

Chapter 13

Immunization and Vaccination



Saira Hussain

Vaccination is considered to be one of the greatest achievements of public health and is the most effective method of preventing infectious diseases. Global vaccination programs have contributed to a decline in mortality and morbidity of various diseases. Widespread immunity due to vaccination is largely responsible for the eradication of smallpox the restriction of polio measles tetanus and many other diseases. The effectiveness of vaccination has been widely studied and verified for example the influenza vaccine the HPV vaccine and the chicken pox vaccine. The World Health Organization (WHO) reports that vaccines are currently available for 25 different preventable infections [1].

The terms *vaccine* and *vaccination* are derived from *Variolae vaccinae* (smallpox of the cow), the term devised by Edward Jenner to denote cowpox. He used this term in 1798 in the title of his *Inquiry into the Variolae vaccinae know as the Cow Pox*, in which he described the protective effect of cowpox against smallpox [2].

S. Hussain (✉)

Department of Psychiatry, North Shore University Hospital,
Manhasset, NY, USA

e-mail: shussai1@northwell.edu

Sometime during the late 1760s, while serving his apprenticeship as a surgeon/apothecary, Edward Jenner learned of the story, common in rural areas, that dairy workers would never have the often-fatal or disfiguring disease smallpox, because they had already had cowpox, which has a very mild effect in humans. In 1796, Jenner took pus from the hand of a milkmaid with cowpox, scratched it into the arm of an 8-year-old boy, and 6 weeks later inoculated the boy with smallpox, afterward observing that he did not catch smallpox [3, 4]. Jenner extended his studies and in 1798 reported that his vaccine was safe in children and adults and could be transferred from arm-to-arm reducing reliance on uncertain supplies from infected cows [2].

In 1881, to honor Jenner, Louis Pasteur proposed that the terms should be extended to cover the new protective and safe inoculations being developed at the time. Prior to the introduction of relatively safe vaccination with material from cases of cowpox, smallpox could be prevented by deliberate inoculation of smallpox virus, a far more dangerous method known as variolation. The second generation of vaccines was introduced in the 1880s by Louis Pasteur who developed vaccines for chicken cholera and anthrax, [5] and from the late nineteenth century on, vaccines were considered a matter of national prestige, and first compulsory vaccination laws were passed.

The twentieth century saw the introduction of several successful vaccines, including those against diphtheria, measles, mumps, and rubella. Major achievements included the development of the polio vaccine in the 1950s and the eradication of smallpox during the 1960s and 1970s. As vaccines became more common, many people began taking them for granted. However, vaccines remain elusive for many important diseases, including herpes simplex, malaria, gonorrhea, and HIV.

There are different types of vaccines that have been developed and used in the community. Some of the types include inactivated, attenuated, toxoid, subunit, and conjugate vaccines. Inactivated vaccines contain inactivated, but previously virulent organisms that have been destroyed by chemicals, heat, or radiation [6]. Examples include the polio vaccine,

hepatitis A, and rabies. Attenuated vaccines contain live, active viruses that have been cultivated under conditions that disable their virulent properties, or use closely related but less dangerous antigens to produce a broad immune response. Examples include yellow fever, measles, mumps, rubella, and typhoid. Toxoid vaccines are made from inactivated toxic compounds that cause illness rather than the microorganism. Examples include tetanus and diphtheria. Protein subunit vaccines contain fragments of the inactivated or attenuated microorganism to create an immune response, and these include hepatitis B, HPV.

The efficacy of a vaccine is dependent on a number of factors including the disease itself, the strain of vaccine, whether the vaccination schedule has been properly observed. Assorted factors such as ethnicity, age, and genetic predisposition play a role as well. In 1958, there were 763,094 cases of measles in the United States; 552 deaths resulted [7]. After the introduction of new vaccines, the number of cases dropped to fewer than 150 per year [8]. In early 2008, there were 64 suspected cases of measles. Fifty-four of those infections were associated with importation from another country, although only 13% were actually acquired outside the United States; 63 of the 64 individuals either had been vaccinated against measles or were uncertain whether they had been vaccinated [8].

As long as the majority of people are vaccinated, it is much more difficult for an outbreak of disease to occur, let alone spread. This effect is called *herd immunity*. Polio, which is transmitted only between humans, is targeted by an extensive eradication campaign that has seen endemic polio restricted to only parts of three countries—Afghanistan, Nigeria, and Pakistan [8].

Vaccines also prevent the development of antibiotic resistance. For example, by greatly reducing the incidence of pneumonia caused by *Streptococcus pneumoniae*, vaccine programs have greatly reduced the prevalence of infections resistant to penicillin or other first-line antibiotics [9].

Vaccinations given during childhood are generally safe [10]. Adverse effects, if any, are mostly mild. The rate of side

effects depends on the vaccine in question. Some common side effects include fever, pain around the injection site, and muscle aches [11]. Some individuals may be allergic to particular ingredients in the vaccine. Severe side effects are, however, extremely rare. Varicella vaccine is rarely associated with complications in immunodeficient people and rotavirus vaccines are moderately associated with intussusception [10].

In order to provide the best protection, children are recommended to receive vaccinations as soon as their immune systems are sufficiently developed to respond to particular vaccines, with additional booster shots often required to achieve “full immunity.” This, in turn, has led to the development of complex vaccination schedules. In the United States, the Advisory Committee on Immunization Practices, which recommends schedule additions for the Centers of Disease Control and Prevention, recommends routine vaccination of children against hepatitis A, hepatitis B, polio, mumps, measles, rubella, diphtheria, pertussis, tetanus, HiB, chickenpox, rotavirus, influenza, meningococcal disease, and pneumonia [12]. A large number of vaccines and boosters recommended (up to 24 injections by age 2) have led to problems with achieving full compliance. Various notification systems have been instituted and a number of combination injections are now marketed (e.g., pneumococcal conjugate vaccine and MMRV vaccine) to simplify schedule and improve compliance. Besides recommendations for infant vaccinations and boosters, many specific vaccines are recommended for other ages or for repeated injections throughout life—most commonly for measles, tetanus, influenza, and pneumonia. Pregnant women are often screened for continued resistance to rubella. The human papillomavirus vaccine is recommended in the United States (as of 2011) [13] and the United Kingdom (as of 2009) [14]. Vaccine recommendations for the elderly concentrate on pneumonia and influenza, which are more deadly to that group. Other countries may have vaccines in place to address diseases endemic to that area.

The principal challenge in further vaccine development is economic. Many of the diseases most demanding a vaccine, including HIV, malaria, and tuberculosis, exist principally in

poor countries. Pharmaceutical firms and biotechnology companies have little incentive to develop vaccines for these diseases, because there is little revenue potential. Even in more affluent countries, financial returns are usually minimal, and the financial and other risks are great. Most vaccine development to date has relied on “push” funding by government, universities, and nonprofit organizations [15]. Many vaccines have been highly cost-effective and beneficial for public health. The number of vaccines actually administered has risen dramatically in recent decades. This increase, particularly in the number of different vaccines administered to children before entry into schools, may be due to government mandates and support, rather than an economic incentive.

Many vaccines need preservatives to prevent serious adverse effects such as *Staphylococcus* infection, which in one 1928 incident killed 12 of 21 children inoculated with a diphtheria vaccine that lacked a preservative [16]. Several preservatives are available, including thimerosal, phenoxyethanol, and formaldehyde. Thimerosal is more effective against bacteria, has a better shelf-life, and improves vaccine stability, potency, and safety; but, in the United States, the European Union, and a few other affluent countries, it is no longer used as a preservative in childhood vaccines, as a precautionary measure due to its mercury content [17]. Although controversial claims have been made that thimerosal contributes to autism, no convincing scientific evidence supports these claims [18].

The development of new delivery systems raises the hope of vaccines that are safer and more efficient to deliver and administer. Lines of research include liposomes and *ISCOM* (immune-stimulating complex) [19]. Other notable developments in vaccine delivery technologies have included oral vaccines. An oral polio vaccine, for example, turned out to be effective even when vaccinations were administered by volunteer staff without formal training; the results also demonstrated increased ease and efficiency of administering the vaccines. Effective oral vaccines have many advantages; for example, there is no risk of blood contamination. Vaccines intended for oral administration need not be liquid, and as solids, they commonly are more stable and less prone to

damage or to spoilage by freezing in transport and storage [20]. Other promising, simplified approaches uses microneedles or needle-free delivery via patches [21, 22].

Vaccination policy is another critical element in attaining immunity at the international or global level. Such policies are mostly prerogatives of national authorities and can vary across the world. Some international agencies such as WHO or EU also affect the immunization agenda. In the European Union, for example, The European Commission assists member countries with the coordination of policies and programs and, in April 2018, it proposed a Council Recommendation to strengthen the EU cooperation on vaccine-preventable diseases. The initiative aims to tackle vaccine hesitancy, improve coordination on vaccine procurement, support research and innovation, and strengthen EU cooperation on vaccine-preventable diseases.

EU countries are encouraged to develop and implement national vaccination plans with initiatives to improve coverage and to introduce routine vaccination status checks. In addition, the Commission supports EU countries in maintaining or increasing rates of vaccination by promoting seasonal flu vaccination to at-risk groups. Though European vaccination rates are high overall, measles continues to spread where vaccination rates have declined, the World Health Organization warned in 2016.

In the United States, there is a similar program, with individual states creating their own individual schedules and requirements, and federal bodies, such as CDC, providing recommendations and guidelines. In the rest of the world, similarly, many countries rely on the guidelines and recommendations provided by the WHO, but are free to set their schedules and regulate immunizations as they see fit.

Vaccination in the Context of a Pandemic Outbreak

Vaccination, if available, will likely be a principal part of multifaceted public health response to the future emergence of a

pandemic illness. In addition to other measures designed to respond to and control a pandemic, such as surveillance, communication plans, quarantine, and disease treatment, the deployment of effective vaccines has the biggest potential to protect lives and limit disease spread. Not all disease threats, however, have a corresponding vaccine, and for those that do, there are significant challenges to their successful use in a pandemic.

In the case of influenza viruses, for example, existing vaccines may not be effective against new strains. Though production methods and infrastructure for influenza vaccines are well established, each new influenza strain requires a new vaccine. Thus, any new pandemic influenza vaccine will take about 4–6 months to produce in large quantities [23]. For other newly emerging threats without licensed vaccines, such as SARS, Marburg virus, Nipah virus, and the like, the time required to develop and produce a safe, effective vaccine is unknown and would depend on the nature of the threat and the state of current vaccine research for that threat. In almost all cases, several months would be needed to respond with the first doses of vaccines. Until a safe, effective vaccine was ready, other public health and medical measures, such as social distancing, quarantine, and use of antiviral medications, would need to be employed to try to limit disease spread.

A variety of US federal, state, and local agencies are involved in public health emergency preparedness and response. The US Congress funds the Centers for Disease Control and Prevention's Office of Public Health Preparedness and Response (PHPR) to build and strengthen national preparedness for public health emergencies caused by natural, accidental, or intentional events. Part of the CDC's funding supports the Strategic National Stockpile, which manages stores of vaccines and drugs that may be deployed in national emergencies.

The US Department of Health and Human Services (HHS) includes several offices involved in pandemic and bioterror response. The Office of the Assistant Secretary for Preparedness and Response (ASPR) was created after Hurricane Katrina and is responsible for leadership in

prevention, preparation, and response to the adverse health effects of public health emergencies and disasters. ASPR conducts research and builds federal emergency medical operational capabilities. Within ASPR, the Biomedical Advanced Research and Development Authority (BARDA) is responsible for the development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies [24].

State and local health departments, as well as public and private hospitals and local law enforcement agencies, would also be involved in responding to a pandemic public health emergency. Their roles are outlined in national response plans as well as delineated by organization-specific plans. The US FDA is involved in establishing a research agenda pandemic response, and it controls the pathway to licensure for vaccines, treatments, diagnostic tests, and other tools for responding to biological threats. The regulatory requirements for the licensure of a vaccine are complex and apply to a multistep process of safety, immunogenicity, efficacy testing, and post-licensure surveillance [24].

In situations when a new vaccine is needed quickly, the FDA has developed alternative pathways to licensure. One is an accelerated pathway to approval that might apply in the case of life-threatening disease when a new process will produce a vaccine with a meaningful therapeutic benefit over existing options. In other, more drastic threats, the so-called animal rule might be used—if research toward a vaccine or treatment would necessitate exposing humans to a toxic threat, then animal studies may be sufficient for approval. To date, these two rapid pathways have not been invoked for vaccines.

The US Emergency Use Authorization (EUA) is an option in pandemic response. After a declaration of emergency by the Department of Health and Human Services secretary, this program allows for use of an unapproved medical product (or a product that has been approved but not for the specific use applicable to the situation at hand) that is the best available treatment or prevention for the threat in question. EUAs

were issued for antiviral treatments, a respirator, and a PCR diagnostic test during the 2009 A/H1N1 pandemic [25].

In all pandemic situations in which a vaccine is available or potentially available, a large supply of vaccine would be necessary and would be needed quickly. Currently, the US Strategic National Stockpile includes several types of influenza vaccines, including an H5N1 vaccine [26]. The stockpile also holds millions of doses of other vaccines, antibodies, antiviral medications, and other medical supplies. Should any of these stockpiled vaccines directly relate to an emerging pandemic, they would be deployed. Chances are, however, that an emerging pandemic illness will require a new vaccine and that will require time and resources to develop.

Another complicating factor to pandemic influenza vaccine production involves how the vaccine is made. Since the 1940s, seasonal and pandemic influenza vaccines have been produced in chicken eggs. The virus is introduced in the allantoic fluid of the fertilized egg (this is the fluid that bathes the embryo and yolk sac), and it replicates in the membrane surrounding the fluid. After about 3 days, the virus-containing fluid is harvested from each egg and the rest of the manufacturing process proceeds [27]. Dependence on egg-based vaccine production is, however, problematic even with non-pandemic seasonal influenza vaccine. First, eggs must be available in large quantities when vaccine production is to begin. Any disruption in egg supply—such as disease affecting chickens, or bad weather interfering with the shipping of eggs—can mean a delay in vaccine production. Second, some influenza strains grow more slowly or less robustly than others, which can result in delays or in lower yields of vaccine virus from each egg. Third, it is possible that some viral vaccine strains, given the origin of some influenza viruses in birds, may be toxic to eggs. In that case, egg-based influenza vaccine production methods would be useless. Even under the best of circumstances, the influenza vaccine production can provide vaccines for less than half the global population.

Other promising technologies are being explored for the development of a universal influenza vaccine, which is the

ultimate goal for many influenza vaccine programs, and would serve as a paragon for any future pandemic. Such a vaccine might need to be given only once, rather than every year as with current seasonal vaccines. Such a universal vaccine would ideally provide protection against all, or at least most, of the many strains of influenza capable of making people sick, including future pandemic influenzas. Plant-produced influenza vaccines are in clinical trials and may prove to be a useful alternative to egg- and cell-based vaccines.

In the event of a pandemic, the public and private sectors will mobilize to produce and distribute the vaccine, if one is available, as quickly as possible. The CDC's Advisory Committee on Immunization Practices and other governmental and advisory groups will issue national guidelines prioritizing who should be vaccinated. State and local health departments will develop local modifications to the recommendations as needed. These public health departments will need to make decisions about how to distribute the vaccine to providers within their jurisdictions equitably and efficiently with the goal of reaching the priority groups first.

Methods for distributing the vaccine in a pandemic are outlined in the HHS Pandemic Influenza Plan, which details public sector pandemic response [28]. The plans are designed to provide guidance to public health coordinators, but also to be flexible enough to adapt to the unique conditions of the particular pandemic situation. For example, prior to the 2009 H1N1 pandemic, the most recent pandemic influenza emergency response plans had been based on H5N1 influenza. Planners accordingly projected that healthcare providers would be overwhelmed with caring for the sick and would not have the capacity to administer the vaccine. Distribution plans primarily relied on public entities, such as public health departments and hospitals, to receive the vaccine and vaccinate most of the targeted population. But because 2009 H1N1 influenza did not cause such severe disease, public health authorities realized early on that providers would have the capacity to vaccinate patients. And so vaccine was, for the most part, shipped directly to providers based on the distribution system for the federal Vaccines for Children (VFC) pro-

gram. This required a few changes to usual VFC procedures, most notably to include non-VFC providers, such as retail pharmacies, corporations with occupational health clinics, and non-pediatric healthcare providers, that received and administered vaccines.

Most aspects of vaccine distribution were executed smoothly in the 2009 H1N1 pandemic, especially considering that limited supplies of vaccines had to be allocated fairly and that initial demand was high [29]. The role of certain private vaccine providers attracted media attention and raised some public concern, especially when a few large high-profile private employers received the vaccine before some public entities did. No wrongdoing was alleged, but the situation drew attention to the mechanism of vaccine distribution when a variety of public and private provider types are included. However, public health authorities support the use of private occupational health clinics to vaccinate in a pandemic, since they are able to identify and reach many people in high-priority groups.

Reports by state health departments after the pandemic assessing the H1N1 vaccination program suggest a few areas of improvement in a future pandemic: two issues that surfaced frequently in the reports were the need for accurate supply forecasts to inform vaccine ordering and subsequent distribution, as well as the need for clear communication about priority groups for vaccination [30].

The US federal government conducts periodic simulations of biologic emergencies to assess the effectiveness of the public health response and to identify areas where response needs to be improved.

The European Union currently has a tool to respond to pandemic influenza threats that the United States has not yet employed. Oil-in-water adjuvants have been used in the influenza vaccine in the European Union since 1997 and have an established safety record. But, while plans were made to use adjuvant in the US 2009 H1N1 vaccine, authorities abandoned those and instead approved only unadjuvanted vaccines. Even if the adjuvanted influenza vaccine were released, the US public might be reluctant to take the unfamiliar vaccine, in spite of its safety record in the EU.

Vaccine acquisition, distribution, and uptake issues are substantially different in the developing world. Less wealthy countries typically do not widely use influenza vaccine for a variety of reasons, perhaps the most prominent of which is the need to devote health funds to more pressing concerns. In the event of a deadly influenza pandemic or other disease outbreak requiring mass vaccination, governments of developing countries will face significant challenges such as meeting supply needs, funding vaccine acquisition and ensuring uptake of vaccine in places where influenza vaccination is not commonly practiced.

Under the guidance of the World Health Organization and with the support of various governments, many middle-income and developing countries (Brazil, Egypt, India, Indonesia, Iran, Mexico, Republic of Korea, Romania, Serbia, Thailand, and Viet Nam) have established influenza vaccine manufacturing capacity, or are making progress to develop this capacity. The US and Japanese governments have funded influenza vaccine manufacturing capacity in several countries in Latin America and Asia in an attempt to build readiness in the event of an influenza pandemic. Efforts will help to establish seasonal influenza vaccine production that could then be harnessed in an influenza pandemic. WHO officials note that global seasonal influenza capacity has increased from 350 million doses in 2006 to more than 800 million doses in 2011. Because the seasonal vaccine is trivalent (that is, it includes three strains of influenza virus), pandemic vaccine capacity should be roughly triple that of seasonal influenza capacity—2.4 billion doses. This is still far short of total global need, but it is evident that global influenza vaccine production capacity is increasing.

Mental Health Aspects of Immunization and Vaccination

Several claims about the neuropsychiatric adverse effects of vaccinations have been staked over the past two decades,

stirring considerable public debate and affecting the immunization rates in some communities [31].

One evidence-based study where some temporal relationship was found was a pilot study, from Penn State and Yale University researchers, looking at medical private insurance claims in a large database and comparing children and adolescents aged 6–15 years prior year’s vaccination records with the new diagnosis of a number of neuropsychiatric disorders over 5 years [32].

The temporal association was found for several diagnostic entities, the most relevant one for anorexia nervosa. Children who had been vaccinated within the prior 3 months had an 80% elevated risk of getting a new diagnosis of the eating disorder that has been increasing in recent years, compared to controls. Less pronounced association was found between vaccinations and OCD, tic disorders, and anxiety disorders.

Incidentally, in the control group, children with broken bones were also slightly more likely to have received the influenza vaccine during the previous year, but by a much smaller percentage. Curiously, children with major depression and bipolar disorder were *less* likely to have received the influenza vaccine, but again with smaller hazard ratios.

The researchers found correlations for one vaccine in particular: the influenza vaccine, which was associated with higher rates of OCD, anorexia, anxiety disorder, and tic disorder. The study emphasized that there was no “proof of a causal role” in vaccines for any of the conditions.

A biological explanation for these correlations has not been found, but a potential mechanism could lie in the body’s immune response to vaccines, the study suggested. Cross-reactivity has been explored as one of the hypotheses providing a possible connection. Cross-reactivity occurs when vaccine-induced antibodies react against not only the intended pathogen proteins but also against human proteins. For example, a 2015 study published in *Science Translational Medicine* discovered that antibodies elicited by the pandemic influenza vaccine cross-reacted with a human brain protein—hypocretin receptor 2.

Autoimmunity, in which antibodies attack human proteins, occurs independently of immunization and also may play a role in normal brain development and in early-onset psychiatric disorders [33]. Some authors (Leckman) hypothesize that, if children were experiencing inflammation—a process that promotes autoimmunity—at the time of vaccination, the combination of inflammation and vaccination could have deleterious effects on brain development [34].

In modern society, any potentially serious adverse event attributed to vaccination is likely to be snapped up by the media, particularly newspapers and television, as it appeals to the emotions of the public. Thus, for example, considerable attention was devoted to the publication of Andrew Wakefield's article, which linked measles vaccination to pervasive developmental disorders and nonspecific colitis, [35] and to the case of Heather Whitestone, who was elected Miss America despite her deafness, which had erroneously been attributed to the diphtheria, tetanus, and pertussis vaccine [36]. The widespread news of the alleged adverse events of vaccination has helped to create the "urban myth" that vaccines cause serious neurological disorders and has boosted anti-vaccination associations. These movements and associations, however, are nothing new. They can be traced back to the nineteenth century, with the foundation of the National Anti-Vaccination League in 1896 in Britain and the Anti-Vaccination Society of America in 1879 in the United States were established. By the end of the twentieth century, opposition to vaccinations had strengthened in most developed countries because diseases preventable by vaccinations had become increasingly rare. Thus, with regard to the subject of vaccinations, ethical, social, religious, and legal issues cannot be ignored.

When Mumps/Measles/Rubella (MMR) vaccines are concerned, the *British Medical Journal* defined the main study that linked these vaccines to autism as a "deliberate fraud" [37]. This conclusion resulted from an investigation conducted by the investigative journalist Brian Deer into the research originally published in 1998 by the journal the

Lancet, before being withdrawn in February 2010. The paper had associated the administration of MMR vaccine with a new syndrome characterized by autism and ileal lymphoid hyperplasia associated with nonspecific colitis. According to Fiona Godlee, the editor in chief of the BMJ, the article by Wakefield “was based not on bad science but on a deliberate fraud.” The US Institute of Medicine (IOM) also concluded that “The evidence favors rejection of a causal relationship between MMR vaccine and autism” [38].

When the relationship between vaccines and schizophrenia is concerned, no epidemiological studies have shown the existence of a causal link. In addition, Short et al. have demonstrated that babies born to rhesus monkeys infected with the flu virus during pregnancy have both significantly smaller brains than normal and other brain abnormalities seen in schizophrenia [39]. These results are consistent with the findings of Mednick et al. [40], who reported an increased risk of schizophrenia in persons who had been in the fetal stage in 1957—the time of the pandemic known as the “Asian” pandemic—and with the study by Byrne et al. [41] Vaccination should therefore be considered a valuable tool, particularly during pregnancy, in that it may also help reduce schizophrenia. Indeed, the CDC recommends influenza vaccination in any period of gestation.

Acceptance of vaccines is a major driver of uptake, along with issues of access, affordability, and awareness. In the past decade, parents have been questioning the need for and safety of vaccines, and as a result, vaccination rates have fallen to dangerously low levels in certain communities. The effects of vaccine hesitancy are widespread. Community pediatricians who interact regularly with vaccine-hesitant parents report a higher level of burnout and lower levels of job satisfaction. Vaccine hesitancy has been linked to increased emergency department use, morbidity, and mortality. Nonacceptance of vaccination is a phenomenon that concerns global agencies. In 2012, a World Health Organization (WHO), a working group, was formed to address vaccine hesitancy and its implications [42]. Vaccine hesitancy is best

viewed on a spectrum of parental beliefs and concerns. From the perspective of medical providers, vaccine hesitancy is demonstrated by increased requests for alternative vaccination schedules or by altogether postponing or declining vaccines. The percentage of parents who refuse all vaccines is small in comparison to alternative schedules.

Overall childhood vaccination rates remain relatively high in the United States. Rates of undervaccination in children younger than 2 continue to rise. In Oregon, for example, rates of alternative schedules have quadrupled. Poland and Jacobson point out that “since the 18th century, fear and mistrust have arisen every time a new vaccine has been introduced” [43]. Even amidst the deadly smallpox epidemic, increasing resistance to smallpox vaccine led to mandated vaccination in the United Kingdom. The United States dealt with its own opposition to mandatory smallpox vaccinations, eventually leading to Supreme Court Case *Jacobson v. Massachusetts*, 197 U.S. 1 (1905).

There is a broad spectrum of individuals who choose not to have themselves or their children vaccinated. They are most commonly referred to as “vaxxers” or “vaccine deniers.” These range from individuals who are solidly anti-vaccine, often termed “vaccine rejectors” (VRj), to those who may accept or even advocate for most vaccines but have concerns over 1 or more vaccines [44]. Hagood and Mintzer Herlihy suggested a 3-category model, characterizing individuals as vaccine rejectors (VRj), vaccine-resistant (VR), or vaccine-hesitant (VH) [45]. Vaccine rejectors are those who are “unyieldingly entrenched in their refusal to consider vaccine information,” prone to conspiracy theory thinking, and may eschew traditional medical providers altogether in favor of “complementary” or “alternative” medical practices. The VRs are those who may currently reject vaccination but are still willing to consider information, and they have a lower incidence of belief in conspiracy theories than VRj individuals. The VH individuals tend to have anxiety about vaccinations but are not committed to vaccine refusal. These groups correspond roughly to the “refusers,” “late/selective vaccinators,” and “the hesitant.” Interventions targeted at changing minds or attitudes to

increase vaccine acceptance need to take into consideration the wide spectrum of beliefs regarding vaccines to be properly tailored to the individual, rather than assuming that all individuals with vaccine concerns have a single belief system.

The reasons for the increasing prevalence of vaccine hesitancy are numerous. Vaccines have become, as many have described, “victims of their own success.” An article in *The Economist* further argues that “the risks of the vaccine are visible; its benefits are not” [46]. Vaccines have been seen as so highly effective and are no longer seen as necessary by many parents, because the diseases they prevent are virtually unknown to the general population. As rates of vaccine-preventable diseases dwindle, caregivers may grow to fear the vaccine more than the disease it prevents, thus leading to decreased vaccination rates [47].

Additionally, highly publicized anti-vaccine arguments have caused a tremendous public backlash against vaccines. The best-known argument originated in an article in *The Lancet*, in which Wakefield falsified data to establish a link between MMR vaccine and autism. Although the article was later retracted, and Wakefield’s license was removed, the damage to the public was already done. There has been no shortage of celebrities, including Jenny McCarthy, Alicia Silverstone, Jim Carey, Kirstie Alley, and President Donald Trump who have expressed concern regarding vaccines, not directly opposing vaccines. As concerns for vaccines rise, there is growing popular interest in alternative remedies and products which has led many parents to question toxins in vaccines. Other parental concerns include multiple needlesticks, and too many vaccines for the immune system to handle [47].

Trust in institutional medicine has become lower than ever before, and medical providers’ relationships with patients are changing. More parents have come to value and expect a shared decision-making model with their pediatrician. These cultural shifts have occurred in the context of a vaccine schedule that has become more crowded with a substantial increase in the number of vaccines given to a child before age 2 since 1994. Parental concerns regarding the number of

vaccines received at a single visit is a well-documented reason for delaying or refusing vaccines [47].

The Internet has played a pivotal role in enhancing parental concerns over vaccines in the last decade as well. Even if parents attempt to educate themselves about the risks and benefits of vaccines, they are often left feeling confused and frustrated due to mixed messages presented on social media and Internet sources. The Internet is filled with blogs, websites, and articles touting the dangers of vaccines, leaving parents uncertain of which sources to trust. A search of the term *vaccination* on the Internet can lead to more anti-vaccination materials than pro-vaccination materials, and even returns carefully crafted YouTube videos as the top query results [48].

The proportion of parents who are vaccine-hesitant varies substantially across the United States and geographic clustering of nonmedical vaccination exemptions has been well documented. Although this clustering effect is not entirely understood, one may hypothesize that the culture of a local population, influenced by characteristics such as socioeconomic status, race, ethnicity, and education level, may play a role. Data from the National Immunization Survey from 1995 to 2001 demonstrated that unvaccinated children were more likely to be white, to have a married, college-educated mother, to belong to higher income households, compared to undervaccinated children [47].

The well-publicized 2014–2015 Disneyland measles outbreak was a stark reminder of the direct influence of vaccine hesitancy and refusal. However, we have seen the influence over the decades in the United States. In a nationally representative survey, 48% of pediatricians and family doctors reported spending less than 10 minutes discussing vaccines with parents who had concerns about vaccines. Considering that the average well-child visit is 18 minutes long, families with concerns about vaccines are likely missing out on other anticipatory guidance [49].

Glanz et al. have done extensive work on direct risks of vaccine refusal on actual vaccination rates and the incidence of disease. Children whose parents refuse pertussis-containing

vaccines are 23 times more likely to be diagnosed with pertussis, children whose parents refuse varicella vaccine are nine times more likely to be diagnosed with chicken pox, and children whose parents refused the pneumococcal vaccine are 6 times more likely to be hospitalized for invasive pneumococcal disease or lobar pneumonia. Numerous studies have shown that states and communities with higher rates of vaccine exemptions are more prone to outbreaks of vaccine-preventable diseases such as measles, mumps, and pertussis [50].

One of the factors that interrelate with individuals' vaccine rejection is the use of complementary and alternative medicine (CAM) Eve Dube et al. 2013. Katie Attwell et al. found with 20 parents who had refused or delayed some of or all of their children's vaccines had a "do it yourself ethic" and personal agency enhanced by CAM use [51]. These parents viewed vaccines as being toxic, profit motive, and embraced CAM as a protective strategy for immune systems before, during, and after an illness. Parents were inclined to pursue CAM care due to their upbringings, or recommendations from within their social community, where vaccine questioning was prominent. Parents or their children experienced specific health problems (not necessarily vaccine related), whereby Western Medicine was viewed "to hit a wall," and CAM filled the gap, generating questions about the vaccines. Parents who prefer CAM, an approach sometimes also euphemistically called "health-promoting" or "salutogenic," tend to cluster in certain parts of the United States, such as rural northern Idaho, or urban pockets of Seattle, Spokane, Portland in the Pacific Northwest, as well as some other urban regions in the country [52].

Immunization hesitancy can also be identified among some religiously conservative populations in the United States that turned out to be receptive audiences for anti-vaccine social media activists. In 2017, after being targeted with misinformation about vaccine risks which led to lower immunization rates, Somali-Minnesotan community experienced a measles outbreak [53]. In 2018, a small measles outbreak was recorded among children in Orthodox Jewish communities in and around New York City [54].

There have been extensive efforts to develop strategies to address vaccine-hesitant parents. To date, there are a few effective evidence-based strategies for communication with parents or for addressing vaccine hesitancy at the community level. There is robust literature showing that simply providing information often does not lead to people changing their views and may even create a dynamic in which a patient or parent is actually less receptive to information a provider may impart [55]. It is clear that medical providers play a crucial role in influencing parents' decision to vaccinate. A recent Cochrane Review revealed that parents wanted more, unbiased vaccine information than they had been receiving. The review also showed that poor communication and poor relationships with providers had the ability to negatively influence vaccine decisions. Building a trusting relationship with parents and patients can promote vaccine acceptance and also influence other important aspects of care [56].

To a rational healthcare provider, particularly in times of emergency, vaccine hesitancy may seem irrational and non-sensical. As irrational, and unfounded as it may be, it must not be dismissed. Failure to address vaccine hesitancy may as well translate into a catastrophic failure to immunize, even in times of dire need. It is a serious issue that needs to be addressed in a serious manner.

There is no single intervention strategy that addresses all instances of vaccine hesitancy. Based on the Systematic Review of Strategies to Address Vaccine Hesitancy, the most effective interventions addressing the outcome of vaccination uptake are multicomponent interventions versus single component. These interventions should be dialogue-based and directly targeted at the unvaccinated or undervaccinated populations [57].

The interventions should address the specific determinants underlying vaccine hesitancy, which may include the following:

- Engagement of religious or other influential leaders to promote vaccination in the community
- Social mobilization
- Improving convenience and access to vaccination
- Mandating vaccination/sanctions for non-vaccination

- Employing reminder and follow-up
- Communications training for HCW
- Non-financial incentives
- Aim to increase knowledge, awareness about vaccination

Motivational interviewing has been a particularly helpful approach with hesitant parents. Motivational interviewing is the process of engaging in open-ended discussion with an individual to assess an individual's readiness to change with the goal of drawing upon the person's own desire and motivation to change, rather than the provider's motivation. In the 2016 Clinical Report on Countering Vaccine Hesitancy by the American Academy of Pediatrics, motivational interviewing is listed as a potential communication technique that may be helpful as pediatricians discuss vaccines with hesitant parents [58]. In a recent cluster randomized trial, motivational interviewing was shown to be effective at increasing uptake of HPV vaccine [59].

Immunization hesitancy represents a considerable and growing obstacle toward achieving appropriate levels of immunization under everyday circumstances. It is virtually impossible to anticipate in what manner and to what extent immunization hesitancy would interfere with immunization rollout during a pandemic. In addition to paramount legal, ethical, and logistical challenges to mounting a response to a pandemic outbreak, immunization hesitancy may seem irrational, unnecessary, and capricious. In case of an outbreak, however, it will not be trivial, and anyone who fails to take it seriously will jeopardize any success in fighting a deadly pandemic outbreak.

References

1. World Health Organization. Global vaccine action plan 2011–2020. Geneva; 2012.
2. Baxby D. Edward Jenner's inquiry; a bicentenary analysis. *Vaccine*. 1999;17(4):301–7.

3. Stern AM, Markel H. The history of vaccines and immunization: familiar patterns, new challenges. *Health Aff.* 2005;24(3):611–21.
4. Dunn PM. Dr Edward Jenner (1749–1823) of Berkeley, and vaccination against smallpox. *Arch Dis Child Fetal Neonatal Ed.* 1996;74(1):F77–8.
5. Pasteur L. Address on the germ theory. *Lancet.* 1881;118(3024):271–2.
6. Sinha JK, Bhattacharya S. A text book of immunology (Google book preview). Academic Publishers. p. 318. ISBN 978-81-89781-09-5. Retrieved January 09, 2014.
7. Orenstein WA, Papania MJ, Wharton ME. Measles elimination in the United States. *J Infect Dis.* 2004;189(Suppl 1):S1–3.
8. Measles—United States, January 1 – April 25, 2008. *Morb Mortal Wkly Rep.* 2008;57(18):494–8.
9. Abbott A. Vaccines promoted as key to stamping out drug-resistant microbes. 2017 July 19. Immunization can stop resistant infections before they get started, say scientists from industry and academia.
10. Maglione MA, Das L, Raaen L, Smith A, Chari R, Newberry S, Shanman R, Perry T, Goetz MB, Gidengil C. Safety of vaccines used for routine immunization of US children: a systematic review. *Pediatrics.* 2014;134(2):325–37.
11. Possible Side-effects from Vaccines. Centers for disease control and prevention. Retrieved February 24, 2014.
12. ACIP Vaccine Recommendations Home Page. CDC. 2013 Nov 15. Retrieved January 10, 2014.
13. HPV Vaccine Safety. Centers for Disease Control and Prevention (CDC). 2013 Dec 20. Retrieved January 10, 2014.
14. HPV vaccine in the clear. NHS choices. 2009 Oct 02. Retrieved January 10, 2014.
15. Olesen OF, Lonnoth A, Mulligan B. Human vaccine research in the European Union. *Vaccine.* 2009;27(5):640–5.
16. Thimerosal in vaccines. Center for Biologics Evaluation and Research, U.S. Food and Drug Administration. 2007 Sept 06. Retrieved October 01, 2007.
17. Bigham M, Copes R. Thiomersal in vaccines: balancing the risk of adverse effects with the risk of vaccine-preventable disease. *Drug Saf.* 2005;28(2):89–101.
18. Offit PA. Thimerosal and vaccines—a cautionary tale. *N Engl J Med.* 2007;357(13):1278–9.
19. Morein B, Hu KF, Abusugra I. Current status and potential application of ISCOMs in veterinary medicine. *Adv Drug Deliv Rev.* 2004;56(10):1367–82.

20. Khan FA. Biotechnology fundamentals. CRC Press; 2011 Sept 20. p. 270. ISBN 9781439820094.
21. Giudice EL, Campbell JD. Needle-free vaccine delivery. *Adv Drug Deliv Rev.* 2006;58(1):68–89.
22. Australian scientists develop ‘needle-free’ vaccination. *The Sydney Morning Herald.* 2013 August 18.
23. http://www.who.int/csr/disease/swineflu/notes/h1n1_vaccine_20090806/en/
24. <https://www.historyofvaccines.org/content/articles/vaccines-pandemic-threats>
25. <https://www.cdc.gov/h1n1flu/cdcresponse.htm>
26. <http://www.cidrap.umn.edu/news-perspective/2008/04/hhs-adds-h5n1-clade-22-vaccine-stockpile>
27. <https://www.historyofvaccines.org/content/blog/us-cell-line-facility-produce-pandemic-influenza-vaccine>
28. <https://www.cdc.gov/flu/pandemic-resources/planning-preparedness/national-strategy-planning.html>
29. Huang H-C. Equalizing access to pandemic influenza vaccines through optimal allocation to public health distribution points. *PLoS One.* 2017;12(8):e0182720.
30. <https://www.hsdl.org/?view&did=714799>
31. Dubé E, Laberge C, Guay M, Bramadat P, Roy R, Bettinger J. Vaccine hesitancy: an overview. *Hum Vaccin Immunother.* 2013;9(8):1763–73.
32. Leslie DL, Kobre RA, Richmand BJ, Aktan Guloksuz S, Leckman JF. Temporal association of certain neuropsychiatric disorders following vaccination of children and adolescents: a pilot case–control study. *Front Psych.* 2017;8:3. <https://doi.org/10.3389/fpsyg.2017.00003>.
33. Raevuori A, Haukka J, Vaarala O, Suvisaari JM, Gissler M, Grainger M, et al. The increased risk for autoimmune diseases in patients with eating disorders. *PLoS One.* 2014;9(8):e104845. <https://doi.org/10.1371/journal.pone.0104845>.
34. Leckman JF, Vaccarino FM. Editorial commentary: “what does immunology have to do with brain development and neuropsychiatric disorders?” *Brain Res.* 2015;1617:1–6. <https://doi.org/10.1016/j.brainres.2014.09.052>.
35. Wakefield AJ, Murch SH, Anthony A, Linnell J, Casson DM, Malik M, Berelowitz M, Dhillon AP, Thomson MA, Harvey P, Valentine A, Davies SE, Walker-Smith JA. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet.* 1998;351(9103):637–41.

36. Gasparini R, Panatto D, Lai PL, Amicizia D. The “urban myth” of the association between neurological disorders and vaccinations. *J Prev Med Hyg.* 2015;56(1):E1–8.
37. Godlee F, Smith J, Marcovitch H. Wakefield’s article linking MMR vaccine and autism was fraudulent. *BMJ.* 2011;342:c7452.
38. IOM (Institute of Medicine). Adverse effects of vaccines: evidence and causality. Washington, DC: The National Academies Press; 2011.
39. Short SJ, Lubach GR, Karasin AI, Olsen CW, Styner M, Knickmeyer RC, Gilmore JH, et al. Maternal influenza infection during pregnancy impacts postnatal brain development in the rhesus monkey. *Biol Psychiatry.* 2010;6:965–73.
40. Mednick SA, Machon RA, Huttunen MO, et al. Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry.* 1988;45:189–92.
41. Byrne M, Agerbo E, Bennedsen B, et al. Obstetric conditions and risk of first admission with schizophrenia: a Danish national register based study. *Schizophr Res.* 2007;97:51–9.
42. https://www.who.int/immunization/sage/meetings/2014/october/SAGE_working_group_revised_report_vaccine_hesitancy.pdf
43. Poland GA, Jacobson RM. The age-old struggle against the antivaccinationists. *N Engl J Med.* 2011;364(2):97–9. <https://doi.org/10.1056/NEJMp1010594>.
44. Tara CS. Vaccine rejection and hesitancy: a review and call to action. *Open Forum Infect Dis.* 2017;4(3). <https://doi.org/10.1093/ofid/ofx146>.
45. Hagood EA, Mintzer Herlihy S. Addressing heterogeneous parental concerns about vaccination with a multiple-source model: a parent and educator perspective. *Hum Vaccin Immunother.* 2013;9(8):1790–4.
46. The needle and the damage done. *The Economist.* 2002. <http://www.economist.com/node/987833?zid=318&ah=ac379c09c1c3fb67e0e8fd1964d5247f>. Accessed Oct 2018.
47. McClure CC, Cataldi J, T’Oleary S. Vaccine hesitancy, where we are and where we are going. *Clin Ther.* 2017;39:1550–62.
48. Wakefield MA, Loken B, Hornik RC. Use of mass media campaigns to change health behaviour. *Lancet (London, England).* 2010;376(9748):1261–71.
49. Kempe A, Daley MF, McCauley MM, Crane LA, Suh CA, Kennedy AM, Basket MM, Stokley SK, Dong F, Babbel CI, Seewald LA, Dickinson LM. Prevalence of parental concerns

- about childhood vaccines: the experience of primary care physicians. *Am J Prev Med.* 2011;40(5):548–55.
50. Phadke VK, Bednarczyk RA, Salmon DA, Omer SB. Association between vaccine refusal and vaccine-preventable diseases in the United States: a review of measles and pertussis. *JAMA.* 2016;315(11):1149–58.
 51. Attwell K, Ward P, Meyer SB, Rokkas PJ, Leask J. “Do-it-yourself”: vaccine rejection and complementary and alternative medicine (CAM). *Soc Sci Med.* 2017;196. <https://doi.org/10.1016/j.socscimed.2017.11.022>.
 52. Olive JK, Hotez PJ, Damania A, Nolan MS. The state of the antivaccine movement in the United States: a focused examination of nonmedical exemptions in states and counties. *PLoS Med.* 2018;15(6):e1002578. <https://doi.org/10.1371/journal.pmed.1002578>.
 53. Hall V, Banerjee E, Kenyon C, et al. Measles outbreak—Minnesota April–may 2017. *MMWR Morb Mortal Wkly Rep.* 2017;66:713–7. <https://doi.org/10.15585/mmwr.mm6627a1>.
 54. Levine A. *NY Times.* New York Today: Measles in Brooklyn. Oct 22, 2018.
 55. National Academies of Sciences, Engineering, and Medicine. In: Gadsden VL, Ford M, Breiner H, editors. *Parenting matters: supporting parents of children ages 0–8.* Washington, DC: The National Academies Press; 2016. <https://doi.org/10.17226/21868>.
 56. Ames HM, Glenton C, Lewin S. Parents’ and informal caregivers’ views and experiences of communication about routine childhood vaccination: a synthesis of qualitative evidence. *Cochrane Database Syst Rev.* 2017;2(2):CD011787. d.
 57. http://www.who.int/immunization/programmes_systems/vaccine_hesitancy/en/.
 58. Leask J, Kinnersley P, Jackson C, Cheater F, Bedford H, Rowles G. Communicating with parents about vaccination: a framework for health professionals. *BMC Pediatr.* 2012;12:154. <https://doi.org/10.1186/1471-2431-12-154>.
 59. <https://www.pm360online.com/motivational-interviewing-for-hpv-vaccination-well-accepted-by-doctors/>.