Reemerging Viral Infections: Implications of Lack of Vaccination

7

Ritu Swali, Claire Wiggins, Sahira Farooq, Radhika A. Shah, and Emily Limmer

Abbreviations

AIDS	Acquired immunodeficiency syndrome
CCHF	Crimean-Congo hemorrhagic fever
CDC	Centers for Disease Control and Prevention
CRS	Congenital rubella syndrome
CSF	Cerebrospinal fluid
DFA	Direct fluorescent antibody
DNA	Deoxyribonucleic acid
ELISA	Enzyme-linked immunosorbent assay
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HI	Hemagglutinin inhibition
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HPV	Human papillomavirus
HZ	Herpes zoster
IFN	Interferon
Ig	Immunoglobulin
MMR	Measles-mumps-rubella
MMRV	Measles-mumps-rubella-varicella
NSAID	Nonsteroidal anti-inflammatory drug
PCR	Polymerase chain reaction
PHN	Postherpetic neuralgia
PRN	Plaque reduction neutralization
RNA	Ribonucleic acid
RV	Rubella virus
SARS	Severe acute respiratory syndrome
SPS	Shingles Prevention Study
STI	Sexually transmitted infection
UV	Ultraviolet
VZV	Varicella-zoster virus
WHO	World Health Organization

R. Swali (✉)
Department of Dermatology, University of Nebraska Medical Center, Omaha, NE, USA

C. Wiggins
Baylor College of Medicine, Houston, TX, USA

S. Farooq
McGovern Medical School and UT Health, Houston, TX, USA

R. A. Shah
Texas A&M University, Dallas, TX, USA

E. Limmer
University of Texas Southwestern Medical Center, Dallas, TX, USA

Introduction

Mucocutaneous manifestations of viruses result from the replication of viral organisms either primarily in the epidermis or as a secondary effect of viral replication elsewhere [1]. Along with being the largest physical barrier against pathologic microorganisms, the skin has an innate antiviral immune system composed of endogenous antiviral proteins, e.g., interferons as well as interferon-independent pathways, and environmental factors [2]. However, in certain populations, a loss, lack of, or suppression of antiviral proteins will make way for viral diseases to manifest. Patients with inflammatory skin conditions, at extremes of age, and with an immunocompro-

S. K. Tyring et al. (eds.), *Overcoming Antimicrobial Resistance of the Skin*, Updates in Clinical Dermatology, https://doi.org/10.1007/978-3-030-68321-4_7

mised status could benefit from enhanced antiviral immunity [2].

The advent of vaccinations changed the face of modern medicine in 1796 when Edward Jenner noted that milkmaids who had bouts of cowpox did not contract smallpox. At the time, smallpox had a 30% mortality rate and left survivors with debilitating scars, including corneal scars, resulting in blindness [3]. After several years, he published his research in "On the Origin of the Vaccine Inoculation," documenting that variolation could, and would, eventually lead to the eradication of the "speckled monster" [3]. The smallpox vaccine with public health measures led to eradication of the number one infectious disease killer in the history of the world (until the last smallpox patient was treated in 1977). Since then, the development of vaccines for other infections has markedly reduced morbidity and mortality from multiple fatal infectious diseases in many parts of the world (Fig. 7.1) [4].

Vaccines provide active immunity by introducing a modified component of a pathogen to the host, thus stimulating the host's immune system to memorize how to identify and attack the virus upon re-exposure. Passive immunity is developed by transferring antibodies from one host to another, giving the host tools to attack the virus without the ability to recognize it. Many primary and secondary viral skin diseases predominantly have been prevented with active immunization strategies [1].

The recent anti-vaccination movement is rooted in the miseducation of social media influ-

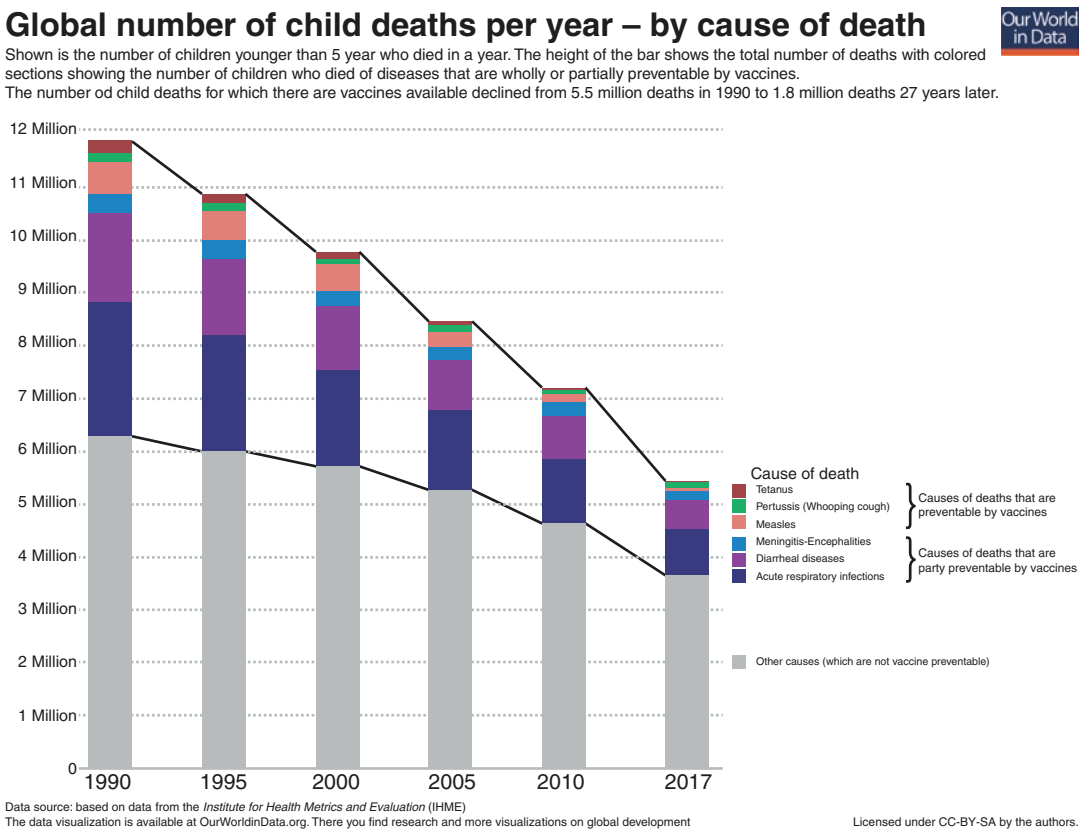

Fig. 7.1 Based on data from the Institute for Health Metrics and Evaluation, vaccine-preventable deaths have dramatically decreased over the past few decades. (Reprinted from Our World in Data: Vaccination, by Vanderslott S, Dadonaite B, and Roser M., 2015. https://ourworldindata.org/vaccination. Link to license: https://creativecommons.org/licenses/by/4.0. No changes were made to the original content)

encers combined with vulnerable parenting. A large role played by the healthcare industry was the publication of a paper in *The Lancet* in 1998 by British physician Andrew Wakefield, who suggested plausibility in the link between autism and the measles-mumps-rubella (MMR) vaccine [5]. The paper was retracted in 2010, accompanied by a detailed commentary in *The British Medical Journal* by Deer et al. the following year, documenting that Wakefield had been paid by anti-vaccine lobbyists to make false proclamations of the dangers of the MMR vaccine [6]. Wakefield subsequently lost his license to practice medicine in the United Kingdom; however, widespread fear of vaccinations had already spread throughout the world, resulting in vaccination refusal [7–10]. Common tactics used by "anti-vaxxers," including skewing science, censoring opposition, attacking critics, and claiming that vaccines are toxic, have been very effective in continuing this trend [11].

Consequentially, unfounded fears of vaccination are often attributed to Wakefield's discredited publication and to general distrust of the medical and pharmaceutical establishments. Fears of adverse effects and vaccine safety far outweigh other societal beliefs to avoid vaccinations (Fig. 7.2) [12]. Other facts, however, may play a role such as the fact most persons currently having children did not suffer these illnesses because their parents had them vaccinated [12]. Therefore, they have no firsthand knowledge of the morbidity and mortality that can result from measles or rubella infections. Furthermore, distrust of western medicine due to political reasons has prevented children from receiving MMR, polio, and other vaccines in conflict zones. For example, Doctors Without Borders were forced to leave certain areas of the Democratic Republic of Congo in 2019, because rebel groups burned their clinics and murdered healthcare workers [13]. Therefore, neither MMR nor the recently approved Ebola vaccine reached the susceptible individuals. Surprisingly, recent surveys on vaccine safety demonstrated higher percentages of distrust in vaccines in regions associated with higher education levels, such as Western Europe and North America, versus regions perceived to have lower education rates, including Africa and Central America (Fig. 7.3) [14].

Another reason that some persons avoid life-saving vaccines may be apathy or the belief that they are not susceptible to a particular infection [12]. The 2019–2020 influenza season is an example: thus far, >12,000 Americans, including 27 children, have died of influenza [15]. Many persons still will not receive the vaccine, citing such pseudo-reasons from previous influenza seasons that the vaccine was not 100% effective; therefore, "it is not worth the pain of the injection." Others may state that the "flu-like syndrome resulting from vaccination is worse than the flu." This statement is extremely misleading, because the cytokine storm that may result from vaccination is not fatal, but influenza kills [12].

Today, previously eliminated viral infections have reemerged, and implications of decreased herd immunity are becoming increasingly apparent.

Reemerging Primary Viral Infections of the Skin

Varicella-Zoster Virus: Primary Varicella (Chickenpox)

Primary varicella-zoster virus (VZV), or varicella, is a highly contagious member of the *Herpesvirus* family. Although only one serotype is known, five viral clades have been identified, spanning Europe (1, 3, and 5), Asia (2), and Africa (4) [16]. The virus evolved alongside early human ancestors, likely originating in Africa and spreading worldwide [17]. VZV is highly host-specific, naturally infecting only humans, primarily affecting pre-adolescent children. Varicella does not have a predilection for any race or gender [18]. The number of chickenpox cases is on the decline after the utilization of effective vaccines; however, as vaccination rates fall, the number of cases will subsequently increase [19, 20].

Historically, varicella was regarded as one of childhood's rites-of-passage, a mere nuisance compared to the threat of the similar appearing, but more sinister, smallpox. However, with small-

Fig. 7.2 Various reasons for vaccine hesitancy versus vaccine support reported in the literature. (Reprinted from Attitudes to vaccination: A critical review., by Yaqub O, Castle-Clarke S, Sevdalis N, and Chataway J. https://wellcome.ac.uk/reports/wellcome-global-monitor/2018/chapter-5-attitudes-vaccines. No changes were made to the original content)

pox long eradicated, the notion of varicella as innocuous was challenged. In the setting of medical advances in pediatric cancer treatments in the 1960s, immunocompromised children, newly cured of cancer, were now at risk for severe morbidity and mortality from VZV [23]. Dr. Thomas Weller was the first to isolate and cell-culture VZV in 1954 and confirm that herpes zoster (HZ) and varicella are caused by the same vector (VZV) [24]. Dr. Michiaki Takahashi from Japan created the first live attenuated VZV vaccine, approved in 1986. Japan and South Korea were among the first countries to vaccinate for chickenpox in 1988, with the United States following suit in 1995 [25]. The varicella vaccine is licensed and available worldwide but is only used routinely in a subset of countries. In the United States in 1995, there were over 120,000 cases of

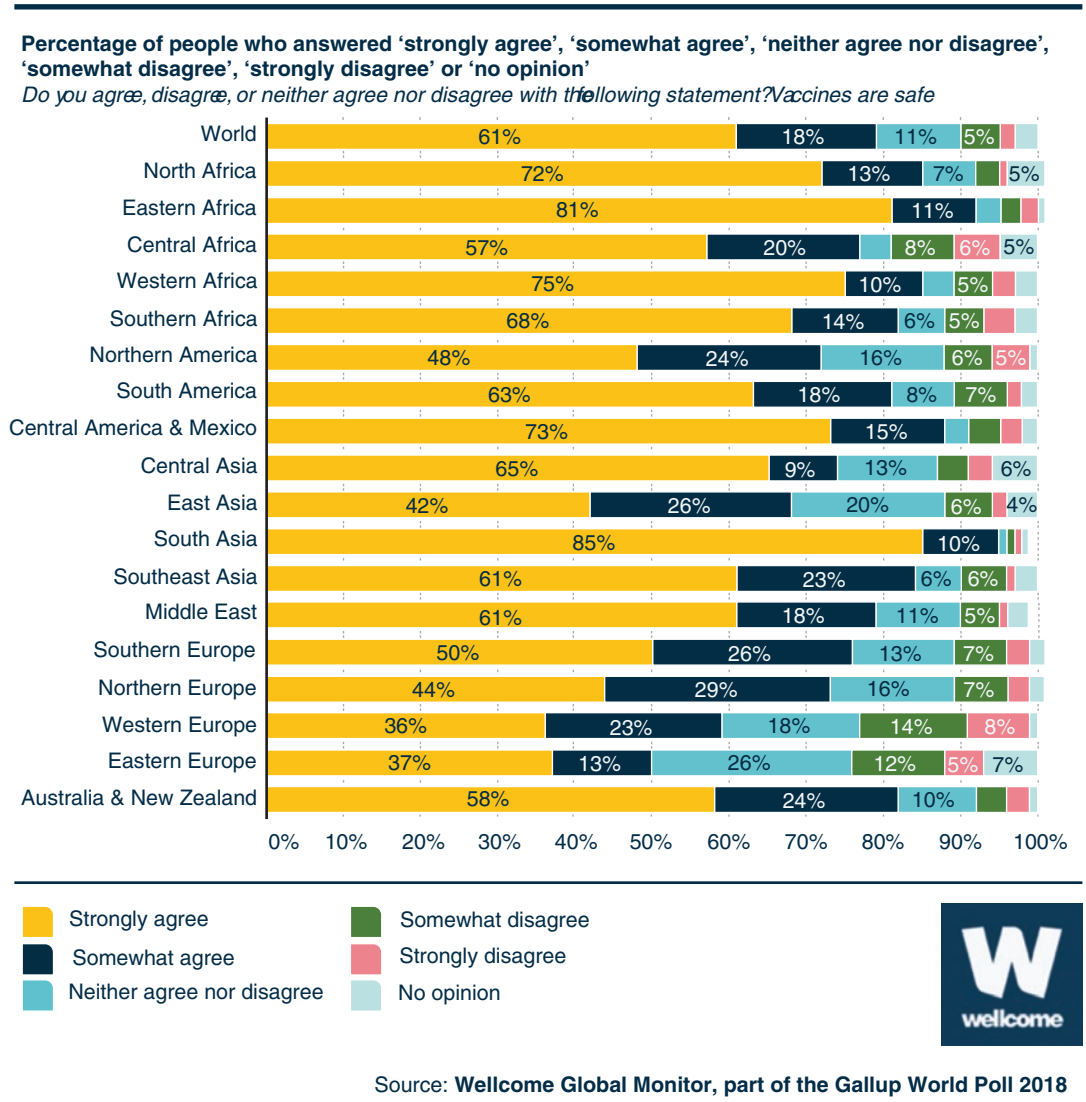

Fig. 7.3 Perceived safety of vaccines by region. (Reprinted from Wellcome Global Monitor 2018: Chap. 5: Attitudes to vaccines, by Wellcome Global Monitor. https://www.sciencedirect.com/science/article/pii/S0277953614002421. Link to license: https://creativecommons.org/licenses/by/3.0/. No changes were made to the original content)

chickenpox and 115 deaths attributed to the virus. Less than 50,000 cases have been reported after 1998 and less than 40 deaths annually since 2000, due to the advent of the chickenpox vaccine [26].

Varicella initially manifests after a prodrome of fever, malaise, and loss of appetite. Over the next week, generalized pruritic papules develop and evolve into vesicles with surrounding erythema, pustules, and lastly crusted papules until resolution occurs with residual hypopigmentation. Lesions appear in a series of crops so that the different stages of lesion development may be observed at one point in time. Distribution of the lesions is concentrated centrally rather than on distal extremities. In previously healthy patients, the symptoms usually last about 3–7 days. The scabs may take several weeks to heal, however, often leaving behind scars. The severity of dis-

ease can range from a barely noticeable rash to hundreds of vesicles. Complications include bacterial superinfection of skin lesions, pneumonia, sepsis, cerebellar ataxia, and encephalitis. Diagnosis is made clinically, but polymerase chain reaction (PCR) for VZV DNA is the laboratory test of choice to confirm the diagnosis when the presentation is atypical [23].

Although it is debated whether or not VZV is transmitted via respiratory droplets, the vesicular fluid is highly contagious. The transmission rate is directly proportional to the number of cutaneous lesions, with no spread of disease in the absence of lesions [27]. Once the virus reaches a susceptible host, the respiratory tract and adjacent lymphatics become infected. VZV then infects T lymphocytes, which migrate to the keratinocytes, among other cells in the body [28]. Although the innate immune system fights back against the virus with the production of alpha-interferon, viral proliferation surmounts this effort, resulting in the production of cutaneous lesions [29]. The incubation period for VZV can be several weeks, mediated by cell-to-cell spread rather than extracellular viral dissemination. It is for this reason that patients who lack a sufficient cell-mediated host response are particularly vulnerable to VZV, as T lymphocyte response is more important than the production of specific antibodies. During primary infection, the virus establishes dormancy in sensory ganglia, where it can be reactivated years later [30, 31].

Primary VZV infection is most common in unvaccinated children, although when it affects unvaccinated adolescents or adults, the clinical course is more severe. Vaccine effectiveness for preventing disease with one dose ranges from 55% to 87%, while two doses prevent 84% to 98% of disease. The United States and Canada are among the few countries that schedule two routine doses of the vaccine [19–22]. Prior to this vaccination policy in the United States, there were 100–150 annual deaths from VZV [32]. The vaccine has proven to be very safe and can even be used safely in select immunocompromised patients [19]. The most common reaction is a mild rash several weeks after vaccination, which occurs in about 5% of patients [32]. More critical side effects, such as severe rash, pneumonia, and neurological symptoms, have been documented rarely around the globe in children who were immunocompromised without knowledge of this status prior to vaccination [23].

Because vaccination rates remain moderate to high, major decreases in varicella disease burden have been seen. However, as expansion of the vaccination programs continues, concern has been raised that vaccination produces weaker immunity than would be naturally derived through infection. This may translate to increased cost and morbidity associated with herpes zoster (HZ). The effects of preventing primary infection have yet to be fully realized, particularly in the setting of additionally vaccinating for HZ. There have been studies showing up to 72% reduced risk of HZ after VZV vaccine in pediatrics [33].

Therapy for varicella previously was supportive care to reduce inflammation and pruritus; however, well-tolerated oral antiviral medications, such as acyclovir, are commonly used today. Acyclovir-resistant VZV is rare, but in such cases foscarnet may be alternatively used. In healthy patients less than 12 years of age, antiviral treatment is not typically recommended, but is cost-effective, because it allows the child and parent to return to school and work sooner. Potential complications of varicella include bacterial superinfection of lesions, neurological symptoms, and maternal pneumonia and congenital transmission in pregnant women. Prognosis with treatment is favorable but is worse in immunocompromised and elderly patients [34].

Varicella-Zoster Virus: Herpes Zoster (Shingles)

Recognition of the dermatomal rash of herpes zoster (HZ)—also known as shingles—dates back to ancient times. HZ has been aptly named across cultures: in Spanish, Culebrilla literally means “small snake”; in Norwegian, Helvetesild translates to “hell’s fire”; in German, Gürtelrose is “belt of rose(thorns)”; and in Arabic, Hezam

innar describes a "belt of fire" [35]. In 1888, von Bokay suggested a relationship between chickenpox and HZ after he observed that children without varicella immunity developed chickenpox following exposure to HZ [36, 37].

HZ is highly prevalent and, per some studies, increasing in age-adjusted incidence worldwide, although precise epidemiologic data is difficult to obtain [38, 39]. Data from different populations within several countries estimate a median zoster incidence of 4 to 4.5 per 1000 person-years. In immunocompetent individuals, this rate is estimated at 1.2 to 3.4 cases per 1000 person-years, with an increased risk in those older than 65 years of age at 3.9 to 11.8 cases per 1000 person-years [35, 40]. Approximately 1 million cases of HZ occur annually in the United States, with 8% of those cases in immunocompromised patients. HZ risk increases with age. The average age of onset in adults is 50 years. Postherpetic neuralgia (PHN), the most common HZ complication, also increases with age, with 80% of cases occurring in patients older than 50 years [35]. As the percentage of elderly people in the global population increases, it is likely that more cases of HZ will be seen each year. Other than age and immune status, a family history of HZ is the best predictor of shingles [41, 42]. Through strategic adult vaccination for HZ, boosting the aging immune system to protect against viral reactivation, HZ complications can be prevented.

In contrast to varicella, which is caused by an acute varicella-zoster virus (VZV) infection, HZ is caused by a reactivation of the same virus, which commonly lies dormant in the dorsal root ganglia, autonomic ganglia, and cranial nerve ganglia [35]. VZV reactivation events are typically suppressed by T-cell-mediated immunity and remain subclinical [43]. However, in immunosuppressed or immunosenescent individuals with weakened cell-mediated immunity, VZV reactivation yields clinical HZ. Viral replication results in ganglionitis and local destruction of tissue, producing an inflammatory response that is the likely cause of the classic prodromal pain of HZ [35].

HZ patients typically experience a prodromal pain, often described as "burning," "stabbing," or "shooting," the cause of which becomes apparent once dermatomal skin lesions become visible days later [44]. The time from the onset of pain to the outbreak of skin lesions represents the transit time for the virus to spread from the ganglia, down the nerve endings, to the epidermal-dermal junction to finally replicate at the skin's surface. First, an erythematous, macular phase develops which progresses into papules and vesicles. HZ lesions can be seen at all stages of development once the vesicular phase is reached. Vesicular pustulation occurs within a week of rash onset, and after several more days, lesions ulcerate and crust over. These crusts take longer to resolve, usually after several weeks, potentially leaving behind areas of hypo-/hyper-pigmentation or scarring. If vesicular lesions continue to erupt for longer than a week, or if there is extensive involvement of multiple dermatomes, investigation for an underlying immunodeficiency should be conducted [35].

HZ is generally diagnosed clinically based on the characteristic rash and other accompanying signs and symptoms. However, in some cases, the diagnosis may be less obvious. The rash may be absent (as in zoster *sine* herpete), limited, or, in the case of immunocompromised patients, atypical [45]. These situations warrant further diagnostic testing. Polymerase chain reaction (PCR) is the preferred method as it provides results in about a day and is the most sensitive and specific laboratory test for detecting VZV [36]. PCR can test lesions of all stages and can aid in the diagnosis of vaccine-modified infection [46]. It can also test non-cutaneous specimens such as CSF and blood [45, 46]. If PCR is not available, direct fluorescent antibody (DFA) is an alternative, though it is significantly less sensitive than PCR and less useful if scrapings are from late-stage lesions [36, 45]. Viral culture is also less sensitive than PCR and requires a longer turnaround time [36]. Additionally, viral proteins remain after viral replication has ceased, so PCR and DFA can be positive when viral culture is negative [36].

Serologic tests such as the latex agglutination assay and enzyme-linked immunosorbent assays (ELISA) can be used to screen for immunity to varicella [36].

Latent VZV is kept from reactivation by a competent immune system. Increasing age correlates with a reduction in VZV-specific cell-mediated immunity and is the most important risk factor for herpes zoster and its complications, followed by a family history of shingles. The estimated lifetime risk in the general population is about 30% with risk increasing dramatically past the age of 50 [48]. On the opposite end of the age spectrum, varicella infection that occurs at a time when cellular immunity is not fully matured (i.e., in utero or early infancy) is associated with risk for pediatric herpes zoster [45]. Disease-related immunosuppression in HIV/AIDS, diabetes mellitus, or malignancies such as leukemia and lymphoma also increase risk [45, 48]. Organ or hematopoietic stem cell transplant patients as well as patients with autoimmune diseases (e.g., inflammatory bowel disease, rheumatoid arthritis, systemic lupus erythematosus, etc.) are also at increased risk due to use of immunosuppressant therapy. Additionally, risk of herpes zoster is reported to be higher in Caucasians more than those of African ancestry and in pregnant women. It is markedly higher in unvaccinated individuals and in those with a family history of herpes zoster [45, 47].

HZ can result in significant complications. PHN, defined as unresolved pain months after rash onset, occurs in about 20% of patients with HZ [49]. Both peripheral and central nervous system components can contribute to PHN, explaining the variety of pain types described by patients, such as burning, electric-shock-like, throbbing, and allodynia [50]. Thought to be due to a different mechanism, postherpetic itch is also a common complication. Significant physical and emotional disability associated with PHN and postherpetic itch is common, leading to impaired patient quality of life and increased healthcare costs. In the United States, gabapentin, lidocaine patches, pregabalin, tricyclic antidepressants, and opioid analgesics are often used as first-line treatments, but many patients report inadequate symptom control with one or more of these treatments [50]. Acute and chronic VZV encephalitis is a rare but serious complication of HZ which can occur before or after rash onset, characterized by delirium and other neurological symptoms. Particularly in HZ ophthalmicus, VZV can invade the large cerebral arteries and cause necrosis, producing transient ischemic attacks or strokes several weeks after the initial disease. VZV can also directly invade the spinal cord, leading to myelitis, or invade the retina and cause retinitis [50].

In light of these complications and widespread incidence, defense against HZ is critical to public health. A live attenuated varicella vaccine was developed in Japan in 1974 and became the first licensed shingles vaccine in the United States in 2006 [36]. The Food and Drug Administration licensed Zostavax® (zoster live vaccine) which is now indicated for adults ages 50 and over [37]. The CDC has recommended that unless a contraindication exists, all adults age 60 and older should receive one dose of the shingles vaccine regardless of past varicella infection or immunity status. Contraindications to the vaccine include pregnancy, significant allergy to a vaccine component, and an immunocompromised state. The vaccine was derived from the original primary VZV vaccine after it was noted that, with increased potency, the Oka-derived varicella vaccine could improve T-cell-mediated immunity in older adults and thus protect against HZ outbreaks [51]. The Shingles Prevention Study (SPS) studied 38,546 immunocompetent subjects over 60 years old who were randomized to receive either a dose of the Oka/Merck VZV vaccine or a placebo injection. This multi-center trial revealed that the vaccine led to a 51.3% decrease in HZ, 39% decrease in PHN in those who did develop HZ, and overall decrease in disease burden by 61.1%. The vaccine was overall very well tolerated with mild side effects including injection site rash, headache, and zoster-like rash occurring several weeks after vaccination [51]. Additionally, a new recombinant zoster vaccine

approved in 2017, Shingrix, is the current recommended vaccine for shingles in the United States due to the lack of live vaccine-related adverse effects and improved efficacy [52]. It is recommended for persons aged 50 years and older. A heat-treated vaccine, created from the same Oka/Merck viral strain as in Zostavax, is under development for use in immunocompromised patients.

Clinicians face common vaccination barriers in the prevention of shingles, especially since many patients do not recall episodes of primary VZV during childhood. However, nearly all adults have serologic evidence of prior VZV exposure and thus should be vaccinated regardless of prior chickenpox history. Even more so, now that there is increased refusal for the primary varicella vaccine, the incidence of shingles is expected to increase as this population ages. As the burden of disease is significant, cost coverage of the HZ vaccine is also advisable in order to provide coverage for all patients [49].

Treatment for HZ in immunocompetent patients should include systemic antiviral therapy and as-needed pain medication for patients over 50 years of age, with moderate to severe pain or moderate to severe rash. Gabapentin has shown to decrease chronic pain if initiated at acute onset of the rash [53]. Treatment with antiviral medications has been shown to decrease pain duration in multiple randomized and controlled clinical trials. Brivudine (not available in the United States), famciclovir, and valacyclovir have demonstrated greater efficacy than acyclovir in clinical trials, although other issues such as cost, dose frequency, and patient frailty should be considered. There is currently no evidence for the use of antiviral treatment after 72 hours of rash onset, unless vesicles are continuing to form. In immunocompromised patients, intravenous rather than oral acyclovir is the standard treatment, as there is limited data for outpatient oral medication use in these populations. HIV-positive patients need treatment until all lesions have healed due to increased risk for relapse. HZ ophthalmicus treatment should be overseen by an ophthalmologist with cool ocular compresses, antibiotic ophthalmic ointments, and topical steroids. Pregnant women can be treated when the benefit of antivirals outweighs the risk of harm to the fetus, while breast-feeding mothers are also treated cautiously, as acyclovir can be transmitted via breast milk [50].

Human Papillomavirus

Human papillomavirus (HPV) is the most common sexually transmitted infection; however, vaccines against the virus have shown to be very safe and effective in preventing disease. The bivalent, quadrivalent, and nonavalent vaccines prevent cervical and other anogenital cancers as well as some oral and other HPV-associated cancers, with the quadrivalent and nonavalent vaccines additionally protecting against condyloma accuminatum or anogenital warts. The World Health Organization (WHO) has recommended that HPV vaccines be included in all national immunization schedules since April 2009 [54]. Public and private organizations, such as Gavi, the Vaccine Alliance, have worked to provide subsidized and free vaccines to low- and low-middle-income countries given the extensive impact of preventing HPV-associated disease [55].

Although great policy strides have been made to promote HPV vaccines, about 35,000 cases of HPV-associated cancer and millions of other cases of non-cancerous disease are diagnosed in the United States annually [56]. Even when vaccines are made available to adolescent males and females, the ideal candidates for vaccination, they remain underutilized [57]. This is unfortunately due to gaps in guardian vaccine education, provider hesitancy to make strong recommendations for vaccination, and guardian refusal due to perceived stigma associated with the HPV vaccine [58–62]. The vaccine was initially approved for cervical cancer, so it is often mistaken to be only for females [61, 62]. Furthermore, guardian hesitancy related to the vaccine is in part due to the stigma of sexually transmitted infections (STIs) and reluctance to consider the minor in their care to be at risk for STIs [58–60].

Healthcare providers may not educate patients and their families appropriately on the vaccine [58–60]. Due to reasons such as these, only about half of recommended adolescents receive the vaccine [60]. More than 70% of adults are not aware the HPV causes cervical, oral, penile, and anal cancers [60]. Although screening via pap smears has greatly decreased cervical cancer rates, other forms of HPV-induced cancers are on the rise [60]. Men received healthcare provider recommendation for the HPV vaccine 19% of the time, where women received a recommendation 31.5% of the time [57]. Productive education about the relevance of HPV vaccination for cancer prevention is critical given the current lack of understanding [60].

If adolescent vaccination rates fail to improve in the United States, more than 4000 girls annually will develop cervical cancer later in life [63]. In addition to the devastating public health consequences, the financial burden of failing to vaccinate against HPV would be astounding. Additional provider visits; procedures such as pap smears, bronchoscopies, and colposcopies; and treatments for cancers and warts could be prevented through successful vaccination programs [64]. Improving provider training to encourage adolescent HPV vaccination rates is essential in protecting public health [65].

Although adverse effects (AE) following HPV vaccination are rare and generally no different than those following vaccination with a placebo, the perception of AEs has been distorted by social media. While serious AEs are exceedingly rare, a single report on social media, even if unsubstantiated, can instill fears on large segments of society, thus preventing vaccination or even official recommendations for vaccination [66].

Reemerging Systemic Diseases with Cutaneous Manifestations

Measles

Rubeola, more commonly known as measles, has been documented historically since the ninth century and likely dates back 5000–10,000 years. Strides in measles pathophysiology began in 1957 with Dr. Francis Home's discovery of measles as a hematologic infectious process [67, 68]. A vaccine for measles was established by John Enders in 1963, after he and Dr. Thomas C. Peebles isolated blood-borne measles. The current US measles vaccine is a live, attenuated adaptation of this vaccine established in 1968 [67]. The CDC initiated serious efforts to eliminate measles in the late 1970s [67].

At the end of the twentieth century, over 1000,000 persons died from measles each year. The majority of these deaths were in unvaccinated, often malnourished, children. Deaths were usually secondary to measles pneumonia and/or secondary bacterial infections. From 2000 to 2015, the worldwide number of both measles cases and deaths fell by 70% and 79%, respectively [68]. However, while efforts in vaccination were able to logistically eliminate measles in the United States in 2000, the incidence of measles in the United States is on the rise, from 63 reported cases in 2010 to 372 reported cases in 2018, with most cases in unvaccinated patients [67]. Due to the "Anti-Vaxx" movement, there has been more resistance to vaccine use, especially in the United States since 2014 [69]. While trepidation with regard to vaccines is certainly not a new phenomenon, current momentum is largely rooted in the since-retracted and discredited 1998 article by Andrew Wakefield that linked autism to the MMR vaccine [69]. In the United States, it is thought that the most salient factor in measles outbreaks is travel to other countries (particularly Ukraine, Mexico, Cuba, Israel, Japan, Thailand, and the Philippines) and lack of vaccination [70]. From January 1 to December 31, 2019, there were 1282 cases of measles reported in the United States (including cases in 31 states), with approximately three quarters of cases diagnosed in Orthodox Jewish communities near New York City; this is the highest incidence rate of measles seen in the United States since the 1990s [67]. Yet, these numbers are miniscule compared to the epidemic that crippled the Democratic Republic of Congo in the same year, counting over 230,000 incidences and more than 6000 deaths [67]. According to 2019 preliminary

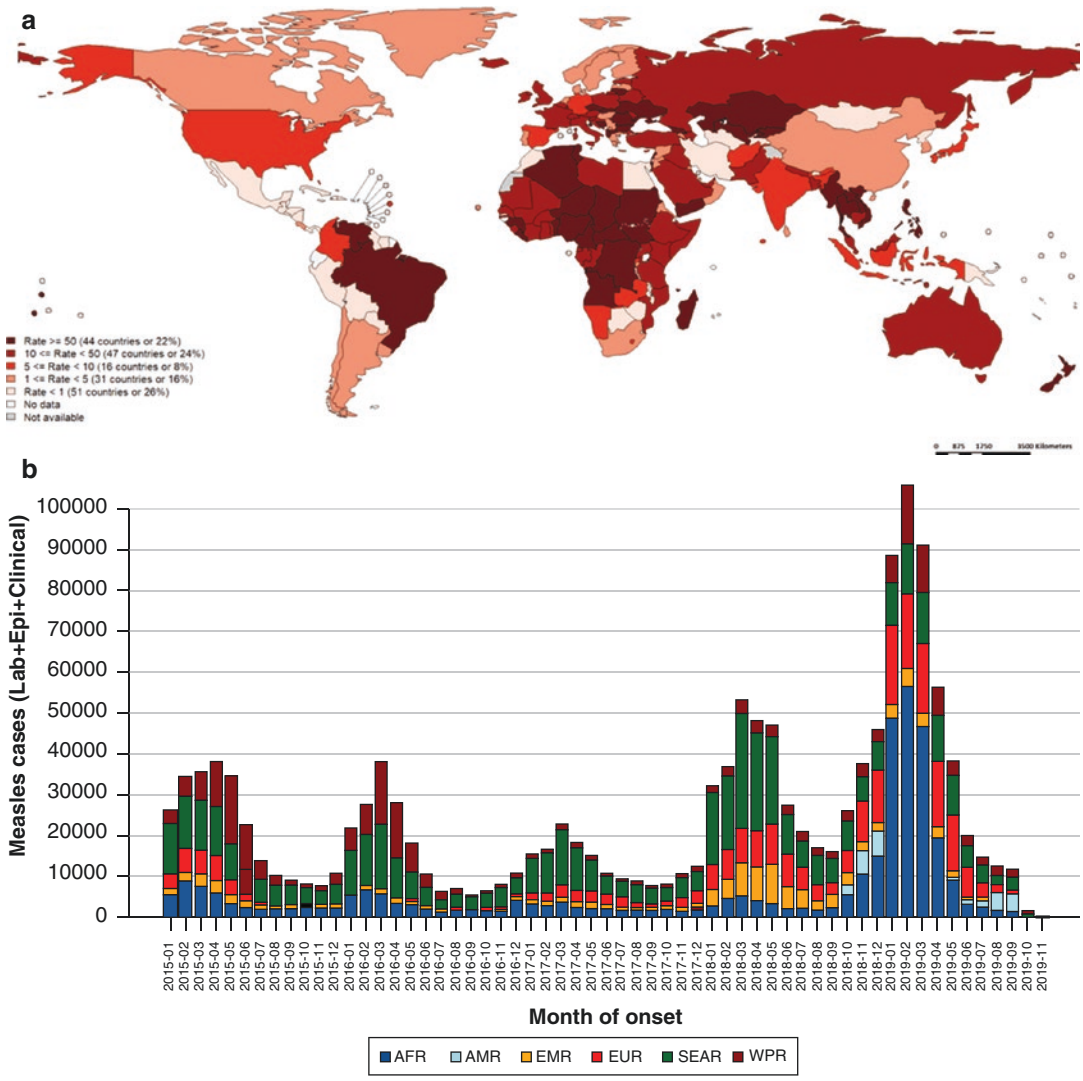

Fig. 7.4 (**a**, **b**) Incidence rate of measles across the world, per 2019 WHO measles surveillance data. Global Measles and Rubella Monthly Update. World Health Organization; [2020]. License: CC BY-NC-SA 3.0 IGO

WHO surveillance data, measles cases have hit a record high across the world (Fig. 7.4) [71].

Measles is a highly contagious viral illness of the *Paramyxoviridae* family. This negative-sense RNA virus is single-stranded and enveloped [68]. Transmission is through airborne inhalation of respiratory droplets containing the virus [67]. While the incubation period has been documented to be highly variable, it is roughly 10 days [68]. One to two weeks after exposure to the virus, pulmonary symptoms as well as viral manifestations like fever and coryza appear. Conjunctivitis can also be present, completing the "three Cs": cough, coryza, and conjunctivitis [67, 68]. In the immediate 2 to 3 days following the onset of the previously described symptoms, small, white macules known as Koplik spots can be found on mucosal membranes of the oral cavity on an erythematous base [67]. The measles exanthem appears 3–5 days after the onset of symptoms. The rash consists of red macules and papules that spread in a craniocaudal manner; macules may coalesce [67]. Fever often breaks during the cutaneous exanthem [68]. The infec-

tious period is defined as 4 days prior and following this exanthem [67]. Measles is transmitted from people with active infections to others; it does not remain latent [68]. Once a person has had measles, production of IgG antibodies to hemagglutinin is protective against subsequent infection [68].

Diagnosis is typically made clinically. Laboratory tests to confirm the diagnosis include detection of IgM or IgG antibodies in serum. Reverse transcriptase polymerase chain reaction (RT-PCR) can confirm diagnosis earlier with samples from the oropharynx, nasopharynx, or urine [68].

While measles generally resolves approximately 1 week after the cutaneous eruption appears, complications are often seen in patients less than 5 or greater than 20 years old or who are pregnant [67, 68]. Immunocompromised state and vitamin A deficiency are also risk factors for complications [68]. Less severe complications include pneumonia, laryngotracheobronchitis, otitis media, diarrhea, and keratoconjunctivitis. Pneumonia and diarrhea are often due to secondary viral or bacterial infections. In pregnant women, additional complications include spontaneous abortion, low birth weight, and intrauterine fetal death; the mother is also at increased risk of death [68]. Severe complications are less likely but more devastating. These include acute disseminated encephalomyelitis, measles inclusion body encephalitis, and subacute sclerosing panencephalitis [68]. Two recent studies on blood of unvaccinated Dutch children who contracted measles detail the concept of "immune amnesia," which explains that measles virus impairs on average 20% of previously acquired immunity by killing memory B cells. Additionally, measles virus was found to decrease the diversity of nonspecific naive B cells, leading to impaired ability to form new immune memory [72]. This discovery helps explain the previously epidemiological observation that unvaccinated children who suffer from measles are subsequently more susceptible to unrelated infections compared to children vaccinated against measles [73].

Prevention of measles is achieved through vaccination. Vaccination options include the MMR (measles-mumps-rubella) and MMR-V (measles-mumps-rubella-varicella) immunization series [67]. The CDC guidelines recommend vaccination for children initially between 12 and 15 months and then again between 4 and 6 years old. Vaccination is highly protective of measles. The initial vaccine is 93% effective, while the second dose achieves 97% efficacy [67]. For the remaining 3%, herd immunity is essential to provide maximum protection. Unlike vaccines for viruses with low transmissibility, vaccines for highly infectious diseases like measles have a low threshold to becoming ineffective, requiring 96–99% of the population to be vaccinated to confer immunity. Once this is achieved, herd immunity extends to those who are not adequately vaccinated, including young infants and the immunocompromised [74].

There is currently no targeted antiviral drug despite numerous attempts due to a combination of factors from pragmatic cost of manufacturing and shelf-life to trouble in biochemical antiviral design [75]. Without a specific drug therapy, measles treatment is often supportive and directed at complication management. Treatments include vitamin A and appropriate antibiotics for secondary bacterial infections. With severe cases, antivirals such as ribavirin and interferon alpha can be helpful [68]. In studies, IFN-alpha and ribavirin have been shown to improve outcomes, especially through decreasing complication risk; likewise, vitamin A has been shown to be effective, particularly in patients less than 2 years old [75]. While complications from measles are quite common, cited in approximately 30%–40% of cases, death from measles or measles complications is rare, at 0.2% in the United States, but common in resource-limited parts of the world [76]. During outbreaks, methods such as isolation of infectious persons and persons who are not immune have been proved efficacious in decreasing the number of people who get the disease. Additionally, vaccinating outbreak populations even after exposure to the virus has been

proven to be effective in limiting the number of diseased individuals. Use of immunoglobulin has also been shown to decrease risk of measles and should especially be considered in the immunocompromised [77].

Rubella

Rubella virus is the causative agent in rubella disease, also known as "German measles," which was first described in the 1750s by German physicians De Bergen and Orlow. In 1866, Scottish physician Henry Veale coined the term "rubella," which he derived from the Latin word "rubellus," meaning "reddish" [78]. The virus was first isolated in culture in 1962, and in 1967, its structure was observed under electron microscopy using antigen-antibody complexes. Infection with the virus typically results in a self-limiting, measles-like disease; however, if the virus infects the fetus, especially during the first trimester, miscarriage or congenital rubella syndrome (CRS) may result. Maternal rubella infection and CRS were first linked by Dr. Norman Gregg, an Australian ophthalmologist [79].

Before the measles-mumps-rubella (MMR) live, attenuated vaccine was introduced, rubella manifested as an acute disease in children and young adults. Due to vaccine implementation strategies since 1969, the number of rubella cases worldwide has been greatly reduced. Widespread epidemics have since become extinct, and since 2009, endemic transmission in the World Health Organization's (WHO) Region of the Americas has come to a halt. The peak age of incidence during the pre-vaccination era was 5 to 14 years but has now shifted to 15 to 19 years [80]. In the period immediately before conception or during the first 8–10 weeks of gestation, infection with rubella can lead to multiple fetal defects, such as fetal wastage or stillbirth, in up to 90% of cases [79].

Rubella virus is a single-stranded positive-sense RNA virus and belongs to the *Togaviridae* family and *Rubivirus* genus. Person-to-person spread occurs via the respiratory route [79]. Detergents, temperatures greater than 56 °C (132.8 ° F), UV light, and pH extremes less than 6.8 but greater than 8.1 can easily destroy the virus. Rubella clinically manifests as an erythematous, pruritic, papular rash, appearing approximately 1 week after viremia and lasting 1 to 3 days [80, 81]. Onset of rash occurs concomitantly with the appearance of antibodies and resolution of viremia. The rash initially develops on the face and then spreads to the extremities, covering the entire body within a day, and typically resolves by the third day [80]. Diagnosing rubella clinically is a challenging feat, as the exanthema can take on an atypical, scarlatiniform, or morbilliform presentation, resembling that of other viral infections such as parvovirus B19 or roseola due to human herpesviruses 6 and 7 [81].

Since the manifestation of rubella disease can resemble several other infectious processes, it is important to use clinical features and specific viral testing, such as throat swabs, oral fluids, or nasopharyngeal secretions, to diagnose rubella through virus detection [80]. Other specimens, including cataract tissue and urine, may also be used. In postnatal rubella, the timing of specimen collection is vital. On the first day of the rash, RV-IgM is present in sera in only 50% of cases; however, RV-IgM is detectable approximately 5 days after the rash in most cases and disappears in 4 to 12 weeks [81]. Several tests that exist to detect viral RNA from clinical specimens, including RT-PCR, ELISA, hemagglutinin inhibition (HI), and plaque reduction neutralization (PRN), are available to detect RV-IgG. Since incidence has greatly decreased, most rubella testing is for immunity to the virus through antibody titers [79].

The biggest risk factor for rubella infection is the absence of vaccination. These individuals, especially expectant mothers and children, are not only at greater risk for infection but also at greater risk for CRS and other complications. Conditions associated with rubella infection include postnatal rubella, CRS, and maternal rubella [78]. CRS usually results from primary infection, and it may persist for months to years. Signs and symptoms of CRS can be grouped into

three categories—transient (thrombocytopenic purpura), permanent (heart defects, cataracts, hearing loss), and developmental (behavioral disorders). The most common finding in CRS is deafness, which presents in up to 67% of cases. The classic cutaneous manifestation of CRS is a "blueberry muffin" purpuric rash, which represents extramedullary hematopoiesis [80]. Other complications that can result from infection include arthralgia or arthritis, carpal tunnel syndrome, tenosynovitis, miscarriage and intrauterine fetal death in pregnant women, hemolytic anemia, thrombocytopenia, purpura, orchitis, uveitis, Guillain-Barré syndrome, and post-infectious encephalopathy [78].

The key to rubella infection prevention continues to be immunization against the virus through vaccination. Rubella vaccines may be given subcutaneously as a single component, but they are most often given as combination vaccines, such as measles-mumps-rubella-varicella (MMRV) or MMR [78]. All children should receive their first dose of the MMR vaccine at 12 to 15 months and the second dose at 4 to 6 years [80]. The vaccine is 95% effective in prevention after just one dose and almost 100% effective after both [78]. Since the MMR vaccine is a live attenuated vaccine containing the RA 27/3 strain of rubella virus, it should not be administered to pregnant women or immunocompromised persons. The vaccination should be administered to women of childbearing age before conception. These women are also advised to avoid pregnancy for 1 month following vaccination. Rubella-susceptible women who have not yet been vaccinated and become pregnant should be vaccinated in the immediate postpartum period [78]. Moreover, in children with CRS, disease can be transmitted for as long as the child sheds virus, up to the age of 1 in 20% of children. Exclusion from daycare or school is necessary for confirmed cases of rubella. Until these individuals have two negative throat swab or urine cultures, they should be kept in isolation [78].

Treating rubella becomes a consideration in individuals who have acquired the infection but have not been vaccinated. Postnatally acquired rubella is typically self-limiting, and treatment is symptomatic through use of NSAIDs for associated arthralgia and arthritis. In gravid individuals, treatment depends on the age of gestation at the time of infection. When termination of pregnancy is not an option, immune globulin may be administered in women with known rubella exposure. Treatment of CRS is managed similarly to postnatally acquired rubella, with focus on symptom management and organ-specific treatment. Children should be monitored with audiologic, ophthalmic, and neurodevelopmental follow-up on a long-term basis, since manifestations of the disorder may be delayed. Prognosis of rubella disease is variable, depending on the severity and number of organs affected. In children with CRS, those with thrombocytopenia, hepatosplenomegaly, pulmonary hypertension, and interstitial pneumonia have a high risk of mortality [78]. No effective antiviral treatment currently exists to treat rubella infection [82].

Looking Forward: The Future of Viral Infections

Common Cutaneous Viruses

As we move forward with our vaccination efforts, it is important to remember that areas of progress, if not maintained, can easily regress. Viruses for which we have vaccines, such as human papillomavirus and hepatitis B, would likely flourish without the use of vaccines or medical therapies.

Hepatitis B virus (HBV) is a major cause of disease worldwide, with an estimated 200–300 million people chronically infected [83]. In addition to the classic symptoms of acute hepatitis such as fever, fatigue, and anorexia, a serum sickness-related rash is not uncommonly observed [84]. Long-term sequelae of untreated infection include cirrhosis and hepatocellular carcinoma, demonstrating the need for coordinated vaccine and treatment efforts. Reduction in new cases of HBV over the past several decades has been achieved through safer sexual and drug

practices as well as widespread vaccination efforts. The Centers for Disease Control and Prevention recommends a three-shot series for children: the first soon after birth, the second at 1–2 months, and the third at 6–18 months. Vaccination has proven to be a safe, effective, and inexpensive method of preventing disease; however, if vaccination efforts are discontinued, rates of maternal-fetal transmission of HBV would certainly rise [85].

The success and acceptance of the HBV vaccine can provide guidance for promotion of the HPV vaccine. For example, both viruses can be sexually transmitted, but neither vaccine is promoted as preventative for a sexually transmitted disease. In the case of HBV, the vaccine is viewed as preventative for liver failure and liver cancer. Likewise, if the HPV vaccine is viewed as prevention for cancer, acceptance may improve.

Vaccines in Development

As we struggle to keep reemerging viruses at bay, our ability to prevent other life-threatening viruses also remains tenuous. Since the start of the anti-vaccination movement, fighting to reeducate the public has also posed new obstacles. Antiviral vaccine development has been a challenge on the scientific forefront due to pathogen variability, escape from vaccine-induced immune responses, short effector memories, reactogenicity, and various environmental factors, among other reasons [86]. Availability of vaccines globally has been limited due to not only costs but also the logistics of delivery. Funding for vaccine development is often based on economic viability rather than need. For example, even though scientists have been aware of the Ebola virus since 1976, only in recent years has sufficient funding become available to accelerate vaccine development. Even once a vaccine has been discovered, product development and licensing to bring it to market costs between 500 million and 1 billion dollars over an average of 11.9 years [86]. The World Health Organization (WHO) has listed pathogens that are of top priority for research and development, several of which are viral illnesses such as Crimean-Congo hemorrhagic fever (CCHF), Ebola virus, Marburg virus, SARS, and Rift Valley fever virus [87]. With increasing international networking and collaboration, efforts to bring about needed vaccines and strategic planning in the event of viral epidemics are underway.

Development of new viral vaccines requires dedicated research and creative thinking. Many RNA viruses, such as hepatitis C virus (HCV) and human immunodeficiency virus (HIV), undergo extremely rapid rates of mutation, making effective vaccine development difficult [88, 89]. Human genetic variability also impacts vaccine efficacy. For example, certain human leukocyte antigen (HLA) allele variants have been associated with decreased antibody generation to several vaccines [90]. This is relevant in the case of patients with certain HLA class II alleles who are completely unresponsive to the hepatitis B vaccine [91]. Further understanding of both viral and human biology is required to create effective new vaccines.

Improving current vaccines and expanding the number of serotypes covered is another area of development. In the elderly, defending against immunosenescence requires effective vaccines. For example, combining different immunostimulatory factors has shown improvement in the zoster glycoprotein vaccine by including the $AS01_B$ adjuvant system in a Phase III clinical trial, which led to herpes zoster risk reduction in adults greater than 70 years old [92]. In the field of tropical disease, a vaccine for dengue virus called Dengvaxia, a tetravalent dengue chimeric live attenuated vaccine, has been approved in several countries and recommended by WHO in ages 9 and older [93]. However, due to dengue virus's four different serotypes, each able to stimulate a cross-reactive and disease-enhancing antibody response against the other three serotypes, creating a very efficacious vaccine has been challenging [94, 95]. Therefore, the currently available quadrivalent dengue vaccine is recommended only for persons already infected with one strain of dengue [96].

Conclusion

The good news is that even with this resurgence of previously eradicated viruses, we are still at a mortality rate of less than 5%, compared to a century ago when infectious diseases were attributable to 50% of the nation's deaths. Advances in technology have foreseen bypasses for many of the hurdles our society faces with vaccinations today. For instance, genome editing tools that reprogram the immune system's B cells to produce antibodies against viruses may be the answer to random failure of vaccine-induced DNA rearrangement [97, 98]. To minimize the need for human resources and to maximize safety, needle-free delivery of vaccines, such as aerosolized routes, jet injectors, and microneedles, is being implemented [99]. Hopefully, with ease of accessibility and increased engagement of health benefits resulting in increased demand, the affordability of vaccinations can decrease the health burdens propagated by infectious diseases.

References

1. Vander straten M, Tyring SK. Mucocutaneous manifestations of viral diseases in children. Clin Dermatol. 2002;20(1):67–73.
2. Handfield C, Kwock J, Macleod AS. Innate antiviral immunity in the skin. Trends Immunol. 2018;39(4):328–40.
3. CDC. History of Smallpox. Centers for Disease Control and Prevention. https://www.cdc.gov/smallpox/history/history.html. Published 30 Aug 2016.
4. Vanderslott S, Dadonaite B, Roser M. Vaccination. Our World in Data. https://ourworldindata.org/vaccination. Published May 10, 2013. Accessed 19 Jan 2020.
5. Wakefield AJ, Murch SH, Anthony A, Linnell, Casson DM, Malik M, et al. Ileal lymphoid nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet. 1998;351:637–41 [retracted].
6. Editors of the Lancet. Retraction: ileal lymphoid nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. Lancet. 2010;375:445.
7. Deer B. How the case against the MMR vaccine was fixed. BMJ. 2011;342:c5347.
8. Deer B. Secrets of the MMR scare. The Lancet's two days to bury bad news. BMJ. 2011;342:c7001.
9. Maisonneuve H, Floret D. Wakefield's affair: 12 years of uncertainty whereas no link between autism and MMR vaccine has been proved. Presse Med. 2012;41(9 Pt 1):827–34.
10. Battistella M, Carlino C, Dugo V, Ponzo P, Franco E. Vaccines and autism: a myth to debunk? Ig Sanita Pubbl. 2013;69(5):585–96.
11. Hussain A, Ali S, Ahmed M, Hussain S. The anti-vaccination movement: a regression in modern medicine. Cureus. 2018;10(7):e2919.
12. Chapter 5: Attitudes to vaccines. Wellcome. https://wellcome.ac.uk/reports/wellcome-global-monitor/2018/chapter-5-attitudes-vaccines. Accessed 6 Feb 2020.
13. DRC: MSF shuts down Ebola treatment center following violent attack. Doctors without borders - USA. https://www.doctorswithoutborders.org/what-we-do/news-stories/story/drc-msf-shuts-down-ebola-treatment-center-following-violent-attack. Published February 26, 2019. Accessed 19 Jan 2020.
14. Yaqub O, Castle-Clarke S, Sevdalis N, Chataway J. Attitudes to vaccination: a critical review. Soc Sci Med. https://www.sciencedirect.com/science/article/pii/S0277953614002421. Published April 16, 2014. Accessed 6 Feb 2020.
15. CDC. 2019–2020 U.S. Flu season: preliminary burden estimates. Centers for Disease Control and Prevention. https://www.cdc.gov/flu/about/burden/preliminary-in-season-estimates.htm. Published January 10, 2020. Accessed 19 Jan 2020.
16. Breuer J, Grose C, Norberg P, Tipples G, Schmid DS. A proposal for a common nomenclature for viral clades that form the species varicella-zoster virus: summary of VZV nomenclature meeting 2008, Barts and the London School of Medicine and Dentistry, 24–25 July 2008. J Gen Virol. 2010;91:821–8.
17. Wagenaar TR, Chow VT, Buranathai C, Thawatsupha P, Grose C. The out of Africa model of varicella-zoster virus evolution: single nucleotide polymorphisms and private alleles distinguish Asian clades from European/North American clades. Vaccine. 2003;21(11–12):1072–81.
18. Sadzot-Delvaux C, Merville-Louis M-P, Delree P, Marc P, Moonen G, Rentier B. An in vivo model of varicella-zoster virus latent infection of dorsal root ganglia. J Neurosci Res. 1990;26:83–9.
19. Spackova M, Wiese-posselt M, Dehnert M, Matysiak-klose D, Heininger U, Siedler A. Comparative varicella vaccine effectiveness during outbreaks in day-care centres. Vaccine. 2010;28(3):686–91.
20. Vázquez M, Larussa PS, Gershon AA, et al. Effectiveness over time of varicella vaccine. JAMA. 2004;291(7):851–5.
21. Mahamud A, Wiseman R, Grytdal S, et al. Challenges in confirming a varicella outbreak in the two-dose vaccine era. Vaccine. 2012;30(48):6935–9.
22. Shapiro ED, Vazquez M, Esposito D, et al. Effectiveness of 2 doses of varicella vaccine in children. J Infect Dis. 2011;203(3):312–5.

23. Gershon AA, Gershon MD. Pathogenesis and current approaches to control of varicella-zoster virus infections. Clin Microbiol Rev. 2013;26(4):728–43. Weller T, Stoddard MB. 1952. Intranuclear inclusion bodies in cultures of human tissue inoculated with varicella vesicle fluid. J. Immunol. 68:311–319
24. Takahashi M, Asano Y, Kamiya H, et al. Development of varicella vaccine. J Infect Dis. 2008;197(Suppl 2):S41–4.
25. CDC. Reported Cases and Deaths from Vaccine Preventable Diseases, United States, 1950-2013. Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/appendices/E/reported-cases.pdf. Published May 2019. Accessed 1 Sept 2014.
26. Tsolia M, Gershon AA, Steinberg SP, Gelb L. Live attenuated varicella vaccine: evidence that the virus is attenuated and the importance of skin lesions in transmission of varicella-zoster virus. National Institute of Allergy and Infectious Diseases Varicella Vaccine Collaborative Study Group. J Pediatr. 1990;116(2):184–9.
27. Arvin AM, Moffat JF, Sommer M, et al. Varicella-zoster virus T cell tropism and the pathogenesis of skin infection. Curr Top Microbiol Immunol. 2010;342:189–209.
28. Ku CC, Zerboni L, Ito H, Graham BS, Wallace M, Arvin AM. Varicella-zoster virus transfer to skin by T cells and modulation of viral replication by epidermal cell interferon-alpha. J Exp Med. 2004;200(7):917–25.
29. Malavige GN, Jones L, Kamaladasa SD, et al. Viral load, clinical disease severity and cellular immune responses in primary varicella zoster virus infection in Sri Lanka. PLoS One. 2008;3(11):e3789.
30. Jean-philippe P, Freedman A, Chang MW, et al. Severe varicella caused by varicella-vaccine strain in a child with significant T-cell dysfunction. Pediatrics. 2007;120(5):e1345–9.
31. Plotkin SA, Orenstein WA, Offit PA. Vaccines E-book. 6th Ed. Philadelphia: Elsevier Health Sciences-Saunders; 2012.
32. Galea SA, Sweet A, Beninger P, et al. The safety profile of varicella vaccine: a 10-year review. J Infect Dis. 2008;197(Suppl 2):S165–9.
33. Weinmann S, Naleway AL, Koppolu P, et al. Incidence of Herpes Zoster among children: 2003-2014. Pediatrics. 2019;144:1.
34. Kim SR, Khan F, Ramirez-fort MK, Downing C, Tyring SK. Varicella zoster: an update on current treatment options and future perspectives. Expert Opin Pharmacother. 2014;15(1):61–71.
35. Yawn BP, Gilden D. The global epidemiology of herpes zoster. Neurology. 2013;81(10):928–30.
36. CDC. Epidemiology and Prevention of Vaccine-Preventable Diseases. Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/pubs/pinkbook/index.html. Published 2017. Accessed 1 Sept 2019.
37. Voelker R. Increasing cases of Shingles in the eye raise key questions. JAMA. 2019;322:712.
38. Mullooly JP, Riedlinger K, Chun C, Weinmann S, Houston H. Incidence of herpes zoster, 1997-2002. Epidemiol Infect. 2005;133(2):245–53.
39. Yawn BP, Saddier P, Wollan PC, St sauver JL, Kurland MJ, Sy LS. A population-based study of the incidence and complication rates of herpes zoster before zoster vaccine introduction. Mayo Clin Proc. 2007;82(11):1341–9.
40. Brisson M, Edmunds WJ, Gay NJ, Law B, De serres G. Modelling the impact of immunization on the epidemiology of varicella zoster virus. Epidemiol Infect. 2000;125(3):651–69.
41. Hicks LD, Cook-norris RH, Mendoza N, Madkan V, Arora A, Tyring SK. Family history as a risk factor for herpes zoster: a case-control study. Arch Dermatol. 2008;144(5):603–8.
42. Hernandez PO, Javed S, Mendoza N, Lapolla W, Hicks LD, Tyring SK. Family history and herpes zoster risk in the era of shingles vaccination. J Clin Virol. 2011;52(4):344–8.
43. Klein NP, Holmes TH, Sharp MA, et al. Variability and gender differences in memory T cell immunity to varicella-zoster virus in healthy adults. Vaccine. 2006;24(33–34):5913–8.
44. Gnann JW, Whitley RJ. Clinical practice. Herpes zoster. N Engl J Med. 2002;347(5):340–6.
45. Cohen JI. Clinical practice: Herpes zoster. N Engl J Med. 2013;369(3):255–63.
46. Leung J, Harpaz R, Baughman AL, et al. Evaluation of laboratory methods for diagnosis of varicella. Clin Infect Dis. 2010;51(1):23–32.
47. Harpaz R. Do varicella vaccination programs change the epidemiology of herpes zoster? A comprehensive review, with focus on the United States. Expert Rev Vaccines. 2019;18(8):793–811.
48. Schmader K. Herpes Zoster. Ann Intern Med. 2018;169(3):ITC19–31.
49. Willison CB, Morrison LK, Mendoza N, Tyring SK. Shingles vaccine. Expert Opin Biol Ther. 2010;10(4):631–8.
50. Dworkin RH, Portenoy RK. Pain and its persistence in herpes zoster. Pain. 1996;67:241–51.
51. Oxman MN, Levin MJ, Johnson GR, et al. A vaccine to prevent herpes zoster and postherpetic neuralgia in older adults. N Engl J Med. 2005;352(22):2271–84.
52. CDC. Shingrix Shingles Vaccination. What You Should Know. Centers for Disease Control and Prevention. https://www.cdc.gov/vaccines/vpd/shingles/public/shingrix/index.html. Published January 25, 2018. Accessed 15 Aug 2019.
53. Lapolla W, Digiorgio C, Haitz K, et al. Incidence of postherpetic neuralgia after combination treatment with gabapentin and valacyclovir in patients with acute herpes zoster: open-label study. Arch Dermatol. 2011;147(8):901–7.
54. Human papillomavirus vaccines. WHO position paper. Wkly Epidemiol Rec. 2009;84(15):118–31.

55. Gavi, the Vaccine Alliance. More than 30 million girls to be immunised with HPV vaccines by 2020 with GAVI support. 2012. http://www.gavi.org/library/news/press-releases/2012/more-than-30-million-girls-immunised-with-hpv-by-2020/.
56. Dunne EF, Park IU. HPV and HPV-associated diseases. Infect Dis Clin N Am. 2013;27(4):765–78.
57. Suk R, Montealegre JR, Nemutlu GS, et al. Public knowledge of human papillomavirus and receipt of vaccination recommendations. JAMA Pediatr. 2019;173(11):1099–101.
58. Attia AC, Wolf J, Núñez AE. On surmounting the barriers to HPV vaccination: we can do better. Ann Med. 2018;50(3):209–25.
59. Bonanni P, Zanella B, Santomauro F, Lorini C, Bechini A, Boccalini S. Safety and perception: what are the greatest enemies of HPV vaccination programmes? Vaccine. 2018;36(36):5424–9.
60. Patty NJS, Van dijk HM, Wallenburg I, et al. To vaccinate or not to vaccinate? Perspectives on HPV vaccination among girls, boys, and parents in the Netherlands: a Q-methodological study. BMC Public Health. 2017;17(1):872.
61. Apaydin KZ, Fontenot HB, Shtasel D, et al. Facilitators of and barriers to HPV vaccination among sexual and gender minority patients at a Boston community health center. Vaccine. 2018;36(26):3868–75.
62. Radisic G, Chapman J, Flight I, Wilson C. Factors associated with parents' attitudes to the HPV vaccination of their adolescent sons: a systematic review. Prev Med. 2017;95:26–37.
63. Chesson HW, Ekwueme DU, Saraiya M, Dunne EF, Markowitz LE. The estimated impact of human papillomavirus vaccine coverage on the lifetime cervical cancer burden among girls currently aged 12 years and younger in the United States. Sex Transm Dis. 2014;41(11):656–9.
64. Chesson HW, Ekwueme DU, Saraiya M, Watson M, Lowy DR, Markowitz LE. Estimates of the annual direct medical costs of the prevention and treatment of disease associated with human papillomavirus in the United States. Vaccine. 2012;30(42):6016–9.
65. Rahman M, Laz TH, Mcgrath CJ, Berenson AB. Provider recommendation mediates the relationship between parental human papillomavirus (HPV) vaccine awareness and HPV vaccine initiation and completion among 13- to 17-year-old U.S. adolescent children. Clin Pediatr (Phila). 2015;54(4):371–5.
66. Morimoto A, Ueda Y, Egawa-takata T, et al. Effect on HPV vaccination in Japan resulting from news report of adverse events and suspension of governmental recommendation for HPV vaccination. Int J Clin Oncol. 2015;20(3):549–55.
67. CDC. Measles (Rubeola). Centers for Disease Control and Prevention. https://www.cdc.gov/measles/index.html. Published May 13, 2019. Accessed 17 Aug 2019.
68. Moss WJ. Measles. Lancet. 2017;390(10111):2490–502.
69. Benecke O, Deyoung SE. Anti-vaccine decision-making and Measles resurgence in the United States. Glob Pediatr Health. 2019;6:2333794X19862949.
70. Sarkar S, Zlojutro A, Khan K, Gardner L. Measles resurgence in the USA: how international travel compounds vaccine resistance. Lancet Infect Dis. 2019;19(7):684–6.
71. Measles and Rubella Surveillance Data. World Health Organization. https://www.who.int/immunization/monitoring_surveillance/burden/vpd/surveillance_type/active/measles_monthlydata/en/. Published January 10, 2020. Accessed 6 Feb 2020.
72. Petrova VN, Sawatsky B, Han AX, et al. Incomplete genetic reconstitution of B cell pools contributes to prolonged immunosuppression after measles. Sci Immunol. 2019;4(41):eaay6125.
73. Jensen A, Andersen PK, Stensballe LG. Early childhood vaccination and subsequent mortality or morbidity: are observational studies hampered by residual confounding? A Danish register-based cohort study. BMJ Open. 2019;9(9):e029794.
74. Hendrix KS, Sturm LA, Zimet GD, Meslin EM. Ethics and childhood vaccination policy in the United States. Am J Public Health. 2016;106(2):273–8.
75. Plemper RK, Snyder JP. Measles control – can measles virus inhibitors make a difference? Curr Opin Investig Drugs. 2009;10(8):811–20.
76. Bester JC. Measles and measles vaccination: a review. JAMA Pediatr. 2016;170(12):1209.
77. Gastañaduy PA, Banerjee E, Debolt C, et al. Public health responses during measles outbreaks in elimination settings: strategies and challenges. Hum Vaccin Immunother. 2018;14(9):2222–38.
78. Leung AKC, Hon KL, Leong KF. Rubella (German measles) revisited. Hong Kong Med J. 2019;25(2):134–41.
79. Lambert N, Strebel P, Orenstein W, Icenogle J, Poland GA. Rubella. Lancet. 2015;385(9984):2297–307.
80. Vander straten MR, Tyring SK. Rubella. Dermatol Clin. 2002;20(2):225–31.
81. Bouthry E, Picone O, Hamdi G, Grangeot-keros L, Ayoubi JM, Vauloup-fellous C. Rubella and pregnancy: diagnosis, management and outcomes. Prenat Diagn. 2014;34(13):1246–53.
82. CDC. Rubella (German Measles, Three-Day Measles). Centers for Disease Control and Prevention. https://www.cdc.gov/rubella/index.html. Reviewed September 15, 2017. Accessed 1 Sept 2019.
83. Matthews PC, Barnes E. Hepatitis B vaccine shortage: another symptom of chronic neglect? BMJ. 2017;359:j4686.
84. Dienstag JL. Immunopathogenesis of the extrahepatic manifestations of hepatitis B virus infection. Springer Semin Immunopathol. 1981;3(4):461–72.
85. Nemerofsky SL, Akingboye B, Ferguson C, Africa D. Sustained improvement in administration of the Hepatitis B vaccine birth dose: a quality improvement initiative. Am J Med Qual. 2018;33(3):313–20.

86. Pronker ES, Weenen TC, Commandeur HR, Osterhaus AD, Claassen HJ. The gold industry standard for risk and cost of drug and vaccine development revisited. Vaccine. 2011;29(35):5846–9.
87. Lambe T, Bowyer G, Ewer KJ. A review of phase I trials of Ebola virus vaccines: what can we learn from the race to develop novel vaccines? Philos Trans R Soc Lond Ser B Biol Sci. 2017;372(1721):20160295.
88. Cuevas JM, Geller R, Garijo R, López-aldeguer J, Sanjuán R. Extremely high mutation rate of HIV-1 in vivo. PLoS Biol. 2015;13(9):e1002251.
89. Ribeiro RM, Li H, Wang S, et al. Quantifying the diversification of hepatitis C virus (HCV) during primary infection: estimates of the in vivo mutation rate. PLoS Pathog. 2012;8(8):e1002881.
90. Posteraro B, Pastorino R, Di giannantonio P, et al. The link between genetic variation and variability in vaccine responses: systematic review and meta-analyses. Vaccine. 2014;32(15):1661–9.
91. Li ZK, Nie JJ, Li J, Zhuang H. The effect of HLA on immunological response to hepatitis B vaccine in healthy people: a meta-analysis. Vaccine. 2013;31(40):4355–61.
92. Cunningham AL, Lal H, Kovac M, et al. Efficacy of the Herpes Zoster subunit vaccine in adults 70 years of age or older. N Engl J Med. 2016;375(11):1019–32.
93. Torres JR, Falleiros-arlant LH, Gessner BD, et al. Updated recommendations of the International Dengue Initiative expert group for CYD-TDV vaccine implementation in Latin America. Vaccine. 2019;37(43):6291–8.
94. Khetarpal N, Khanna I. Dengue fever: causes, complications, and vaccine strategies. J Immunol Res. 2016;2016:6803098.
95. Anderson KB, Endy TP, Thomas SJ. The dynamic role of dengue cross-reactive immunity: changing the approach to defining vaccine safety and efficacy. Lancet Infect Dis. 2018;18(10):e333–8.
96. Wilder-smith A. Dengue vaccine development: status and future. Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 2020;63(1):40–4.
97. Plotkin SA. Increasing complexity of vaccine development. J Infect Dis. 2015;212(Suppl 1):S12–6.
98. Lau CH. Applications of CRISPR-Cas in bioengineering, biotechnology, and translational research. CRISPR J. 2018;1:379–404.
99. National Vaccine Advisory Committee, Enhancing the work of the HHS National Vaccine Program in global immunizations. 2013. www.hhs.gov/nvpo/nvac/reports/index.html.