It is a widely recognized fact that after clean water, vaccination is the most successful and effective public health intervention of all time in terms of lives saved, preventing up to an estimated 3 million deaths per year. Vaccination not only protects the individual by stimulating immune response in the body, but also protects communities through herd immunity. The concept had been first conceptualised in the 17th century in China when cowpox on skin tears would be inoculated on the skin of those with smallpox to confer immunity. However, the word vaccination and the scientific process of vaccination was first coined and studied by Edward Jenner in 1796, when he inoculated in Gloucester a young boy with vaccinia virus (cowpox) to immunise her against smallpox. From then until today, the WHO recognizes licensed vaccines for 29 vaccine-preventable infections.

In 1974, the Expanded Programme on Immunization (EPI) was initiated in order to scale up immunisation programs globally. This was done at a time when less than 5% of children in low-and-middle-income countries were receiving a third dose of DTP (Diphtheria, Pertussis and Tetanus) and polio vaccines.

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*[This document forms part of a series of discussion notes addressing fundamental questions about global health. Its purpose is to transfer scientific knowledge into the public conversation and the decision-making process. These documents are based on the best information available and may be updated as new information comes to light]*

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Photo: Bill Weener / Unsplash

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1. Vaccines and Immunization.

2. A Brief History of Vaccination.

Today immunisation is a key element in the prevention and control of infectious diseases, and it is a critical part of primary health care.⁴

Alongside this, an immunisation system of performance was established with the completion of three doses of DTP (DTP3) vaccine by age 12 as a principal indicator of immunisation coverage.⁵

The WHO defines the following as elements of a strong immunisation programme: ⁶

- Reaching every person
- Staff training and capacity building.
- Organisation, planning and supervision
- Monitoring, surveillance and response systems
- Supply chain systems
- Cold chain, storage and handling systems

All elements must be equally met and functional for a successful immunisation programme. The COVID-19 pandemic affected each of these elements putting years of remarkable gains at risk. For example, the WHO has announced that 18 million children did not receive any vaccines in 2021. ⁷

Source: WHO.
COVID-19 pandemic fuels largest continued backslide in vaccinations in three decades.

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⁵ World Health Organization, ‘Vaccines and Biologicals: WHO Vaccine-Preventable Diseases: Monitoring System; 2002 Global Summary’.

⁶ WHO Regional office for Europe, The Elements of a Strong Immunization Programme - and Why We Need to Invest in Them.
English physician-scientist Edward Jenner inoculates eight-year-old James Phipps with matter from a cowpox sore – proving that inoculating a person with cowpox pus can create smallpox immunity.

Harvard physician-scientist Benjamin Waterhouse performs first smallpox vaccinations on his four children.

U.S. Vaccine Agency established – then and now, continues to ensure safety, efficacy of vaccines.

Drastic decrease in smallpox mortality after vaccination begins.

French biologist Louis Pasteur develops technology for attenuated vaccines (uses weakened viruses).

Spanish physician Jaime Ferrán develops a cholera vaccine – first against a bacterial disease.

Gaston Ramon, a veterinarian at the Pasteur Institute in France, develops diphtheria toxoid; working independently at the Wellcome Research Laboratories in London, physician Alexander Thomas Glenny does likewise.

Harvard physician-scientist Benjamin Waterhouse performs first smallpox vaccinations on his four children.

Influenza vaccine approved for civilians.

Polio vaccine made widely available.

Combination measles, mumps, rubella (MMR) vaccine released after the individual vaccines were released in 1963, 1967, and 1969, respectively.

Scientists begin exploring how to simplify vaccines using mRNA, discovering it can create a stronger immunity by training the immune system to make antibodies and killer T-cells which kill cells infected with an intruder.

BioNTech clinical trial in Germany shows mRNA vaccine effective against melanoma.

Moderna plant opens in Massachusetts to manufacture mRNA vaccines for cancer clinical trials.


In February, FDA issues EUA for viral vector COVID-19 vaccine from Johnson & Johnson/Janssen.
To date, **only smallpox infection has been eradicated** as a result of a successful coordinated and global immunisation campaign (WHO declared smallpox eradication in 1980). This raised hopes of eradicating other vaccine preventable diseases. Polio, measles, mumps, chickenpox, yaws and tetanus are on the list of potentially diseases to be eliminated globally, but there is still need for **concerted interventions** to eradicate them.\(^7\) For some of them, the availability of highly effective vaccines is a massive advantage.

The initial EPI focused on **four childhood vaccine-preventable diseases** and today it has expanded to include vaccines for older children, adolescents and adults.\(^8\) Whereas initially most vaccines were live-attenuated strains of the disease agent, today molecular genetics have taken centre stage in vaccine development with increased scientific understanding of immunology, microbiology and genomics.

Vaccination campaigns are common in all countries and are routinely carried out in the health facilities, in schools and in the community through outreach initiatives in order to reach all communities, including the most vulnerable populations and those rural, remote and hard to reach areas. Importantly, vaccines are among the most equitable public health interventions. Immunizations **have averted an estimated 37 million deaths between 2010 and 2019.**\(^9,10\)

Despite the great advances made in the last decades, **in 2019 the vaccination coverage had reached a plateau.** Between 2010 and 2019, the global coverage of DTP3, first polio dose and first measles dose has lingered between 84% and 86%. In 2019, a reported 19.7 million children (the majority in LMIC countries) were not vaccinated with 3rd dose DTP and more worrisome, 70% of these children were **zero-dose** children (they had never been vaccinated by age 12). The DTP1 to DTP3 dropout was 6% globally (9% in the African region). In the interval between 2010 to 2019, the number of zero-dose children kept increasing in the African region (by 0.7 million), the Americas (by 1 million) and the Western Pacific region (by 0.3 million). Seventy seven percent of these children were in countries eligible for GAVI (Vaccine Alliance) support (financial assistance to buy vaccines and strengthen the health system) and a majority lived in 10 LMIC (Nigeria, India, Democratic Republic of Congo, Pakistan, Ethiopia, Brazil, Philippines, Indonesia, Angola and Mexico).

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\(^7\) Vaccine-Preventable Disease.

\(^8\) Essential Programme on Immunization. [https://www.who.int/teams/immunization-vaccines-and-biologicals/essential-programme-on-immunization](https://www.who.int/teams/immunization-vaccines-and-biologicals/essential-programme-on-immunization)


The coverage of second dose of measles vaccine increased by 29% from 2010 to 2019; but the African region reported 69% coverage for first dose of measles and 33% second dose measles vaccine in 2019. Moreover, vaccination coverage of previously underutilised vaccines increased in this time period especially for rotavirus, pneumococcal conjugate, rubella, *Haemophilus influenzae* type b, hepatitis B vaccine and human papillomavirus vaccines. 

Reasons for these pre-COVID-19 vaccination gaps are well explored in a *Lancet* paper by Galles et al. Their systematic analysis found that although the Global Vaccine Action Plan had made huge progress in ensuring access to vaccines by all countries, it did not address the issues around delivery of immunisation services to the children. This means that challenges such as the financial capacity of a family to get to the vaccination centre, awareness of the community on importance of childhood vaccines, health centre capacity to store vaccines under ideal conditions, supply chain challenges and other country level obstacles were not addressed by the action plan and prevented the “last mile” delivery of vaccine doses. Additionally, countries which were previously supported by GAVI, The Vaccine Alliance, as low-income countries were left with limited support as they developed and transitioned to become middle income countries. These countries encountered challenges in access to vaccines as they no longer were eligible to GAVI. 

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**Figure 3.** Estimated number of zero-dose children* among the 10 countries with the most zero-dose children and cumulative percentage of all incompletely vaccinated children accounted for by these 10 countries — worldwide, 2019.

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Table 1. Vaccination coverage, by vaccine and World Health Organization (WHO) region — worldwide, 2019.

<table>
<thead>
<tr>
<th>Vaccine</th>
<th>No. [%] of countries with vaccine in schedule</th>
<th>Global</th>
<th>Africa</th>
<th>Americas</th>
<th>Eastern Mediterranean</th>
<th>Europe</th>
<th>South-East Asia</th>
<th>Western Pacific</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacille Calmette-Guérin</td>
<td>156 (80)</td>
<td>88</td>
<td>80</td>
<td>83</td>
<td>87</td>
<td>92</td>
<td>93</td>
<td>96</td>
</tr>
<tr>
<td>First dose of diphtheria and tetanus toxoids and pertussis</td>
<td>194 (100)</td>
<td>90</td>
<td>81</td>
<td>90</td>
<td>89</td>
<td>97</td>
<td>94</td>
<td>95</td>
</tr>
<tr>
<td>Third dose of diphtheria and tetanus toxoids and pertussis</td>
<td>194 (100)</td>
<td>85</td>
<td>74</td>
<td>84</td>
<td>82</td>
<td>95</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>Birth dose of hepatitis B</td>
<td>111 (49)</td>
<td>43</td>
<td>6</td>
<td>55</td>
<td>34</td>
<td>41</td>
<td>54</td>
<td>84</td>
</tr>
<tr>
<td>Third dose of hepatitis B</td>
<td>189 (97)</td>
<td>85</td>
<td>73</td>
<td>81</td>
<td>82</td>
<td>92</td>
<td>91</td>
<td>94</td>
</tr>
<tr>
<td>Third dose of Haemophilus influenzae type B</td>
<td>192 (98)</td>
<td>72</td>
<td>73</td>
<td>85</td>
<td>82</td>
<td>79</td>
<td>89</td>
<td>24</td>
</tr>
<tr>
<td>Final dose of human papillomavirus†</td>
<td>106 (55)</td>
<td>15</td>
<td>19</td>
<td>55</td>
<td>0</td>
<td>24</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>First dose of measles</td>
<td>194 (100)</td>
<td>85</td>
<td>69</td>
<td>88</td>
<td>82</td>
<td>96</td>
<td>94</td>
<td>94</td>
</tr>
<tr>
<td>Second dose of measles</td>
<td>178 (91)</td>
<td>71</td>
<td>33</td>
<td>75</td>
<td>75</td>
<td>91</td>
<td>83</td>
<td>91</td>
</tr>
<tr>
<td>Third dose of pneumococcal conjugate</td>
<td>148 (74)</td>
<td>48</td>
<td>70</td>
<td>83</td>
<td>52</td>
<td>80</td>
<td>23</td>
<td>14</td>
</tr>
<tr>
<td>Third dose of polio</td>
<td>194 (100)</td>
<td>86</td>
<td>74</td>
<td>87</td>
<td>83</td>
<td>95</td>
<td>90</td>
<td>94</td>
</tr>
<tr>
<td>First dose of rubella</td>
<td>173 (87)</td>
<td>71</td>
<td>33</td>
<td>88</td>
<td>46</td>
<td>96</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>Final dose of rotavirus§</td>
<td>108 (52)</td>
<td>39</td>
<td>50</td>
<td>74</td>
<td>49</td>
<td>25</td>
<td>37</td>
<td>2</td>
</tr>
</tbody>
</table>

* BCG coverage is based on 156 countries with BCG in the national schedule, whereas coverage for all other vaccines is based on 194 countries (global) or all countries in the specified region. Administrative coverage is the number of vaccine doses administered to those in a specified target group divided by the estimated target population. During vaccination coverage surveys, a representative sample of households are visited and caregivers of children in a specified target group (e.g., aged 12–23 months) are interviewed. Dates of vaccination are transcribed from the child’s home-based record, recorded based on caregiver recall, or transcribed from health facility records. Survey-based vaccination coverage is calculated as the proportion of persons in a target age group who received a vaccine dose.

† Number of doses to complete the HPV series depends on age of recipient.

§ Number of doses to complete the rotavirus series varies among vaccine products.

Source: Centers for Disease Control and Prevention
https://www.cdc.gov/mmwr/volumes/69/wr/mm6945a7.htm#T1_down
In order to reduce the infections and resulting mortality from COVID-19, a series of lockdowns and restrictive preventive measures were implemented worldwide. These measures had a negative impact on primary health care services and most particularly routine immunisation programs around the world putting millions of children’s lives at risk of vaccine preventable diseases.

The COVID-19 pandemic affected routine vaccinations in the following manner:\textsuperscript{13}

1. Routine immunisation campaigns and services:
In the early months of the pandemic, the WHO initially recommended an interruption of the routine immunisation services and outreach activities in order to reduce the social interaction, thereby protecting healthcare workers and children from COVID-19. The Global Polio Eradication Initiative equally recommended suspension of vaccinations until the second half of 2020. Vaccinations are time sensitive, as they are age specific and children must take advantage of the vaccinations within the age-specific window to benefit from lifelong immunity. So, this initial recommendation came at a very high cost as the data below show (See Figure 4).

The WHO quickly revised its initial recommendation and advised countries to continue immunisation services, however, observing all COVID-19 preventive measures such as protective equipment for healthcare workers, necessary distancing and so on. Studies were also increasingly showing that the benefit of vaccination outweighs the risk of death by COVID-19. One particular study\textsuperscript{14} showed that for every death by SARS-CoV-2 during a routine immunisation clinic visit, 84 deaths from vaccine preventable diseases could be averted by maintaining routine immunizations in Africa.

2. Access to vaccination services
The implemented COVID-19 preventive measures such as lockdowns, social distancing and isolation restricted movement of people and therefore access to vaccination services worldwide. Children were not able to reach health facilities to get their routine vaccinations. Health care workers and community workers were not able to carry out their usual clinic activities and outreach campaigns due to fears of getting infected by clients. As a result of the lockdowns and closing of borders, supply chains for medical supplies were also affected.

There were shortages of personal protective equipment for health care workers to carry out the vaccination services. Supplies of vaccines also faltered as there were delays in delivery due to importation and distribution problems. Vaccine supplies for BCG vaccine were at one point of the pandemic affected by the then prevailing hypothesis that BCG vaccine could have some non-specific effects that would reduce COVID-19 mortality.


To those clinics that were opened, especially in LMICs, if they had few children coming, there was fear of opening multi-dose vials (such as BCG and Measles & Rubella vaccines) as it would lead to wastage.

Examples of this is seen in countries such as South Africa where the lockdown reduced clinic visits from 11.8 to 4.5 visits per day and clinic,15 and in Pakistan the clinic visits dropped by more than 50% in the week that the lockdown was implemented.16

3. Availability of healthcare workers:

Lack of transport affected not just the distribution of medical supplies but also affected both community members and health care workers in reaching health facilities or outreach community sites. Mitigation of the COVID-19 pandemic involved the redirection of health care workers towards COVID-19 testing and treatment. This left a shortage of providers for other essential services like routine immunizations. In LMICs, where there is usually a generalised shortage of health personnel, this meant that certain immunisation centres were closed due to lack of staff. In addition, COVID-19 affected primarily health care workers, adding to the overall shortage of staff.

4. Management

With increased focus on mitigation of the COVID-19 in already debilitated health systems, it became a huge challenge for health managers in LMICs to prioritise services in order to avert catastrophe. There was limited awareness of the importance of routine vaccinations, and so this was not prioritised as it should have been. Additionally, as resources were being directed to COVID-19, the much-needed training activities of routine vaccination did not take place in order to find local solutions to adapt to the COVID-19 emergency without foregoing years of gains with routine vaccinations. As the health personnel were not receiving adequate training and information, the population was also not being adequately informed.

As a result of all the above, about 30 million children missed their 3rd DPT doses and 27.2 million missed their MCV1 doses as the global coverage decreased from 86% in 2019 to 83% in 2020. It is estimated that 23 million children below age 1 did not receive the basic vaccines, taking the coverage back to 2009 levels. About 3 million children were zero-dose children. This means that an additional 8.5 million children missed their DTP3 doses and an additional 8.9 million missed their MCV1 doses compared to the expected estimates for 2020.17

Vaccine coverage in 2020 fell below the expected estimates – DTP3 coverage was 7.7% lower and MCV1 (1st dose of Measles-Containing-Vaccine) was 7.9% lower than the expected 2020 estimates. The reductions were more drastic in April 2020 with a decrease of 31.3% for DTP3 doses and 30.1% for MCV1 doses compared to expected estimates. The South Asia region experienced the biggest drop in coverage (58.3% for DTP3 and 43.1% for MCV1). From May 2020, with the WHO recommendation to resume vaccination activities, there was an observed monthly improvement of coverage worldwide.18

Sub-Saharan Africa experienced relatively mild disruptions with decreases by 3.8% for DTP3 and 4.4% for MCV1 compared to 2020 expected estimates. However, since before the pandemic this region had lower vaccine coverage, at the end of 2020 they had low DTP3 coverage at 66.1% and 68.4% for MCV1.19

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Figure 4. Global DTP3* coverage 1980-2020.
Basic immunization coverage dropped to 83% in 2020, leaving 3.7 million more children un-or under vaccinated than in 2019.

* DTP3 = vaccine protecting against diphtheria, tetanus, and pertussis

Source: Unicef
The vaccine coverage target is dependent on the basic reproductive rate \( (R_0) \) of a specific organism (the ability of the organism to spread). The higher the \( R_0 \), the more the organism can easily spread and the higher the vaccination coverage needed to control or prevent the spread. For example measles, the most infectious virus globally, has a \( R_0 \) of around 18, so the vaccination coverage needs to be above 95%, different from infections such as diphtheria that have lower \( R_0 \). 20

Before the COVID-19 pandemic, vaccination coverage was already falling at an alarming pace around the world primarily due to vaccine hesitancy and resource shortages. So much so, that measles mortality was at a peak in 2019 with over 200,000 deaths. The COVID-19 pandemic came to make the decline worse and to increase the annual accumulated immunity gap, especially with the disruptions that impacted the delivery of vaccination services. 21, 22

As a result of the millions of children who missed measles vaccination in 2020, the world is again seeing a quick resurgence of measles, and as a result, by April 2022 the WHO reported 21 large measles outbreaks in the last year especially in Africa and the East Mediterranean region. Measles cases increased globally by 79% in the first two months of 2022 compared to the same time in 2021. However, for Africa the increase was more dramatic as 17,500 cases were reported from January to March 2022 (corresponding to a 400% increase compared to a similar period in 2021). 21, 22

A similar phenomenon is being observed for other vaccine preventable diseases, notably yellow fever and polio. Yellow fever resurgence is being observed in Africa with countries such as Kenya reporting cases after 25 years without a case. For polio, Africa was declared free of wild polio in August 2020 after a 4 years period of no reports. However, to date cases have been reported in Malawi and Mozambique. Both cases were linked to a wild poliovirus type 1 strain circulating in Pakistan (one of the few countries where the disease is still active), and considered as imported cases. Additionally, Africa is seeing an increase in vaccine derived polio cases as a result of gaps in the herd immunity. These events have kicked off a major vaccination campaign to reach 23 million children below the age of 5 years in Malawi, Mozambique, Tanzania, Zambia and Zimbabwe. 25, 26
The goals of the Global Vaccine Action Plan 2011 to 2020 were not reached as the figures presented above adequately show.

In August 2020, WHO launched a new ambitious Immunization Agenda 2021-2030, which draws on lessons learnt from the challenges of the previous plan as well as the COVID-19 pandemic. This new agenda is people centred, country owned, partnership based and data guided. Countries are expected to set their own targets based on the local context and evidence.

It aims to:
1. Reduce by 50% the number of children missing out on all vaccines (zero-dose children).
2. Achieve 90% coverage for all essential vaccines given in childhood and adolescence.
3. Introduce 500 new vaccines in low and middle-income countries.

Figure 5. Goals of the Decade of Vaccines (2011–2020).


This agenda is expected to halt the resurgence of vaccine preventable diseases such as measles and polio; and put the world back on track to the elimination and eventual eradication of these dangerous diseases.

Additionally, a costing study was done in LMICs considering the added challenges brought on by the COVID-19 pandemic (such as personal protective equipment for health workers, infection control measures for immunisation clinics and sites, physical distancing and COVID-19 screening during immunisations, vaccine delivery strategy changes and others).

The study found that countries should consider an additional start-up cost per facility of $466 - $799 for routine fixed immunisation sites, $12 - $220 for routine outreach sites and $12 - $108 per immunisation campaign site. They should also consider an additional monthly cost of $137 - $1,024 per facility for fixed-site, $152 - $848 per facility for outreach site and $0.32 - $0.85 per dose per campaign site. Thus, countries should consider this additional budget required for implementation of recovery measures within the framework of the new Immunization Agenda 2030.

Equally important is the issue of vaccine hesitancy in LMICs. Historically, vaccine hesitancy was not a problem in LMICs as previous studies show. The 2018 Wellcome Global Monitor (a global survey of 140 countries) reported that the great majority of the participants (more than 90%) in South Asia and East Africa thought vaccination was effective, compared to 59% in Western Europe. However, this may change due to the COVID-19 pandemic and countries’ response to it - a study published in Nature showed high acceptance rates in LMICs - but this was carried out while COVID-19 vaccines were still in clinical trials.

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“The legacy of the COVID-19 pandemic is a tragic immunity gap, especially in LMICs among the most vulnerable populations and this requires urgent action in order to reverse it.”

5. Recommendations

The legacy of the COVID-19 pandemic is a tragic immunity gap, especially in LMICs among the most vulnerable populations and this requires urgent action in order to reverse it:

- Countries need to ensure that standard immunisation programs remain as little disrupted as possible. Given that COVID-19 infection poses a much smaller risk of complications and lethality for children and youth than measles (and other VPDs), ensuring accessibility to life saving interventions such as vaccines during infancy remains necessary, even if against the general lockdown recommendations. It is vital to start planning and implementing catch-up vaccination campaigns to address the missed doses during the COVID-19 disruptions as well as pre-existing gaps.

- The new vaccines must be integrated into the EPI so that they can routinely benefit children.

- Invest in effective disease surveillance systems to detect disease outbreaks in a timely manner and prevent spreading by mass vaccination campaigns.

- Improve the routine immunisation data systems in order to closely monitor trends on doses and coverage to ensure timely responses to challenges.

- Review the logistical and supply chain problems to ensure timely and equitable delivery of vaccines across the globe and especially to the areas most in need.

- Invest in community based, comprehensive strategies to decrease vaccine hesitancy.
TO LEARN MORE:

- Rebecka Jonsson, María Lafuente. La salud infantil en el mundo debe ser un objetivo de la nueva Cooperación Española. El País. 5 July 2022.

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