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## Original Article

## Elucidating causes of COVID-19 infection and related deaths after vaccination

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## ABSTRACT

**Background and aims:** Symptomatic or asymptomatic COVID-19 infection has been reported in vaccination. In the current article, we try to elucidate various causes behind COVID-19 infection and mortality following COVID-19 vaccination and suggest possible strategies to counteract this threat.

**Methods:** We carried out a comprehensive review of the literature using suitable keywords such as 'COVID-19', 'Pandemics', 'Vaccines', 'Mortality', 'deaths', 'infections', and 'India' on the search engines of PubMed, SCOPUS, Google Scholar, and ResearchGate in from January to May 2021. Epidemiology, risk factors, Adverse Events Following Immunization (AEFI) and mortality after COVID-19 vaccination were assessed.

**Results:** A number of factors have been associated with symptomatic or asymptomatic COVID-19 infection reported after vaccination. A high viral load, comorbidities, mutant strains, Variants of Concern (VOC) leading to Vaccine escape and casual attitude towards COVID Appropriate Behaviors appear to be the most important factors for infection and deaths after COVID-19 vaccination.

**Conclusions:** COVID-19 Infection and mortality after COVID-19 vaccination are of great concern. Application of COVID Appropriate Behaviour (CAB) before and after vaccination is essential for the population. Effective Vaccines against mutant strains and enhanced vaccination drive are key strategies to avoid this quintessential threat. Early medical intervention in high-risk groups can prevent overall mortality.

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## 1. Introduction

The second wave of COVID -19 has gripped around all Indian States and Union territories in just a few months [1]. As of May 28, 2021, more than 27 million cases of COVID-19 have been reported with more than 300,000 deaths attributed to the disease in India [2]. Increased incidence of new COVID-19 infections and deaths have been reported since the onset of the second wave. It has been observed that the second wave is different from the first wave due to its high infectivity rates [3].

Vaccination roll-out across the world have shown the introduced COVID-19 vaccines have been effective against serious COVID-19 infection across all ages in preventing symptomatic and

asymptomatic SARS-CoV-2 infections and COVID-19-related hospitalizations, severe disease, and death [4,5]. Recent study and reports by Public Health England suggest both the Pfizer-BioNTech and Oxford-AstraZeneca vaccines are highly effective in reducing symptomatic COVID-19 infections among older people aged 70 years and over. Further the data suggests these COVID-19 vaccines are effective in preventing hospitalization, the risk of serious illness and mortality due to SARS-CoV-2 infection in even older patients [6,7]. Researchers worldwide have tried to develop effective vaccines that can provide individual protection and introduce herd immunity in the population. Vaccination against COVID-19 was launched in India in January 2021. Currently, roll-out vaccines for restricted emergency use are from Covishield (Oxford-AstraZeneca vaccine) Covaxin, (Bharat Biotech) and Sputnik V (Moscow's Gamaleya Institute) [8]. The efficacy rate of vaccines varies. The Covaxin and Covishield have a reported efficacy rate of approximately about 81% and 70%, respectively [9]. Though the Ministry of Health and Family Welfare, Government of India (MOHFW, GOI) has undertaken an unprecedented vaccination drive, in a populous

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country like India with more than 1.3 billion people, it is just a fraction of the people who are vaccinated to provide individual immunity and current vaccination program is not enough to develop herd immunity.

More worryingly, breakthrough infections can occur and have been noted since COVID-19 vaccines do not offer 100% protection. An early Indian Council of Medical Research (ICMR) report suggests that 0.13% and 0.07% have been found to have COVID-19 infection following the two doses of Covaxin and Covishield, respectively [10]. Similarly, a hospital-based observational study from Apollo hospital, India reported that 97.8% of vaccinated Health Care Workers (HCW) are protected from COVID-19 infection, and in only 0.06% patients, hospitalization was required.

In another study, majority of persons with breakthrough infections; post-vaccination, were asymptomatic with only two persons needing hospitalization following COVID-19 infection and one death [11].

These breakthrough infections are usually mild [12]. However, despite these positive data regarding the efficacy of vaccines, more severe Adverse Events Following Immunization (AEFI) such as anaphylaxis, Bell's Palsy, Vaccine-Induced Immune Thrombotic Thrombocytopenia (VITT) and deaths have been reported in persons who have already received one or two doses of the vaccines [13–15].

Consequently, these serious adverse effects, SARS-CoV-2 infection and deaths after COVID-19 vaccination have raised concerns and a question mark on the efficacy of the existing vaccines. We explore the possible reasons for these below and suggest some strategies to mitigate them.

### 1.1. Centre for Disease Prevention and Control (CDC) surveillance definition of breakthrough infection

Though the currently introduced COVID-19 vaccines provide a high level of vaccine efficacy, a proportion of vaccinated population develop symptomatic or asymptomatic infections with SARS-CoV-2. According to the recently published CDC surveillance report, a vaccine "Breakthrough infection" is defined as the detection of SARS-CoV-2 RNA or antigen in a respiratory specimen collected from a person  $\geq 14$  days after receipt of all recommended doses of an FDA-authorized COVID-19 vaccine [16].

### 1.2. Possible reasons of COVID-19 infection, AEFI and mortality after COVID-19 vaccination

**1. Infection acquired before vaccination:** One of the common reasons could be the person may have contracted the SARS-CoV-2 infection few days prior to the immunization schedule and may have been asymptomatic. The patient then shows features of COVID-19 disease before the COVID-19 vaccine has initiated an immune response in the patient.

**2. Infection acquired before antibody formation:** The response to a vaccine in the human body depends on the duration and number of antibodies formed. Similar to the first reason, a person may develop COVID-19 if there is insufficient immune response and subsequent low production of antibodies against SARS-CoV-2 [17]. This has been reported previously with severe acute respiratory syndrome (SARS) in 2007 [18]. Jacobson et al. suggest a great majority of post-vaccine SARS-CoV-2 cases occurred prior to the expected onset of full, vaccine-derived immunity. The first two weeks following the vaccination are crucial and most of their patients acquired during this period [19]. Authors recommended persons should continue infection control measures particularly in the early days post-vaccination.

### 3. Mutation, Variants of Concern (VOC) and Vaccine escape:

Recently, Variants of Concern (VOC) B.1.617.2 strain has drawn attention and seems to be one of the main reasons of second wave in India. It has two mutations (L452R and E484Q) that have been related to increased transmissibility and an ability to evade immune defense system [20–22]. ICMR data suggests both Covishield and Covaxin appear to be only half effective in producing antibodies against the B.1.617 strain of SARS-CoV-2 [10]. This could perhaps explain the resurgence of COVID-19 infection and vaccine escape. There is a rising need for the efficacy of the Covishield and Covaxin vaccines to be proven against the "SARS-CoV-2" viral variants. Evaluation of vaccine-escape, antibody therapies and fast-growing mutations using comprehensive genetic analysis have been suggested for detecting infectious variants [23].

**4. Short life of immunity or protection after vaccination:** The exact duration of immunity following COVID-19 vaccination is still being assessed. Some of COVID-19 infection could be due to waning immunity and antibody titers [24,25]. The need for future booster doses is being evaluated [26].

**5. Immuno-suppression and use of steroids:** Patients already on immune-suppressants or use of a high dosage of steroids following COVID-19 hampers the antibody formation and adversely affects the vaccine response [27].

**6. Challenging Vaccination Drive and Coverage:** The GOI vaccination drive initiative has been challenging due to the population coverage needed for an effective control of COVID-19 with incomplete immunity in partially immunized individuals at risk of SARS-CoV-2 infection. The situation India is also hampered due vaccine hesitancy, mutant strains, and availability of sufficient vaccines [3,22].

**7. Supply chain challenges in distribution of Vaccine:** Improper Cold-chain infrastructure, storage, and transportation of vaccines make them ineffective. These may lead to incomplete immunity with a false sense of security.

8. High viral loads, pandemic fatigue especially amongst HCW and workers on COVID duty: They have overall higher risk of exposure to SARS-CoV-2. A recent Indian Medical association report suggests deaths of about 329 doctors since the beginning of the second wave of COVID-19, which is much higher than the deaths reported in the first wave [28].

**9. Mortality after COVID-19 vaccination:** More concerningly have been emerging reports of deaths following the various available COVID-19 vaccines. A Norwegian expert group has noted mortality in frail patients vaccinated with the Pfizer-BioNTech vaccine and advocate a risk-benefit analysis in this cohort of patients [29]. There have been multiple other reasons attributed to deaths with these vaccines including fatal anaphylaxis and a paradoxical syndrome of blood clots and thrombocytopenia (VITT) [14,15]. VITT has been predominantly noticed following the first dose of the Oxford-AstraZeneca COVID-19 vaccine and this has led to change in vaccine strategy with the CDC panel including various national governments advocating avoiding Oxford-AstraZeneca COVID-19 vaccine in specific age groups and women [30].

Post vaccination deaths due to COVID-19 have been reported in older individuals with multiple co-morbidities [31]. It has been reported that vaccine effectiveness is generally lower in such groups [32].

**10. Role of Genealogy:** It has been certainly clear that Black and Ethnic Minority (BAME) population have been disproportionately affected by COVID-19 [33]. What is still being evaluated is

the effect of COVID-19 vaccine and its relationship with genetic configuration.

The studies elucidating these mechanisms for COVID-19 infection and mortality after commonly used COVID-19 vaccinations are summarized in Table 1. The studies where the incidence of breakthrough infection post vaccination has been evaluated across various countries is summarized in Table 2.

1.3. Suggested strategies to mitigate COVID-19 infection, severe adverse effects and mortality following COVID-19 vaccination

1. **Data Surveillance and longitudinal studies** of hospitalized patients or who died due to COVID-19 infection after vaccination is an important strategy to explore the reasons of post-vaccination infection, risk factors, AEFI and mortality.
2. **Variant surveillance and Genomic studies** in post-vaccine SARS-CoV-2 cases are imperative in order to anticipate and control future surges of infection and deaths. Diagnosis and evaluation of mutant strains in patients who acquire infection after COVID-19 vaccination could give some insight into the cause of the infection.
3. **National seroprevalence and vaccine efficacy survey:** A nationwide survey regarding the efficacy of vaccines is a viable option. Further investigation about COVID-19 vaccine effectiveness over a large population such as in India will provide invaluable data, complement global efforts to control the current and better prepare for future pandemics.
4. **Vaccine studies against Mutant strains and Variants of Concern:** These are imminently necessary as we observe new, emerging strains across the world to investigate features of vaccine escape resulting in COVID-19 infection and

- prevent avoidable deaths or serious complications due to vaccines such as VITT.
5. **COVID-19 Appropriate Behavior and Vigilance** before and after vaccination is critical to prevent such infection and deaths.
6. **Stringent public health control strategies** across the nation and internationally to prevent the spread of viral transmission.
7. **Effective Vaccination Drives:** Accelerated, enhanced national and global vaccination drive with collaborative projects such as COVAX, WHO initiative to support the population [34]. Use of emerging technologies such as Artificial Intelligence (AI) and the Internet of Things (IOT) for distribution of vaccine [35].
8. **Enhanced Supply chain management:** Maintenance of the Cold chain, proper storage, and transportation of vaccines.
9. **Promoting vaccine uptake and tackling vaccine hesitancy:** Promotion of high vaccination coverage among all health care providers even to the extent of evaluating the possibility of mandatory vaccination in HCW provided there are no contraindications may be a way forward [33,36].
10. **Vaccine Policy:** The principle of two doses of COVID-19 vaccine at appropriate interval will bolster immune response in most people against serious COVID-19 infection.

2. Conclusion

COVID-19 Vaccination is the main strategy to eradicate SARS COV-2 related current pandemic in India and globally. Though COVID-19 infection is being reported following vaccination, predominantly these have been minor and not requiring hospitalization or invasive therapy. Pre- and post-vaccination appropriate COVID behavior including enhanced vigilance are required to

Table 1  
Reasons of COVID-19 infection and mortality after commonly used COVID-19 vaccinations.

Name of vaccine/References	Manufacturer Company/organization/ Institute of origin	Type/Features of Vaccine	Reasons of COVID-19 infection and mortality
1 AZD1222 (ChAdOx1) [13,14,15, WHO, CDC]	Oxford/AstraZeneca COVID-19 vaccine University of Oxford, UK	Chimpanzee adenoviral vector ChAdOx1, with the SARS-CoV-2 spike glycoprotein antigen.	1) Vaccine escape 2) Ineffective against some Mutant strains 3) Very rare <1/10000 of VITT
2 BNT162b2 [29, CDC 37]	Pfizer-BioNTech USA, Germany (Pfizer, Inc., and BioNTech)	mRNA vaccine encoding SARS-CoV-2 spike glycoprotein.	1) Vaccine escape 2) Ineffective against some Mutant strains 3) Myocarditis and pericarditis 4) Death in Frail, elderly population 5) Anaphylaxis may lead to death due to ingredient in mRNA Vaccine e.g. polyethylene glycol (11.1 cases per million doses administered after receipt of the first dose of the Pfizer-BioNTech vaccine)
3 mRNA-1273 [37] [CDC 37]	ModernaTX, Inc USA	mRNA vaccine encoding SARS-CoV-2 spike glycoprotein	1) Myocarditis and Pericarditis 2) Anaphylaxis may lead to death due to ingredient in mRNA Vaccine e.g. polyethylene glycol (2.5 cases per million Moderna COVID-19 vaccine doses administered)
4 JNJ-78436735 [37] [9, CDC 37]	Janssen Pharmaceuticals Companies of Johnson & Johnson, USA	Viral Vector- Adenovirus Ad26.COV2.S encoding SARS-CoV-2 spike glycoprotein	1) Vaccine escape 2) May be ineffective against some Mutant strains 3) Anaphylaxis may lead to death due to ingredient in the J&J/Janssen COVID-19 vaccine (such as polysorbate) 4) Risk of blood clots with low platelets after vaccination, especially in younger Females
5 ChAdOx1 [8,10,38,39].	Covishield, Serum Institute Pune, India	Chimpanzee adenoviral vector ChAdOx1, with the SARS-CoV-2 spike glycoprotein antigen.	Like Oxford/AstraZeneca COVID-19 vaccine University of Oxford, UK
6 BBV152 [39]	COVAXIN, Bharat Biotech/ICMR India	Whole-virion inactivated SARS-CoV-2 vaccine	Not available

WHO=World Health Organisation; CDC= Centre for Disease Prevention and Control; VITT= Vaccine-Induced Immune Thrombotic Thrombocytopenia; RNA = Ribo-nucleic acid; USA= United States of America; NA= Not available?.

**Table 2**  
Studies from countries which have reported breakthrough COVID-19 infection post vaccination.

Country	Vaccine and manufacturer	Total SARS-CoV-2 vaccine breakthrough infections	Asymptomatic or mild disease	Age	Deaths
USA [40]	BNT162b2 mRNA COVID-19 vaccine mRNA-1273 SARS-CoV-2 vaccine Ad26.COV2.S vaccine	10,262 out of 101 million persons	2725(27%) were asymptomatic; 995 (10%) hospitalized; and 160 (2%) patients died.	The median age of patients who died was 82 years	28 (18%) decedents were asymptomatic or died from a cause unrelated to COVID-19.
USA [41]	Moderna COVID-19 vaccination	22 out of 627 possible breakthrough infections $\geq$ 14 days after their second dose of vaccine.	Two thirds of persons were asymptomatic. A minority had mild to moderate COVID-19-like symptoms; two COVID-19-related hospitalizations and	61.5 years	one death occurred. Yes, COVID-19 related
USA [42]	second dose of BNT162b2 (Pfizer –BioNTech) or mRNA-1273 (Moderna) vaccine	2/417 2 women with vaccine breakthrough infection			
USA [43]	BNT162b2 (Pfizer –BioNTech) or mRNA-1273 (Moderna) vaccine	379 tested positives for COVID-19 (0.05%.)	Data not available	health care workers in the study were young	No death
India [12]	(Covaxin, 28, Covishield, 85)	113 vaccinated	Asymptomatic infection in 98. Among 15 having symptoms, 14 had mild disease and only 1 required hospitalization	All vaccine recipients were >45-year-old as per Indian vaccination regulations	No death
UK [44]	BNT162b2 (Pfizer –BioNTech) or mRNA-1273 (Moderna) vaccine	Among symptomatic patients (1823), 40% (729) developed covid-19 symptoms in 1st week and 19% (352) developed symptoms in 2nd week post-vaccination.	2019 of 3842 were asymptomatic	82 of the 113 deaths were in the high risk “frail elderly” group.	113 died with COVID-19.
UK [45]	Pfizer-BioNTech (BNT162b2) and the Oxford-AstraZeneca (ChAdOx1 nCoV-19)	3106 of 103,622 vaccinated tested positive for SARS-CoV-2 infection	Data not available	overall mean age of the vaccinated was higher than that of the general population (40.3 years)	24 Not mentioned
Israel [46]	BNT162b2 mRNA vaccine	10,561 infections were documented (0.6 infections per 1000 person-days),	43% were asymptomatic	Mean age was 45 years	229 were severe cases of COVID-19, and 41 resulted in death.
India [47]	Covishield	86 (18.65%) got infection in 461 study population	No data on asymptomatic. Disease was Mild in 69(80.2%), moderate in 10(11.62%), severe in 6(6.97%) and critical in 1(1.16%)	All health care workers	mortality was 1 out of 86 cases
USA [48]	either mRNA vaccine (Pfizer, Moderna)	Multicenter observational cohort analysis across eight hospitals among 11834 patients	10880 unvaccinated, 825 partially vaccinated, and 129 fully vaccinated Emergency department patients.	Average age was 53.0	death occurred in 384 (3.5% of 10880) Unvaccinated patients, 50 (6.1% of 825) Partially vaccinated patients, and 8 (6.2% of 129) Fully vaccinated patients.
Italy [49]	2 doses of BNT162b2(Pfizer)	33 breakthrough infections in 3694 health care workers	mildly symptomatic in 16 (48%) and asymptomatic in 17 (52%)	All health care workers	Not available
India [50]	Covaxin or covishield	37 (11.3%) infections in 325 worekrs	Most breakthrough infection cases (94.4%) were mild	Mean age of 29 years old health care workers	Not available

thwart infection. Data surveillance of mutant virus, effective vaccines against VOC will prevent phenomenon of vaccine escape and COVID-19 infection.

However, deaths reported after vaccination has raised several questions about the safety and efficacy of current vaccines. More rigorous evaluation of COVID-19 vaccines is necessary to avoid deaths such due to VITT including strategies such as ring-fencing specific vaccines for appropriate age and or gender groups.

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## Declaration of competing interest

None declared.

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