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REVIEW

Addressing COVID-19 vaccine hesitancy

George Kassianos[1,2], Joan Puig-Barberà[3], Hannah Dinse[4], Martin Teufel[4], Özlem Türeci[5], Shanti Pather[5]

[1]Royal College of General Practitioners, London, UK; [2]The British Global and Travel Health Association, London, UK; [3]Fundación para el Fomento de la Investigación Sanitaria y Biomédica de la Comunidad Valenciana, Valencia, Spain; [4]University of Duisburg-Essen, Clinic for Psychosomatic Medicine and Psychotherapy, LVR University Hospital, Essen, Germany; [5]BioNTech SE, Mainz, Germany

Abstract

Immunization programmes have been globally recognized as one of the most successful medical interventions against infectious diseases. Despite the proven efficacy and safety profiles of coronavirus disease 2019 (COVID-19) vaccines, there are still a substantial number of people who express vaccine hesitancy. Factors that influence vaccine decision-making are heterogenous, complex, and context specific and may be caused or amplified by uncontrolled online information or misinformation. With respect to COVID-19, the recent emergence of novel variants of concern that give rise to milder disease also drives vaccine hesitancy. Healthcare professionals remain one of the most trusted groups to advise and provide information to those ambivalent about COVID-19 vaccination and should be equipped with adequate resources and information as well as practical guidance to empower them to effectively discuss concerns. This article seeks to summarize the currently available information to address the most common concerns regarding COVID-19 vaccination.

Keywords: boosters, coronavirus, COVID-19, hesitancy, infectious disease, public health, SARS-CoV-2, vaccination.

Citation

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Introduction

Vaccines are known to be one of the most robust tools against the transmission of infectious diseases in terms of providing disease control, mitigation of disease severity, herd immunity and reducing healthcare/societal costs.[1] Vaccines that have been approved for coronavirus disease 2019 (COVID-19) by regulatory bodies, such as the Medicines and Healthcare products Regulatory Agency (MHRA), United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have proven effective and well tolerated in the prevention of infection and disease severity,[2] and global vaccine coverage is a crucial factor to ensure the success of vaccination programmes during a pandemic. The chance of achieving herd immunity, which leads to disease eradication or elimination, has been a controversial topic during the SARS-CoV-2 outbreak and is thought to be unlikely given that COVID-19 is now so widespread.[3] However, high levels of background population immunity or indirect protection are possible through vaccination[4] but are hindered due to a number of factors, including the emergence of highly transmissible virus variants, the extent to which vaccines prevent transmission and their duration of protection, adherence to social distancing and mitigation measures, and vaccine hesitancy.[3] Although vaccination is known to reduce hospitalizations and severe disease compared with those who are unvaccinated,[5] there is a substantial proportion of the population that expresses vaccine hesitancy; up to 28% of individuals in Europe[6] and 22% in the United States are undecided about or unwilling to receive a COVID-19 vaccine.[7]

Vaccine hesitancy is multifactorial and may be due to confidence, complacency, and convenience in regards to vaccination or vaccines,[8] fear, and cultural or political factors.[9] Lack of information or even misinformation is one of the most influential yet preventable causes[8] and has contributed to a decrease of up to 6.4% in vaccination intent among those who would otherwise get vaccinated, including those who would normally not be vaccine hesitant.[4] More recently, the emergence of variants of concern (VOCs), such as Omicron (B.1.1.529), which has been shown to have a higher transmissibility *versus* the wild-type strain[10] and less severe disease,[11] could further drive vaccine complacency or hesitancy.

Healthcare professionals play a leading role in vaccine decision-making and equipping them with tools and information will facilitate effective conversations with patients. Interventions to combat vaccine hesitancy are most effective when tailored to specific populations and if they address specific concerns,[12] and it is important to discuss these concerns, fears and other reasons for vaccine hesitancy with unvaccinated individuals.[8]

The aim of this review is to provide scientific information to support effective communication with vaccine-hesitant individuals. We focus on the first four vaccines to receive emergency authorization and/or full approval and with real-world evidence (RWE)[13] available: BNT162b2 (Pfizer–BioNTech), mRNA-1273 (Moderna), AZD1222 (University of Oxford–AstraZeneca), and AD26.COV2.S (Johnson & Johnson [Janssen]).

Methods

Search strategy

A literature search [Title/Abstract] of PubMed and MedRxiv was performed using the search term "COVID-19 vaccines" combined with the following terms: "myths", "misinformation", "misconception", "anxiety", hesitancy", "acceptance", "warp speed", "expedited", "accelerated", "emergency use", "BNT162b2", "mRNA-1273", "AZD1222", "AD26.COV2.S", "ChAdOx1", "safety", "adverse events", "anaphylaxis", "allergic reaction", "reactogenicity", "mRNA", "DNA", "nucleus", "cytoplasm", "DNA modification", "genetically modified", "GMO", "pregnancy", "pregnant", "lactating", "breastfeeding", "lactation", "fertility", "infertility", "menstrual", "syncitin-1", "embryo", "fetus", "sperm", "real-world evidence", "transmission", "transmissibility", "viral load", "variant", "mutating strain", "strain", "motivational interviewing" and "patient communication". This returned 1500 articles in PubMed and 1153 articles on MedRxiv. In addition, information on clinical trials from ClinicalTrials.gov was evaluated as well as articles or documents released by public health bodies and regulators such as the Centers for Disease Control and Prevention (CDC), the EMA, and the FDA. Press releases were also referenced in this article with regards to topics where published information was not yet available.

Inclusion and exclusion criteria

Our search criteria included unique, full-text articles published until 30 March 2022. Articles from PubMed and *MedRxiv* were included if they were primary literature or review articles, and available in English. Where possible, we primarily used publications from randomized control trials, observational studies and registries when discussing data on COVID-19 vaccines and smaller studies and case reports were excluded. If citing reviews, systematic, peer-reviewed articles were given preference.

Review

We can trust COVID-19 vaccines that were developed within short timelines

The relative speed with which COVID-19 vaccines were developed and authorized continues to cause concerns amongst some as to how thoroughly vaccine safety and efficacy were investigated, and if any steps in vaccine development or regulation were bypassed.[14,15] The pressing need to develop vaccines to counter the fast-spreading pandemic was quickly identified by governments, public health bodies (e.g. WHO, CDC, and the European Centre for Disease Prevention and Control), regulators, non-profit organizations, funding bodies and the pharmaceutical industry, who worked together to ensure that safety, quality and efficacy were not compromised during clinical development.[16–22]

International regulatory authorities collaborated early in the pandemic to streamline the vaccine development and authorization process, aligning on the data required to proceed from preclinical to phase III clinical trials and establishing guidelines to maintain the strict standards, procedures and protocols required of all preventive vaccines for infectious diseases.[16–22] Phase I to III trials were conducted in parallel, rather than sequentially, with the agreement of regulatory bodies and national health institutes, and with rolling review cycles to expedite the assessment for accelerated authorization.[16,17,20,21,23–25] The phase III trials were large scale, with some enrolling more than 43,000 participants from demographically diverse populations. This participant size, which is comparable to other phase III vaccine trials,[26] allowed for rapid collection and analysis of safety and efficacy data.[27–29] Due to the scale of the pandemic, the willingness of participants and the public health urgency, recruitment for COVID-19 vaccine phase III trials was rapid (3–7 months)[27–29] compared to other trials, which can take 12–18 months to screen and enrol fewer participants.[30] The high worldwide prevalence of COVID-19 in the population meant that vaccine efficacy could be observed sooner than for a disease where prevalence is lower. Furthermore, pre-existing production processes meant that vaccines could be manufactured rapidly and at a large scale, with vaccines produced at-risk prior to authorization.[17,23]

After vaccines were authorized for emergency use, vaccine manufacturers continued clinical trials, and were required to conduct post-marketing pharmacovigilance activities to monitor longer-term safety, immunogenicity, and efficacy in an expanded population exposed to emerging variants.[16,22,25] Owing to the timely approvals, these postmarketing data were bolstered by RWE, which quickly emerged from countries where vaccines were being rapidly rolled out.[31]

Leveraging research from existing non-clinical data and well-validated vaccine platforms saved considerable time.[20,23] There were pre-existing non-clinical data from other coronavirus

outbreaks, which circumvented the need for some early stages of vaccine development. For example, it had already been demonstrated that the full-length spike glycoprotein of SARS-CoV-1 and Middle East respiratory syndrome-related coronavirus triggers robust immune responses and gives rise to viral protection,[23] and that the prefusion stabilized conformation of the spike was a suitable vaccine antigen.[32] Further, a considerable amount of data that had already been generated on the vaccine platforms prior to the pandemic was leveraged for COVID-19 vaccine development. Viral vector vaccines (i.e. AZD1222 and AD26.COV2.S) are the result of extensive research over the last 30 years.[33] AD26.COV.2 was based on Janssen's AdVac® technology, which was used in the development of the EMA-approved Ebola vaccine (Zabdeno/Mvabea).[34] Similarly, mRNA technologies had also undergone extensive basic research and development for more than 20 years[35] and a number of clinical trials prior to the development of the COVID-19 vaccine had established that mRNA-based vaccines had an acceptable safety profile (e.g. in trials with mRNA-based vaccines in human immunodeficiency virus,[36] prostate cancer[37] and melanoma[38]). Furthermore, prior individualized mRNA cancer vaccine trials (e.g. NCT04486378, NCT03815058, NCT03739931) meant that the process of moving from genetic sequence to vaccine design and manufacturing had been optimized. These factors combined facilitated the expedited development and manufacturing of these novel vaccines, whilst ensuring compliance with the same safety and quality standards applied to all vaccines.

It is becoming increasingly clear that additional doses beyond the primary regimen are needed to extend vaccine protection (refer to 'Booster vaccinations may increase protection when immunity begins to wane' later). Modified versions of the currently available vaccines that are variant-adapted are in development, including Omicron-adapted vaccines, and will be evaluated by regulators when robust first-in-human data are available from the ongoing clinical trials.[39,40] Regulators have emphasized the need for comparator efficacy trials or immunobridging studies to support their use, although consensus on the implementation and adoption of these vaccines will be established once further data are available.[41]

COVID-19 vaccines are well tolerated in the short and long term

The expedited approval processes (e.g. Emergency Use Authorizations by the FDA and MHRA and Conditional Marketing Authorization by the EMA) require independent and rigorous determination that the known and potential benefits of a product outweigh the known and potential risks, with studies using safety evaluation protocols no different than those used for any other preventive vaccine.[21,42] Therefore, any COVID-19 vaccine granted emergency authorization is considered to have an acceptable safety profile and is well tolerated. Large-scale pre-licensure vaccine efficacy and safety trials conducted prior to initial authorization allowed an assessment of both common and uncommon risks.[16] Following submission of further data, manufacturers can apply for full approval; BNT162b2 has now gained full approval (Biologics License Application, BLA) from the FDA in individuals ≥16 years of age and Moderna has completed their BLA submission for mRNA1273.

Data from these large-scale pre-licensure clinical trials demonstrated that immunization with the currently authorized COVID-19 vaccines led to adverse events (AEs) and that these are transient and self-limiting and include, but are not limited to, injection-site reactions, fatigue, headache, muscle pain, chills, joint pain, and fever,[27–29,43] are associated with the desired innate immune activation mediated by vaccines, and are akin to those observed with other infectious disease vaccines.[44,45] Incidences of serious AEs identified in the phase III trials were comparable between vaccinated participants and those in the control arm (BNT162b2: 0.6% *versus* 0.5% in placebo;[29] mRNA-1273: 0.6% in both groups;[28] AZD1222: 0.9% *versus* 1.1% in control [MenACWY];[27] Ad26.CoV2.S: 0.4% *versus* 0.4% in placebo[43]).

The aforementioned trials examined the safety and efficacy of the primary vaccine regimens (i.e. two separate doses for BNT162b2, mRNA-1273, and AZD1222 and one dose for Ad26.CoV2.S) but since then, immunity against both wild-type and VOCs following vaccination has been shown to wane overtime,[46,47] which is also observed with vaccines for other diseases.[48] Thus, an extra administration of the vaccine, that is, a third dose (applicable to the mRNA vaccines and AZD1222) or a second dose (applicable to Ad26.CoV2.S), beyond the primary regimen (also referred to as a 'booster dose') was investigated to ascertain if this can restore levels and clinical trial data and RWE has shown that this gives rise to a safety profile in line with that of the primary regimen and thus far no new safety signals have been identified.[49–54] A third dose of BNT162b2 and mRNA-1273 is classed as a part of the primary regimen for those who are severely immunocompromised.[54,55] Booster dosing is discussed in more detail below.

RWE emerging following widespread vaccine rollout is already providing valuable long-term safety data, and information from national surveillance systems, such as the Vaccine AE Reporting System (VAERS) and the Yellow Card MHRA reporting system, which can be reported by both healthcare professionals and vaccinated persons, is continually collected. RWE analyses have shown low incidences of mostly mild and self-limiting AEs following administration of COVID-19 vaccines, which are expected based on the mode of action of the vaccines and are in line with the observations in late-stage clinical trials.

Anaphylaxis is a serious and rare side effect associated with most vaccines (frequency is 1 case per 1 million doses).[56] It is also rare with COVID-19 vaccines (estimates of 9.9–28.4 cases per 1 million doses; Table 1).[57,58]

Thrombosis with thrombocytopenia syndrome (TTS), a very rare syndrome of blood clotting involving large blood vessels

Table 1. Vaccine-associated adverse events of special interest.

Vaccine	Doses administered (country; data cut-off date)	Cases reported	Estimated cases per million doses	Groups at higher risk (impact of sex, age or ethnicity)
Anaphylaxis/anaphylactoid reactions				
Ad26.COV2.S	7.98 million doses (US; April 12, 2021)[58]	79	Estimate of 9.9 cases per million doses[58] 4 confirmed, 4 under review[58]	
AZD1222	24.9 million first doses; 24.2 million second doses; 64,000 third doses (UK; March 02, 2022)[57]	873	Estimate of 17.8 cases per million doses[57]	• Women may be more prone; of those reporting anaphylaxis aged between 18 and 85 years, it has been shown that the majority are women (1,002/1,183 cases) (EudraVigilance; February 26, 2022)[154]
BNT162b2	26.1 million first doses; 23.4 million second doses; 29.3 million third doses (UK; March 02, 2022)[57]	654	Estimate of 8.3 cases per million doses[57]	• Incidence of anaphylaxis is 2–7 times higher for recipients of mRNA vaccines with a prior history of allergies (VAERS; US)[155] • Women may be more prone (VAERS; US)[155]
mRNA-1273	1.6 million first doses; 1.5 million second doses; 9 0 million third doses (UK; March 02, 2022)[57]	87	Estimate of 7.2 cases per million doses[57]	• Incidence of anaphylaxis is 2–7 times higher for recipients of mRNA vaccines with a prior history of allergies (VAERS; US)[155] • Women may be more prone (VAERS; US)[155]
Thrombosis/major thromboembolic events with thrombocytopenia syndrome[a]				
Ad26.COV2.S	12.6 million doses (US; June 30, 2021)[59]	38	4 deaths	• Highest reporting rates seen in women aged 30–39 years (8.8 cases per one million doses)[59]
AZD1222	24.9 million first doses; 24.2 million second doses; 64,000 third doses (UK; March 02, 2022)[57]	437	Estimate of 8.8 cases per million doses[57] 78 deaths (6 following second dose)[57] 49/437 cases occurred following second dose[57]	• Higher incidence in younger adult population following the first dose compared to the older groups (21.3 per million doses in those aged 18–49 years compared to 11.1 per million doses in those aged ≥50 years) (UK; March 02, 2022)[57]
BNT162b2	26.1 million first doses; 23.4 million second doses; 29.3 million third doses (UK; March 02, 2022)[57]	32	Estimate of 0.4 cases per million doses[57] 4 deaths reported[57]	• The 32 events occurred in 13 women and 18 men aged 18–91 years (UK; March 02, 2022)[57]
mRNA-1273	1.6 million first doses; 1.5 million second doses; 9 0 million third doses (UK; March 02, 2022)[57]	5	Estimate of 0.4 cases per million doses[57] No deaths reported[57]	• The 5 events occurred in adult men <75 years (UK; March 02, 2022)[57]

(Continued)

Table 1. ***(Continued)***

Myocarditis				
Ad26.COV2.S[156]	2.0 million doses (EU/EEA; May 31, 2021)	0	N/A	N/A
AZD1222 (ref.[57])	24.9 million first doses; 24.2 million second doses; 64,000 third doses (UK; March 02, 2022)[57]	221	Estimate of 4.5 cases per million doses[57]	• Number of UK ADR reports associated with suspected myocarditis, pericarditis and other related terms was higher in those aged ≥40 years[57]
BNT162b2 (ref.[57])	26.1 million first doses; 23.4 million second doses; 29.3 million third doses (UK; March 02, 2022)[57]	739	Estimate of 9.4 cases per million doses[57]	• Higher case numbers in male adolescents and young adults[68] • 70.7, 105.9 and 52.4 cases per million in those aged 12–15 years, 16–17 years and 18–24 years, respectively (VAERS; US)[68] • Usually occur following the second dose and within a week of vaccination
mRNA-1273 (ref.[57])	1.6 million first doses; 1.5 million second doses; 9 0 million third doses (UK; March 02, 2022)[57]	212	Estimate of 17.5 cases per million doses[57]	• Higher case numbers in male adolescents and young adults[68] • 56.3 cases per million in those aged 18–24 years (VAERS; US)[68] • Usually occur following the second dose and within a week of vaccination[157]
Pericarditis				
Ad26.COV2.S[156]	2.0 million doses (EU/EEA; May 31, 2021)[156]	1	Estimate of 0.5 cases per million doses	N/A
AZD1222 (ref.[57])	24.9 million first doses; 24.2 million second doses; 64,000 third doses (UK; March 02, 2022)[57]	216	Estimate of 4.4 cases per million doses[57]	• Number of UK ADR reports associated with suspected myocarditis, pericarditis and other related terms was higher in those aged ≥40 years[57]
BNT162b2 (ref.[57])	26.1 million first doses; 23.4 million second doses; 29.3 million third doses (UK; March 02, 2022)[57]	507	Estimate of 6.4 cases per million doses[57]	• Higher case numbers in male adolescents and young adults[157] • Usually occur following the second dose and within a week of vaccination[157]
mRNA-1273 (ref.[57])	1.6 million first doses; 1.5 million second doses; 9 0 million third doses (UK; March 02, 2022)[57]	119	Estimate of 9.8 cases per million doses[57]	• Higher case numbers in male adolescents and young adults[157] • Usually occur following the second dose and within a week of vaccination[157]

[a]Classed as major thromboembolic events (blood clots) with concurrent thrombocytopenia (low platelet counts).
ADR, adverse drug reaction; VAERS, Vaccine AE Reporting System.

combined with low platelet counts, has been reported 1–2 weeks following vaccination with AD26.COV2.S (Table 1).[59] A safety review confirmed 17 cases of TTS following more than 8 million doses, all occurring in women aged 18–59 years (median age 37 years).[58]

The FDA determined that the available data suggested the chance of TTS is very low and that the known and potential benefits of AD6.COV2.S outweighed its known and potential risks in individuals ≥18 years of age.[60] Although a causal relationship between the vaccine and TTS is considered plausible, the mechanism and risk factors for this syndrome are still being investigated. Similar thrombotic events, primarily amongst women aged <60 years, have been described in Europe after receipt of AZD1222, with very few cases reported from non-European countries despite extensive use.[57,58,61]

Thromboembolic events with concurrent thrombocytopenia events have been reported following administration of mRNA COVID-19 vaccines, but these are rare (Table 1).[57] There are a small number (0.8 per million doses of BNT162b2 or mRNA-1273) of immune thrombocytopenia reports that do not exceed the background rate.[62] Of note, severe COVID-19 infection itself, which vaccination protects against, is associated with a high incidence of thrombotic complications (31% of patients in intensive care units).[63]

Reports have suggested that there is an association between COVID-19 vaccination and myocarditis and pericarditis (Table 1).[64,65] The risk of myocarditis and pericarditis following BNT162b2 or mRNA-1273 vaccination had not previously been observed in phase III clinical trials due to the number of participants involved in the trials and the low frequency of these AEs.[28,29] A report from VAERS stated that there were 1,226 reports of myocarditis, pericarditis or myopericarditis during a 6 month period when 296 million doses of mRNA vaccines had been administered.[66] Given this low frequency, the CDC determined that the benefits of vaccination still outweighed the risks,[66] and others have also taken the same approach.[64]

RWE from the largest healthcare organization in Israel (*n*=1,736,832; December 2020 to May 2021) showed that the risk of myocarditis and pericarditis in persons infected with SARS-CoV-2 was substantially increased when compared to vaccinated persons (11 events *versus* 1–5 events per 100,000 persons, respectively).[67] To date, no confirmed signal is established between COVID-19 viral vector vaccines and myocarditis and pericarditis.[64]

As more data have emerged on the short-term and long-term safety of vaccines, demographic analyses have shown that the safety profiles may differ depending on age, sex and ethnicity. A recent analysis of the VAERS database showed that the frequency of AEs post-vaccination is higher in women (73.5% of reported AEs) and in those <60 years (61.4% of reported AEs). Myocarditis reports are higher in young male adults and after the second dose[64,65] and amongst white and Hispanic persons.[68] Table 1 provides further detail on groups at higher risk of adverse events of special interest.

Taken together with the generally acceptable safety profiles and low risks of serious AEs, as well as the emerging safety data from RWE,[69] postmarketing surveillance and phase IV trials (e.g. ENFORCE [NCT04760132]), the potential benefits of COVID-19 vaccination outweigh the potential risks.

Concerns that COVID-19 vaccines alter DNA are unfounded

The lipid nanoparticle-encapsulated mRNA contained in the authorized COVID-19 mRNA vaccines (BNT162b2 and mRNA-1273) encodes the non-infectious SARS-CoV-2 spike (S) protein (found on the surface of SARS-CoV-2 and required for virus attachment and host cell entry).[70,71] Upon entry into the host cell, the mRNA is translated into SARS-CoV-2 S protein by the cell's own protein-producing machinery in the cytoplasm. The S protein is subsequently presented by antigen-presenting cells to T and B cells, priming the immune system for rapid and strong cellular and humoral (antibody) responses upon SARS-CoV-2 exposure and subsequent longer-term protection against SARS-CoV-2 exposure.[35]

mRNA is a transiently expressed intermediate carrier of genetic information required for protein synthesis and is rapidly degraded by normal physiological processes, all features that may contribute to an acceptable safety profile for mRNA therapeutics.[35,71] The mechanisms by which mRNA vaccines generate immunity against COVID-19 do not involve any DNA modification as mRNA is only active in the cytoplasm and does not enter the nucleus, where DNA is located, and does not affect or alter the DNA in any way.[72]

The viral vector vaccines, that is, AZD1222 and AD26.COV2.S, utilize replication-deficient adenovirus vectors (Ads) as carriers for the genetic code of the SARS-CoV-2 S protein.[73] Ads, which have been used for several years as a vehicle for gene delivery, are not capable of producing copies of the genome after delivery as the E1 and/or E3 genes, which are required for replication, are deleted and replaced with the gene of interest.[73] Following administration, the viral vectors are delivered to immune cells, which results in high levels of production of the SARS-CoV-2 S protein carried out by the cell machinery in the cytoplasm. These cells then present the SARS-CoV-2 S protein on their surface and trigger the production of memory T and B cells as well as high-affinity SARS-CoV-2 antibodies, which contribute to protection against SARS-CoV-2 infection.[74] Ads viral vaccines lack the machinery to integrate their genome into the host chromosomes (i.e. they are non-integrating vectors) so cannot modify DNA in any way.[74]

Concerns that COVID-19 vaccines affect fertility are unfounded

Misinformation regarding COVID-19 vaccines has led to the concern that vaccination will affect the fertility of women. One claim suggests that anti-SARS-CoV-2 S protein antibodies

may cross-react with human syncytin 1, a protein involved in placental growth and attachment, leading to infertility or pregnancy loss.[75,76] However, recent studies in women undergoing in vitro fertilization (IVF) treatments showed that there was no difference in IVF cycle outcomes (e.g. oocyte retrieval number and fertilization rate) between prevaccination and postvaccination.[76,77] A prospective study examining the impacts of mRNA vaccination on ovarian reserve found that levels of anti-Müllerian hormone, a measure of ovarian follicular reserve, were not altered, although longer-term data (>3 months post vaccination) are required.[78] Additionally, in the COVID-19 clinical trials, no significant difference was found in the rate of accidental pregnancies in the control *versus* vaccinated groups.[79] A report from the United Kingdom that examined data in the period between 9 December 2020 and 06 October 2021 stated that there is no evidence that vaccination impacts fertility.[57]

A small number of reports have been published examining COVID-19 vaccination and fertility in men. A retrospective study conducted in infertility centres in Italy showed that COVID-19 vaccination (with either mRNA or viral vector vaccines) did not influence sperm quality and fertilization capacity of men undergoing assisted reproductive treatments. The researchers concluded that COVID-19 vaccination does not have any negative association with fertility in men.[80]

COVID-19 infection in pregnancy is known to impact maternal and neonatal outcomes

In a study involving 43 institutions in 18 countries (*n*=2130), pregnant women with COVID-19 had an increased risk of maternal complications, for example, pre-eclampsia/eclampsia (relative risk (RR) 1.76; 95% CI 1.27–2.43), severe infections (RR 3.38; 95% CI 1.63–7.01) and maternal mortality (RR 22.3; 95% CI 2.88–172) compared to pregnant women without COVID-19.[81] Statistics released by National Health Service England in October 2021 showed that 20% of patients with COVID-19 who are critically ill are unvaccinated pregnant women.[82] Analyses from registries (COVI-Preg) have shown that pregnant women with conditions such as hypertensive disorders, diabetes and pulmonary comorbidities are at an increased risk for severe maternal outcomes (adjusted odds ratios: 2.7 (95% CI 1.0–7.0), 2.2 (95% CI 1.1–4.5) and 4.3 (95% CI 1.9–9.5), respectively).[83] Additionally, pregnant women who are overweight and have a COVID-19 diagnosis have an increased risk of maternal and neonatal morbidity[81] and present with more severe symptoms,[83] which, as in the general population, are known to vary depending on the SARS-CoV-2 VOC.[84,85]

Although pregnant women were excluded from preauthorization COVID-19 vaccine trials and contraception was mandatory as per the clinical trial protocol,[86,87] limited data on women who became pregnant during clinical trials (although prohibited) showed that the type and frequency of AEs in these women were similar to those observed in non-pregnant women.[88–90]

Data from developmental and reproductive toxicity non-clinical studies (in accordance with EMA and FDA requirements) for the BNT162b2,[54] mRNA1273,[55] AD26.COV2.S[91] and AZD1222[92] vaccines did not demonstrate any safety concerns in pregnancy. Placebo-controlled trials or observational studies investigating the safety and efficacy of vaccines in pregnancy are ongoing, e.g. mRNA1273 (NCT04958304), Ad26.COV2.S (NCT04765384) and BNT162b2 (NCT04754594) (data pending).

Until these are read out, data on the safety and effectiveness of vaccines in pregnant women are primarily derived from RWE studies or national surveillance systems in countries where pregnant women were vaccinated based on individual benefit–risk assessments. Preliminary findings from a study evaluating mRNA COVID-19 vaccine safety during pregnancy based on data from three US vaccine safety monitoring systems, including VAERS, did not identify any obvious safety signals with respect to pregnancy or neonatal outcomes associated with vaccination in the third trimester of pregnancy.[87] Reactogenicity events of injection-site pain, fatigue, headache and myalgia were the most frequent AEs after either dose and were most frequent after the second dose amongst a cohort of 35,691 pregnant women in the V-safe Surveillance system that received an mRNA vaccine.[87] Amongst the participants with completed pregnancies who reported major congenital anomalies (16 of 724 (2.2%) births), none had received a COVID-19 mRNA vaccine in the first trimester or periconception period; no neonatal deaths were reported.[87] Amongst 221 pregnancy-related AEs reported to the VAERS, the most frequent AE was spontaneous abortion (46 cases, with 37 in the first trimester), which is comparable with published incidences in this population.[87] Data from the UK Health Security Agency, taken between January and November 2021, where 483,677 women had given birth and of these 50,359 and 941 had received at least two and three vaccine doses, respectively, reported no differences between vaccinated and unvaccinated women with regard to rates of stillbirth, low birth weight and premature delivery.[93] A multicentre, retrospective cohort study also showed that vaccination during the third trimester did not impact maternal outcomes and resulted in a two-fold lower risk for adverse neonatal outcomes compared to unvaccinated women; however, women who received the vaccine had higher rates of elective caesareans.[94] An observational, retrospective study showed that the risk of spontaneous abortion in the first trimester following COVID-19 vaccination is not increased compared to unvaccinated women, and this did not differ depending on number of doses administered (1–3 doses).[95]

Although there is concern about the safety of COVID-19 vaccination whilst breastfeeding and if it is harmful to the child, breastfeeding postvaccination has not shown a risk for adverse effects in breast-fed newborns or infants.[54,55] For other vaccines, although there are limited data in breastfeeding, no risk is expected.[91,96] Anti-SARS-CoV-2 immunoglobulin A (IgA)

and immunoglobulin G (IgG) are detected in the breast milk of COVID-19-naive women vaccinated with BNT162b2, mRNA-1273 and AZD1222, with the strongest reactivity observed mainly after the second dose. The potential transfer of protective antibodies against SARS-CoV-2 in breast milk may provide protective benefits to breastfeed infants.[97] Additionally, some studies have shown that, following COVID-19 vaccination, anti-SARS-CoV-2 antibodies are transferred through the placenta to the foetus, likely giving rise to neonatal protection and thus further supporting vaccination in this population.[98,99]

Given the known risks and severity of COVID-19 during pregnancy, advisory committees (e.g. American College of Obstetricians and Gynaecologists, Royal College of Obstetricians and Gynaecologists and the CDC) have stated that COVID-19 vaccines (both the primary regimen and boosters) are strongly recommended and/or should not be withheld from women who are pregnant or breastfeeding as the benefits outweigh the potential risks.[100–102] As the pandemic evolves, new VOCs emerge, and more data become available, the risk–benefit profile of COVID-19 should be continually monitored in pregnant women.

COVID-19 vaccines do not cause infection

The currently available COVID-19 vaccines do not contain the live SARS-CoV-2 virus or any components that can cause infection.[103] The mRNA molecules in BNT162b2 and mRNA-1273 are non-infectious and non-integrating, encoding only part of the virus (the SARS-CoV-2 spike S glycoprotein); therefore, there is no risk of infection or insertional mutagenesis.[35] Vector-based vaccines use a different virus, such as adenovirus, with an altered genome to encode the SARS-CoV-2 S glycoprotein, and are replication deficient (non-integrating).[74] Immunization with COVID-19 vaccines may induce mild and short-term AEs. Such events may be signs that the vaccine is eliciting an innate immune response, are not a sign of infection and are observed with other vaccines.[100,104,105]

Vaccination is important even with the emergence of new COVID19 variants

Various SARS-CoV-2 VOCs have emerged during the pandemic, including Alpha (B.1.1.7), Beta (B.1.3.5.1), Gamma (P.1), Delta (B.1.617.2) and Omicron (B.1.1.529). Overall, data have shown that the vaccines have differing, and sometimes less efficient, neutralization capacities against VOCs compared to the wild-type lineage.[43,47,52,106–108] However, cross-protective efficacy against VOCs by vaccines based on the wild-type lineage has been shown, suggesting that, although neutralizing titres may be lower, they are sufficient to provide protection.[47] AZD1222 vaccine efficacy against symptomatic infection was 70.4% (95% CI 43.6–84.5) for Alpha (B.1.1.7).[106] Vaccine efficacy has been shown with BNT162b2 (100% (95% CI 53.5–100.0) against infection)[47] and Ad26.COV2.S (73.1% (95% CI 40.0–89.4) against severe disease)[43] in South Africa at a time when the Beta (B.1.351) variant was most prevalent.

Delta (B.1.617.2) was globally dominant in mid-2021 and recognized as an important and highly transmissible VOC (reproductive number of 5.08 *versus* 2.79 for the wild type).[109] Immunogenicity against Delta (B.1.617.2) by Ad26.COV2.S and AZD1222 vaccination has been shown, although this is to a lesser degree compared to wild-type or other variants. Ad26.COV2.S elicited a 1.7-fold decrease in neutralizing titres compared to wild-type at 8 months post-vaccination[67] and, similarly, neutralizing titres by AZD1222 showed a 3.2-fold reduction 28 days after the second dose.[51] Both BNT162b2 and mRNA-1273 give rise to neutralizing antibodies against Delta (B.1.617.2), which are decreased compared to the wild-type (1.4-fold and 2.1-fold decrease, respectively).[52,107] Although there is a decrease in neutralizing antibodies, RWE studies have shown that COVID-19 vaccines still have high levels of effectiveness against Delta after two doses.[110]

Omicron (B.1.1.529), the most recent VOC identified in November 2021, has significantly more mutations than other variants of concern and exhibits partial immune escape characteristics.[111] It is known that the initial primary vaccine regimen gives rise to neutralizing titres against Omicron that are lower than those induced against prior VOCs[112,113] and it has been shown to provide insufficient protection against infection.[114,115] Therefore, boosters have become an important vaccination strategy for Omicron (see next section).

The immunogenicity and efficacy (disease severity or infection) of vaccines against VOCs, particularly regarding long-term data, reported from the pivotal randomized controlled trials is still limited. However, RWE supports the available data and demonstrates vaccine effectiveness against VOCs amongst the general population (for a systematic review, refer to Higdon et al.[69]).

Booster vaccinations may increase protection when immunity begins to wane

Prime-boosting is a common vaccination strategy used with other infectious diseases[48,116] to maintain antibody titres above the threshold required for protection. Clinical trials[51,52,117] and observational studies[118] investigating third-dose boosters of COVID-19 vaccines have indicated that these increase neutralizing antibody titres and T cell immune responses and help to maintain efficacy or effectiveness levels observed after the initial vaccine regimen.[51,52,117,118] COVID-19 vaccines administered as boosters are well tolerated, consistent with the primary regimens.[49–53] Neutralizing antibody data have also shown that vaccine booster doses offer a higher protection against the highly transmissible Omicron (B.1.1.529) VOC when compared to the standard two-dose regimen, which elicits reduced effectiveness.[112,113] Memory T and B cells have also been reported to contribute

to the neutralizing breadth of antibodies against Omicron (B.1.1.529) following a booster dose.[113,119] Boosters have also been shown to substantially increase protection against Omicron (B.1.1.529)-related symptomatic disease (administered ≥6 months after second dose)[120] and hospitalization.[138] This effectiveness has been shown to wane after ≥3 months,[138] consistent with UK Health Security Agency[121] and CDC data,[122] which showed that vaccine effectiveness against Omicron-related symptomatic disease decreases despite a booster dose. The current data are based on emerging RWE drawn from multiple studies with different methodologies and limitations, thus further studies are required to fully elucidate their impact.

Owing to their safety and efficacy profiles, both homologous and heterologous booster vaccinations are approved by numerous regulatory authorities, including the FDA, EMA and MHRA, with mRNA vaccines being generally preferred for booster dosing.[123,124] These approvals were initially for healthcare workers and those in high-risk groups, but eligibility has since widened to anyone ≥18 years.[54,55] Second booster (fourth) doses have been approved in certain high-risk populations, such as the elderly population, those who are immunocompromised, and healthcare workers, to improve immunity following waning after the initial booster dose.[125] Second-generation vaccines, which may have a prolonged duration of protection, increased breadth of protection, and an ability to reduce transmission of disease, are currently being investigated in clinical trials.[39,40]

Vaccination is still effective and well tolerated in individuals who have already had COVID-19

Current recommendations, e.g. from the CDC and WHO, suggest COVID-19 vaccination regardless of prior infection.[100,126] Those with symptomatic infection should defer vaccination until symptoms have resolved. Some bodies, such as the UK Health Security Agency, advise that vaccination should occur 4 weeks following symptom onset or, in those who are asymptomatic, 4 weeks after testing positive for SARS-CoV-2.[124] In those who have received passive antibody therapy as part of COVID-19 treatment, vaccination should be deferred for at least 90 days, as reinfection is uncommon in the 90 days after initial infection based on the estimated half-life of these products and their expected time of protection.[100] In a report by the CDC, those with previous COVID-19 infections who were unvaccinated were 2.3 times likely to be reinfected than those who were vaccinated.[127]

Evidence shows that immune responses in individuals who have previously been infected with SARS-CoV-2 are robust after a single dose of BNT162b2, reaching similar IgG titres to those elicited by the full two-dose regimen in COVID-19-naive individuals,[128,129] demonstrating the value of vaccination even after prior infection.

Additionally, although immunological memory may exist after COVID-19 infection, immune responses wane over time.[100] Recent studies have demonstrated immunological memory for up to 8 months postsymptom onset as per IgG levels, whilst SARS-CoV-2-specific memory $CD4^+$ and $CD8^+$ T cells declined with a half-life of 3–5 months.[130] Of note, data are emerging indicating that natural immunity via prior infection may give rise to a lower antibody concentration when compared to vaccination.[131] Additionally, vaccination may prevent long-term sequelae following COVID-19, although further research is warranted to assess how the infection/vaccination sequence may impact this.[132–134] COVID-19 reinfection is becoming increasingly common with COVID-19, particularly following the Omicron surge, including amongst those have been fully vaccinated.[10] Although this may fuel vaccine hesitancy, data have also shown that, whilst previous SARS-CoV-2 infection in unvaccinated individuals can provide moderate protection, booster vaccination can maintain a high level (>70%) of protection against hospitalization and death in those with breakthrough infections.[135]

Although the majority of participants in clinical trials with COVID-19 vaccines did not have prior COVID-19 infection, evidence comparing those with and without COVID-19 infection prior to vaccination shows that it does not impact vaccine efficacy and safety.

Vaccination protects both me and others

The benefits of widespread immunization can be seen in RWE effectiveness data from the broad national immunization programme in Israel, showing declines in case numbers after the primary regimen and additional (third) doses.[31,118] Hospitalization rates, the number of new cases and positivity rates dropped relative to peak values after the initiation of the vaccination campaign. This pattern of decline followed the vaccine prioritization order: the decline was greater in older individuals, with consecutive drops observed in other age groups. Moreover, the effect was greater in cities where a larger proportion of individuals were vaccinated earlier.[31]

Data suggest that a leading driver of SARS-CoV-2 transmission is viral load,[136] which is also associated with COVID-19 severity[137,138] and can vary depending on VOC (e.g. viral load is approximately 1,000 times higher in those infected with Delta [B.1.617.2] *versus* the wild type).[139] COVID-19 vaccines have been shown to remain effective despite this higher viral load. For example, data from the United Kingdom, captured during periods when Alpha (B.1.1.7) and Delta (B.1.617.2) VOCs were prevalent, showed that BNT162b2 and AZD1222 were able to prevent new PCR-positive cases and infections; however, infections that did occur in vaccinated individuals had a similar peak viral load to those in unvaccinated individuals.[140]

Another driver of SARS-CoV-2 transmission is asymptomatic infection, which may account for more than half of all

Box 1. Key considerations for healthcare professionals when conducting a conversation with a COVID-19 vaccine-hesitant individual.[158–160]

Before the conversation starts

- Pay attention to a calm and relaxed atmosphere and to your own body language in the conversation (open, approachable posture)

Start the conversation with open-ended questions

- Open-ended questions allow individuals to respond with more information about their feelings and attitudes, enabling a clearer understanding of their concerns
- Example: *'What are the main reasons that you are concerned (or even anxious) about having the vaccine?'*

Acknowledge anxiety and concerns

- Acknowledging the concern reassures the individual that you are open and helps you to identify the source of their anxiety
- Example: *'It is understandable that there is a lot of information to take in, and some sources do not always present the information in the same way'*

Encourage and give positive feedback

- Encouragement motivates the individual and shows that they are valued
- Example: *'It is clear you have done a lot of research and consideration about the vaccine'*

Actively listen and build trust

- Actively listening gives you the chance to fully understand the point of view of the individual and respond with empathy
- Example: *'I can understand your concern with X, this is a mostly clearable doubt/misconception'*

Share information but do not overwhelm

- Overloading the individual with too much information may cause mistrust or confusion
- Example: *'What do you know about how the vaccines were developed? If you would like, I can share some information about it'*

Present evidence-based information clearly

- Providing evidence-based information and discussing benefits *versus* risks in a succinct and clear manner enhances understanding and builds trust
- Example: *'COVID-19 vaccines prevent X % of hospitalizations'* <u>not:</u> *'X% of people are hospitalized if they have COVID-19 after being vaccinated'*

End the conversation with a summary

- By summarizing the conversation, it is possible to ensure that everything has been understood and whether there are still any unanswered questions
- Example: *'Your concern was X. The concerns are comprehensible in the current context. You said, you already know X about COVID-19 vaccines and we could add X to the knowledge'*

Consider the format of the conversation (e.g. face-to-face *versus* telephone consultation)

- Be cognisant that telephone consultations are less personal, and the individual may disclose less information in this format; allow time for all questions/concerns to be addressed

Other considerations

- Be sure to give evidence-based information, and clearly review the benefits/risks with the patient, and how it may protect the individual as well as the population as a whole

transmissions.[141] A systematic review on EMA-approved vaccines reported that vaccination has an efficacy of 80–90% against infection, including asymptomatic infection.[142] Limiting asymptomatic infection may reduce the risk of transmission, although the extent of this risk reduction is currently uncertain.[143]

Indirect protection via high vaccine uptake is important when considering members of the community who are unable to receive vaccines[144] or individuals where vaccination has been shown to have a lower efficacy, such as haematology cancer patients, those who are immunocompromised, and solid organ transplant recipients, where seroconversion rates following

vaccination are significantly lower.[145] Furthermore, a higher disease prevalence and transmission rate drives the emergence of new SARS-CoV-2 variants, thus lowering prevalence by vaccinating a larger proportion of the population lessens the likelihood of the emergence of VOCs.[146]

Discussion

Providing evidence-based information is crucial to overcoming vaccine hesitancy and there is a rapidly evolving body of evidence on COVID-19 vaccination. For healthcare specialists, and especially the lay public, this information is complex and may be difficult to interpret. Additionally, whilst accurate, simplified sources of information are available to the general public (such as public health body and government resources), the internet, news outlets and social media can be major sources of misinformation and can cause fear, mistrust and confusion about COVID-19 vaccination, fuelling vaccine hesitancy.[147] Healthcare professionals are well placed to disseminate reliable information regarding vaccination and combat misinformation, and doing so in the correct manner is crucial to address concerns adequately and effectively. However, it should also be acknowledged that, whilst vaccines have proven a robust tool to combat the pandemic, COVID-19 will continue to pose many challenges in the future. As mentioned previously, the first vaccines approved have shown disadvantages in terms of duration of protection and, whilst booster doses can restore immune protection against Omicron (B.1.1.529) to previous levels,[148] this may not be the case for future variants. It is still unknown if seasonal/yearly boosters or variant-adapted vaccines to target virus evolution will be required. It must also be acknowledged that vaccines may have different effectiveness depending on the population, for example, in younger paediatric patients (aged 5–11 years),[149] thus could warrant further avenues of research as to how to achieve optimal effectiveness in such populations. Additionally, although vaccine safety continues to be actively surveyed, long-term, 5-year safety data are not yet available for the current vaccines. Furthermore, given the huge proliferation of data since the start of the pandemic, interpretation is challenging and should be conducted with caution as there may be caveats and limitations with study design and conduct. Some pitfalls include incomplete datasets, studies lacking controls or appropriate stratification, the capture of data at different timepoints (which can be misleading, e.g. during different periods of VOC prevalence, different restriction measures depending on country-specific government policies), and biased datasets (e.g. those that do not account for asymptomatic individuals due to lack of testing in this population). Articles that are publicly available that have not yet undergone peer review have steeply increased with the onset of the pandemic due to the rapidly evolving information available and should also be handled with caution. Healthcare professionals should be cognisant and transparent regarding these weaknesses and unknowns of vaccines and the data behind them, as this could also be important to foster trust and public confidence in vaccines.

Debunking beliefs that are not backed by evidence is rarely successful. Rather, the emotion (predominantly fears) behind hesitancy should be acknowledged and addressed to communicate effectively with those who have uncertainties. Discontinuation of contact with vaccination sceptics should be avoided. General guidance on how to communicate effectively with those who may be vaccine hesitant is provided in Box 1.

One possible technique in such conversations for shared decision-making is Motivational Interviewing (MI), which is a patient-centred communication style that engages the patient in conversation and supports their self-efficacy whilst encouraging their internal motivation for attitudinal change.[150–152] Five core skills are involved in MI: asking open questions, affirming, reflective listening, summarizing, and informing and advising, only if prior permission was given by the patient.[151] MI could be a useful tool in encouraging change of attitude in vaccine-anxious persons by effectively communicating risks for both the minor and rare but serious AEs associated with vaccination.[153]

Conclusion

COVID-19 vaccine hesitancy is a worldwide public health challenge and societies are faced with an enormous community and individual burden. Reaching those who are unvaccinated remains a key priority as is the reinforcement of the urgent need to be vaccinated with boosters against highly transmissible variants such as Omicron (B.1.1.529). Providing evidence-based information centrally contributes to the global effort to fight the pandemic. Comprehensible facts as well as individual and culture-adapted shared decision procedures can improve motivation to get vaccinated in COVID-19 vaccine-hesitant individuals.

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Correspondence: Shanti Pather, BioNTech SE, Mainz, Germany. Email: shanti.pather@biontech.de

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