in all cases may have subjective bias and therefore transparency should be practiced. All safety-related information should be shared with the general population either in our country or in any other part of the globe with the same vaccine.

In AEFI, laboratory tests such as RT-PCR and inflammatory markers (ESR, CRP, IL-6, and D-DIMER), chest X-ray, and CT scan of lungs should be done. These all will help in timely management of patients at home or in the hospital as determined by cough, breathlessness, temperature and SpO2 levels.

Conclusion

The emergency usage of COVID-19 vaccines has brought with it issues related to mounting of immune response of differing types. Some mount protective neutralizing antibodies that protect them from fatal infection, while others may not and may land up with an immune response that damages their own body cells. Others have allergic reactions to these vaccines. Broadly, there are AEFIs in the immunized population which need to be accepted and reported and such people should receive urgent and appropriate treatment and further counseling and roadmap should be charted out. It would not be sufficient to just say that there are differing responses. The way ahead is to capture such data from the second wave and makes a blueprint for prevention and management of morbidity and mortality during the predicted third wave. This has to be done rationally and sensitively, to generate reliable data base on which vaccine hesitancies can be fully addressed. Furthermore, the word "vaccine hesitancy" needs to be accepted by all and not put under the carpet then only the immunization campaign will be successful.

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