

REVIEW ARTICLE

Impact that the COVID-19 pandemic on routine childhood vaccinations and challenges ahead: A narrative review

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Abstract

Aim: To document the decline in vaccination coverage in the first months of 2020 as an indirect effect of the COVID-19 pandemic.

Methods: We performed a literature review in medical databases. Overall, 143 articles were initially retrieved, out of which 48 were selected and included in the review.

Results: Our review retrieved similar data in many countries worldwide, and, globally, preliminary data from the first 4 months of 2020 indicate a decline in diphtheria-tetanus-pertussis coverage, generally considered the marker of vaccination coverage across countries. World Health Organization recommends maintaining vaccination services, prioritising primary series vaccinations especially for measles-rubella or poliomyelitis, but it also lets each country decide whether to maintain the immunisation services evaluating the current epidemiology of vaccine-preventable diseases and the COVID-19 local transmission scenario. Successively, recovering of vaccinations should be planned. Moreover, during the pandemic, influenza vaccination should be promoted as a central public health measure.

Conclusion: Future challenges will be to maintain the vaccination programmes, especially in children younger than 2 years old and adolescents, to plan the recovery of vaccinations for subjects who postponed them during the lockdown, and to early identify any vaccine-preventable disease outbreak.

KEYWORDS

children, COVID-19, immunisation coverage, pandemic, SARS-CoV-2, vaccinations

Abbreviations: BCG, bacillus calmette-guerin; CDC, centres for disease control and prevention; COVID-19, coronavirus disease 2019; DTP3, diphtheria, tetanus, pertussis; GAVI, global alliance for vaccines and immunisation; HPV, human papillomavirus; MERS, Middle East respiratory syndrome; MMR, measles, mumps, rubella; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; UNICEF, United Nations international children's emergency fund; WHO, world health organization.

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1 | BACKGROUND

Indirect damage from the current COVID-19 pandemic in the general population, particularly in children, affects many aspects of daily life. Worldwide, the proportion of severe disease directly associated with SARS-CoV-2 infection in the paediatric population seems to be around 1%–2%, and deaths are infrequent¹; on the other hand, children suffer the indirect consequences of the pandemic. During the lockdown, the prolonged school closures, social isolation and general impoverishment lead to physical and psychological abuse in children living in fragile social situations. In children from disadvantaged families, greater difficulty in remote access to the school education system has been also highlighted.

Due to the fear of contracting the infection in the hospital, access to the emergency room has been postponed for children with various types of pathologies for a long time. In March 2020, visits to some Italian paediatric emergency rooms decreased by more than 80%, with delays in diagnosing even severe diseases and, at least in one case, also resulting in a child's death.²

Moreover, the fear of contracting the infection has led the population to postpone the use of other health services, so that, for example, among the indirect effects of the pandemic, a decline in vaccination coverage has been documented all around the world.^{3,4}

On March 2020, the WHO European regional office published the document *Guidance on routine immunization services during COVID-19 pandemic in the WHO European Region* to provide support in the decision to maintain or not the vaccination activity during the pandemic.⁵ The document indicates how to conduct a risk assessment and provides the guiding principles to minimise the exposure to COVID-19 during the immunisation service. The document recommended to maintain vaccination services and prioritise primary series vaccinations especially for measles-rubella- or poliomyelitis vaccines and other combination vaccines.⁵ It also suggested to avoid mass vaccination campaigns in high-risk settings and vaccinate neonates, accordingly to the national immunisation schedule, in maternity hospitals. Relying on the above guiding principles, each country should decide whether to maintain the immunisation services evaluating the current epidemiology of vaccine-preventable diseases, the COVID-19 transmission scenario, the corresponding containment measures in place and the resources available. These principles are further reiterated in a subsequent document, *Guiding principles for immunization activities during the COVID-19 pandemic*, which emphasises the high risk of vaccine-preventable disease outbreaks in case immunisation coverage fell under sub-optimal ranges.⁶

2 | METHODS

A literature review was performed through medical databases, including MEDLINE by PubMed, EMBASE, Google Scholar, Scopus and Web of Science for articles published up to 1 January 2021. Used keywords were as follows: SARS-CoV-2, COVID-19, coronavirus, vaccine coverage, vaccine, children, infant, trained immunity,

Key Notes

- This review investigated the vaccination situation worldwide during the COVID-19 pandemic.
- Data from many countries have indicated a decline in diphtheria-tetanus-pertussis coverage, generally considered the marker of vaccination coverage across countries.
- It is fundamental to plan the recovery of vaccinations for subjects who postponed them.

measles, varicella, rubella, MMR, MMRV, poliomyelitis, diphtheria, tetanus, pertussis, Haemophilus influenza, Hib, Hepatitis B, HBV, DTP, BCG, influenza, HPV and papillomavirus. Relevant articles published in English referring to routine immunisation programmes during the COVID-19 pandemic were included. Duplicates, non-relevant articles and studies pertaining to other coronavirus-related illnesses were excluded, as well as those referring to anti-SARS-CoV-2 vaccines. Two authors (EC and SP) independently performed the literature searches.

Overall, 143 articles were initially retrieved, out of which 48 were selected and included in the present review. Below, we summarise the key findings from reviewed manuscripts, highlighting the major results.

3 | RESULTS

3.1 | A decline of vaccine coverage in general has been reported worldwide

Globally, the World Health Organization (WHO), United Nations Children's Fund (UNICEF) and the World Alliance for Vaccine and Immunisation (GAVI, a cooperation of public and private entities with the aim of improving access to immunisation in poor countries) estimated that at least 80 million children are at risk of vaccination-preventable diseases due to the COVID-19 pandemic. In fact, 75% of 82 countries all over the world have temporarily suspended mass vaccination campaigns^{3,4}; in the WHO European Region, during the first months of the COVID-19 pandemic, routine vaccinations were interrupted in 22% of infants⁷ [Table 1].

An Italian survey including about 1,500 children aged 0–11 years resulted in one in three parents postponing their children's vaccinations during the first months of COVID-19 pandemic.⁸ The mainly affected age group was the 0–2 years, with a decrease in hexavalent, measles-mumps-rubella-varicella (MMRV), anti-meningococcal and anti-pneumococcal vaccines. The lack of information regarding the vaccination centres' safety played a role in the parents' decision to postpone vaccination. On the other hand, in 42% of cases, the vaccination centre postponed the appointment, and the centre was closed in 13% of cases. The WHO and the Italian Ministry of Health

TABLE 1 Main findings of studies investigating vaccination coverage during the first months of COVID-19 pandemic

Country/Region	Reference #	Decrease in vaccination coverage—main findings
Worldwide	3	75% of 82 countries all over the world have temporarily suspended mass vaccination campaigns during the lockdown
Europe	5	22% of infants interrupted vaccinations
Italy	8	One in three children postponed vaccinations; 0–2 years old were the mainly affected group
Tuscany (Italy)	9	31.7% reduction in parents' compliance with mandatory vaccination (hexavalent and MMRV vaccines), and even more (42.3%) with non-mandatory vaccinations
Spain	10	Vaccination coverage declined by 5%–60% depending on children's age and type of vaccine. Most noticeable decline for non-gratuity vaccines
England	12	MMR vaccination coverage decreased by 20% during the first three weeks of the lockdown
Lothian area of Scotland	13	Stable attendance at childhood immunisation clinics during lockdown, since several adaptations were made
Netherlands	14	Limited impact on the routine infant vaccinations, especially after catch-up vaccination programme, with a reduction in MMR participation by 1%–2%
USA	15	Drop of 21.5% in the administration of the measles vaccine during the first four months of 2020; vaccinations against hepatitis, meningitis, polio and rotavirus also showed a decreasing trend
Michigan	16	Overall decline in vaccination coverage of 21.5%
New York	17, 18	In April 2020, 62% decrease in vaccine administration in children aged <24 months, and 96% decrease in those aged 2–18 years. After a sharp decline in vaccine orders during March and April 2020, orders during the second half of May and June were relatively comparable to those from the same period in 2019
United States	21	Decrease in vaccination coverage of 45.7%, with an 83% drop among children age 5 and younger. The human papillomavirus vaccine was among those with the largest drop-off, with 65% lower coverage in 2020
Latin America	4	Vaccination coverage had already suffered a collapse during the last decade, and it will now suffer an even greater decline due to the COVID-19 pandemic
Brazil	27	Reduction in demand for vaccine rooms during the pandemic, even though the service continues to be offered universally and free of charge. By September 2020, Brazil occupied the first place at the Top 10 list of Measles Incidence Rate per Million
Asia	4	Over the past decade Asia made enormous progress in terms of vaccination coverage, and now risks seeing jeopardised all the work done because of the pandemic
Indonesia	24	About 84% of immunisation services have been blocked by the pandemic; 20% of these related to measles and rubella
Pakistan	23, 25	52.5% decline in the daily average total number of vaccinations, with the highest decline observed for BCG vaccine. Increase in poliomyelitis cases was documented
Singapore	26	Herd immunity against measles reduces to 74%–84% among 12-month- to 2-year-olds
Japan	27	The national Haemophilus influenzae vaccination rate decreased to 73% in 2020, and an incremental disease burden was observed
Korea Republic	28	Vaccination rate in children aged 0–35 months did not decrease significantly; for children aged 4–6 years decreased by 1.4%–1.9%
Afghanistan	22	Increase in poliomyelitis cases
Saudi Arabia	30, 31	23.4% of parents postponed the immunisation of their child. Were documented drops in vaccination visits of 49.93%–71.90% compared to previous years
Africa	35	For every one death attributable to SARS-CoV-2 infections acquired during routine vaccination clinic visits, there could be 84 (14–267) deaths in children prevented by sustaining routine childhood immunisation in Africa
Sierra Leone	32	Decrease among 50%–85% in vaccine administration
Sub-Saharan Africa (15 countries)	35	13/15 countries showed a decline in the monthly average number of vaccine doses provided, with 6 countries having more than 10% decline

(Continues)

TABLE 1 (Continued)

Country/Region	Reference #	Decrease in vaccination coverage—main findings
Kenia	36	From December 2020, the probability of a large measles outbreak will increase to 38% (19–54), 46% (30–59) and 54% (43–64) assuming a 15%, 50% and 100% reduction in measles vaccination coverage
Ethiopia	37	Nationwide follow-up measles preventive vaccination campaign, scheduled for April 2020, was postponed

draw up detailed guidelines to limit the risk of transmitting SARS-CoV-2 during vaccination, but 46% of vaccinating physicians declared that they had not received the new safety recommendations. These data were in line with another survey, carried out in Tuscany, Italy, involving 223 primary care paediatricians; 98.2% of them reported a general decline in outpatient visits during the pandemic (65.8% reported a more than 60% reduction).⁹ The study reported that 93.3% of paediatricians continued to vaccinate in the period considered, and, among them, 31.7% reported a reduction in parents' compliance with mandatory vaccination and even more (42.3%) with non-mandatory vaccinations, despite almost all the paediatricians took preventive actions to counter the spread of SARS-CoV-2.⁹ Once available the national Italian vaccination coverage data for the first months of 2020, it will be possible to assess the pandemic's real impact throughout the national territory.

In Spain, vaccination coverage declined by 5%–60% depending on children's age and type of vaccine. The decline was most noticeable for non-gratuity vaccines, such as anti-meningococcal B vaccination, with coverage falling from 40% to 68%.¹⁰ Similarly, in England, over 60% of interviewed healthcare workers reported contact with families who cancelled or postponed the child's vaccinations, so that, for example, MMR vaccination coverage decreased by 20% during the first three weeks of the lockdown.^{11,12} Smaller falls have been reported in Scotland. In particular, in Lothian, attendance at childhood immunisation clinics remained stable in the weeks during lockdown thanks to a very effective vaccination programme, designed in 2018.¹³

In the Netherlands, only limited impact on the routine infant vaccination programme has been documented, while a 75%–97% decreased incidence of several vaccine-preventable diseases was observed, probably linked to COVID-19 preventive measures.¹⁴

In the United States, according to the Centers for Disease Control and Prevention (CDC), vaccination coverage declined in all age cohorts, despite a 2020 policy document stressed the importance of ensuring routine healthcare and continuing vaccination practices, particularly for children aged ≤24 months.¹⁵ Results are consistent across several states such as New York, California, Ohio, Virginia and Michigan, overall declines ranging from 40% to 63%.^{16–18} In Virginia, human papillomavirus (HPV) vaccination rate reduced by 65%. In the State of Michigan, vaccination coverage fell from 66% to 50% and from 76% to 71%, respectively, in the two cohorts of 5- and 16-month-old children, with an overall decline in vaccination coverage of 21.5% in all the paediatric age groups during March 2020, compared to previous years.¹⁹ In parallel, a notable decline, about 75%, in vaccines orders occurred.^{20,21} Afterwards, vaccine

administrations have started to increase in the United States, especially for younger children, thanks to the implementation of public health strategies to promote vaccinations in the pandemic context, including the active recall of children late on the vaccination schedule.¹⁹ One US study with the aim to estimate vaccination coverage for MMR vaccine under a range of scenarios found that a 15% sustained catch-up rate outside stay-at-home orders may be needed to achieve projected vaccination coverage similar to that one observed in previous years.¹⁹

In Asia, a reduced vaccine coverage has been documented in several countries, and worryingly, poliomyelitis cases increased in Afghanistan²² and Pakistan.²³ About 84% of immunisation services suspended their activity in Indonesia, particularly for the MMR vaccine.²⁴ In Pakistan, a 52.5% decline in the daily average total number of vaccinations was evidenced, with the highest decline observed for Bacille Calmette Guérin (BCG) vaccine.²⁵ In Singapore, variable percentages have been reported for most vaccines across the country up to July 2020,²⁶ and in Japan, the national *Haemophilus influenzae* vaccination rate decreased to 73% in 2020 while an incremental disease burden was observed.²⁷ Different findings have been reported in the Korea Republic where drops were not substantial.²⁸

Similar results have been reported in other areas of the worlds, such as Brazil,²⁹ Saudi Arabia^{30,31} and Sierra Leone.³²

Globally, preliminary data from the first four months of 2020 indicate a substantial decline in the number of children who have completed three doses of diphtheria, tetanus and pertussis (DTP3) vaccine, leading to a global reduction in DTP3 coverage, generally considered a reliable marker of vaccination coverage within and across countries.³ Even in countries where the vaccination offer has been maintained, many of the population rejected it for fear of contracting SARS-CoV-2 infection, or due to interruptions in public transport or to economic difficulties. In many countries, there was also a significant reduction in the healthcare workers who can be employed in vaccination services due to the lack of protective equipment or relocation to the assistance and management of patients affected by COVID-19. Inequities in routine vaccination coverage are likely to occur during the pandemic, although they need to be better investigated.³³ In a survey conducted within participant to the IMPRINT, a global network of experts in maternal and neonatal vaccinology, 50% of 48 respondents, most of them working in low-and-middle-income countries, reported issues with vaccine delivery within their country during the pandemic.³⁴ In another study among 15 African countries, those with lower immunisation coverage in the pre-COVID period experienced larger declines during the pandemic,³⁵ and several authors underlined the importance

of supplementary immunisation activities to prevent measles outbreaks during the COVID-19 pandemic in several African countries, including Kenya³⁶ and Ethiopia.³⁷

3.2 | Influenza vaccinations during the COVID-19 pandemic

Although influenza activity in 2020–2021 has been reported to be lower than expected in several countries, following the implementation of physical distancing measures and lockdown,³⁸ it is imperative to promote influenza vaccination as a central public health measure, during the COVID-19 pandemic.

The available literature, although limited, indicates that the spread of influenza vaccination during the coronavirus pandemic could facilitate the differential diagnosis between febrile respiratory syndromes, avoiding overload of health services and thus enabling more efficient use of health resources, especially in the elderly, the most vulnerable to COVID-19.

Petti et al.³⁹ ecological study, including data from thirty-four European countries, found an inverse correlation between the extent of influenza vaccination coverage and the risk of death from COVID-19. Other authors have suggested a reduced risk of SARS-CoV-2 infection in subjects vaccinated with the influenza vaccine. One possible hypothesis would lie in the increased expression of ACE-2 receptors on the respiratory tract induced by influenza viruses.⁴⁰ Several countries have implemented influenza vaccination during the years 2020–2021. In a recent, review-specific recommendations at this regard were identified in 13 countries, including five countries in the WHO regions of America, five in Europe, two in the Western Pacific region and one in the African region.³⁸ UK has recommended expanding the programme to adults aged 50 and over.⁴¹ Influenza vaccine has been freely offered also to people who are on the shielded patient list and their household members; all school year groups up to 7 years of age; people aged over 65, pregnant women; and those with several pre-existing conditions including at risk under 2 years of age.⁴¹

In Italy, several Scientific Society highlighted the urgency to raise influenza vaccination coverage. Thus, the Italian Medicines Agency recommended anticipating the flu vaccination campaign starting from the beginning of October 2020 and offering vaccination to eligible patients at any time during the flu season, even after the usual recommended vaccination time.⁴² It was essential to increase the current vaccination coverage, especially in the elderly and in more susceptible subjects (such as those affected by cardiovascular pathology, diabetes, cancer or immunosuppression) considering that in 2019, vaccination coverage in people aged >65 years in Italy was only 54.6%.⁴¹ In the 2020–21 winter season, the Italian Ministry of Health has extended free vaccination from 60 years of age instead of 65, underlines the crucial importance of vaccinating healthcare workers and institutionalised elderly and suggests immunisation in children, especially those aged six months–6 years.⁴² Since children are considered an important vehicle of infection, paediatric

vaccination will indirectly decrease the spreading of influenza viruses, with a very favourable cost/benefit ratio for both the elderly population and the general population.

4 | DISCUSSION

A significant and deleterious indirect effect of the COVID-19 pandemic first wave was the decline in vaccination coverage, evidenced by epidemiological studies conducted in many countries all over the world and by WHO global immunisation surveillance and monitoring. The scientific community and healthcare providers must be able to send clear messages to the public on the importance of immunisation and to deal with other challenges of routine immunisation during the pandemic. For example, parents could be worried about the eventuality of vaccinating a child during the SARS-CoV-2 incubation period and those infection symptoms could occur shortly after a vaccination. A WHO document affirmed that although specific data regarding the efficacy and safety of vaccinations in subjects infected with SARS-CoV-2 are not yet available, the general principles of vaccination in patients affected by other infectious diseases should be applied.⁵ Therefore, if, inadvertently, a subject with SARS-CoV-2 ongoing infection or during the incubation period receives a vaccination, there is no reason to be concerned that the vaccination will affect the disease's course.

Furthermore, at the moment, there is no evidence that SARS-CoV-2 infection could affect the safety or efficacy of the administered vaccine.

All precautions must be taken during the vaccination to reduce the risk of infection during the procedure and in the waiting room. For this reason, the CDC recommends postponing the vaccinations in SARS-CoV-2 infected subjects, both symptomatic and asymptomatic, until the criteria for ending isolation are met in order to avoid healthcare workers' and patients' exposition to the virus.⁴³

4.1 | Trained immunity and SARS-CoV-2

It is actually under debate whether certain vaccinations, such as BCG, anti-measles or oral anti-poliomyelitis vaccine, can also confer protection against SARS-CoV-2 infection. According to recent studies, the long-term enhancement of the innate immune response (trained immunity) effected by some live-attenuated vaccines would induce a non-specific protective response to heterologous infections. This would be due to epigenetic and transcriptional rewiring of myeloid progenitors of innate immunity cells.⁴⁴

Other authors suggested that even non-live vaccines, including pertussis or influenza vaccines, may trigger immune response, as well. Some data indicate that influenza vaccination may have a favourable effect on COVID-19 and its course. However, more studies are needed at this regard.⁴⁵

Similarly, *Bordetella pertussis* has been found to be more common in adults with COVID-19 pneumonia, suggesting that

pertussis vaccine could be useful to avoid co-infection, but it has been also speculated that pertussis vaccine may play a not specific protective role even towards SARS-CoV-2 by eliciting heterologous adaptive responses.⁴⁶ To date, these hypotheses are mostly theoretical speculations, not yet supported by good-quality controlled studies.

The current SARS-CoV-2 vaccination mass campaign stressed the importance of reinforcing the vaccination supply services and of improving the institutional communication activities to overcome vaccination hesitancy.

4.2 | Limitations

Our literature review may have some possible limitations, including the fact that some references might have been missed, especially considering the rapid growth of articles published during the COVID-19 pandemic.

5 | CONCLUSIONS

In line with WHO's guidance document, a significant decline in vaccination coverage during COVID-19 pandemic was detected in many countries all over the world. Future challenge will be to maintain the vaccination programmes, with particular attention to children younger than 2 years old, planning the recovery of vaccinations for subjects who postponed them during the lockdown. Moreover, a careful epidemiological surveillance needs to be guaranteed, in order to early identify any vaccine-preventable disease outbreak.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

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