Review

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COVID-19: vaccination, therapeutics and a review of the science and public health

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Abstract

COVID-19, stemming from the SARS-CoV-2 virus, has initiated a worldwide respiratory pandemic. Remarkable headway has been made in the realm of vaccination, as nearly every nation has initiated COVID-19 vaccine deployment. However, a mere 32.6% of individuals in low-income countries have received only a single vaccine dose. Unprecedented research and development endeavors have yielded over 170 COVID-19 vaccines, several of which are now in practical use. These vaccines have demonstrated remarkable efficacy in averting severe illness, hospitalization, and fatalities from COVID-19, even against emerging variants. Research pursuits persist, concentrating on novel vaccine technologies, oral and nasal vaccines, broader coronavirus protection, and vaccine combinations. In the realm of therapeutics, there have been significant strides in developing oral antiviral medications and monoclonal antibodies. Nonetheless, challenges in COVID-19 vaccination persist, encompassing issues of hesitancy, accessibility, financial barriers, knowledge gaps, and logistical hindrances. Robust monitoring via global agencies and reporting systems remains pivotal. Strategies for enhancing vaccination efficacy are rooted in fostering trust, countering misinformation, and expanding access. As for therapeutics, the approach involves dedicated research, clinical trials, regulatory streamlining, stockpiling, and international collaboration. Telemedicine and public awareness campaigns play integral roles in this effort, with coordination being the linchpin for preserving lives and mitigating the disease's impact. The global campaign against COVID-19 has witnessed substantial advancements, with an ongoing research focus on developing vaccines and therapeutics that are not only more accessible and affordable but also more effective, particularly for populations in low-income countries and vulnerable communities.

Keywords: barriers, COVID-19, strategies, therapeutics, vaccine

Introduction

In 2019, a new coronavirus, SARS-CoV-2, originating in China, caused the COVID-19 outbreak. The WHO declared it a pandemic in March 2020[1]. COVID-19 is a respiratory illness caused by the novel coronavirus, SARS-CoV-2. It's highly contagious and spreads through respiratory droplets from coughs and sneezes. Common symptoms include fever, cough, shortness of breath, fatigue, muscle aches, headache, sore throat, and congestion[2]. As viruses spread, their genetic material mutates, with most mutations having little impact. Those mutations that do affect the virus are called variants, potentially altering transmission, disease severity, diagnostics, vaccines, and treatments.

HIGHLIGHTS

- Over the time different variants of COVID-19 have emerged, they are summarized in the table.
- Various types of COVID-19 vaccination have developed and are in use. Overall about those vaccines are discussed.
- Barriers to COVID-19 vaccination encompass hesitancy, access issues, financial constraints, knowledge gaps, and logistical challenges.
- Strategies for improving vaccination focus on trust, counteracting misinformation, and enhancing access.
- Monitoring and evaluation of COVID-19 vaccines are focused.

Various variants of SARS-CoV-2, such as Alpha, Beta, Gamma, Delta, and Omicron, exist, each with sub-variants[3].

During COVID-19 pandemic, surplus fatalities (84%) are mainly in South-East Asia, Europe, and the Americas, with 68% in the top 10 countries. Middle-income nations account for 81% of the 14.9 million deaths. High-income and low-income countries make up 15% and 4%, respectively. In 2020 and 2021, the global death toll was higher among older adults and more often in men (57% male, 43% female)[4].

The first COVID-19 vaccination was administered on 8 December 2020[5]. COVID-19 vaccines work by teaching the body's immune system to recognize and fight the SARS-CoV-2 virus. This helps the body to protect itself from infection and to mount a strong immune response if it does become infected[6]. COVID-19 vaccines are safe and effective in preventing serious

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illness, hospitalization, and death from COVID-19[7,8]. There are a number of therapeutics that are being used to treat COVID-19, including monoclonal antibodies and antiviral drugs. Monoclonal antibodies are laboratory-made proteins that mimic the body's own antibodies. They work by binding to the SARS-CoV-2 virus and preventing it from entering cells[9,10]. Antiviral drugs are medications that work by blocking the replication of the SARS-CoV-2 virus[11,12].

Methodology

Literature search process

A wide range of materials like scientific studies, government reports, and data from well-known health organizations were used to understand the latest on COVID-19 vaccines and treatments. Trusted databases and websites, such as PubMed, Scopus, Google Scholar, WHO, CDC, and Our World In Data were used to search the information. The search strategy employed a combination of key terms such as "COVID-19", "vaccination", "therapeutics", "global status", "pandemic", "strategies", and "barriers" to gather all important information.

Data synthesis and analysis

After finding the relevant information, data were sorted to pick out the most crucial and trustworthy data about COVID-19 vaccines and treatments. Close attention was paid to the details of the studies and reports to ensure the information is reliable and relevant. Then, data were organized by themes like vaccine effectiveness, treatment advances, barriers and strategies used worldwide to make sense of the big picture.

Selection criteria for sources

Sources were based on their reliability and authority in the health field. Peer-reviewed articles and reports from key health organizations were focused on because they offer the most accurate and current information. This way, it covered a wide range of scientific research and reflected the global situation regarding COVID-19 vaccination and treatment efforts.

In short, this method aimed to thoroughly and accurately gather and analyze the latest data on COVID-19 vaccines and treatments. By doing so, it helps to provide useful insights for learner's and help guide public health decisions.

History and trend of COVID-19 outbreak

Trends and outbreaks

29 December 2019, marked the beginning of the new coronavirus COVID-2019 outbreak. The new coronavirus COVID-19 is extremely contagious and has impacted a significant number of individuals globally[13]. Within the next four days, 44 similar cases were reported in China, though the cause was still unknown. On January 7, 2020, China announced the identification of a new type of coronavirus, named SARS-CoV-2, and the disease it causes was designated COVID-19 by the WHO. The WHO declared the outbreak a pandemic on 11 March 2020. Upon the onset of the COVID-19 pandemic, China and the cruise liner "Diamond Princess" were thought to be the primary hubs for the virus. However, as of April 2020, the virus was present in over 210 nations and territories, with the USA, Iran, and Europe making up its new virus cluster[14].

With fluctuating prevalence and fatality outbreak trends, it is continually spreading. An earlier-identified novel coronavirus (2019-nCoV), now known as coronavirus (COVID-19), surfaced from Wuhan, China, towards the end of December 2019. It caused difficult epidemics in numerous parts of China and spread throughout the world. The coronaviruses are zoonotic diseases that spread from person to person by touch or droplet exchange. Before they show any outward signs of the illness, infected individuals might spread the infection. This is the primary cause of the disease's potential for rapid global spread from Wuhan, China. The source of the illness cases was seafood, snakes, and bats among Wuhan, China locals and tourists. In 2021, the emergence of new variants, such as Delta and Omicron, led to a resurgence in cases. However, the implementation of public health measures like social distancing, mask-wearing, and hand washing, along with the development and widespread distribution of vaccines, helped to reduce the severity of the pandemic[13].

Types of COVID-19 variants

Over the duration of the pandemic, SARS-CoV-2 has continuously evolved, producing versions that differ from the original virus[15]. Different variants of COVID-19 emerged over time are in the Table 1 below:

Deaths and severely affected countries

COVID-19 had a significant impact on a number of nations, including Iran, Germany, Switzerland, Italy, France, Spain, and the United States of America. The countries with the highest death rates are Iran, Italy, Spain, the United Kingdom, and France[13].

According to information released by the WHO as of 19 May 2024, the pandemic has resulted in 775 522 404 confirmed cases and 7 049 617 deaths worldwide. COVID-19 has had a significant impact on many nations. The countries with the highest death rates are: United States of America: 1.2 million, Brazil: 702 000, India: 534 000, Russia: 403 000, Mexico: 335 000, United Kingdom: 232 000, Peru: 221 000, Italy: 197 000, Germany: 175 000, France: 168 000, Indonesia: 162 000, Iran: 147 000, Colombia: 143 000, Argentina: 131 000, China: 122 000, Spain: 122 000, Poland: 121 000, Ukraine: 110 000, South Africa: 103 000, Turkey: 101 000. the extended pandemic has resulted in over 772.84 million confirmed cases and 6.98 million deaths[16].

Impact on People's lives

The COVID-19 lockdown significantly reduced environmental pollutants[17]. With industries, transportation, and businesses closed, greenhouse gas emissions dropped sharply. In China, shutting down heavy industries cut N_2O and CO emissions by about 50%[18]. Normally, 80% of NO_2 emissions, which contribute to acid rain and respiratory diseases, come from motor vehicles[19]. The European Environmental Agency reported a 30–60% drop in NO_2 emissions in cities like Barcelona, Madrid, Milan, Rome, and Paris due to the lockdown[20]. In the U.S., NO_2 levels fell by 25.5%[21]. In Delhi, India, NO_2 and PM2.5 levels decreased by nearly 70%, and across India, PM2.5 and PM10 levels dropped by 46% and 50%, respectively[22,23].

Table 1

COVID-19 variants.

WHO label	Pango lineage	Current status	Date of designation
NA	Variants containing the F456L spike mutations[a]	VOI	VOI: 1 September 2023
Omicron	BA.2.86	VBM	VBM: 1 September 2023
Omicron	XBB.1.9.1	VBM	VBM: 1 September 2023
Omicron	XBB.1.9.2	VBM	VBM: 1 September 2023
Omicron	XBB.2.3	VBM	VBM: 1 September 2023
Omicron	XBB.1.16	VBM	VBM: 1 September 2023
Omicron	XBB.1.5	VBM	VBM: 1 September 2023
Omicron	CH.1.1	VBM	VBM: 1 September 2023
Omicron	BA.2.74	VBM	VBM: 1 September 2023
Alpha	B.1.1.7 and Q lineages	VBM	VOC: 29 December 2020 VBM: 21 September 2021
Beta	B.1.351 and descendent lineages	VBM	VOC: 29 December 2020 VBM: 21 September 2021
Gamma	P.1 and descendent lineages	VBM	VOC: 29 December 2020 VBM: 21 September 2021
Delta	B.1.617.2 and descendant lineages	VBM	VOC: 15 June 2021 VBM: 14 April 2022
Epsilon	B.1.427 and B.1.429	VBM	VOC: 19 March 2021 VOI: 26 February 2021 VOI: 29 June 2021 VBM: 21 September 2021
Eta	B.1.525	VBM	VOI: 26 February 2021 VBM: 21 September 2021
Iota	B.1.526	VBM	VOI: 26 February 2021 VBM: 21 September 2021
Kappa	B.1.617.1	VBM	VOI: 7 May 2021 VBM: 21 September 2021
NA	B.1.617.3	VBM	VOI: 7 May 2021 VBM: 21 September 2021
Omicron (parent lineages)[b]	B.1.1.529 and descendant lineages	VOC	VOC: 26 November 2021
Zeta	P.2	VBM	VOI: 26 February 2021 VBM: 21 September 2021
Mu	B.1.621, B.1.621.1	VBM	VBM: 21 September 2021

Source: CDC, *SARS-CoV-2 variant classifications and definitions*. https://www.cdc.gov/coronavirus/2019-ncov/variants/variant-classifications.html. Accessed 1 September 2023. 2023.

NA, not applicable; VBM, variant being monitored; VOC, variants of concern; VOI, variant of interest.

[a]Many lineages have acquired the F456L mutation and common examples include EG.5, FL.1.5.1, and XBB.1.16.6.

[b]Omicron parent lineages include BA.1 or similar.

The lockdown also improved water quality. In India, rivers like the Ganga and Yamuna became cleaner without industrial pollution[24]. Italy's Grand Canal cleared up, and aquatic species returned[25]. Water pollution decreased on beaches in Bangladesh, Malaysia, Thailand, the Maldives, and Indonesia[26].

Quarantine measures reduced economic activity, lowering noise levels in many cities[27]. In Delhi, noise levels fell by 40–50% during the lockdown[28]. At the Govindpuri metro station, noise dropped from 100 dB to 50–60 dB, letting residents hear birds at 40–50 dB[29]. The Central Pollution Control Board of India reported noise levels in Delhi's residential areas fell from 55 dB (day) and 45 dB (night) to 40 dB (day) and 30 dB (night)[30].

A UN report stated the pandemic could shrink the global economy by 1% in 2020[31]. In 2019, global merchandise exports declined by 3% to $18.89 trillion[32]. The global stock market lost $6 trillion in a week, with the S&P 500 losing $5 trillion alone[33]. However, remote work led to new job opportunities in freelancing and eCommerce[17].

Domestic violence surged during the pandemic due to limited opportunities for victims to escape, restricted access to support, increased stress, and household tensions from economic losses and work disruptions[34–36]. In the UK, domestic violence deaths doubled between 23 March and 12 April 2020, compared to the average over the previous ten years[37].

Hospital employees faced long hours, causing physical and psychological strain. Many children began drinking alcohol during quarantine. School closures sent students home without proper guidance, leading to a lack of interest in studies[38]. Gym and stadium closures reduced physical activity, leading to a sedentary lifestyle, irregular sleep patterns, overeating, and unbalanced diets due to food shortages. These factors contributed to obesity and other health issues[39,40].

Current status in 2024

With around 292 thousand new cases recorded, the number of new cases fell by 44% globally between the previous 28-day period (8 January–4 February 2024) and the current 28-day period (5 February–3 March 2024). With 6200 new deaths reported, there were 51% fewer deaths than in the 28-day period prior. Over 774 million confirmed cases and over seven million

deaths had been reported worldwide as of 3 March 2024. Between 5 February and 3 March 2024, COVID-19 new hospitalizations and admissions to intensive care units (ICUs) showed a 35% and 64% overall decline, with ~78 000 and 500 admissions, respectively. https://www.who.int/publications/m/item/covid-19-epidemiological-update-15-march-2024

Global status of COVID-19 vaccination

Every country has been affected by COVID-19, with excess mortality estimated at ~15 million lives lost[4]. The first mass vaccination program was started in early December 2020[41].

Significant progress has been made on the vaccination front: nearly every country has implemented COVID-19 vaccines, and the global COVID-19 vaccine supply is now abundant with yearly manufacturing capacity of 11–16 billion vaccine doses,' and ample volumes available for lower-income countries through contracts and donations via the COVAX Facility, regional mechanisms, and bilateral approaches[42]. The data shows that 70.5% of the global population has received at least one COVID-19 vaccine dose, with a total of 13.51 billion doses administered. Currently, 18 512 doses are being administered daily. However, only 32.6% of people in low-income countries have received at least one dose[43]

Types of covid-19 vaccines and their efficacy

Currently, there are 199 candidate vaccines in preclinical development and 183 in clinical stages of development. 50 vaccines are approved for use in 201 countries and 12 Vaccines are granted in Emergency Use Listing (EUL) by WHO[44,45]. Different types of COVID-19 vaccination in use are described below:

Whole virus vaccines: (39/183 vaccines)

Live attenuated vaccines stand out for their ability to generate robust immune responses involving B and T cells, along with their relatively simple manufacturing process, making them strong contenders among vaccine options. A study by Arriola *et al.*[46] conducted in Peru demonstrated effectiveness against symptomatic or asymptomatic SARS-CoV-2 infection as 97% (95% CI 88–99%) for those who received more than 1 dose of the vaccine. This finding is comparable with those reported by WHO, in which BBIBP-CorV vaccine efficacy was estimated at 78.9% (95% CI 65.8–87%) against COVID-19[47]. Similarly, Berik and colleagues found that two immunizations with the inactivated QazCovid-in vaccine achieved 82·0% (95% CI 71.1–88.5) protective efficacy against COVID-19[48].

However, these vaccines may not be suitable for immunocompromised individuals and can occasionally trigger disease. In such cases, the inactivated virus vaccine, in which the entire virus is used as an immunogen, can provide a compensatory solution. Additionally, the overall adverse reaction rate of inactivated vaccines in clinical trials is low, with no reported deaths. A trial conducted by Lazarus *et al.* in the UK (COV-COMPARE) studied the immunogenicity and safety of inactivated whole virus vaccine (VLA2001) by categorizing patients into 3 groups; Open-label VLA2001 group (age 18–29 years), Randomised VLA2001 group (age $\geq$30 years) and ChAdOx1-S group (age $\geq$30 years) and found an incidence of any adverse events to be 92.6%, 88.8% and 98.1%, respectively. However, most of these adverse events were mild to moderate in intensity and only a few were defined as "severe"[49]. This suggests that these vaccines have a good safety profile[50] . One drawback of live attenuated vaccines is the need for repeat booster shots[51]. Notably, reports of eosinophil-related lung pathology are associated with the inactivated virus vaccine[52]. Example: Sinopharm, with Phase III trials demonstrating 78.9% efficacy against COVID[53].

DNA vaccines: (17 /183 vaccines)

Current DNA vaccines against SARS-CoV-2 can trigger both humoral and cellular immune responses targeting the Spike (S) glycoprotein. When the recombinant DNA plasmid is transfected into antigen presenting cells (APCs) like dendritic cells, it is transcribed into mRNA in the nucleus. The mRNA exits the nucleus and translates into the S protein in the cytoplasm, which is processed into smaller peptides presented to naïve B and T cells, activating both humoral and cell-mediated immunity[54].

DNA vaccines have notable strengths, such as the stability of the DNA molecule and the potential for long-term storage through freeze-drying. They are cost-effective, easy to produce, and stable, making them ideal for developing countries with limited resources[55]. Unlike mRNA vaccines requiring extremely low storage temperatures, DNA vaccines can be stored at room temperature, reducing cold chain storage costs and making them suitable for third-world countries[56]. Immune response persistence has been reported up to 48 weeks for the GLS-5310 vaccine and 24 weeks for the AG0302 vaccine, with other DNA vaccines reporting data during post-vaccination study visits[57].

Despite their advantages, human DNA vaccines face significant limitations and have not yet received marketing approval[58]. Concerns about insertional mutagenesis are relieved by the lack of reported cases in SARS-CoV-2 DNA vaccines so far[59] However, long-term immunopathological reactions and risks associated with gene-encoding cytokines remain potential issues. DNA vaccines face two challenges: the need for a device to enhance cellular uptake, increasing costs and delivery complexity, and relatively lower antibody responses compared to other platforms[57]. Future prospects include new platforms like minicircle DNA and Doggybone for DNA vaccination, with ZyCoV-D showing 66.6% effectiveness[60].

Key Highlights of Advanced DNA Vaccines:

- *ZyCoV-D:* Achieved emergency use authorization in India, the first DNA vaccine to gain regulatory approval for human use. A Phase 1/2 trial showed seroconversion rates of 34.8% (1 mg dose) and 90% (2 mg dose) over four weeks[61]. The Phase 3 study with nearly 30 000 participants during the Delta variant outbreak showed 66.6% efficacy in preventing serious illness, leading to emergency use authorization[60].

- *INO-4800:* Evaluated in Phase 1 and 2 trials. In Phase 1, 40 participants received 1 mg or 2 mg of the vaccine at 0 and 4 weeks, with seroconversion rates of 74% and 100%, respectively[62]. The Phase 3 trial was put on hold due to concerns about targeting the ancestral SARS-CoV-2 spike protein, now irrelevant to prevalent Omicron variants. INO-4800 remains part of a WHO Solidarity Trial. https://www.sec.gov/Archives/edgar/data/1055726/000119312522146350/d259881dex991.htm

- *COVID-eVax:* In a Phase 1 study, 80 subjects received 0.5 mg, 1 mg, or 2 mg of the vaccine at 4-week intervals, with a fourth group receiving 2 mg only at baseline. Higher antibody

and T-cell responses were observed in the 1 and 2 mg dose groups[63].

mRNA vaccines: (43/183 vaccines)

Messenger RNA (mRNA) vaccines are a new, highly effective class of vaccines, proving successful in preclinical and clinical studies against infectious diseases. Their synthetic nature and sequence-independent manufacturing allow for rapid and flexible design and production. For example, the development of SARS-CoV-2 mRNA vaccines began just 42 days after the virus's genetic information was shared with Moderna, achieving nearly 90% efficacy in Phase III trials, making them ideal for addressing rapidly emerging outbreaks[64]. Both Pfizer–BioNTech (BNT162b2) and Moderna (mRNA-1273) vaccines received widespread approval and have been in use since December 2020. There are three main types of mRNA vaccines: non-replicating mRNA, self-amplifying mRNA, and circular RNA[65]. Like DNA vaccines, mRNA vaccines stimulate both humoral and cellular immune responses[66]. Unlike traditional vaccines, mRNA vaccines use the genetic information of the antigen to prompt in vivo transcription of the target immunogen. This allows for faster production compared to traditional vaccines[50].

However, mRNA's large molecular weight, negative charge, and proneness to degradation by nucleases necessitate vaccine delivery devices like lipid nanoparticles (LNPs)[65]. Strategies such as using the 5′ cap, UTRs, and 3′ poly-A tail enhance stability and activity[67]. Quality control in mRNA vaccine production involves monitoring raw materials (plasmid, lipid, nucleotide), intermediates, and final products. Plasmid purity, lipid quality, and mRNA content must be scrutinized. The mRNA-LNP complex should be produced with precise calibration and encapsulation efficiency. Ultra-low temperature storage is required due to mRNA instability, with Moderna's mRNA-1273 effective for 6 months at – 20 °C, and Pfizer/BioNTech's BNT162b2 effective for six months at – 60 to – 80 °C. Freeze-drying is a promising technique to improve mRNA vaccine stability[65].

Although mRNA vaccines have reported side effects, they are generally mild to moderate and transient. Common side effects include headache, fatigue, and myalgia, while severe reactions like anaphylaxis are very rare[68–70]. For example, the Pfizer/BioNTech vaccine shows 95.6% efficacy with three doses, and Moderna's vaccine prevents hospitalization in 93% of patients four months after the second dose, decreasing to 58% after six months[53,71].

Moderna

In March 2020, a Phase I trial with 45 individuals showed dose-dependent immune responses and mild to moderate adverse events. A Phase III trial with 30 420 participants showed 94.1% efficacy in preventing COVID-19 and high efficacy (> 90%) after 6 months[64,72,73].

Pfizer/BioNTech

In Phase I trials, participants received two doses (3 weeks apart), showing dose-dependent immune responses and mild adverse events. A Phase III trial with 43 548 volunteers showed 95% efficacy and mild to moderate adverse reactions. In a large study in Israel, the vaccine provided 92% protection against documented SARS-CoV-2 infection and 94% against symptomatic COVID-19, with an 87% reduction in hospitalizations[64,74].

In Israel a study of 596 618 individuals vaccinated with Pfizer/BioNTech showed 92% protection against infection, 94% against symptomatic COVID-19, 92% against severe disease, and 87% reduction in hospitalization[74].

Viral vector vaccines: (25 + 1(VVnr + APC)/183 vaccines)

Viral vector vaccines, including recombinant and whole virus types, are known for their high efficacy. They can elicit strong Th1 cell responses but may cause complications like thrombocytopenia, so monitoring platelet levels in recipients is crucial[50,53]. Examples include AstraZeneca's two-dose vaccine with 76% efficacy, Covishield, which prevents death in 91% of cases, Sputnik Light with 93.5% efficacy, and Johnson & Johnson's (J&J) single dose which initially has 66% efficacy but decreases to 13% over time[53]. These vaccines use adenovirus to carry SARS-CoV-2 spike protein DNA into human cells, triggering humoral and cellular immune responses that produce neutralizing antibodies. This helps the body destroy the SARS-CoV-2 virus upon future exposure[75].

Current adenovirus vector-based vaccines include JNJ-78435735 by Johnson & Johnson, AZD1222 by Oxford-AstraZeneca, Sputnik V and Sputnik Light by Gamaleya Institute, and CanSino vaccine by CanSino Inc. Among these, the FDA has approved the Janssen (JNJ-78436735) vaccine for emergency use[75].

Janssen (JNJ-78436735 or AD26.COV2.S)

It was approved by the FDA on 28 February 2021, but briefly suspended due to rare cases of cerebral venous thrombosis and thrombocytopenia. The suspension was lifted on 23 April 2021. It requires a single 0.5 ml dose administered intramuscularly and can be refrigerated for up to three months at 2–8°C and up to two years at – 20°C[75]. In the Phase 3 ENSEMBLE trial, the vaccine showed 72% efficacy in the US and 66% overall at preventing moderate to severe COVID-19. It provided 85% protection against severe COVID-19 globally and complete protection against COVID-19-related hospitalizations and deaths[76]. The Phase 3 ENSEMBLE 2 study with 6000 UK participants showed two doses provided 100% protection against severe/critical COVID-19, 75% against symptomatic COVID-19 globally, and 94% in the US[77]. Its common side effects includes: Injection site pain, erythema, swelling, headache, fatigue, myalgia, nausea, and fever. Rarely it can cause: Convulsions, tinnitus, peripheral neuropathy, Guillain-Barré syndrome, and Bell's palsy in patients with predisposing conditions[75].

Astrazeneca (AZD1222 or ChAdOx1 nCoV-19)

AZD1222 vaccine formerly called ChAdOx1 nCoV-19 also known by other names as Oxford-AstraZeneca Vaccine, Covishield, and Vaxzevria. AZD1222 was developed by Oxford University. From the phase 1 and 2 clinical trial data, the AstraZeneca vaccine had shown significant efficacy of 64.1% after at least a single dose against symptomatic disease and 70.4% after two doses, with no safety concerns. The phase 3 study showed a vaccine efficacy of 76% at preventing symptomatic COVID-19 infection and 100% efficacy at preventing

severe or critical disease and hospitalizations. The two doses of the AstraZeneca vaccine have shown 61.7% effectiveness against the B.1.1.7 (UK) variant, 10.4% against mild to moderate due to B.1.351 (South Africa) variant, and 77.3% against other variants[78]. Similar to other vaccines, the most common adverse effects are local injection site pain, tenderness, erythema, and swelling, nausea and vomiting, fever with chills, muscle ache, headache, and malaise, which are predominantly seen on the day 1 after vaccination. A rare complication of neutropenia, hemolytic anemia, and transverse myelitis was seen[75].

Subunit vaccines: (59/183 vaccines)

Protein subunit that contains a specific product of the virus rather than complete viral particle is used to elicit immune responses. S protein of SARS-CoV-2 has been shown, to be an ideal target for vaccine development on multiple platforms due to its high antigenicity and potency to induce robust immune responses . However, since only a few viral components are included in the protein subunit vaccine that do not exhibit the full complexity of the virus antigen, their protective effect may be limited and, in some cases, may elicit unbalanced immune responses[79].

These vaccines are regarded as the safest options, particularly when combined with other vaccine platforms. These vaccines have shown the ability to induce mucosal immune responses through nasal and oral administration, potentially preventing virus transmission through the respiratory tract. However, they may not efficiently generate cytotoxic T cells[58,80] . For example Novavax- has efficacy rate of 90.4%[52].

Comparing vaccine efficacy based on relative and absolute risk

Comparing vaccine efficacy based on relative and absolute risk involves assessing the relative risk ratio (RRR) and absolute risk ratio (ARR). The RRR, indicating the risk of an event in the vaccinated group versus the unvaccinated group, reports values like 95% for Pfizer–BioNTech, 94% for Moderna–NIH, 67% for J&J, and 67% for AstraZeneca–Oxford vaccines. However, focusing on RRR may not provide a complete picture. ARR offers a broader perspective, reflecting the difference in attack rates between vaccinated and unvaccinated populations. For example, ARR values include 1.3% for AstraZeneca–Oxford, 1.2% for Moderna–NIH, 1.2% for J&J, and 0.84% for Pfizer–BioNTech vaccines[81].

Three major outcomes, including symptomatic COVID-19, severe disease, and serious adverse events, show variations in vaccine efficacy. For instance, high-certainty evidence supports the reduction in symptomatic COVID-19 for Pfizer, Moderna, AstraZeneca, and Sinopharm-Beijing vaccines, while moderate-certainty evidence associates Novavax with such reduction. Severe disease is largely reduced by Pfizer, Moderna, Sinopharm-Beijing, and Bharat vaccines, with moderate-certainty evidence for Novavax. However, data on the impact of CoronaVac on severe disease remains insufficient. Regarding serious adverse events, Moderna, AstraZeneca, and Sinopharm vaccines likely show no difference compared to placebo, while the evidence is insufficient for Pfizer, CoronaVac, Sinopharm-Beijing, and Novavax vaccines due to low reported serious adverse events[82].

Overview of therapeutics used for COVID-19

Several studies have shown that chloroquine inhibits SARS-CoV-2 entry, but concrete data on its efficacy is lacking. Doses exceeding 5 g of chloroquine have been associated with an increased incidence of ventricular dysrhythmias and cardiovascular collapse[83,84]. Hydroxychloroquine has been shown to increase the risk of diarrhea and nausea or vomiting[85] . APN01 is a recombinant human ACE2 protein is under investigation for its efficacy. It has been associated with unintended immunogenicity[83,84].

Nucleotide Analogs Remdesivir is currently approved for COVID-19 but offers limited advantages, such as a median recovery time of 10 days compared to 15 days in the ACTT-1 trial. Metabolic acidosis can occur, and about 5% of patients experience bone marrow suppression[83,84,86]. For individuals with non-severe COVID-19, remdesivir is likely to reduce the need for hospitalization. However, its impact on mortality is unclear. There is no evidence to suggest that remdesivir increases the risk of adverse side effects that would lead to discontinuation of the drug[85]. Favipiravir is a nucleoside analog that inhibits RNA-dependent-RNA-polymerase. It reduces the viral load in the upper respiratory tract and in the lungs[84].

The WHO GDG panel found no evidence that lopinavir-ritonavir (Protease Inhibitors) improved patient-important outcomes, such as reduced mortality, need for mechanical ventilation, or time to clinical improvement questioning its efficacy . However, one study demonstrated reduced mortality and the incidence of ARDS when lopinavir-ritonavir (AbbVie) was used in combination with ribavirin compared to ribavirin alone. Although overdose with protease inhibitors is uncommon, it can happen[84,86].

SARS-CoV-2–targeting neutralizing monoclonal antibodies (mAbs) like Bamlanivimab plus Etesevimab, Casirivimab, offer a targeted approach, reducing off-target toxicity but potentially making them susceptible to emerging viral variants. In the RECOVERY trial, hospitalized SARS-CoV-2 seronegative patients treated with mAbs showed reduced 28-day mortality[83,84].

Anti-inflammatory therapies like Corticosteroids are commonly used in COVID-19 management. Large trials like REMAP-CAP and RECOVERY have demonstrated a mortality benefit for hospitalized patients receiving glucocorticoid therapy[83,84] Corticosteroids are not associated with an increased risk of adverse events, other than a likely increase in the incidence of hyperglycemia and hypernatremia[85].

Barriers to COVID-19 vaccination and its solutions

Hesitation to get vaccinated

The biggest hurdle in getting more people vaccinated against COVID-19 is vaccine hesitancy. This hesitation isn't about just one thing; it's a mix of worries. Some people are concerned about whether the vaccine is safe, if it really works, and what side effects it might have. Then there's a lack of trust in the government and health organizations, which doesn't help. On top of all this, there's a lot of false information floating around on the internet and social media, making people doubt the vaccine even more[87]. Clear, transparent communication from trusted community leaders and healthcare providers can help. Sharing evidence-based

information, including benefits and possible side effects, can address concerns. Encouraging open dialog and providing platforms for people to ask questions and get reliable answers are key. Examples include town hall meetings or social media campaigns featuring medical professionals[88].

Trouble accessing vaccines

Getting to a vaccine appointment isn't easy for everyone. For some, it's a struggle because there's no easy way to get to the places where vaccines are given. Others find that the times vaccines are available don't fit with their schedules, or they might face language barriers that make the whole process even more challenging[89]. Mobile vaccination units and community-based strategies have been effective in reaching underserved communities, improving access by addressing geographical, linguistic, and operational barriers. For example, in Ohio, Partners In Health identified gaps in vaccine access through mapping and deployed mobile vaccination units accordingly, successfully targeting communities of color and providing vaccinations in accessible locations like community centers[90]. Similarly, in Cheshire and Merseyside, UK, mobile units targeted disadvantaged communities, offering walk-in vaccinations without appointments, significantly increasing uptake among those who might have faced barriers accessing conventional vaccination sites[91].

Cost concerns

Even though the vaccine is supposed to be free for everyone, there are still cases where people have to pay, which can be a big problem for those who don't have insurance or whose insurance doesn't cover much. This makes the vaccine seem out of reach for many[92]. Solutions can be the clear communication about the cost-free nature of vaccines is vital. For incidental costs, community funds or government programs could offer support. Insurance companies should be encouraged to cover any related costs, ensuring the vaccine is genuinely free for everyone. https://www.cdc.gov/vaccines/programs/bridge/index.html

Not knowing enough

A lot of people just don't have enough information about the COVID-19 vaccine. This might be because they don't know where to find reliable information, there's a language barrier making the available information inaccessible, or the medical jargon is too complicated. Without clear and understandable information, deciding to get vaccinated becomes harder[93]. It can be overcome by conducting Educational campaigns using simple language and visuals can help demystify vaccine information. Translating materials into multiple languages and using various media channels can reach a wider audience. Partnerships with community organizations can facilitate workshops or informational sessions to educate residents. https://www.who.int/europe/activities/supporting-vaccine-safety/strengthening-community-acceptance-of-vaccines-through-educational-interventions. https://www.cdc.gov/vaccines/covid-19/vaccinate-with-confidence/community.html.

Logistical issues

Even if people decide to get the vaccine, there can be logistical nightmares like long lines at vaccine sites, trouble finding an appointment time that works, or not having someone to watch your kids while you go. These problems can make the process so frustrating that some people might just give up[73]. The solution could be simplifying the appointment process through online systems and walk-in options can alleviate scheduling issues. Providing childcare services at vaccination sites or offering vouchers for childcare can remove a significant barrier for parents[94].

Monitoring and tracking

Monitoring and tracking the progress and impact of COVID-19 vaccination efforts are crucial for ensuring that the vaccines remain safe and effective for public use. This process is multilayered, involving the analysis of vaccination rates, identifying areas with low vaccine uptake, and keeping a vigilant eye on the vaccines' safety and efficacy[95,96].

To specifically address concerns around vaccine safety, systems like the vaccine adverse event reporting system (VAERS) in the United States and the European Medicines Agency (EMA) safety reporting system in the European Union are integral[97,98].

Vaccine adverse event reporting system

The VAERS is a U.S.-based system for monitoring the safety of vaccines after they're approved for public use. It functions as a national early warning system to detect possible safety issues with vaccines. VAERS is co-managed by the CDC and the FDA, allowing healthcare professionals, vaccine manufacturers, and the general public to report any adverse events or side effects that occur after vaccination. The reports can include a wide range of health problems or symptoms, from mild side effects like sore arms to more serious health outcomes that could be related to a vaccine. Once a report is submitted, experts analyze the data to look for unusual patterns or trends that might indicate a vaccine safety concern. This system plays a crucial role in maintaining public health by ensuring vaccines remain safe and effective for everyone[95,97,98].

European Medicines Agency (EMA)

The EMA plays a critical role in the regulation and supervision of medicinal products within the European Union. Its function unfolds in a structured, step-by-step process aimed at ensuring the safety, efficacy, and quality of medicines available to EU citizens. Initially, pharmaceutical companies submit an application to the EMA for the evaluation of new medicines, providing detailed data from clinical trials and other studies. The EMA's scientific committees, composed of experts from across the EU, then assess this data to determine the medicine's benefits and risks. This evaluation involves a rigorous review of the clinical trial results, safety information, and the medicine's effectiveness for its intended use. If the benefits outweigh the risks, the EMA recommends granting marketing authorization to the European Commission, which has the final say on approval for the EU market. Once a medicine is approved, the EMA continues to monitor its safety through pharmacovigilance activities, including the collection and analysis of adverse event reports, to ensure ongoing safety and efficacy in the broader population. This comprehensive process underscores the EMA's commitment to safeguarding public health by regulating access to safe and effective medicines across the EU[96,99,100].

These systems are pivotal in identifying any unexpected patterns or significant safety concerns that could suggest issues with the vaccines. The data they collect informs ongoing public health recommendations and adjustments to vaccination strategies as needed.

Evaluating the impact of monitoring systems

The effectiveness of these monitoring systems is continually assessed through a variety of methods, including statistical analyses to detect patterns, trends, and anomalies in the reported data. Evaluations also consider the system's reach and the reliability of the data captured. By continuously refining these systems, health authorities can enhance their responsiveness to any emerging safety concerns, thereby bolstering public confidence in the vaccination process. https://www.ema.europa.eu/en/about-us/what-we-do/crisis-preparedness-management/vaccine-monitoring-platform[101].

The CDC operates systems like VAERS and VSD to analyze vaccine safety data and identify potential issues. The FDA, in collaboration with CDC, CMS, and others, uses both passive and active surveillance to ensure vaccine safety, participating in global pharmacovigilance efforts with organizations like ICMRA and WHO. The EMA, with ECDC, has established the VMP to oversee post-authorization studies on vaccine safety and effectiveness in the EU. https://www.ema.europa.eu/en/about-us/what-we-do/crisis-preparedness-management/vaccine-monitoring-platform. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/reporting-systems.html.[101]

To figure out how well these vaccine monitoring systems are working, experts use a few steps. First, they dive into the data with statistical tools to spot any unusual patterns, trends, or oddities in the reports about vaccine side effects. They also check how far-reaching these systems are—basically, how much of the population they're covering—and how reliable the gathered data is. By regularly tweaking and improving these systems based on what they find, health authorities make sure they're always on top of any new safety issues that emerges. This constant vigilance helps keep the public's trust in vaccines strong. https://www.ema.europa.eu/en/about-us/what-we-do/crisis-preparedness-management/vaccine-monitoring-platform. https://www.cdc.gov/coronavirus/2019-ncov/vaccines/reporting-systems.html.[101].

The role of public participation

Public involvement in these reporting systems is invaluable. Individuals who receive the vaccine play a crucial role in safety monitoring by reporting any adverse effects they experience. To contribute, individuals can report their experiences directly to VAERS or the EMA's safety reporting system via their respective websites. When individuals who get vaccinated report any side effects they encounter, they're directly contributing to the vast pool of data that helps track the safety and effectiveness of vaccines in the real world, beyond what clinical trials can show. By streamlining the reporting process, authorities aim to lower any barriers to participation, underscoring the importance of every individual's contribution. https://vaers.hhs.gov/reportevent.html. https://www.cdc.gov/vaccinesafety/ensuringsafety/monitoring/vaers/index.html

Strategies to improve COVID-19 therapeutics

Enhancing COVID-19 therapeutics requires a comprehensive approach. This includes investing in research and development, conducting global clinical trials, expediting regulatory processes, stockpiling critical medications, and fostering international collaboration[83,102]. Additionally, telemedicine can expand access, while ensuring equitable distribution is vital. Monoclonal antibodies should be developed and distributed for early treatment, and adaptive research is essential to address emerging variants[103]. Public awareness campaigns should educate the public about available therapeutics. A coordinated effort involving governments, healthcare systems, and the scientific community is paramount, emphasizing flexibility, data-driven decision-making, and a focus on saving lives and reducing disease severity[104]

Conclusions

In conclusion, the identified knowledge gap pertains to the unequal distribution and accessibility of COVID-19 vaccines, particularly in low-income countries, and the associated challenges of hesitancy, financial barriers, and logistical issues. Addressing this gap will contribute to existing literature by promoting equitable health solutions, advancing novel vaccine technologies, improving therapeutic options, and developing effective strategies to enhance vaccine uptake and public trust. Ongoing research is directed toward more accessible and effective vaccines and therapeutics, with a focus on reaching low-income countries and vulnerable populations. The commitment to international collaboration and coordinated efforts remains paramount in the collective goal of saving lives and reducing the impact of this pandemic.

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Consent

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