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A Review of the Resurgence of Measles, a Vaccine-Preventable Disease, as Current Concerns Contrast with Past Hopes for Measles Elimination

Authors' Contribution:
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Funds Collection G

BCDEF **Dinah V. Parums**

Science Editor, Medical Science Monitor, International Scientific Information, Inc., Melville, NY, USA

Corresponding Author: Dinah V. Parums, e-mail: dinah.v.parums@isi-science.com

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On 22 February 2024, the World Health Organization (WHO) stated that, following the recent resurgence of measles cases in Europe, more than half the world's countries could expect significant measles outbreaks this year. Measles is a highly infectious virus with a primary case reproduction number (R0) of 12-18. Measles infection can be severe, resulting in pneumonia, and also more rarely in subacute sclerosing panencephalitis (SSPE), which occurs in 1 child out of every 1,000 and can be fatal. Until the 1990s, the hope of eliminating measles seemed possible following the successful development of effective vaccines, given individually or in the combined measles, mumps, and rubella (MMR) vaccine. Vaccine hesitancy due to misinformation about possible vaccine side effects, reduced vaccine uptake during and after the COVID-19 pandemic, and lack of awareness of the severe consequences of measles infection have contributed to low vaccine uptake, resulting in vulnerable communities. This article aims to review the recent resurgence of measles cases in the US, Europe, and the UK, to provide a reminder of the potential severity of measles, and to consider the causes of the failure to eliminate this vaccine-preventable viral infection.

Keywords: **Measles • MMR Vaccine • Vaccine Hesitancy • Review**

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Background

Due to the recent resurgence of cases of measles in the European region, on 22 February 2024, the World Health Organization published a statement that more than half the countries of the world could expect significant measles outbreaks during 2024 [1]. Measles is a highly infectious virus transmitted via respiratory droplets and aerosols, with a basic case reproduction number (R0) of 12-18 [2,3]. Approximately 90% of susceptible individuals will become infected with measles after exposure to the virus [3]. Measles causes a lengthy and unpleasant acute illness and can result in serious long-term illness in children and adults [3]. Until the 1990s, the hope of eliminating measles seemed possible following the successful development of effective vaccines, given individually or in the combined measles, mumps, and rubella (MMR) vaccine [4-6]. However, from the 1990s, false claims that the MMR vaccine was associated with childhood autism resulted in vaccine hesitancy, including in developed countries [4-6]. Non-evidence-based claims regarding the side effects of the measles vaccines persisted but diminished until, by the last decade, many clinicians had not seen a case of measles [4-6]. The ongoing outbreaks of measles that threaten the potential for the elimination of measles may now be due to multiple factors that include persisting parental vaccine confidence, lack of awareness of the serious nature of measles infection, and factors associated with the recent COVID-19 pandemic, resulting in groups of unvaccinated individuals [7,8]. This article aims to review the recent resurgence of measles cases in the US, Europe, and the UK, to provide a reminder of the potential severity of measles, and to consider the causes of the failure to eliminate this vaccine-preventable viral infection.

The History of Measles Virus Infection

The measles virus is a member of the genus *Morbillivirus* (family, P*aramyxoviridae*) [9,10]. The human measles virus probably has a zoonotic origin from rinderpest, a cattle viral infection [11]. The first description of measles and its distinction from chickenpox and smallpox is attributed to the Persian physician Muhammad ibn Zakariya al-Razi (860 to 932 AD), who published *The Book of Smallpox and Measles* [12,13]. Between 1100 and 1200 AD, the measles virus fully diverged from rinderpest to become a human viral infection [12]. At this time in history, medieval European cities had grown to the required size to sustain an epidemic, with populations of >500,000) [13]. In 1757, a Scottish physician, Dr Francis Home, showed that measles was caused by an infectious agent in the blood [12]. Worldwide, until effective vaccines were developed, measles was an endemic disease, continually present in the population, with resistance acquired through prior infection [12]. Between 1855 and 2005, before vaccination programs were implemented, it was estimated that measles infection caused the death of 200 million people worldwide [12].

Clinical Presentation, Diagnosis, and Differential Diagnoses

The measles virus is highly infectious, with an incubation period of between 6 and 21 days [10]. The measles virus enters the respiratory tract or conjunctivae, spreads to the lymph nodes, and includes viremia [10]. Measles is highly contagious 5 days before the appearance of a skin rash and up to 4 days after the ash disappears [10]. Koplik spots were originally described in 1896 and are small (millimeter-sized) erythematous, white, or grey lesions seen on the buccal mucosa [14]. Koplik spots are typical of the prodromal phase of measles, often occurring before the skin rash in 50-70% of patients with measles [10,14]. Patients with measles virus infection are asymptomatic during the incubation period, and a second viremia occurs several days after the first, coinciding with the appearance of symptoms and the start of the prodromal or symptomatic phase of measles [10]. Because both humoral and cellular measles virus-specific immunity are required for viral clearance and lasting immunity, children with defects in immune function have high infection rates and mortality [10]. Acquired immunity after measles virus infection is usually lifelong, but a modified form of measles is an attenuated infection that occurs in individuals with immunity from infection or vaccination and is not highly contagious [15]. Secondary infections and co-infections are common and are mainly due to parainfluenza virus, adenovirus, *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Streptococcus pyogenes*, and reactivation of tuberculosis [16,17]. Also, measles-associated immune dysfunction may persist for up to three years following measles virus infection [15].

The diagnosis of measles virus infection requires a positive serologic test for serum levels of measles IgM antibody, a significant rise in IgG antibody levels between acute and convalescent titers, isolation of the measles virus in culture, or by detection of measles virus RNA by a reverse transcription polymerase chain reaction (RT-PCR) test [16,17]. Laboratory confirmation of measles virus infection is essential at this time, as there are several infections in the differential diagnosis, some of which are also on the rise in the post-COVID-19 pandemic era (**Table 1**) [10]. The treatment of measles is mainly supportive, and there are currently no approved specific antiviral therapies.

Complications of Measles

There is concern that healthcare professionals and populations have forgotten how severe measles infection can be [18]. Although measles can be a severe infection in all age groups,

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Table 1. Childhood diseases in the differential diagnosis of measles [10].

Childhood disease	Clinical diagnosis
Dengue fever	Dengue has a similar presentation to prodromal and post-rash measles. Relevant epidemiology and serologic testing can diagnose dengue
Childhood respiratory viruses, including rhinoviruses, parainfluenza, influenza, adenovirus, and respiratory syncytial virus (RSV)	Fever due to measles infection is usually more severe than for other childhood respiratory viruses, diagnosed from nasal swab using polymerase chain reaction (PCR)
Childhood viral infections with skin rash include varicella, human herpesvirus 6 (roseola infection), parvovirus B19 (erythema infectiosum), and rubella	Measles has a distinctive clinical progression of the rash, which can be brown, blanches on pressure, and is associated with coryza and conjunctivitis. Serology can diagnose other childhood virus infections
Group A *Streptococcus* infections, including scarlet fever and toxic shock syndrome	Scarlet fever presents with an erythematous skin rash and pharyngitis. Toxic shock syndrome results in hypotension and organ system dysfunction. Isolation of group A Streptococcus is diagnostic
Meningococcemia can include a petechial rash, fever, vomiting, headache, and sepsis	*Meningococcal* infection is confirmed by bacterial culture
Rocky Mountain spotted fever can include a maculopapular rash	Rocky Mountain spotted fever is associated with tick exposure and diagnostic serology or skin biopsy
Mycoplasma pneumoniae respiratory tract infection can present with an erythematous maculopapular or vesicular rash	The diagnosis of *Mycoplasma pneumoniae* may be difficult, but pneumonia is the main feature
Infectious mononucleosis can result in a generalized maculopapular, urticarial, or petechial rash	Infectious mononucleosis includes fever, fatigue, pharyngitis, and lymphadenopathy and is diagnosed by serology and virology
Exanthematous drug eruption can resemble a measles rash	A history of recent drug exposure, with resolution of the rash after drug withdrawal
Fordyce spots (small yellow/white granules on the buccal mucosa) are benign ectopic sebaceous glands. In early measles infection	Fordyce spots can be confused with Koplik spots in early measles infection
Multisystem inflammatory syndrome in children (MIS-C) from SARS-CoV-2 includes fever, abdominal pain, conjunctivitis, and rash	The diagnosis of MIS-C can be confirmed by RT-PCR testing for SARS-CoV-2

some individuals are more susceptible to complications, including children <5 years of age, adults >20 years of age, pregnant women, people who are immune suppressed (including patients with HIV/AIDS), and patients with chronic co-infections (such as tuberculosis) [18]. In the US, 1 in 5 unvaccinated people who contract measles will require hospitalization [18]. Mild complications following the initial acute illness include ear infections in 10% of cases, skin rashes, and diarrhea (<10%) [18]. Serious complications, such as pneumonia (5%) and encephalitis, can occur [18]. Pneumonia is the most common cause of death in children following measles infection [18].

Subacute Sclerosing Panencephalitis (SSPE)

Subacute sclerosing panencephalitis (SSPE) occurs in 1 child out of every 1,000 and can be a fatal complication of measles [18]. Between 1 and 3 children per 1,000 infected with measles will die from pneumonia or neurologic complications [18]. Although SSPE is a very rare complication that affects the central nervous system, it can be fatal and usually results from measles infection in early childhood, particularly in infants <2 years of age [18]. After recovery from the initial illness, SSPE can develop between 7 and 10 years after initial infection [18]. Since the elimination of measles in the US in 2000, there have been very few reported cases of SSPE [18]. However, the recent resurgence of measles infection is likely to be associated with an increase in future cases of SSPE [1,18]. The previous name for SSPE was Dawson's inclusion body encephalitis, as Dawson reported cellular inclusion in the brains of affected children as early as the 1930s [19]. Electron microscopy in the late 1960s identified paramyxovirus in the CNS [19]. SSPE is characterized clinically by cognitive decline, chorioretinitis, blindness, gait abnormalities, periodic myoclonus, and total loss of cognitive

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Table 2. US Recommendations: Measles, mumps, and rubella (MMR) vaccination [23].

Population groups	Vaccination recommendations
Children between 12 to 15 months of age	First dose of the MMR vaccine
Children between 4 to 6 years of age	Second dose of the MMR vaccine (the second dose can be given earlier if given after at least 28 days after the first dose)
Children between 12 months and 6 years of age	The measles, mumps, rubella, and varicella (chickenpox) (MMRV) vaccine as a single dose
Students in higher educational institutions without presumptive evidence of measles virus immunity	Two doses of MMR vaccine, separated by at least 28 days
Adults without presumptive evidence of measles virus immunity	A single dose of MMR vaccine
Adults without presumptive evidence of measles virus immunity who are at increased risk of infection: students at higher education institutions; healthcare personnel; international travelers	Two doses of MMR vaccine, separated by at least 28 days
Non-pregnant women of childbearing age who do not have presumptive evidence of immunity	At least a single dose of MMR vaccine
Women who are breastfeeding and do not have presumptive evidence of immunity	At least a single dose of MMR vaccine while breastfeeding, as the vaccine is not passed to the baby in breast milk
Contraindications for MMR vaccination	
• Allergy to the vaccine components • Pregnancy • Immune suppression (including HIV/AIDS) • Coagulopathies • Current chronic infection (including TB) • Recent history of receiving another live vaccine in the previous four weeks • Recent transfusion of blood products	

Modified from: Centers for Disease Control and Prevention (CDC), 26 January 2021 [23].

function (vegetative state) [20]. Electroencephalography (EEG) changes include characteristic periodic discharges, and neuroimaging identifies loss of periventricular white matter, followed by cerebral atrophy [20]. The definitive diagnosis of SSPE requires the identification of elevated measles antibody titers in the cerebrospinal fluid (CSF) [20]. SSPE may be caused by a mutated form of the measles virus [20].

Several population studies have shown that SSPE may be more common than previously thought or could be diagnosed as cases of childhood encephalitis due to other causes. For example, in 2017, Wendorf and colleagues published a population study from California that reviewed reported cases from 1998 to 2015 to estimate the incidence and risk factors for SPPE [21]. This study identified cases of SSPE by diagnostic symptoms on review of medical records, state death certificates, and detection of measles antibodies in cerebrospinal fluid (CSF) [21]. This study had limitations but showed that SSPE cases in California occurred at an increased rate among unvaccinated children, mainly when measles was contracted during infancy [21]. The incidence of SSPE was 1 per 1,367 for children <5 years and 1 per 609 for children <12 months at the time of initial measles infection [21]. The diagnosis of SSPE was made in children with a median age of 12 years (range, 3-35 years) and with a latency period of 9.5 years (range, 2.5-34 years) [21]. The authors advised that protection of unvaccinated infants should include avoiding travel to endemic areas or early vaccination between 6 and 11 months of age before travel [21]. These findings are relevant to the present global situation where vaccine hesitancy is prevalent, and economic necessity, conflict, and climate change are leading to increased population migration [1,22].

Presumptive (Presumed) Measles Virus Immunity

People born before 1957 have only presumptive acquired immunity to measles, mumps, and rubella [23]. Before vaccines were available, almost everyone was infected during childhood [23].

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However, healthcare personnel born before 1957 without laboratory evidence of immunity or disease should be considered high-risk groups and receive two doses of MMR vaccine (**Table 2**) [23]. Reports have shown that despite high population immunity to the measles virus, imported measles transmission can occur in healthcare workers with presumed immunity [24]. Therefore, newly appointed healthcare workers and those who work with and for their community should be considered at risk and offered further MMR vaccination [24].

Elimination of Measles

Maintaining measles virus infection in a population requires a critical number of susceptible individuals, so public health vaccination initiatives can potentially eliminate measles infection [25]. Mathematical modeling studies have shown that outbreaks of measles virus infection require an immune naïve population of between 250,000 and 500,000 [13]. The World Health Organization (WHO) defines measles elimination as "*the absence of endemic measles virus transmission in a defined geographical area for at least 12 months in the presence of a surveillance system that has been confirmed as performing well*" [25,26]. The measles virus has characteristics required for infection elimination. Previous infection or vaccination can confer lifelong immunity, and there is no animal reservoir for the human measles virus [25]. Also, the measles virus does not cause a latent or persistent infection, except for the rare complication of SSPE [18,25].

The History of Measles Vaccination and the MMR Vaccine

In 1796, Edward Jenner, FRS, FRCPE (1749-1823), first tested a method to prevent smallpox by inoculation into the skin of an 8-year-old boy with matter from a cowpox sore from the hand of a dairy maid [27]. By the late 1940s, large-scale vaccine production was possible, which began the era of infection control and elimination by vaccination [28]. By the early 20th century, vaccines were available for pertussis (1914), diphtheria (1926), and tetanus (1938), which were combined in 1948 as the DTP vaccine [28]. From the 1940s, smallpox vaccination and public health initiatives would eliminate smallpox [28]. After 1972 and successful smallpox eradication efforts, the vaccine was no longer recommended for use [28]. Until the 1950s, as urban populations grew and travel increased, polio epidemics were common, resulting in severe illness, neurological complications, and fatalities [28]. Jonas Salk invented the first polio vaccine, which was licensed in the US in 1955 [28]. The first measles vaccine was developed in 1963, followed by a mumps vaccine in 1967 and a rubella vaccine in 1969 [28]. In 1971, Maurice Hilleman combined the measles, mumps, and rubella (MMR) vaccines, which is still the most common vaccine combination used to provide long-term protection from measles [28].

In September 2005, the combined measles, mumps, rubella, and varicella (MMRV) vaccine (ProQuad) (Merck & Co., Inc.) was licensed in the US for children aged 12 months to 12 years [29]. In June 2009, the CDC ACIP recommended that the combined MMRV should be used instead of the MMR vaccine (M-M-RII) (Merck & Co., Inc.) and varicella vaccine (VARIVAX) (Merck & Co., Inc.) for children aged 12 months to 12 years, using a two-dose schedule [29]. The CDC ACIP revised its recommendations following reports of an increased risk for febrile seizures 5-12 days after the first vaccine dose of MMRV in children aged between 12-23 months when compared with age-matched children who had received a first dose of MMR vaccine, with the varicella vaccine administered separately [29]. Because of the low rate of reported cases of febrile seizures of 1 per 2,300-2,600 children, updated recommendations express no preference for using the MMRV vaccine or separate injections of equivalent component vaccines for both the first and second scheduled doses [29]. However, a contraindication for the MMRV vaccine for the first and second doses is a personal or family history of seizures [29]. Annual updates for childhood and adult immunization schedules offer guidance to healthcare providers and are reviewed in the US by committees of experts from the CDC, the American Academy of Pediatrics (AAP), and the American Academy of Family Physicians (AAFP) [30]. The first formal adult immunization schedule was published in 2002 and is updated annually [30].

Protective Immune Responses from Infection and Vaccination

The measles virus causes infection by fusing with respiratory tract cells in a receptor-dependent manner, targeting alveolar macrophages in the lungs via the signaling lymphocytic activation molecule (SLAM) [17]. Macrophages can transport copies of the measles virus to the nearest lymph nodes for dissemination and present viral antigens to memory T and B lymphocytes [17]. Infection with the measles virus also has immunosuppressive effects by depletion of T and B lymphocytes [16,17]. Therefore, measles vaccination may have long-term benefits, preventing further infectious disease by preventing measles-associated immune memory loss [17]. Population vaccination programs provide herd immunity from measles and might also offer polymicrobial herd immunity [16,17].

Measles in the United States (US)

In 1912, measles became a nationally notifiable disease in the US, with an average of 6,000 measles-related deaths reported

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in each year of the following decade [11]. Before the MMR vaccine became available in 1963, almost all children in the US contracted measles before they reached 15 years of age [11]. In the US, before 1963, there were between 3 to 4 million

people infected annually, with an average of approximately 550,000 annual reported cases of measles, resulting in between 400 to 500 annual deaths, 48,000 annual hospitalizations, and 1,000 annual cases of measles-associated encephalitis [11]. Elimination of measles in the US was declared in 2000, with the absence of continuous disease transmission for >12 months, due to improved control of infection transmission and high vaccine uptake rates [25]. The US maintained measles elimination status for almost 20 years [25].

As of 26 January 2021, the US CDC updated its recommendations and patient information for the MMR vaccine to protect against measles, mumps, and rubella (MMR) (**Table 2**) [23]. Currently, two MMR vaccines are available in the US, M-M-R II and PRIORIX, which are interchangeable for all indications [23]. The CDC recommends that all children be given two doses of the MMR vaccine [23]. The first dose of MMR vaccine is given at 12-15 months of age and the second dose at 4-6 years of age (**Table 2**) [23]. Teenagers and adults should also ensure they are up to date with their MMR vaccinations [23]. Children between 12 months and 12 years of age may also receive the MMRV vaccine, which protects against measles, mumps, rubella, and varicella (chickenpox) (**Table 2**) [23].

Measles Vaccination, Elimination, and Resurgence in the US

Hemagglutinin on the surface of the measles virus envelope binds the virus to the host cell surface, and a fusion protein facilitates viral uptake into the host cell. Several live, attenuated measles vaccines have been available, initially as monovalent vaccines or combined with rubella and mumps vaccines (the MMR vaccine) [6]. Many current attenuated measles virus strains are derived from the Edmonston strain, first isolated in 1954 [6]. The history of measles vaccination in the US began 60 years ago, on 21 March 1963, when the first two measles vaccines were licensed [31]. Other live attenuated vaccine strains include CAM-70, TD 97, Shanghai 191 (Ji-191), and Leningrad-16 [6]. Attenuated measles virus replication occurs in primary chick embryos or cell cultures, and the virus is harvested and clarified before being lyophilized. The reconstituted lyophilized measles vaccine is administered by subcutaneous or intramuscular injection [6].

In 1962, President John F. Kennedy Jr. signed the Vaccination Assistance Act, the first law directing federal funds to US states to support immunization programs beginning in childhood [31]. In 1965, the US Congress renewed the program and extended it to cover measles [31]. The history of measles vaccination in the US began 60 years ago, on 21 March 1963, when the first two measles vaccines were licensed [31]. Six months into the 1967 US measles vaccination campaign, the number of measles cases fell from an average of 1,000 to 200 cases per week [31]. However, within the next decade, it became clear that measles vaccination protected some but not all communities [31]. By the early 1970s and into the early 1980s, the implementation of school mandates for childhood vaccination was a significant legacy of the early measles eradication era [31,32]. In 1977, the President Carter administration launched the National Childhood Immunization Initiative to encourage mass immunization with the implementation of state immunization laws to cover polio, diphtheria, pertussis, tetanus, mumps, rubella, and measles, and immunization rates among children rose to almost 90% [31]. By 1981, 96% of all schoolchildren were vaccinated against measles, as the new combined measles, mumps, and rubella (MMR) vaccine simplified immunization protocols in the US [31,32].

In 1993, during President Bill Clinton's first year in office, access to childhood vaccines was at the forefront of health reform efforts, which resulted in the Comprehensive Child Immunization Act and an entitlement program, Vaccines for Children (VFC) [32,33]. President Clinton's last year in office was 2000, when measles was officially declared eliminated from the US and no longer endemic, with the only remaining cases being imported from abroad or spread by imported cases [33,34]. However, from 2000, with the increased availability of online social media, vaccine-hesitant groups increased and focussed on the measles component of the MMR vaccine, with fears of links to childhood autism, sudden infant death syndrome, and immune dysfunction [31]. As autism rates increased, a single study was published in *The Lancet* (retracted in 2011) that claimed to provide research evidence for the association between autism and the MMR vaccine, which drove vaccine hesitancy [35]. In the following 20 years, until the COVID-19 pandemic, vaccine hesitancy was combined with vaccine apathy [31]. This situation starkly contrasted to the pre-vaccine era, when social awareness of the severity of measles and the wait for effective vaccines drove populations to take all possible preventive measures, and vaccines were welcomed, making measles elimination briefly possible in the US in 2000 [31].

Measles in Europe

On 16 February 2024, the European Centre for Disease Prevention and Control (ECDC) published a public health response to the rise of reported measles cases in the European Union and European Economic Area (EU/EEA) [36]. In 2020, Wilder-Smith and colleagues reported a resurgence in European measles cases due to suboptimal MMR vaccine coverage [7]. They undertook a systematic literature review of European publications between 2011 and 2019 [7]. These authors identified 20 high-quality European studies and found that vaccine hesitancy or refusal was associated with concerns about vaccine safety and effectiveness, perception of minimal measles risk, and mistrust of medical opinion [7]. In Europe, childhood vaccines are free and accessible for most communities, except traveler communities [7]. Factors encouraging MMR vaccine uptake included awareness and a sense of responsibility for child and community health, trust in medical experts and vaccine efficacy, and an understanding of measles severity [7]. The authors also concluded that healthcare professionals should understand individual attitudes and ongoing barriers to vaccine uptake [7]. Several sources have recommended improved infection surveillance to identify non-vaccinated populations, and vaccination outreach programs have also been recommended to enhance vaccine accessibility and uptake in identifiable vulnerable groups [7]. In 2023, Novilla and colleagues published the findings from a systematic literature review to identify the social and parental determinants for MMR vaccine hesitancy [8]. Analysis of 115 publications from seven databases identified a geographic clustering of MMR vaccine hesitancy [8]. This finding supports that social factors drive parental perceptions and their decisions on vaccinating their children [8]. Vaccine hesitancy to childhood vaccines, including the MMR vaccine, showed clusters in middle-income to high-income areas and mothers with at least a college-level education [8]. Vaccine hesitancy was associated with mothers who sought health information from the Internet rather than their physician or pediatrician [8]. A lack of perceived and trustworthy vaccine information resources and fear of autism as a vaccine complication were still identified as the most common reasons for MMR hesitancy [8]. From this 2023 systematic review, the authors concluded that multiple social drivers of vaccine hesitancy should be recognized and addressed by healthcare, education services, and international government policy and healthcare economists [8,36].

Measles in the United Kingdom (UK)

Measles is a notifiable disease in the UK, which means that any suspected cases must be reported to local health protection services, and diagnostic laboratories must report confirmed cases [37,38]. Confirmed measles cases in the UK have only been recorded officially since 1995 [37,38]. However, data for measles notifications and deaths have been available in England since 1940, when statutory reporting of measles was introduced [37,38]. A measles vaccine was first introduced in the UK in 1968 [10]. In 1988, the measles, mumps, and rubella vaccine (MMR) was introduced in England as a single-dose schedule at 12 to 13 months [10]. Before 1968, annual measles notifications in the UK ranged from 160,000 to 800,000, with biannual peaks [10]. Also, at that time, more than 90% of adults had serological or clinical evidence of previous measles infection, and there were up to 100 recorded annual deaths from acute measles [10].

In 1988, the MMR vaccine program began for all children in the UK and achieved 90% coverage, resulting in low reported cases and deaths [10]. In 1988, with 90% coverage levels, measles cases and deaths became very low [10]. A second-dose MMR vaccine program began in 1996, which was given as a preschool booster vaccination to maintain infection control and as an attempt to eliminate measles [10]. National campaigns in the UK were introduced to target specific age groups and social groups where vaccine coverage was identified as low [38,39]. Successful herd immunity was achieved for measles in the UK by 2017, reaching the WHO 95% coverage target for the first MMR dose, resulting in the UK's measles elimination status [38,39]. Measles elimination is defined as the absence of endemic measles transmission within a defined geographical area for at least 12 months [6]. However, infection elimination can only be verified if a high-quality surveillance system capable of testing at least 80% of suspected measles cases is in place and shows that elimination has been sustained [6]. Due to the high infectivity of the measles virus, a high level of herd immunity is necessary to prevent measles transmission. Herd, or community, immunity can be achieved by reaching 95% MMR coverage, a target that the WHO set in 2001 [6]. However, eliminating viral infection can only be sustained by maintaining immune coverage from the MMR vaccine in children and by vaccinating older children and adults who may have missed being vaccinated in childhood [37-39]. In response to the rise in measles cases during 2023 and 2024, the UK Health Security Agency (HSA) updated the national measles guidelines in February 2024 to provide updates on measles outbreaks and information for primary healthcare providers on the importance of implementing vaccination programs [40].

The COVID-19 Pandemic and Measles Resurgence

During and since the COVID-19 pandemic, the success of vaccine development for SARS-CoV-2, and the implementation of vaccination programs for adults and children, the incidence and patterns of respiratory virus infections have changed [41-44]. The increase in reported cases of measles has been driven by several factors, including social restrictions during the COVID-19 pandemic, post-pandemic vaccine hesitancy, and non-evidence-based fears of the association between the MMR vaccine and autism, which may persist and compound vaccine hesitancy

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and by the complacency of populations and healthcare professionals who may not remember how severe measles infection and its long-term sequelae can be [2,4,7,41-44].

The control and elimination of measles requires high population immunity to interrupt transmission. All six WHO regions have committed to eliminating measles but have yet to achieve and sustain this [45]. A recently published global report has described the progress toward global measles elimination from 2000 to 2022 [45]. The estimated measles coverage following the first dose of a measles vaccine increased from 72% to 86% but then declined to 81% in 2021 during the COVID-19 pandemic [45]. Only 72 of the 144 countries in the WHO regions that reported measles cases achieved the measles surveillance indicator target in 2022 [45]. Between 2021 and 2022, there was an estimated increase in measles cases by 18%, from 7,802,000 to 9,232,300 [45]. Also, between 2021 and 2022, the number of countries experiencing measles outbreaks increased from 22 to 37, and deaths from measles increased by 43%, from 95,000 to 136,200 [45]. However, between 2021 and 2022, an estimated 57 million measles deaths were estimated to have been prevented by measles vaccination [45]. By the end of 2022, global surveillance data showed some recovery from measles vaccination hesitancy due to the COVID-19 pandemic [45]. However, in low-income countries, years of suboptimal immunization coverage left millions of children at increased risk of measles infection [45]. This report supports that reversing the setbacks to measles vaccine coverage experienced during the COVID-19 pandemic could be achieved by renewed efforts to vaccinate all children with two vaccine doses and by increasing infection surveillance to prevent measles outbreaks and restart progress toward measles elimination [45].

In 2023, Flaxman and colleagues reported the findings from a national population epidemiological analysis of data between 2019 and 2022 from the US CDC Wide-Ranging Online Data for Epidemiologic Research (WONDER) database on causes of death in the US to rank mortality from COVID-19 in the 0 to 19-year age group [4,46]. Mortality from non-infectious causes included accidental injury (18.4%), assault (6.9%), and suicide (6.8%) [46]. In the 0 to 19-year age group, between 2019 and 2022 in the US, death due to COVID-19 was ranked fifth in disease-related causes of death and first in deaths caused by infectious diseases and respiratory diseases [46]. When they compared deaths from COVID-19 with deaths from other vaccine-preventable diseases before implementation of vaccination programs, mortality from COVID-19 was significantly greater than for rotavirus, varicella, and measles [46,47]. However, the immediate post-COVID-19 pandemic era is now experiencing the effects of outbreaks of vaccine-preventable virus infections, including measles [1]. The recent predictions and warnings from the WHO regarding the likelihood of significant global measles outbreaks during 2024 may be associated with outbreaks of other vaccine-preventable viral diseases, including RSV, mumps, and rubella [1,41,42].

Global Responses

Rapid measles outbreak responses have begun in the Northern and Southern hemispheres, which are critical to protecting millions of vulnerable children [1]. In 2023, the increase in measles cases in Europe resulted in emergency responses to promote vaccination and educate populations and healthcare professionals regarding the dangers of measles infection and the effects of reduced immunity within communities [36,37]. On 26 July 2023, the WHO published the Big Catch Up, a global immunization recovery plan for 2023 and beyond [48]. This recovery plan aims to get global immunization programs back on track following the reduced uptake of vaccines during the COVID-19 pandemic [48]. The WHO recovery plan has three components: catch up, restore, and strengthen [48]. This coordinated effort includes the WHO, the United Nations International Children's Emergency Fund (UNICEF), the Vaccine Alliance, and the Immunization Agenda 2030 (IA2030) Partnership [48,49]. Following a recent statement from the WHO regarding the recent resurgence of measles cases and a warning that more than half the countries of the world could expect significant measles outbreaks during this year, a global preparedness response is required [48-51].

Conclusions

This article has highlighted how measles, a vaccine-preventable viral infection, has gone from a state of potential elimination to a resurgence within 40 years. During this time, a 'perfect storm' of multiple factors has brought about a global resurgence of reported cases, hospital admissions, and fatalities from measles, particularly in developed countries, including within Europe. Decades of false claims of vaccine adverse events that have included a misleading association with autism, vaccine complacency and hesitancy, and reduced childhood vaccination rates during and after the COVID-19 pandemic have all contributed to the current resurgence of measles cases in 2024. Public health and primary care initiatives are urgently required in all countries to raise awareness of the dangers of measles infection and the importance of adherence to vaccination programs.

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