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Vaccines, Vaccination, and Vaccine-preventable Diseases in Humanitarian Settings, 2022

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ABSTRACT

Vaccines, Vaccination, and Vaccine-preventable Diseases in Humanitarian Settings, 2022

By Ahmed Haji Said

Introduction: Vaccines and vaccination are fundamental to prevent significant morbidity and mortality and protect vulnerable populations from vaccine-preventable diseases (VPDs) in complex humanitarian emergencies (CHEs). Communities in these settings are at heightened risk for infectious disease transmission due to crowded conditions with inadequate shelter; poor water, sanitation, and hygiene; and limited access to healthcare services. Numerous VPDs elimination and eradication efforts exist globally; for the systematic review, I focused on VPDs in CHEs published extensively including cholera, measles, meningitis, yellow fever, poliomyelitis, diphtheria, tetanus, pertussis, and hepatitis A.

Methods: Literature on VPDs, vaccine hesitancy, and promising practices for future immunization delivery in complex humanitarian emergencies were searched using four electronic databases (PubMed™, Embase™, Web of Science™, and the grey literature). Abstracts from Jan 1, 2022, to Mar 1, 2022, were reviewed in contrast to predefined inclusion and exclusion criteria. All citations were managed and exported to EndNote X9®, where duplicates were removed.

Results: A total of 936 articles met the criteria to be reviewed once all duplicates were removed. Of those, 124 qualified for full-text review, 60 articles were not eligible, and a cumulative of 64 articles were eligible to be included. Research articles that did not meet the inclusion criteria were excluded because they did not examine a VPD or did not discuss the research population.

Discussion: VPDs persist in humanitarian and fragile settings due to low levels of immunity and challenges with reaching vulnerable populations. According to the literature, efforts must be made to reach these communities, and substantial funding is needed to understand vaccine hesitancy in CHEs. This is important because the views, concerns, and underlying barriers of individuals, communities, and groups are critical to addressing and improving vaccine uptake.

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ACCRONYMS

CHE	Complex Humanitarian Emergency
DPT	Diphtheria, Pertussis (whooping cough), and Tetanus
EPI	Expanded Program on Immunization
GAVI	Global Alliance for Vaccination and Immunization
GHS	Global Health Security
GTFC	Global Task Force on Cholera
GPEI	Global Polio Eradication Initiative
HAV	Hepatitis A Virus
IASC	Inter-Agency Standing Committee
IDMC	Internal Displacement Monitoring Centre
IDPS	Internally Displaced Persons
LMICs	Low- and Middle-income Countries
MCV	Measles-containing Vaccine
MoH	Ministry of Health
MR	Measles-Rubella
NIDs	National Immunization Days
OCV	Oral Cholera Vaccine
PHS	Public Health Surveillance
SAGE	Strategic Advisory Group of Experts on Immunization
SIA	Supplementary Immunization Activities
UN	United Nations
VPDs	Vaccine-preventable Diseases
WHO	World Health Organization
WPV	Wild Poliovirus
YF-VAX	Yellow Fever Vaccine

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Chapter 1. Introduction

Purpose

Immunization is a significant medical achievement in global health and development by protecting people from deadly diseases and averting up to 3 million deaths annually. [1] Global vaccination coverage against deadly infectious diseases has intensified with the establishment of the Global Alliance for Vaccination and Immunization (GAVI Alliance) in 2000 and the World Health Organization (WHO) Expanded Program on Immunization (EPI) in 1976. [2] There have been many impactful vaccines developed against numerous pathogens. This achievement is not only dependent on one classification of a vaccine, but rather on various subunits of vaccines, attenuated live vaccines, and non-replicating whole-virus or whole-bacteria vaccines. [3] After receiving an immunization series, vaccines create long-term protection and immunity.

According to WHO, approximately 4-5 million deaths are averted annually by childhood immunization. [4] In the 73 countries supported by GAVI Alliance, statistical modeling projected immunization programs averted 23.3 million deaths from 2011 – 2020. [3]

Definition of terms

According to the Inter-Agency Standing Committee (IASC), a **Complex Humanitarian Emergency (CHE)** is defined as a *humanitarian crisis in a country, region, or society where there is a total or considerable breakdown of authority resulting from internal or external conflict and which requires an international response that goes beyond the mandate or capacity of any single agency and/or the ongoing UN country programme.* [5] While the terms **refugees** and **migrants** are used similarly by the public, there is a distinction: *refugees* are *persons who are outside their country of origin for reasons of feared persecution, conflict, generalized violence, or other circumstances that have seriously disturbed public order and, as a result, require international protection.* [6] There is a general agreement that a *migrant* is an *individual who changed their country of primary residence, regardless of their legal or migration statu*s. [7]

According to the Guiding Principles on Internal Displacement, **internally displaced persons (IDPS)** *are persons or groups of persons who have been forced or obliged to flee or to leave their homes or places of habitual residence because of or in order to avoid the effects of armed conflict, situations of generalized violence, violations of human rights or natural or human-made disasters, and who have not crossed an internationally recognized border*. [8]

Vaccine is defined as *a preparation that is used to stimulate the body's immune response against diseases. Vaccines are usually administered through needle injections, but some can be administered by mouth or sprayed into the nose*. **Vaccination** is *the act of introducing a vaccine into the body to produce protection from a specific disease.* [9] **Immunization** *is a procedure in which a person becomes protected from disease through vaccination.* Immunization will be used interchangeably with vaccination. [9]

Background and significance

Countries grappling with CHEs caused by war, conflict, civil unrest, natural disasters, or other crises that result in human suffering or death have major disruptions to routine immunization programs, which threaten existing progress and coverage. [10] According to the Internal Displacement Monitoring Centre (IDMC), by late 2020, > 55 million individuals were internally displaced due to conflict or human rights violations. [11]

Data published by WHO and UNICEF in 2020 indicate that ≥ 23 million children missed routine immunizations. [12] Those in impoverished communities (i.e., refugee, migrant, or displaced populations) are disproportionately unprotected and overlooked regarding immunization and essential healthcare. As the CoVID-19 pandemic continues to burden fragile health systems and populations in CHEs, especially those in low-income countries, routine immunization programs are at risk of a setback. Significant progress to reach children and vulnerable populations with a wide range of vaccines is also impeded. This will lead to an increase in vaccine-preventable diseases (VPDs) and

mortality. Maintaining coverage and re-establishing routine vaccination programs should be a goal for immunization programs during CHEs.

There is a large gap in access to immunization between low- and high-income economies, refugees, and populations in CHEs, including internally displaced persons and stateless people. The populations in CHEs deal with heightened barriers to life-saving services. Communities in these settings are at risk for infectious disease transmission due to crowded conditions with inadequate shelter; poor water, sanitation, and hygiene; and access to healthcare services. To combat this, WHO's Strategic Advisory Group of Experts on Immunization (SAGE) in 2013 developed a framework to help decision-makers prioritize immunization programs during acute humanitarian emergencies. [13]

The framework presents decision-makers with a rigorous process to determine vaccination options during CHEs by evaluating epidemiologic threats of vaccine-preventable diseases and epidemic outbreak-prone diseases (e.g., meningococcal meningitis, cholera, polio, and yellow fever). [13, 14] This guidance aims to fill the gaps in the literature and proposes three steps for decision-makers to 1) conduct an epidemiologic risk assessment to categorize and determine the grade of risk of each VPD; 2) assess the primary distinction of vaccines (i.e., availability, affordability, and suitability to carry out vaccination campaigns); and 3) evaluate contextual considerations. [13]

WHO identified vaccine hesitancy in 2019 as one of ten threats to global health security (GHS). [15] After CoVID-19 was declared a pandemic by WHO, there has been a sharp increase in hyper-nationalism and protectionism. [16] The issue, as it pertains to historical non-region-led vaccine development and its role in previous outbreaks, received limited attention from organizations involved in the roll-out of the CoVID-19 vaccine across many regions. [17] Vaccination acceptance is critical in emergency-affected settings; factors that influence vaccine hesitancy must be addressed immediately. The global health community has a paramount role in amplifying scientific

and reliable information to emergency-affected communities to validate their questions and concerns. [18]

Rationale and objectives

A standardized approach is no longer acceptable to improve immunization coverage for populations in CHEs. Various factors are needed, not only among but also within countries. If all people are to have equitable access to vaccines, immunization services must be delivered in all settings that are secluded socially, culturally, and geographically. At the subnational level, multiple perspectives and approaches from varied stakeholders increase immunization coverage for hard-to-reach populations.

As global economies aim to recover from the CoVID-19 pandemic, we have an opportunity to review lessons learned; in humanitarian contexts, we should derive lessons learned from reinstated immunization campaigns despite their reach and impact. It is important now to understand the challenges and opportunities faced by hard-to-reach communities with vaccinations and to bring equitable solutions to the forefront of future vaccine delivery.

The objectives of this systematic review are to review available scientific evidence to …

- evaluate routine immunization coverage and identify populations affected by VPDs in settings where humanitarian emergencies occur.
- identify approaches or promising practices that are feasible while engaging with communities during immunization delivery in humanitarian settings.
- understand vaccine hesitancy in emergency settings and position immunization programs as an equitable solution to improve health outcomes.

Chapter 2. Literature Review

The CoVID-19 pandemic has caused massive disruptions for migrants, refugees, and displaced populations across the global migration cycle. [19] It generated significant economic and social obstacles for CHE's due to fragile governance, displacement, mistrust of authority, and variable compounding challenges. The 2022 World Migration Report revealed 281 million international migrants globally; a staggering number that increased by 3.5% in 2020 and continues to rise due to CoVID-19. [19] According to migration data, 89.4 million people live in displacement, of which 26.4 million are refugees, 4.1 million are asylum seekers, 3.9 million are displaced, and 55 million are internally displaced. [19] The countries impacted by the largest refugee population are Afghanistan, Burundi, Central African Republic, Democratic Republic of the Congo (DRC), Eritrea, Myanmar, Somalia, South Sudan, Sudan, and Syria. [19]

Complex Humanitarian Emergencies (CHEs) – regardless of type – have an increased risk for VPDs due to forced and continuous migration, resettlement, overcrowding, impoverishment, and substandard access to healthcare. [20] The objectives of immunization programs differ from routine programs and those for CHEs. In routine immunization programs, the goal is to provide security to the population and long-term defense of vaccines and increase immunity. However, in CHEs, vaccination programs or campaigns focus on reducing excessive preventable deaths. [20] There is an emphasis placed on mass vaccination campaigns to reach vulnerable age groups including children, elderly, and to vaccinate against pathogens with epidemic potential. In camps and camp-like settings, VPDs have the potential to be exacerbated and cause significant mortality or lead to an epidemic. [20]

Due to the CoVID-19 pandemic, there is a heightened risk of VPD outbreaks and disruption to health services. There are numerous VPD elimination and eradication efforts ongoing globally. However, VPDs which occur in CHEs and have been published extensively in the literature include cholera, measles, meningitis, yellow fever,

poliomyelitis, diphtheria, tetanus, pertussis, and hepatitis A. [21] These VPDs are not comprehensive, however, they are the most pertinent to emergency settings.

Cholera

Cholera is a fatal bacterial disease if it is not treated promptly and can cause harm to the small intestines. In CHE's, cholera has been linked to inadequate drinking water, sanitation facilities, poor hygiene, and overcrowding. [22] Cholera outbreaks are a considerable threat and most of the outbreaks occurring in the last decade have been in humanitarian settings. [23] Severe cholera epidemics are evident in countries with continued political fragility, instability, and displacement including Zimbabwe, South Sudan, Tanzania, Somalia, and Sierra Leone. [24]

Global Task Force on Cholera (GTFCC) was launched in 2017 and developed *A Global Roadmap to 2030* which aimed to harmonize strategies for cholera control and elimination, utilize oral cholera vaccine (OCV), and strengthen WASH strategies in low- and middle-income countries (LMICs) and humanitarian settings. [25] The OCV stockpile was set up in 2013 to provide immediate access of OCV to high-risk and conflict-affected settings where cholera is endemic. [26] The first OCV distributed from the global reserve was distributed to South Sudan due to an increased risk of cholera and a large displacement from the civil war in 2014. [27]

WHO reported 1.2 million cholera cases in 2017 and 5,654 deaths globally. [28] The United Nations (UN) declared an emergency in Yemen because they accounted for 84% of cases and 41% attributed deaths, making Yemen's outbreak the worst recorded epidemic globally. [28] However, these figures are not an accurate representation of the global burden of the disease since numerous nations do not self-report cholera cases and deaths (due to poor public health surveillance [PHS]). [28] Before the Yemen cholera outbreak, the country did not have a cholera preparedness and response plan despite prior outbreaks and endemicity. This challenge was exacerbated by an ongoing humanitarian crisis and airstrikes that damaged water systems. The gap led to 1 million suspected cholera cases to occur across two waves from Sep 2016 to Mar 2018. [29]

During the first wave, a response plan was established; however, it failed to prioritize delivering OCV and initiate an effective supply chain coordination. [24] This was similar to other CHEs that have had challenges in delivering OCV. [30] At the peak of the second wave, Yemen utilized lessons learned from the first wave and scaled up OCV, designed an information management system, and increased community-based WASH services. [28]

Somalia is overburdened with an ongoing, prolonged conflict. Continuous drought has exhausted water sources; increased malnutrition cases in internally displaced communities led the country to declare famine and emergency across 55 districts. [31] Due to these challenges, in 2017, the Ministry of Health (MoH) implemented the first OCV campaign to reach > 1.1 million displaced people in one year across 11 districts impacted by CHEs. [31] From Jan to Nov 2017, Somalia reported 79,172 suspected cholera cases with 1,159 deaths. [31]

This campaign was the most wide-reaching OCV campaign to date in sub-Saharan Africa and was supported by UNICEF, WHO, and the GAVI Alliance. [32] During the campaigns, the MoH followed WHO protocols, and OCV was used to control the outbreak and curb the spread of the epidemic. [32] The achievement of the OCV campaign was accredited to substantial communication, collaboration, and planning between the MoH and stakeholders before the campaign was launched. Somalia utilized lessons learned from ongoing polio campaigns and their implementation, existing data systems, and door-to-door vaccination strategies to supplement vaccination sites. [33] Before the campaigns started, the MoH and global partners utilized community mobilizers to teach communities about the benefits of OCV. This effort benefitted a large number of displaced communities who took the vaccine once the roll-out was widely implemented across the country.

Dec 27, 2021 the DRC launched a campaign targeting 2 million children aged > 1 year in regions with ongoing outbreaks and fragility. [34] The DRC had previously reported

8,279 suspected cases and 153 deaths across 16 of 26 districts located across the country during 2021. [34]

Measles

A highly contagious and deadly viral infection, measles has no cure. The virus is extremely harmful and has a rapid person-to-person transmission through respiratory droplet. Globally, measles cases have continued to increase in CHEs despite a measles-containing vaccine (MCV) being widely available. [35] Unvaccinated young children and pregnant women continue to be at heightened risk for the virus and its complications, including death. Despite significant progress, coverage has been stagnant at 85% in 2010, and in 2016, efforts began to expand activities to decrease the virus in Gavi-eligible economies. [36] Measles-Rubella (MR) vaccine and MCV2 campaigns have been introduced, and measles cases decreased to 65% in 2019. [36] In 2020, WHO introduced the *Measles Outbreak Strategic Response Plan* 2021 – 2023 because of the virus's uptick in 2018 and 2019 causing substantial cases and deaths. [37] The strategic plan guides preparedness, prevention, and control efforts, and improved coordination, communication, and collaboration among countries and stakeholders.

The *Immunization Agenda 2030* (IA2030) indicated that measles incidence is a way to measure the effectiveness of immunization programs, particularly in fragile settings. [38] The *Measles Outbreak Strategic Response Plan* and *Measles-Rubella Strategic Framework* advocated for consolidated PHS to measure immunity gaps, and identify fundamental causes for lack of vaccination in order to develop tailored and targetted approaches for missed communities with vaccines. WHO recommends 95% coverage of the two MCV doses, and the first and second doses should be administered between 9, 15, and 18 months, respectively. [39] In CHEs, measles may present with pneumonia and diarrhea which can contribute to infant mortality. [39, 41]

Supplementary Immunization Activities (SIA) for measles is important for individuals who are 6 months to 14 years old to help with preventative measures and increase

immunity, if there are outbreaks or a decline in immunization coverage. [39] While SIAs have their benefits, they are a substitution rather than complementing routine immunization programs, an approach that is critical for measles elimination. [39] In Yemen, several SIAs conducted used an integrated outreach system; they administered MCV five times in a year and increased vaccination coverage up to 70%. [40]

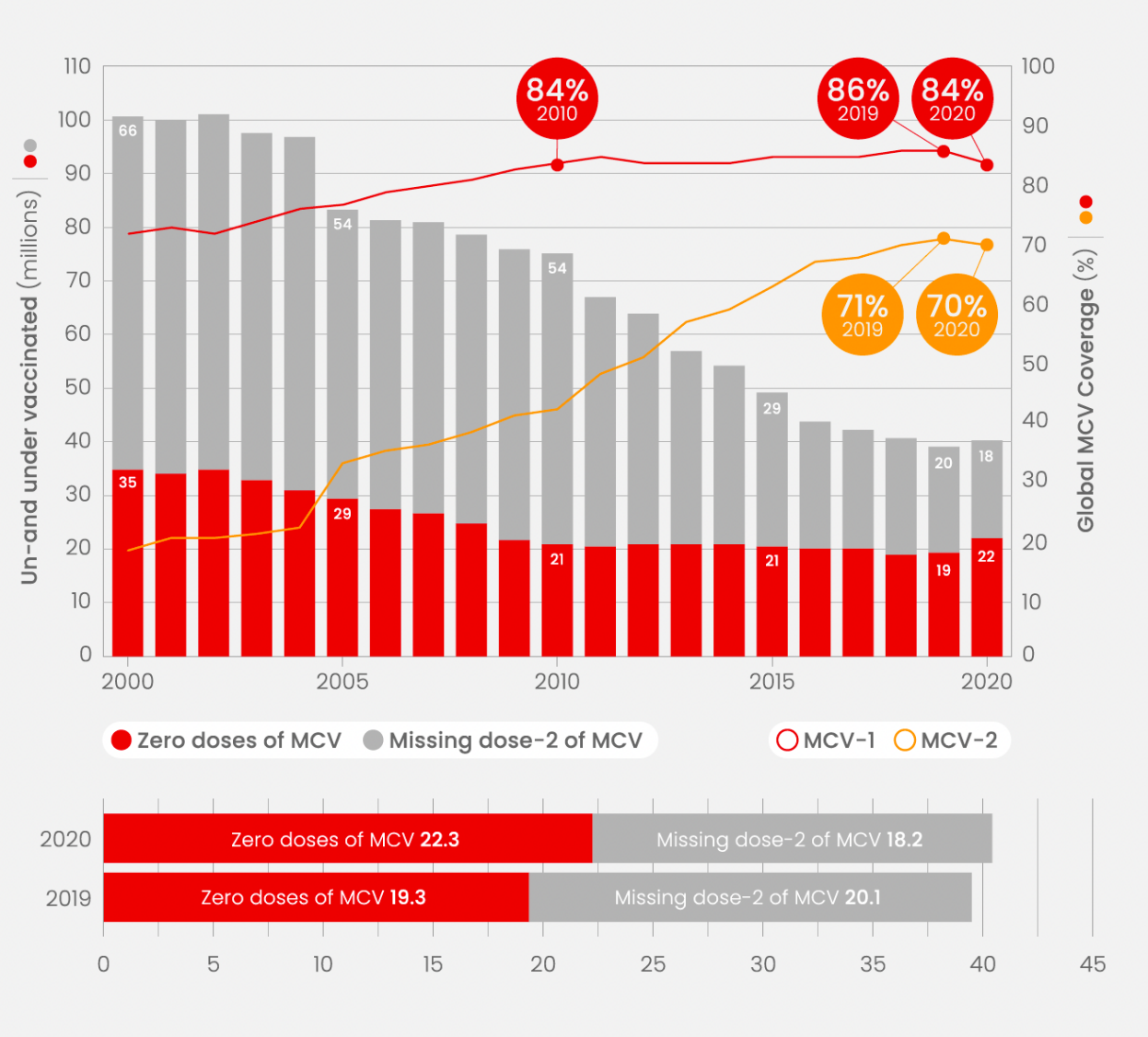
In 2020, the coverage rate for MCV-1 dropped to 84% bringing it to 2010 levels. [43] This decline left > 22 million children unprotected against measles, and only 18.2 million received MCV-1 but not MCV-2 through the measles protection program. [43] The decline was attributed to CoVID-19. Most children were in areas affected by conflict, urban slums, and remote rural areas in 10 countries: Afghanistan, Angola, Brazil, the Democratic Republic of the Congo, Ethiopia, India, Indonesia, Nigeria, Pakistan, and the Phillippines. [43] Countries have begun SIA campaigns to guarantee children receive the 2 doses of MCV.

Dr. Kate O'Brien, MD, MPH, Director of WHO's Department of Immunization, Vaccines, and Biologicals said in a joint WHO-CDC Statement ... *Evidence suggests we are likely seeing the calm before the storm as the risk of outbreaks continues to grow around the world.* [43]

Dr. Ephrem Tekle Lemango, Associate Director for Immunization at UNICEF, added...

Even before the pandemic, we were seeing how even small pockets of low measles immunisation coverage could fuel unprecedented outbreaks, including in countries where the disease had been considered eradicated. And now, CoVID-19 is creating widening gaps in coverage at a pace we haven't seen in decades. If we do not act, gaps will become outbreaks, and many children will be exposed to a preventable but potentially deadly disease. [43]

Figure 1. Global Measles-containing Vaccine Coverage (%) in Un-and-under Vaccinated Children (millions) (source: WUENIC, 2020)



The first dose of MCV dropped in 2020; 70% of zero-dose children received their second dose of MCV, which is below the 95% coverage required to protect populations from the virus. [44] Adding to this challenge, 23 countries that were positioned to implement 24 campaigns postponed their efforts, citing CoVID-19 as a challenge and leaving more than 93 million individuals at risk for measles. [45]

Dec 4, 2021, Cameroon rolled out a measles campaign on its northern border with Nigeria, intending to reach 67,000 children aged 6 months to 9 years. [46] Most of the population were former child fighters escaping Boko Haram terrorists and became infected at a demobilization center. Cameroon announced 79 of 190 district hospitals reported measles epidemics in 2020, and approximately 1,500 were confirmed infections. [46]

A challenge with routine measles coverage in humanitarian settings is using population-based surveys due to difficulty in administration, bias, and diplomatic controversies. [38] Communities in CHEs are prone to incorrect sampling frames, inflation of population data, and exclusion of certain groups by religion or ethnicity. [39] Humanitarian organizations have historically conducted small-scale surveys during CHEs intending to make it available for use to stakeholders. Nonetheless, the biggest challenge which remains is tracking ongoing and sudden large population migration after conflict, because surveys cannot be administered due to difficulty with access and evidence of vaccination. [39] To overcome this challenge, flexible funding streams must be developed to advance research and overcome the existing barrier for this demographic.

Meningitis

Meningitis is a viral, bacterial, or fungal infection causing inflammation around the brain and spinal cord. [20] Globally, it can be debilitating causing devastating social, economic, and physical well-being. *Neisseria meningitides*, also referred to as meningococcus, is a bacterial meningitis that has an epidemic potential causing death, with one in five patients having disability after infection. [49] Meningitis is a severe disease for all age groups, but children < 5 years are the most at risk with half the cases and deaths. [49] During CHEs, meningitis has been recorded to transmit to adolescents and adults. [20, 49] Meningococcemia and meningococcal meningitis are known to spread widely in refugee camps albeit the two agents have not been differentiated since the 1970s. [48] Meningitis cases and deaths are preventable in CHEs with life-saving vaccines, however, progress has stalled behind other VPDs. [49]

In 1997, The International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control was established and commissioned with responding to global epidemics and maintaining the vaccine stockpile. [20] The *Global Roadmap to Defeat Meningitis by 2030* was developed to eliminate bacterial meningitis epidemics and reduce deaths by 70%. Meningococcal meningitis in CHEs has been recorded in Ethiopia during 1989 and 1993; the Democratic Republic of the Congo in 1994 and 2001; Guinea in 1993; Sudan during 1985, 1989, 1999, and 2007; Thailand in the 1980s; Uganda in 1994. [47-49] Bacterial meningitis has been recorded in Chile, Fiji, Kyrgyzstan, Niger, and Nigeria. [47]

During CHEs, campaigns deliver meningococcal vaccines for outbreak response and prevention. [48] Experts recommend implementing mass campaigns once the epidemic threshold has passed, targeting refugees and non-refugees within four weeks using vaccines that are suitable for the causative serogroup. [47] Polysaccharide vaccines, polysaccharide-protein conjugate vaccines, and protein-based vaccines against serogroup B vaccines are used to prevent meningitis. [47, 50] Meningococcal conjugate vaccine (ACWY) offers protection against four types of meningococcal bacteria (A, C, W, and Y), and monovalent serogroup A vaccines, and are useful in the African meningitis belt. [52]

Between 2000 – 2018, DRC reported > 118,000 cases of meningitis with a mortality rate of 11.5%. [53] In 2021, DRC declared the deadliest meningitis outbreak on record in Tshopo, a north-eastern province, where 2,662 and 205 deaths were recorded. [51] DRCs national health authorities – with the support of WHO – conducted a rapid response by strengthening PHS, deploying emergency response teams, implementing vaccination campaigns, and mobile health clinics for communities. As a result, the case-fatality ratio decreased significantly from 85% to 10% within a few weeks. [49] Historically, meningitis has been a challenge to control in DRC due to lacking diagnostics, data sharing, unstable telecommunication networks, vaccine hesitancy and

witchcraft, and challenging terrains with poor roads to reach vulnerable communities. [54, 55]

Yellow Fever

Yellow fever is a mosquito-borne disease transmitted by the *Aedes species and Haemogogus* species. The disease is endemic in 44 countries and the geographic region most affected is Africa and people living in the yellow fever belt. [56, 57] Communities in CHEs with limited nutrition, inadequate shelters, substandard sanitation and hygiene, and deficient vector control activities are at high risk for the disease. [59] The sequelae of yellow fever include high fever, bleeding into the skin, and cell death in the kidney and liver. [58] Yellow fever has no treatment or cure, however, the disease can be prevented with the life-saving yellow fever vaccine (YF-VAX). YF-VAX is recommended to infants > 9 months who are living in endemic areas. Most countries provide YF-VAX in combination with MCV as part of their EPI program. Global estimates show approximately 610 million individuals across 32 African countries, of which 219 million are urban dwellers remain most at risk for yellow fever. [58] WHO estimates 200,000 cases and 30,000 deaths annually, of which 90% occur in Africa. [58] Yellow fever cases in Africa are underreported and the burden of the disease is underestimated. [58]

WHO, UNICEF, GAVI Alliance, and partners published *Eliminate Yellow Fever Epidemics (EYE) 2017 – 2026* with three key objectives: 1) to protect vulnerable populations, 2) avert global spread, and 3) prevent outbreaks quickly. [60] The guidance urges prioritization for urban outbreaks due to migration, crowding, and an increase in transmissibility with epidemic potential.

In 2021, the World Health Organization Regional Office for Africa (WHO AFRO) reported cases of yellow fever in the Republic of Congo, Niger, Nigeria, DRC, Ghana, Center African Republic (CAR), Côte d'Ivoire, and Cameroon. Six of these countries reported 66 deaths (Ghana = 42; Cameroon = 8; Chad = 8; Nigeria = 4; Congo = 2; DRC = 2) and most of the cases occurred in conflict-affected or fragile settings with

existing decreased population immunity. [61] Most of these settings lack active PHS, preparedness, and response which lead transmission to spread to other countries as seen in CAR, Cameroon, and Chad. [61] In 2016, yellow fever outbreaks in urban settings spread rapidly in DRC and Angola.

Vaccination coverage in Africa has been inadequate to provide herd immunity and decrease the likelihood of transmission. In 2020, WHO and UNICEF data on YF-VAX showed 44% coverage across Africa, lower than the 80% coverage needed for herd immunity. [61] In endemic areas where coverage is low, communities in CHEs are the most impacted with low vaccination coverage. This indicates a susceptible demographic at risk of continued transmission of the disease. A single dose of YF-VAX is adequate to afford individual protection against the disease, and a future booster is not required. [61] Inoculation with the YF-VAX provides immunity in 10 days for 80-100% of people, and 30 days for 99% of people who become vaccinated. [61]

Hepatitis A

Hepatitis A occurs in the liver caused by the hepatitis A virus (HAV). It is linked to insufficient food, poor water, sanitation, hygiene, and oral-fecal transmission from an infected individual. [62] Globally, HAV is a growing concern in refugee camps with an estimated incidence of 1.5 million symptomatic cases. [63] HAV infection occurs without symptoms in CHEs due to high endemicity and isolation. The virus is common in men who have sex with men (MSM). Children in refugee camps are often asymptomatic and develop immunity, however, adults present with clinical symptoms such as jaundice and dark urine. Immunity to HAV has been credited to improved immunization coverage. [63, 64]

During the Syrian crisis in 2013 and 2014, increased cases of HAV were reported in Lebanon due to a large influx of refugees who sought shelter in refugee settlements and camps. [63] The Syrian civil war led to more than 6.5 million refugees being internally displaced. Approximately 1 million Syrian refugees were registered in the Northern

states of Lebanon. Refugees live in roughly 990 informal tented settlements across Lebanon. [63] Existing fragile water systems and untreated sewages led to a rapid spread of HAV disease.

In Croatia, inadequate sanitation and hygiene coupled with a higher number of refugees led to an HAV outbreak among children in a refugee camp. The camp was populated by 284 displaced Croats from Kosovo. [64] Existing conflict in bordering countries prompted an increase in HAV cases, accompanied by an already susceptible demographic. [64] Vaccination, health education, and improved sanitation were central to the response efforts to hamper the outbreak. [20] Serological tests were conducted, and eligible children who were anti-HIV positive received a vaccine. Researchers concluded vaccination is a critical component to decreasing HAV transmission in CHEs. [20, 64]

Poliomyelitis

Polio, or poliomyelitis, is a deadly acute communicable disease caused by the poliovirus serotype 1, 2, and 3. Polio is transmitted from person-to-person contact, through the fecal-oral route, and presents with flu-like symptoms. The population most at risk of the disease are children < 5, particularly in humanitarian and fragile settings. Polio infection can lead to irreversible paralysis in the legs in approximately one out of 200 cases. [65] Polio can invade the central nervous system in a few hours and cause complete paralysis of the respiratory system.

During World Polio Day, Oct 24, 2019, a historic announcement was made by experts on the eradication of wild poliovirus type-three (WPV3), marking the eradication of wild poliovirus type-two (WPV2) and WPV3. [66] The WHO Africa Region was declared free of wild poliovirus Aug 2020, WHO South-East Asia Region in 2014, WHO European Region in 2002, WHO Western Pacific Region in 2000, WHO Region of the Americas in 1994. [65] However, Angola, Myanmar, Malaysia, the Philippines, and Zambia remain at risk due to poor PHS and immunity. [68]

Polio can only be prevented through inactivated poliovirus vaccine (IPV) and oral polio vaccine (OPV). Pakistan and Afghanistan are the last two countries with Wild Poliovirus Type 1 (WPV1) transmission. Nigeria has recently become polio-free and has not reported any cases of the wild poliovirus since Aug 25, 2020. [69] The risk of polio resurgence exists globally until both countries become polio-free.

In 1988, the WHO (during the World Health Assembly) pledged to eradicate polio by launching the Global Polio Eradication Initiative (GPEI) to eradicate and contain wild, Sabin polioviruses, and vaccine-related polio. [70, 71] Before GPEI was launched, polio was endemic in > 125 countries and caused approximately 350,000 cases; polio incidence has since decreased by 99.9%. [71] GPEI launched the *Polio Eradication Strategy 2022–2026,* supporting global eradication by increasing vaccination efforts, integrating services, transitioning polio programs to government ownership, and reaching communities in fragile and inaccessible settings. [72] GPEI has made significant progress on polio eradication, however, poliomyelitis continues to take place in displaced communities.

In 2001, the humanitarian crisis in Afghanistan led Afghani refugees to seek shelter in neighboring Pakistan, causing concern between the two nations. [21] Before the humanitarian crisis, Afghanistan made significant progress to eradicate polio from the nation; however, fragile health systems, political, and socioeconomic challenges have created obstacles. [71] In 2008, the Taliban banned door-to-door OPV SIAs, leading to approximately 3.4 children missing out on polio vaccines. [71] Most of these households reside in rural and humanitarian settings where health and immunization services are non-existent. On Nov 8, 2021, the Taliban agreed to restart polio immunization programs, allowing WHO, and other key organizations to provide immunization to > 3 million children. [74]

To eradicate poliomyelitis from Afghanistan, every child < 5 years must receive a vaccine, however, instability and the CoVID-19 pandemic continue to be the biggest challenges. Data reported from the National Immunization Days (NID) during Jan 2020

showed 2,655,821 children < 5 years were unreachable. [71] In Mar 2019, SIA coverage reported 399,969 children as reachable but missed due to campaign failures; 299,977 cases were reported from Nov 2019 to Jan 2020; and 22,035 in Jul 2020, with most children reported to be in fragile settings. [77] Children who do not receive OPV during SIAs are categorized as unreachable due to safety concerns. To accelerate eradication in the country and improve security for healthcare workers during immunization campaigns, the Taliban and community must work together as partners, by providing security, and preventing violence during campaigns.

A polio campaign was conducted across Afghanistan on Nov 21 reaching 8.5 million children < 5 years, and 2.4 million of these children were reached for the first time in 3 years. [75] Afghanistan and Pakistan reported the lowest polio cases in 2021, and they used re-start campaigns as the best opportunity to work towards disease eradication. [75]

Polio is endemic in Pakistan and poses a significant risk to global eradication efforts. Pakistan's polio elimination and eradication efforts are conducted through routine programs, campaigns, and SIAs which have proven to be challenging to carry out due to operational restrictions and oversight, security, migration, instability in war-affected humanitarian settings where healthcare workers have been under attack. [76] Historically, Pakistan's polio program has undergone a close watch due to being the primary driver for wild polio spread globally. This has been attributed to ongoing conflict and instability, hindering the effectiveness of SIAs and campaigns. Insufficient surveillance, vaccination, vaccine hesitancy and misconceptions, operations including adequate storage and transportation, and coordination with Afghanistan regarding increased immunity are substantial challenges. [76]

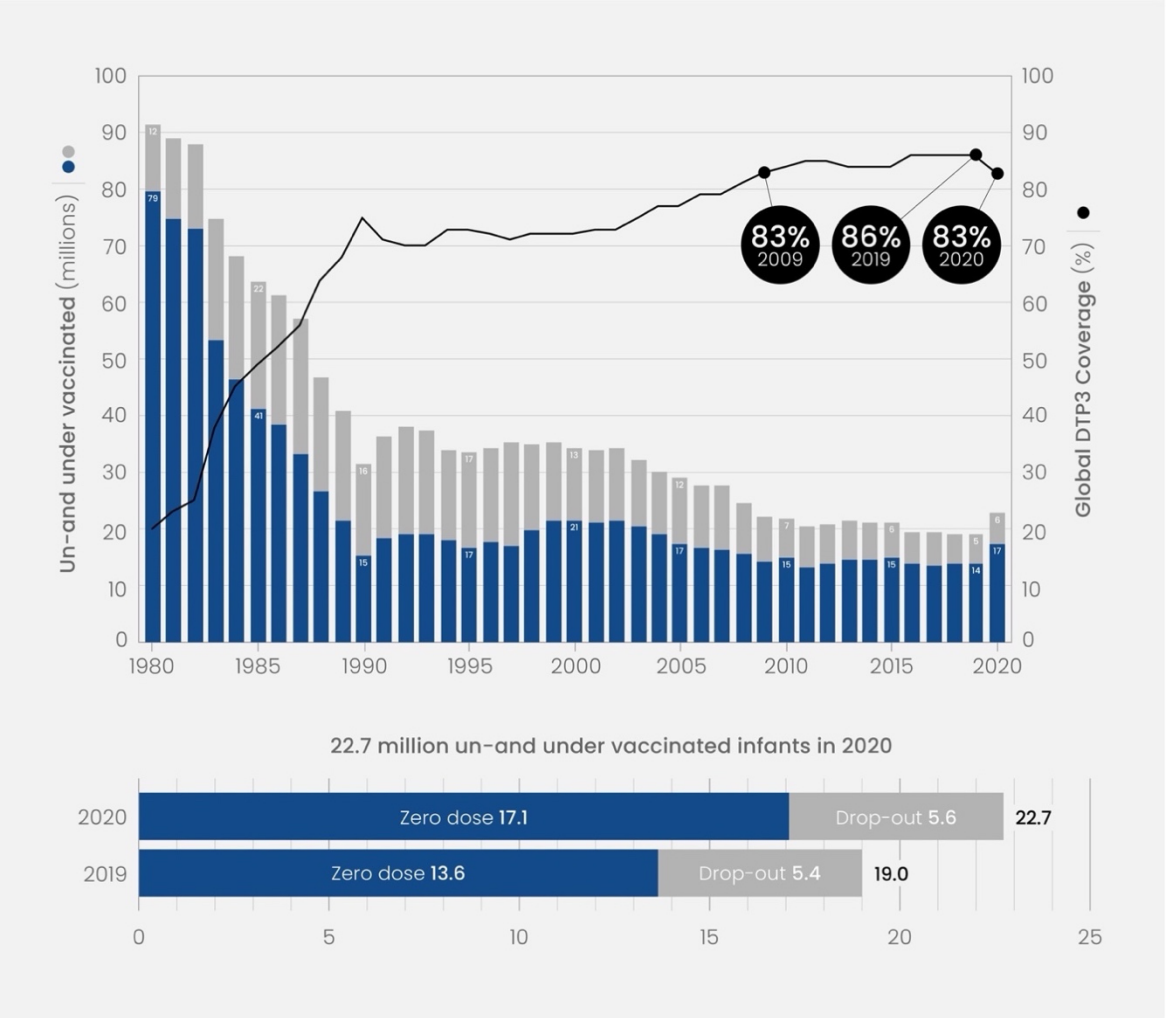
Jan 17, 2022 a Sub-National Immunization Days (SNIDs) polio campaign was launched, reaching > 22.4 million children < 5 years, covering 70 municipals, and six districts with ongoing heightened risks due to fragility. [75] Pakistan's government engaged more than 150,000 workers who inoculated children from door to door. The considerable

success from this campaign generated Pakistan to plan another nationwide campaign on Feb 28, 2022, and to work towards being polio-free. [75]

Diphtheria, Pertussis, and Tetanus

Diphtheria, pertussis, and tetanus (DPT) are contagious vaccine-preventable bacterial diseases. Diphtheria can cause respiratory issues, paralysis, and even death. Tetanus leads to locking of the jaw, and pertussis, also known as whooping cough, is an extremely infectious respiratory infection. [76] Children require three doses of the DPT vaccine to build immunity against diphtheria, tetanus, and pertussis. Those engaged in immunizations, for performance purposes, use DPT1 as an indicator to pinpoint children who have not received other vaccines and essential healthcare services, referred to as zero-dose children. [78] Around 1 in 10 children in 68 Gavi-supported economies do not receive a single dose of routine immunization. [79] Many of these children live in resource-constrained households in fragile and humanitarian settings. Zero-dose children are not only deprived of vaccines but wider services (e.g., education, basic nutrition, WASH, sexual and reproductive health).

Figure 2. Global Diphtheria, pertussis, and tetanus (DPT-3) coverage (%) in Un-and-under Vaccinated Children (millions) (source: WUENIC, 2020)



In 2020, global coverage estimates showed 22.7 million infants were (un)under vaccinated of DPT3, dropping immunization coverage rates back to 2009 levels, specifically 83%. Globally, pertaining to children who were un-and-under vaccinated, 3.7 million were zero-dose children. [12] In 2020, approximately 16 million of the 72.9 million children targeted with Gavi funding did not receive the first dose of DPT. In total, 12.4 million (78%) of zero-dose children did not receive a single inoculation of DPT. Moreover, 16 million children in the 68 Gavi-eligible economies did not receive the third dose of DPT, referred to as under-immunized. [80]

Among the 68 countries in Gavi's portfolio, 18 are classified as fragile nations with ongoing humanitarian crises. In fragile settings in 2019, 62% coverage of DPT3 was reached compared to 81% in other nations. Approximately 50% of children who lose their lives due to VPD's in Gavi-eligible economies are zero-dose, albeit composed of 13% of the total demographic. [80] The CoVID-19 pandemic caused coverage to drop in Q2 2020, and countries began resuming their routine immunization campaigns and program at the end of 2020. Due to CoVID-19 related challenges, there is an increased risk of disease outbreaks and child death. According to a study that examined the immunization cascade of zero-dose children, they found that over two-thirds of children who received one dose of DPT went on to become fully vaccinated with MCV, Polio, and BCG. [81]

Vaccine Hesitancy

Vaccination against VPDs in humanitarian and fragile settings is believed to be a panacea for reducing significant mortality and morability. Despite the increase recognition that children and vulnerable communities must be prioritized during delivery, there is emerging evidence that vaccine hesitancy poses a challenge in improving coverage. Inequities in access to healthcare services are among the drivers of vaccine hesitancy in some communities. Countries are increasingly focused on protecting their citizens and have neglected their obligations and commitments to protecting refugees and displaced populations which live in their borders.

During an OCV campaign in Juba, South Sudan, vaccine hesitancy posed a significant threat to immunizing displaced populations. This objection was attributed to skepticism that the national institutes were engaged in ethnic cleansing, and ultimately led to vaccine refusal from IDPs. [82] Individuals who received OCV in the past, the flavor and scent contributed to vaccine hesitancy. However, social behavior influences, political will, and philosophical ideologies contributed to existing challenges. IDPs believed that Cholera occurred due to God's will, and others believed that politics contributed to the root cause of the disease. Taking OCV with medication or alcohol also contributed to

hesitancy. [82] These findings suggest addressing skepticism, adverse reactions, and effectively communicating the benefits of the vaccine is important during delivery. It is also important to understand social influence in the context of understanding the communities needs.

Polio has been associated with vaccine hesitancy in Afghanistan and Nigeria. [83] In both countries, rumors, misinformation, and rejection of the vaccination program was a growing challenge. Campaign activities and CHWs were rejected by community members, especially in insecure areas such as the Pakistan-Afghanistan border. Due to the region being controlled by the Taliban, a house-to-house strategy was ineffective. The community believed the government were camoflouging themselves and bringing unnecessary attention to their homes or were planning for drone attacks. [83]

Myths, misinformation and rumors about several issues such as vaccine safety and efficacy, politics, science, etc., are major drivers of vaccine hesitancy in CHEs. [83] They instill fear in people and negatively influence their intention to receive effective immunizations. Prompt, coordinated, and community-oriented messaging is important for countering rumors, misinformation, and disinformation about vaccines.

Chapter 3. Methods

Introduction

The objective of the systematic review was to synthesize available scientific evidence on routine immunization coverage in CHEs, identify populations that are most affected by vaccine-preventable diseases, and explore approaches or promising practices that are feasible for immunization delivery in fragile settings. A search strategy, which incorporated Medical Subject Headings (MeSH) and text-based terms associated with vaccine-preventable diseases and complex humanitarian emergencies, was established with the support of a librarian at Emory University. This research study did not require a review by the Institutional Review Board (IRB).

Search Strategy

We searched the literature for articles published from Jan 1, 2002, to Mar 1, 2022, providing a 20-year review of VPDs in CHEs. The systematic literature review was composed of searching for published articles in PubMed™, Embase™, and Web of Science™. While PubMed™ served as the primary research database, and due to the multifaceted nature of this research, the ("grey") literature was also utilized. Articles in the grey literature included academic research papers, government reports, and scientific committee reports, among others. An inclusion and exclusion criteria were developed and applied during the literature search process across the three databases, and the grey literature. Research articles and grey literature suitable and met the inclusion criteria were synthesized during the literature review. Broad terms relating to VPDs in CHEs were utilized in the search strategy to ensure a breadth of articles were captured. A search strategy with the subsequent key terms was used. (Figure 3)

Figure 3. Literature Search Inclusion and Exclusion Criteria, 2002 – 2022

Database	Key Search Terms
Pubmed™ Embase™ Web of Science™ Grey Literature	*Vaccine OR Vaccine OR Immunization OR Vaccination* *Immunization Campaign OR Supplemental Immunization Activities* *Vaccine Preventable Diseases OR VPDs* *AND* *Humanitarian Crisis OR Humanitarian Emergency Crisis OR Armed Conflict* *Camp OR Warfare OR Emergency Shelter* *Refugee OR Internally Displaced Person OR Displaced Person OR IDP OR Displace*

After conducting a search in the databases, all citations were managed and exported to EndNote X9®, where all duplicates were removed. All abstracts were carefully reviewed in contrast to the inclusion and exclusion criteria developed before conducting the systematic literature review.

Inclusion Criteria

- Research articles that address at least one of the following vaccine-preventable diseases (e.g., cholera, measles, meningitis, yellow fever, hepatitis A, poliomyelitis, diphtheria, pertussis, and tetanus) in humanitarian settings
- Population includes those affected by a humanitarian crisis (e.g., migrants, refugees, internally displaced persons)
- Articles must be available through accessible databases or the Emory library

- Published between 2002 and 2022
- Published in English

Exclusion Criteria

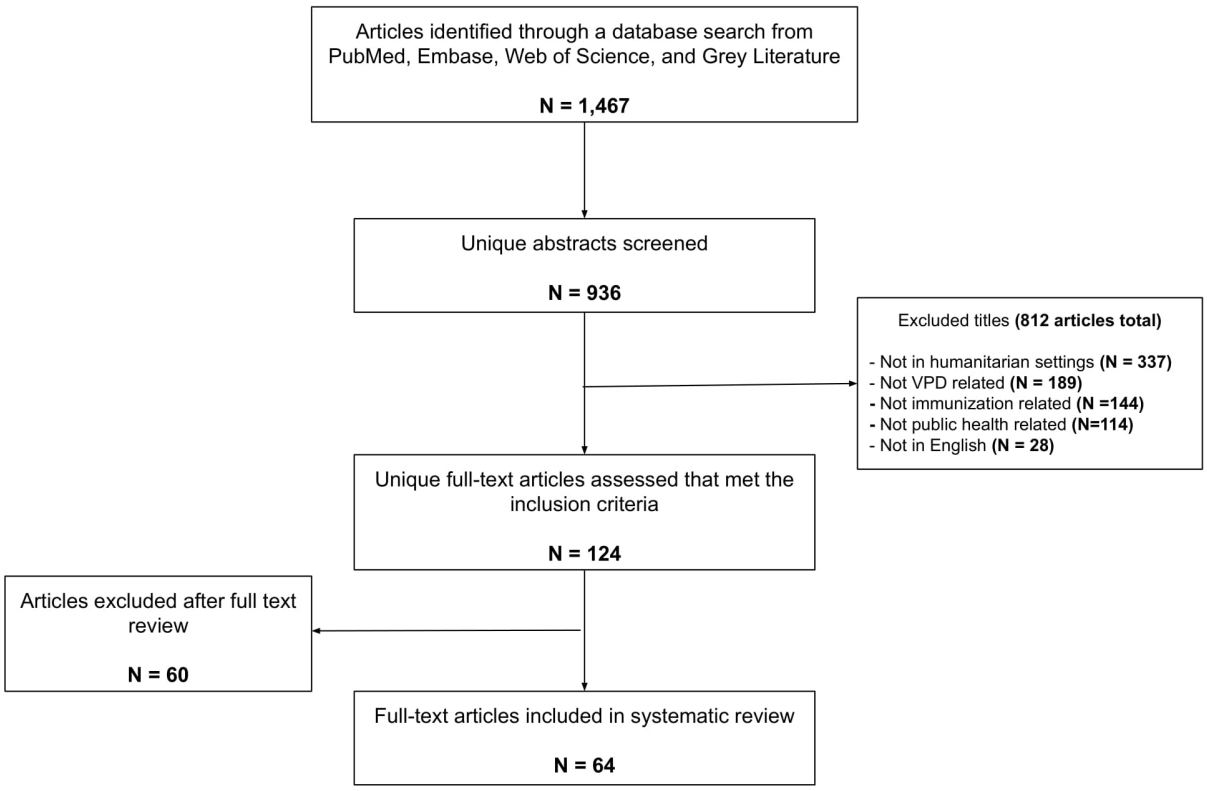
- Studies not addressing at least one vaccine-preventable disease in humanitarian settings
- Editorial letters, articles and reviews that did not include any abstracts
- Research articles that did not include the study population
- Research studies published before 2002
- Studies not in English
- Studies not available through databases or through the Emory library

Chapter 4. Results

Introduction

For the systematic review, a total of 936 articles met the criteria to be reviewed once all duplicates were removed. Of those articles, only 124 articles qualified for full text review, 62 articles were not eligible, and a cumulative of 64 articles were eligible to be included in the systematic review. (Figure 4)

Figure 4. Diagram of Study Search & Selection Process, 2002 – 2022



Research articles that did not meet the inclusion criteria were excluded because they did not examine a VPD or the research population. (Figure 5)

Figure 5. Articles of Population and Vaccine-preventable Diseases, 2002 – 2022

Disease	Internally Displaced Persons	Refugees
Cholera	5	4
Measles	9	8
Meningitis	8	6
Yellow Fever	4	5
Hepatitis A	4	3
Poliomyelitis	8	7
Diphtheria, Pertussis, and Tetanus	5	6
Total	43	39

Description of Eligible Literature

Among the studies included for the systematic review, they discussed the vaccine-preventable diseases of interest according to the following: cholera (n=12), measles (n=18), meningitis (n=11), yellow fever (n= 5), poliomyelitis (n=12), diphtheria, tetanus, pertussis (n=5), and hepatitis A (n=5).

Immunization coverage

In general, the authors expressed that the principal of any effective immunization program that aims to prevent the spread of VPDs in CHEs must provide clean water, sanitation, hygiene, and access to essential health services. [21, 28, 30, 58, 61] To determine which vaccines can be used for implementation, a decision-making tool has been designed by WHO's SAGE. The tool encompasses disaster types, geographic representation, and host factors to determine which vaccines are appropriate for

delivery during an emergency. [13] The instrument has been important for the prevention and control of VPDs; however, it has been criticized that it's complicated and excludes vaccines that can be used in emergency settings. [83]

Measles is often the biggest threat to emergency settings, and MCV is a priority vaccine in CHEs. [13, 83] MCV is typically co-delivered with polio, and for optimum vaccine coverage, a needs assessment needs to be done to decide on the age groups that will be targeted for campaigns. A coverage rate that is below 90% in <15 years is often the standard for mass vaccination campaigns. [83] SAGE guidelines propose selecting primary sampling units and drawing a representative sample using probability proportional to size (PPS) and randomly selecting households from the population. [13]

In the literature, the vaccines that were proposed for immediate delivery during a CHE were polio, measles, and DPT. [13, 14, 20, 21, 39, 43] Concerning VPDs with epidemic potential, meningitis, hepatitis A, and yellow fever are recommended for immediate delivery, polio, and measles are recommended to be used as preventative measures during the beginning of a CHE. DPT-3 is highly recommended to be delivered through routine immunization programs, especially for zero-dose children. [79, 80] The meningococcal vaccine has been used to prevent meningitis across the sub-Saharan Africa meningitis belt, particularly when at the beginning of an outbreak.

Recommendation for future delivery

An important priority after a CHE's recovery phase is to rebuild and implement routine vaccinations through the national EPI services. [13] This indicates the health system has steadily been reinstated, and the VPDs was corresponding to the circumstances of the CHE. Important lessons from previous CHEs underline the significance of establishing an appropriate framework for emergency response before they occur. Trained health workers, staff, and pre-defined population targets lead to a successful campaign during a CHE.

The need for multi-sectoral partnerships is not well-documented in our systematic review. However, a multisectoral partnership with the contribution of several stakeholders across sectors such as nutrition (vitamin A) is important during delivery. [79, 81] Stakeholders must communicate, collaborate, and coordinate through a collective partnership and not in silos. Competing interests must be worked through between partners and which partners will allocate which resources. However, the collective goal must be to reduce significant morbidity and mortality. Co-delivering integrated health services with immunization are cost-effective for service delivery and will strengthen attendance from the population.

Chapter 5. Discussion, Limitations, and Recommendations

Discussion

This systematic review utilized publications with quantitative, qualitative, and mixed methods approaches. We synthesized these articles to evaluate routine immunization programs and the impact of VDPs in the population and regions where humanitarian emergencies occur. We identified approaches or promising practices that are feasible while engaging with communities during delivery of immunization services, the negative impact of vaccine hesitancy, and the need to improve health outcomes for this population.

Immunization programs are cost-effective and successful in reducing significant morbidity and mortality in humanitarian and fragile settings. However, there are routine short- and long-term disruptions of immunization programs impacting many refugees and IDPs thereby leaving them prone to VPDs. Continuous displacement, crowding, migration, and poor access to immunization services impact the ability to obtain high immunization coverage and decrease morbidity and mortality. These challenges have been exacerbated by the CoVID-19 pandemic which has caused delays in campaigns, thus increasing concerns in re-emerging VPDs and more populations being negatively impacted.

To overcome these challenges, multisectoral partnerships, political buy-in, and engaging communities during implementation and delivery will be necessary. Multisectoral partnerships will allow for immunization to integrate with other services, and communities will have the opportunity to benefit from services they likely missed out on due to the pandemic.

Strengths

The primary strength of the systematic review is that it provided progress made on VPDs in CHEs within the last 20 years. The study highlighted the critical need for understanding the role of vaccine hesitancy in emergency and fragile settings

considering this subject matter is not well published. An additional strength of this study's methodology was the inclusion criteria. While analyzing the literature, we classified publications according to which population was discussed.

Limitations

Given VPDs in humanitarian settings are considerable and rapidly changing, there may have been research articles excluded unintentionally. This systematic review only utilized three databases and the grey literature. We considered databases only available through the Emory library system; there were some articles unable to be retrieved due to limited resources. Taking into consideration that the grey literature can be broad even with an inclusion and exclusion criteria, some articles may have been missed. We also narrowed our search to articles published in English and within the last 20 years. However, the systematic review informs the recent, available, and relevant literature regarding VPDs in humanitarian and conflict effected settings.

Moreover, the VPDs we focused on (cholera, measles, meningitis, yellow fever, poliomyelitis, diphtheria, tetanus, pertussis, and hepatitis A) are not the only diseases that occur in humanitarian settings, however, we focused on these diseases because they are the most widely published. [20, 21]

Recommendations

Strengthening communication and community engagement during immunization delivery for VPD's is important. Coordinated, consistent, and targeted community engagement is necessary to increase vaccine uptake. It is important to increase demand by increasing the understanding of science, safety, and efficacy of issues raised by the population who are receiving immunizations. Engaging community members on their beliefs and attitudes regarding vaccines is important for tailored and targeted approaches. Continuous engagement with community members regarding their interests and concerns will help build trust and confidence. When communities are involved in the decision-making process and are allowed to share their input, they are likely to take the vaccines.

The critical need for training in communication and community engagement for everyone involved in supporting the immunization programs, including the healthcare workers, cannot be overemphasized. Community health workers, humanitarian workers, and healthcare workers need to understand the social, behavioral, and scientific importance of vaccines, and how to communicate this to the community. These officials are depended on by community members and are in the best position to communicate the importance of vaccine safety, efficacy, and adverse reactions.

There is limited research of understanding vaccine hesitancy in humanitarian and fragile settings. Substantial funding is needed towards understanding vaccine hesitancy in humanitarian and fragile settings. This is important because the views, concerns, and underlying barriers of individuals, communities, and groups are important to address to improve vaccine uptake.

Most current research is from high-income economies, thus investments should be tailored and targeted towards developing appropriate tools and methods that are applicable to campaigns and routine immunization programs in humanitarian and fragile settings. This is a crucial undertaking to understand the necessary development of evidence-based strategies that are necessary to address vaccine hesitancy. Context-specific tools that can be used for socio-behavioral, community engagement, and demand generation around vaccine hesitancy is essential.

Collaboration between spiritual leaders and humanitarian aid workers can enhance understanding of vaccine hesitancy towards VPDs. This will help identify sustainable solutions since spiritual leaders are a trusted voice within a community and could potentially play a positive role in sensitizing their communities about their behavior towards seeking immunizations. Engagement with spiritual and community leaders should, however, be based on scientific research and anthropologic evidence so that consultations can be relevant to the needs of the targeted communities.

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