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MINI-REVIEW

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# Impact of the COVID-19 pandemic on routine vaccine landscape: A global perspective

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**ABSTRACT**

The coronavirus disease (COVID-19) threat is subsiding through extensive vaccination worldwide. However, the pandemic imposed major disruptions in global immunization programs and has aggravated the risks of vaccine-preventable disease (VPD) outbreaks. Particularly, lower-middle-income regions with minimal vaccine coverage and circulating vaccine-derived viral strains, such as polio, suffered additional burden of accumulated zero-dose children, further making them vulnerable to VPDs. However, there is no compilation of routine immunization disruptions and recovery prospects. There is a noticeable change in the routine vaccination coverage across different phases of the pandemic in six distinct global regions. We have summarized the impact of COVID-19 on routine global vaccination programs and also identified the prospects of routine immunization to combat COVID-like outbreaks.

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## Introduction

Worldwide, more than 610 million confirmed cases of coronavirus disease (COVID-19) and 6 million deaths have been registered to date. As of October 1, 2022, about 3,565,278 of the world population are vaccinated against COVID-19, with 4,79,994 belonging to upper-middle-income countries, 102,048 to low-income countries, and 1,941,569 to lower-middle-income countries.[1] However, the pandemic has resulted in the disruption of routine vaccinations in at least 68 countries, affecting more than 80 million children worldwide, especially in the lower-middle-income regions (LMIRs). Although sustainable catch-up immunization programs have recommenced in affluent countries to mitigate disruptions, this is not the case in LMIRs, impeding global sustainable recovery.[2] An African study has projected a horrifying 100 child deaths that could be prevented by sustained routine immunizations compared with each death caused by COVID-19 acquired from an immunization visit.[3] Reduced vaccination rates for children even for brief periods could result in an increasing number of vulnerable people and elevate the danger of outbreaks of vaccine-preventable diseases (VPDs) like measles, polio, diphtheria, and pertussis. Besides, immunization disruptions jeopardize the 90–95% vaccination coverage, which is imperative for herd immunity in general. Therefore, vaccine disruptions potentiate the accumulation of unimmunized children, leading to circulating vaccine-derived viral strains (such as polio) that endanger future outbreaks of VPDs. Intriguing reports of polio from human infections and sewage systems from the United Kingdom, United States, and Israel are alarming.[4] Furthermore, vaccination hesitancy including the fear of COVID-transmission during clinic visits is another obstacle to be dealt with.[5–7] Low uptake has also been reported in maternal vaccination which is a promising strategy in preventing newborn severe infections.[8] Here, we attempt to present comprehensive information on the impact of COVID-19 on routine vaccine coverage that will not only address the surrounding issues but also identify gaps and solutions in the event of futuristic COVID-like outbreaks.

## The COVID vaccine scenario and impact

The COVID-19 vaccine coverage too varied from nation to nation. During the course of pandemic, multiple variants in the process of adapting to the host evolved, making the vaccine design more dynamic, and challenging. The WHO classified these variants into variant of concern (VOC) and variant of interest (VOI).[9,10] With the emergence of variants during vaccine development and clinical trials, the primary goal was to incorporate the new variants to combat emerging strains, which further demanded continuous surveillance, research, and production. Pharmaceutical industries employed this goal as their driving force to get their vaccine into clinical trials and subsequently to the market. Scaling up the COVID vaccine worldwide in order to control the pandemic was the immediate and prime action. Consequently, the production and dissemination of non-COVID vaccines suffered a setback owing to the increasing pressure on the pharmaceutical sector to

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escalate COVID-vaccine production.[11] This globally hampered the routine immunization schedule among children, vulnerable adults, and pregnant women during and after the pandemic.

## Global perspectives on routine vaccine disruptions

### *Population coverage of routine vaccines*

Global immunization is the key to the primary health and development as the various immunization programs have prevented more than 20 life-threatening diseases around the globe.[12] The WHO established the extended immunization program and aimed to ensure universal access to four vaccines, namely BCG (Bacillus Calmette–Guerin), DTP (diphtheria, tetanus toxoid, and pertussis), Pol, and MCV (measles-containing vaccine) which protect against tuberculosis; diphtheria, tetanus, and pertussis; poliomyelitis; and measles, respectively.[12,13] Other vaccines that are restricted to certain populations are rotavirus vaccines (rota), pneumococcal conjugate vaccine (PCV), rubella-containing vaccine (RCV), *Haemophilus influenzae* type b vaccine (HiB), Hepatitis B vaccine (HepB), and Human papillomavirus vaccine (HPV).[13] The key objective of the immunization agenda 2030, by the World Health Assembly in 2020, is to cover zero-dose children, i.e., children who have not even got part-vaccination of DTP as well as the under-immunized children.[14,15] However, the immunization program was severely affected during the pandemic, resulting in an interruption to the global vaccination coverage.[12]

To understand the stark difference in the global immunization coverage, we have classified the immunization programs covered up to the year 2019 as pre-COVID phase and year 2020–2021 as COVID phase and year 2022 as COVID-19 recovery phase.

### *Pre-COVID-19 phase*

The global coverage of full vaccination of diphtheria, tetanus toxoid and pertussis (DTP1) was around 89–90%, while the part-vaccinations of DTP (DTP3), polio vaccine, and MCV (MCV1) were estimated to be in the range between 84% and 86% during 2010–2019.[14,15] The part-vaccination of MCV (MCV2) was increased to 71% from 42% in 2019.[16] The underused routine vaccines were estimated to have a global coverage of 39% for rota vaccine, 48% for PCV, 71% for RCV, 72% for Hib, 43% for Hep B, and 15% for HPV in 2019.[17] The overall vaccine coverage statistics in 2019 comprising eight routine vaccines administered globally indicated highest average vaccine coverage in the American region (~77.8%) and lowest in the African region (~52.8%). The other regions such as Europe, South-east Asian (SEA), Eastern Mediterranean (EM), and Western-Pacific (WP) regions had average vaccine coverage of 76%, 70%, 64.8%, and 63.1%, respectively (Figure 1). It can also be observed that DTP, Hib, and Pol vaccines have high uniform global coverage among the rest. MCV and RCV coverages substantially are low in Africa and EM regions. The disparity in vaccine coverages widens the regional outbreak risks, especially if there are major disruptions.

### *COVID-19 phase*

The global vaccination coverage of DTP3 markedly suffered showing a critical reduction from 86% in 2019 to 83% in 2020 and 81% in 2021.[15] The part-vaccination of MCV suffered a sharp decline over the last 2 years, leaving 24.7 million children unvaccinated, while the population coverage of MCV2 was dropped from 86% to 83% in 2020 and 81% in 2021 accounting for 14.7 million deprived of MCV2.[16] Global coverage of other routine vaccines was also reduced by 2–3% compared with 2019; however, polio and HPV immunizations suffered a reduction by ~9%.[18] An estimate of 25 million

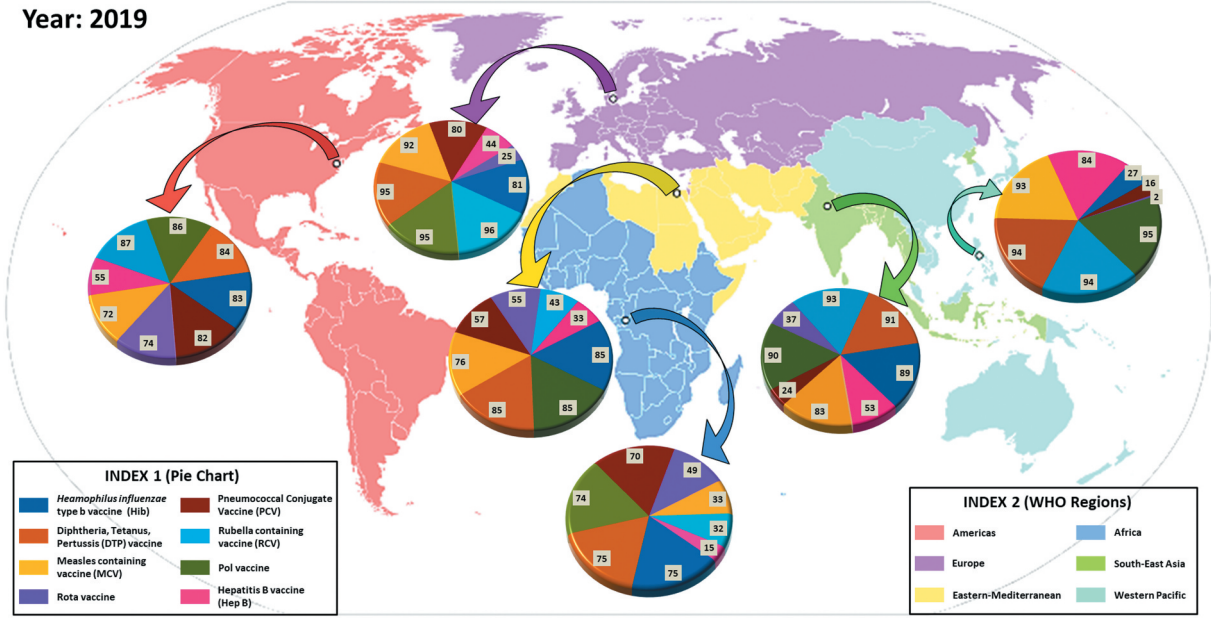


**Figure 1.** Global vaccine coverage (in percentage) of routine vaccines in 2019 (pre-pandemic).

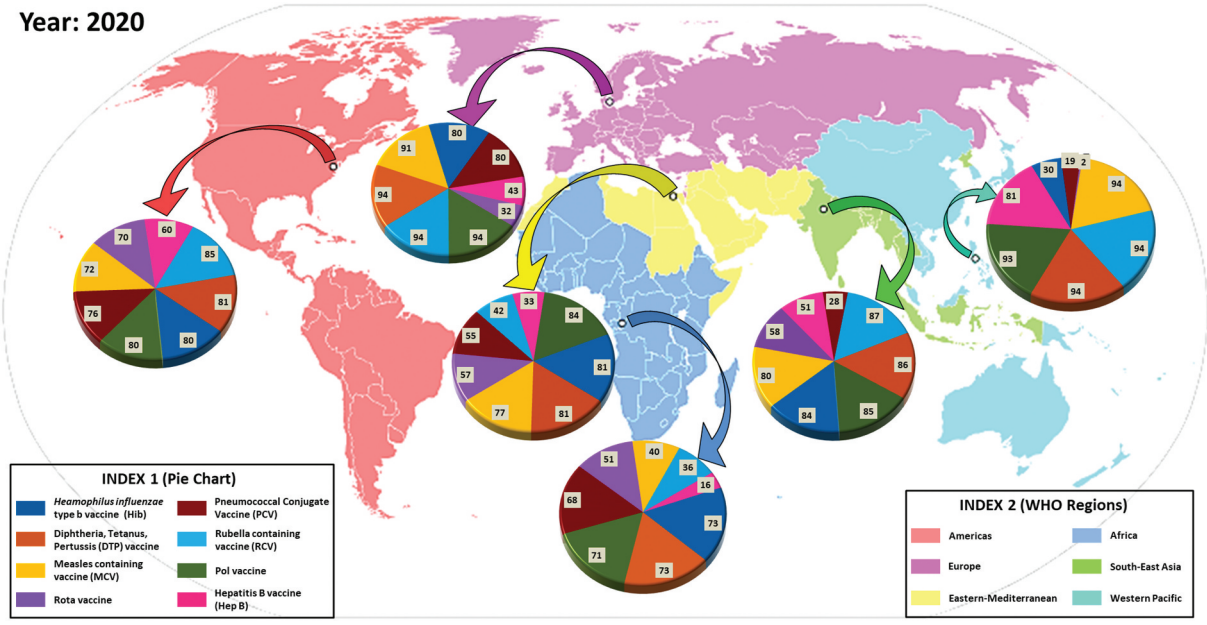


**Figure 2.** Global vaccine coverage (in percentage) of routine vaccines in 2020 (pandemic-peak phase).

children of age group of 1 and under missed their routine immunizations which accounted for 5.9 million lower compared with that in 2009. This also marks the highest number of failed vaccination coverage since 2009.[18] As far as the overall average vaccine coverage is concerned during this phase, SEA (66%) and American region (75%) witnessed the major reduction than pre-COVID phase (Figure 2) than the other regions. The drastic decrease in MCV coverage in SEA during COVID-19 phase potentiated the regional outbreaks of measles.[19]

### *COVID-19 recovery phase*

In terms of overall average vaccine coverage in this phase, recovery of the vaccine coverage after the COVID was not observed in the WP (61.2%) and American (74.8%) regions as compared with pre-COVID phase especially for the DTP and Pol vaccines (Figure 3). European region showed remarkable consistency in terms of vaccine coverage all through (76%). The other regions also showed steady recovery in the overall average vaccine coverage.

Effective public health campaigns, vaccination implementation and evaluation programs have enabled recommencing the routine vaccination. Vaccination status in the COVID-19 recovery phase is slowly trickling in and scientific data on this are limited. In spite of vaccine hesitancy widespread across the globe especially post pandemic, COVID-19 and Influenza vaccine uptake has been significantly increased.[20] It was observed that the flu-vaccine coverage in the North

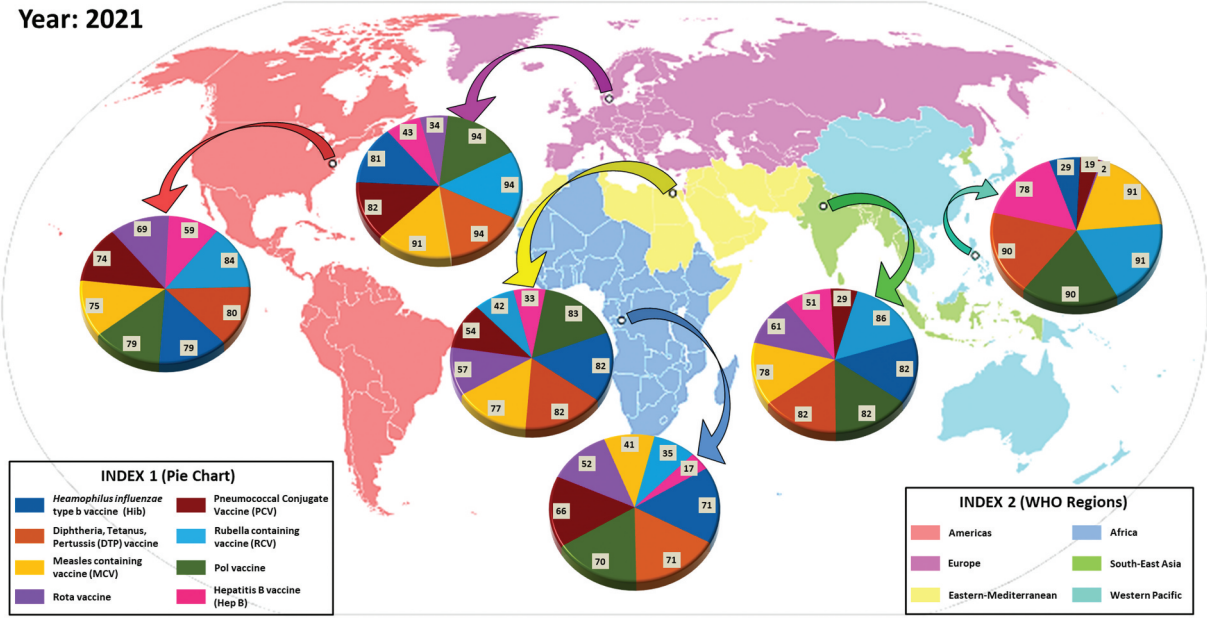


**Figure 3.** Global vaccine coverage (in percentage) of routine vaccines in 2021 (pandemic-recovery phase).

American region during the early half of the pandemic (mid-2020) increased in children, young adults, and elderly (cumulative increase by 12–15%) as compared with the pre-pandemic times (2018–19).[1] Similar trends, especially in elderly (>65 years), were observed in the WP region (increase by ~9%) and EM region (increase by ~9%).[2] This may be driven by the notion that getting vaccinated for flu might lead to cross-protection against COVID-induced flu-like symptoms. However, with the advent of COVID vaccines in the latter half of the pandemic (late 2020–21), there was a decline (~3–10%) in the flu vaccine administration in the aforementioned regions. European regions being vulnerable to seasonal flu maintained consistent flu vaccination coverage throughout the pandemic.[2] Similar trend was observed for the Hib (bacterial) vaccination coverage globally. It was observed that South-East Asia, Africa, regions of the Americas, and East Mediterranean region have noticeable decline in vaccination coverage. South-East Asia showed decline from 89% to 82%, whereas African region reduced from 75% to 71% when compared in the years 2019 and 2021. Similarly, there is a decrease in vaccination coverage in the regions of the Americas, where 83% coverage was reduced to 79%, while EM region was reduced from 85% coverage to 82% in the same time period (Figure 4).

There was a 79% increase in measles cases worldwide during the first part of 2022, as compared with 2021. This probably may be attributed to the usage of double-dose monovalent measles vaccines (MCV 1 and 2) or manufacturing/marketing issues. Ineffective revamping vaccinations might be due to the reliance on very limited vaccine manufacturers. UNICEF has taken an initiative to increase the market health by 2023 with more manufacturers and diversifying the suppliers. Furthermore, the Measles and Rubella Initiative (MRI) in 2020, a new measles and rubella strategic framework (MSRF) for 2021–2030, under the umbrella of WHO's global 'Immunization Agenda 2030 (IA2030)' has devised several strategies toward global immunization. However, measles immunizations (with *Rubella*) in the vulnerable populations of DR Congo, Ethiopia, and Nigeria cannot be anticipated before 2025, which deprives 14 million children with a two-dose routine immunization schedule and demands ardent efforts. The other less populous African nations with measles outbreak have been brought under strategic coverage by 2022–2023.[21] Despite socio-political conflicts, establishing a global uniformity in routine vaccine coverage can constrict the long-lasting effects of immunization disruptions. Interestingly, unlike the measles outbreak in certain parts of the globe, influenza cases showed a drastic decline globally during the pandemic period. The drop in influenza cases is attributed by compromised intervention and surveillance during the pandemic period. The real scenario will soon be understood after the complete recovery and resumption of influenza surveillance program by the WHO member states.[4,5]

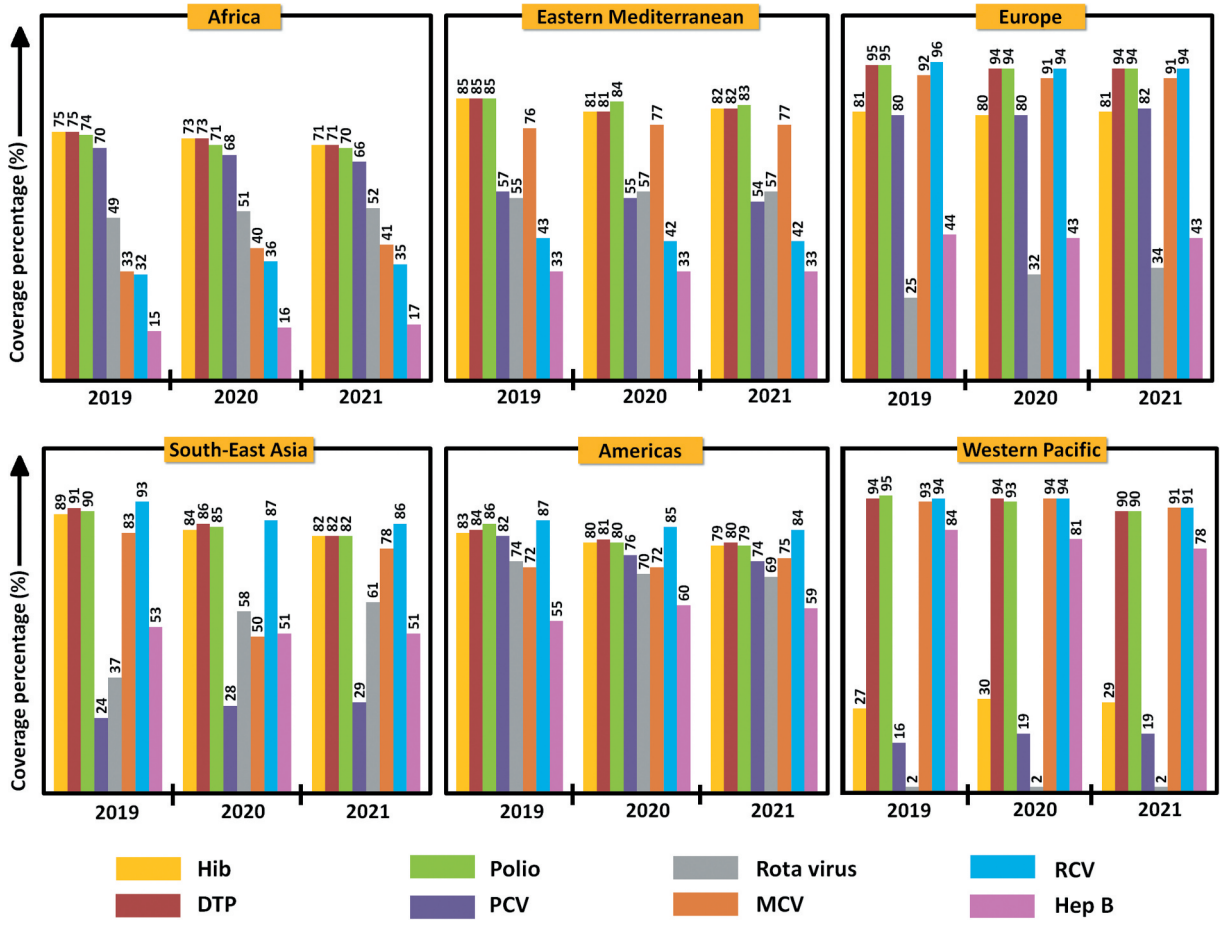


**Figure 4.** Trends in global vaccine coverage between 2019 and 2021.

## Routine vaccine disruptions in specific regions

The pandemic has witnessed a varied number of zero-dose children around the globe with an increase to 7.7 million from 7.1 million in African region; 1.7 million from 1.6 million in American region; 2.3 million from 1.8 million in EM; and 4.1 million from 2.0 million in South-East Asia.[18]

Considering the routine vaccine coverage (2019–2021), Hib vaccine coverage globally was reduced by ~3% with major variation in American region (~5%), EM region, and South-East Asia region (~8%). Similarly, Hepatitis B vaccine coverage globally was reduced by ~6% with evident reduction in South-East Asia (~10%). MCV, RCV, and OPV coverage suffered an evident reduction in South-East Asia (~9%, ~8%, and ~9%, respectively). The PCV coverage was evidently reduced by ~10% in the regions of America. The DTP3 immunization worldwide witnessed a decline of ~6%, with major impact on South-East Asia (~10%).[12] From Figure 4, we can visualize the trends of non-COVID coverages across the WHO regions. Besides restoring the immunization programs in these regions, healthcare authorities should also be prepared to combat any potential outbreaks of VPDs resulting from major disruptions. The majorly affected regions (SEA and Americas) can particularly be focused upon to escalate the recovery measures as well as VPD-outbreak preparedness. The disruption period and percent-affected ratio can help in formulating vaccine-stocking strategies, thereby preventing future disruptions.

## Causes and consequences of vaccine disruptions

> Even as countries clamor to get their hands on COVID-19 vaccines, we have gone backwards on other vaccinations, leaving children at risk from devastating but preventable diseases like measles, polio or meningitis. Multiple disease outbreaks would be catastrophic for communities and health systems already battling COVID-19, making it more urgent than ever to invest in childhood vaccination and ensure every child is reached.
>
> Dr Tedros Adhanom Ghebreyesus, WHO Director-General

Women and children are severely affected due to the disruptions in routine vaccinations. As per the WHO and UNICEF reports, zero-dose children increased drastically in geo-politically vulnerable areas with communal and social conflicts. School closings in some nations of South-East Asia and EM region have significantly reduced (by ~13%) the administration of human papillomavirus (HPV) vaccination, which would have protected girls from cervical cancer later in life.[22] In Africa, more than 60% of the WHO member states faced disruption due to vaccine supply pertaining to transport restrictions and vaccine misinformation.[12,23,24] In Europe, 23% of the nations faced disruptions in routine vaccinations due to unavailability of workforce and challenges in vaccine supply. In South-east Asia, there were vaccine supply issues coupled with reduction in health workforce availability in 45% of the countries.[6,12] Besides routine immunization disruptions, as many as 57 mass vaccination campaigns for measles, polio, yellow fever, and other diseases were postponed in 66 countries, affecting millions of people.[6,25] The accumulation of unvaccinated children due to immunization gaps may lead to higher disease burden and deaths, especially in the low-income regions. Polio and measles vaccine disruptions in countries like Pakistan and Afghanistan, where the persistence of polio can further be escalated by the circulating vaccine-derived poliovirus (cVDPV) Type 1. Type 2 poliovirus was reported in Chad, Ethiopia, Pakistan, and Ghana.[6,26] The occurrence of cVDPV is mainly due to poor vaccination strategies, as OPV and IPV require multiple doses and failure of the same may lead to the outbreak of cVDPV. This was further indicated by the escalation of cVDPV cases in developing countries spanning Africa and Asia to 1079 cases in 2022 from 533 cases in 2017–2019, which clearly shows the detriment, the disruptions due to pandemic caused in these areas. As per the latest report released by the WHO on cVDPV, there are zero cases reported on cVDPV during 2019–2020, while an isolated cases was reported in China in 2019 with no follow-up or any outbreaks reported thereafter.[27,28] The disruptions also led to a new polio outbreak in Nigeria.[6,7] Similarly, diphtheria cases have increased in Venezuela, Nepal, Pakistan, Yemen, and Bangladesh.[5–7,29] Although the pandemic has been tackled in most of the countries with extensive vaccination, the efforts to minimize the risks of concurrent outbreaks of VPDs still persist in various lower-middle-income countries.

## Can routine immunization alleviate COVID-like outbreaks?

Several hypothetical studies have suggested routine immunizations toward mitigation of COVID-19-induced disruptions and prevention of COVID-like outbreaks. Reduction in SARS-COV -2 severity in children who have had their routine immunizations had been strongly proposed by several studies, although lacking experimental documentation. Since these routine immunizations are being used in children for several years with low to none major side effects, they can be tested for cross-protection against COVID-19.[30] Studies have suggested a possible beneficial effect of MMR vaccine in lowering the severity of COVID-19 symptoms.[31] The findings were corroborated with Gold *et al.* (2020), suggesting that the MMR vaccines negatively correlate with the severity of COVID-19 symptoms.[32] The effect of live vaccines such as MCV and BCG on COVID-19 disease severity in children has been debated by several studies. In a national-level analysis in USA, Ogimi *et al.* (2021) showed that COVID-19-related mortality was higher in countries where *Mycobacterium bovis* BCG vaccination is not routinely administered, proposing the cross-protective nature of the BCG vaccine.[33,34] Tetanus toxoid vaccine has also been hypothesized to lower the severity of COVID-19 symptoms.[35] A single dose of bivalent oral polio vaccine (bOPV) has been demonstrated in a recent randomized clinical trial to reduce the incidence of COVID-19 cases by ~40%.[36] Due to the symptomatic coherence between pneumococcal infections and COVID-19, pneumococcal vaccination in the COVID-19 pandemic has become extremely critical for reducing the SARS-CoV-2 risk factors. Their observed correlational effect can potentially decrease mortality and morbidity *via* co/secondary infections and super-infections.[37] Using deterministic dynamic transmission model in Japan, a probable incremental disease burden of invasive Hib disease was recorded in children under 5 years old if reduced COVID-19

vaccination rate persisted.[38] Similar to many live-attenuated vaccines, influenza vaccines have also been widely reported to lower the risk of SARS-CoV-2 infections, but their association has not been well elucidated[39] Additionally, pertussis vaccines can be administered to prevent co-infection; however, it has also been speculated that pertussis vaccine might induce a nonspecific protective role toward SARS-COV-2 by its cytokine storm damping effect and eliciting heterologous adaptive responses.[40] A global surveillance indicated a substantial link between COVID-19 and HBV vaccines for chronic liver disease; however, more evidence on their relationship need to be explored.[41] Although disruptions and speculations regarding routine immunization and COVID-19 vaccines exist on parallel tracks, understanding immunological associations of SARS-CoV-2 vaccines with other routine vaccines can bridge the gaps to understand the physiological impact on routine-vaccine disruption, especially in the pandemic recovery scenario. Furthermore, 'pandemic-preparedness' as a part of 'disaster management' should be enforced taking into account the long-lasting consequences due to health-service disruptions, demographic factors, and scientific predictions.[42] The region-specific rise of some of the VPDs during the course of the pandemic has been depicted in Figure 5, as per the data published by the WHO (2022). Latest report on the outbreak of measles and diphtheria in South-East Asia has been attributed due to the evident decline in the vaccination coverage due to the COVID-19 pandemic.[19] The present review can be instrumental in highlighting the severely affected parts of the world to

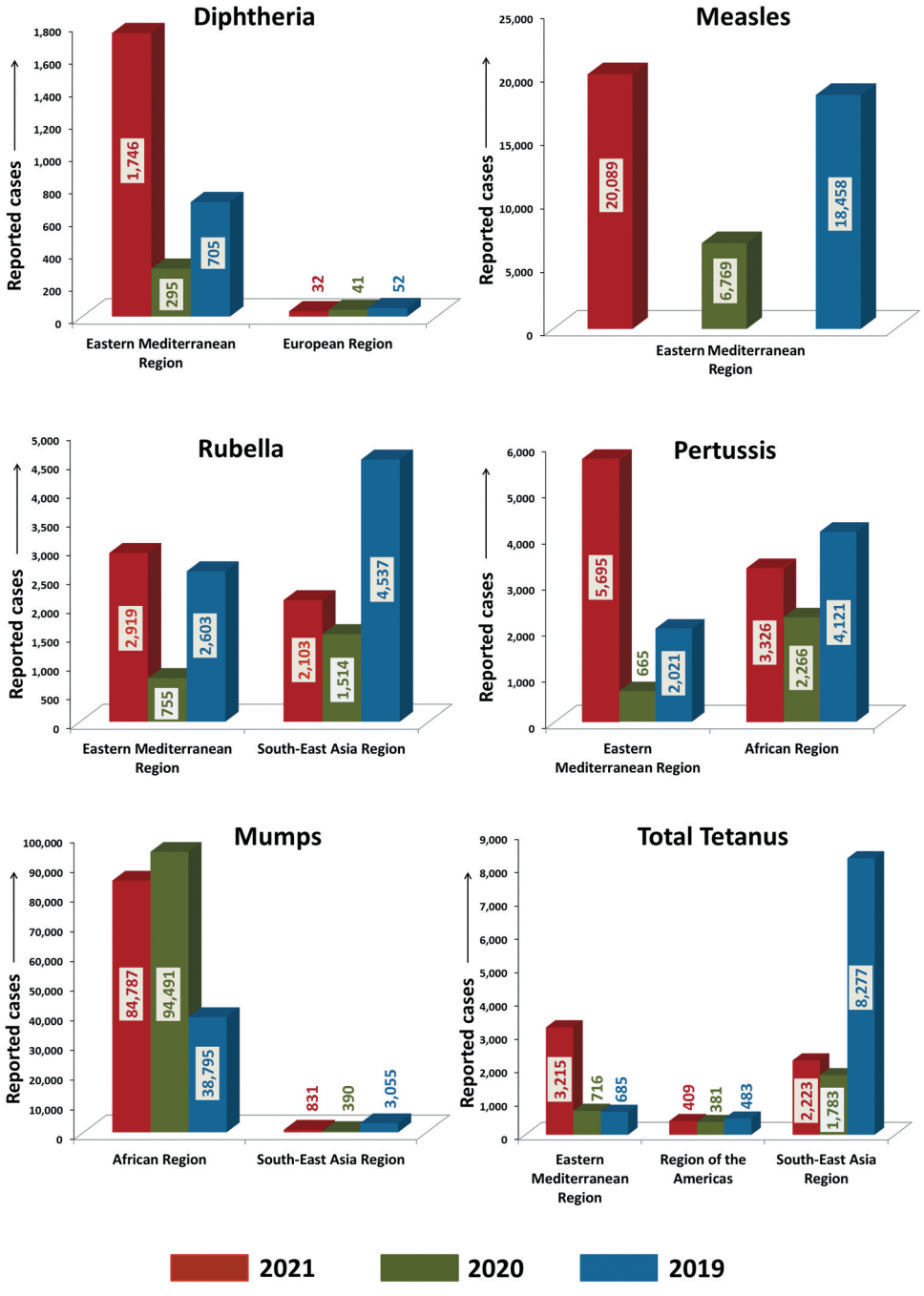


**Figure 5.** WHO-region-specific rise of some of the VPDs during the course of the pandemic.

endemic outbreaks as a consequence of variable routine vaccination coverage due to future COVID-like pandemics. The detailed data by the WHO on the incidence of various VPDs during various phases of the pandemic are given in Table S1.

## Recovery and preparedness

UNICEF, WHO, and partners like Gavi, the Vaccine Alliance are encouraging efforts to strengthen immunization systems by restoring vaccine services, identifying gaps in vaccine coverage, reducing the accumulation of unvaccinated communities (especially children), ensuring safety of healthcare personnel, and ensuring that childhood vaccination services can be conducted alongside COVID-19 vaccinations.[24,43]

However, to ensure effective recovery from routine vaccine disruptions and mitigation of resultant hazards, rigorous surveillance and updated epidemiology map of global vaccination scenario have to be designed.[44] Setting up large-scale vaccine production (and storage) units in the LMIRs as counterparts of leading vaccine producers with cooperation from governmental partners will further help in the mitigation and recovery from the outbreaks by eliminating the risks of disrupted international supply chains.[45]

## Conclusion

Disruptions in routine immunization have made majority of the population in LMIRs vulnerable to various outbreaks of VPDs like measles, polio, and diphtheria. Although recovery through catch-up immunization drives has shown promise, vaccine misinformation and hesitancy persist. The demographic impact of COVID-19 on routine immunization programs clearly depicted the lack of uniformity in vaccine coverage around the globe. This information can help in finding thrust population to provide essential vaccination services. Furthermore, the prospects of repurposing existing vaccines and/or cross-protection benefits of routine immunization to combat COVID-like outbreaks were addressed. The review identified lasting issues as a result of pandemic-mediated immunization disruptions and encourages preparedness for similar future scenarios.

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***Soumya Basu***: Study design, Literature review, Compilation, Writing – Original draft preparation. ***Gayathri Ashok***: Study design, Literature review, Data curation, Writing – Original draft preparation. ***Reetika Debroy***: Literature review, Visualization, Writing – Original draft preparation. ***Sudha Ramaiah***: Conceptualization, Writing – Review and editing. ***Anand Anbarasu***: Conceptualization, Validation, Supervision, Writing – Review and editing. ***Paul Livingstone***: Conceptualization, Validation, Writing – Review and editing.

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