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OVERVIEW OF KEY LEGAL, POLITICAL, AND SOCIAL CHALLENGES FACING GLOBAL VACCINATION EFFORTS

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Despite the proven safety and effectiveness of vaccines, they are not utilized as widely as they should be. This article provides a high-level overview of five key challenges affecting the global vaccine uptake. First, availability is affected by the research costs and counterfeit vaccines. Second, accessibility is affected by distribution not being proportionate to need, and by poor infrastructure. Third, affordability is affected by intellectual property protections and costs of manufacturing and distribution. Fourth, appropriateness is affected by the way vaccine effectiveness varies and presents risks for immunocompromised populations. Fifth, acceptability is affected by controversies regarding risks and cultural objections.

Malgré l'innocuité et l'efficacité prouvées des vaccins, ils ne sont pas utilisés aussi largement qu'ils le devraient. Cet article fournit un aperçu de haut niveau de cinq défis clés affectant l'adoption mondiale de vaccins. Premièrement, la disponibilité est affectée par les coûts de recherche et les vaccins contrefaits. Deuxièmement, l'accessibilité est affectée par une distribution non proportionnée aux besoins et par une infrastructure médiocre. Troisièmement, l'abordabilité est affectée par les protections de la propriété intellectuelle et les coûts de fabrication et de distribution. Quatrièmement, la pertinence est affectée par la façon dont l'efficacité du vaccin varie et présente des risques pour les populations immunodéprimées. Cinquièmement, l'acceptabilité est affectée par les controverses concernant les risques et les objections culturelles.

INTRODUCTION

Hailed as one of the greatest public health achievements of the 20th century (Centers for Disease Control and Prevention, *Ten Great Public Health Achievements*), childhood vaccinations have prevented more than 100 million cases of serious disease from 1924 to 2012 (Gostin). Despite the proven safety and effectiveness of vaccines, they are not utilized as widely as they should be. Most recently, uptake concerns have garnered renewed media interest in response to the 2019 measles outbreaks in the United States—764 individual cases reported in 23 states from January 1 to May 3, 2019 (Centers for Disease Control and Prevention, *Measles Cases and Outbreaks*). This is the greatest number of measles cases reported in the US since the elimination of the virus in 2000 (Centers for Disease Control and Prevention, *Measles Cases and Outbreaks*).

There are numerous legal, political, and social factors that contribute to the limited uptake of vaccinations worldwide. This article provides a high-level overview of key challenges facing global vaccination uptake, utilizing the "5A Framework" of (1) Availability, (2) Accessibility, (3) Affordability, (4) Appropriateness, and (5) Acceptability to systematically organize the issues (Jackson). *Availability* is affected by the costliness of research and counterfeit vaccines. *Accessibility* is affected by distribution not being proportionate to need and poor infrastructure in many areas of the world. *Affordability* is affected by international intellectual property protections and costs of manufacturing and distribution. *Appropriateness* is affected by the way vaccine effectiveness varies and presents risks for immunocompromised populations. Finally, *acceptability* is affected by controversies regarding risks and benefits and cultural objections.

AVAILABILITY

Availability questions the existence of vaccines in an accessible location and inadequate supply (Jackson). Vaccine availability is influenced by vaccine development (i.e., funding for certain diseases and clinical challenges in research) and by vaccine

distribution (i.e., management of health systems, monitoring, and supervision). Both vaccine development and production have significantly increased since the early 2000s. Major challenges to vaccine availability include barriers to developing cost-effective vaccines, such as immunological complications, market factors, and high research costs.

Vaccines represent one of the fastest growing sectors of industry, having almost tripled since 2000, and were valued at over US$24 billion in global revenue in 2013 (Kaddar). This trend will most likely continue, as the global market for vaccines is projected to reach US$100 billion by 2025 (Kaddar). Most of this expansion is due to the development of newer, more costly vaccines, accounting for more than half of the total value of vaccine sales worldwide (Maurice and Davey). Furthermore, demand for existing vaccines has grown in response to well-funded global initiatives pushing to eradicate polio and reduce the burden of measles and tetanus (Maurice and Davey). Finally, the availability of vaccines can differ between high- and low- or middle-income countries both in terms of the combination of vaccines licensed and vaccine types (Smith et al.).

Despite growth in the global vaccine market, many challenges to producing cost-effective vaccines remain. For example, a variety of immunological complications have caused considerable barriers to the vaccine development process. Among them are a deficiency in the availability of the antibodies that confer protection against specific infections, significant immunological differences between animal test models and humans, and the possibility of less responsive immune systems in the real world (Oyston and Robinson). Vaccines against viruses with high mutation rates and multiple variants, such as the human immunodeficiency virus (HIV), may not be effective in destroying the microbe as resistant viral variants rapidly evolve (Zhou et al.). These immunological complications can discourage research and development endeavours.

Vaccine research and development has also proven to be extremely costly, estimated at about US$1-2 billion per vaccine (Watson and de Goër). This high cost is mostly due to the high failure rate, as only 1

in 5,000-10,000 vaccine formulations will receive approval from government regulatory agencies like the US Food and Drug Administration and Health Canada (Oyston and Robinson; Light et al.). While the high failure rate itself acts as a barrier to research and development, additional market factors deepen costs. Pharmaceutical companies, for instance, have little economic incentive to develop vaccines for common infections faced by poorer populations in developing countries, especially for tropical diseases such as hookworm infections and Chagas disease (Oyston and Robinson). This is because most medical research and development is incentivized by patents, which typically give the patent-holder a 20-year government-enforced monopoly on the sale of resulting products that allows them to charge high prices, recoup their research investments, and earn profit before other vaccine producers enter that market. Even costs associated with the production of generic vaccines are markedly different from those of the comparable market of generic medicines, as clinical testing must be repeated before the production of generic vaccines, but not medicines (Ridley et al.). The impact of cost on vaccine availability can be demonstrated by a 2016 study from the United States, which found that lower vaccine prices were associated with higher probabilities of vaccine shortages (Ridley et al.). Availability and affordability are both challenged by the fact that there has been an overall decrease in the number of vaccine companies investing in research and development, from 14 in the 1990s to 4 in 2016 (Watson and de Goër).

If a vaccine manufacturer is willing to undertake the costs associated with vaccine production, there remain other availability concerns, such as the time between discovery and distribution, and the need for region-specific research. Pfizer, one of the largest biopharmaceutical companies, reported that each new vaccine generally requires its own exclusive manufacturing site, which can take roughly 5 years to build, with an added 2 years before distribution (Ridley et al.). Research targeted to developing countries is needed, not just for vaccines that are only required in developing countries, but also for vaccines already researched and implemented in developed countries, as clinical efficacy data from developed countries is likely not representative of results in developing countries. Research has shown that the trivalent polio vac-

cine has a per-dose efficacy of over 50% in Europe and North America, but only 21% in India (Serazin et al.). These needs in developing countries are further challenged by limited medical research and regulatory capacity, which make it difficult to conduct rigorous and ethical clinical trials (Oyston and Robinson).

Those who are perhaps seeking to take advantage of these availability concerns have created a growing problem: the proliferation of counterfeit vaccines, particularly in developing countries. This includes instances where unauthorized versions of a vaccine are sold illegally by non-patent-holders (thereby undercutting legitimate companies' incentives for developing vaccines) and, more importantly, where fake or substandard products are passed-off as genuine, thereby denying immunological protection, potentially causing harm, and in turn decreasing the acceptability of vaccines overall. Counterfeit vaccines can create dangerous global health crises ; a prime instance was the 1995 Nigerian meningitis epidemic, where 50,000 people were administered fake vaccines, resulting in 2,500 deaths (World Health Organization, *General Information on Counterfeit Medicines*).

ACCESSIBILITY

While vaccine availability is about the existence of a vaccine for a population, accessibility refers to the ease and convenience of obtaining and using it (Jackson). Vaccine distribution systems vary from country to country, especially between developed and developing countries. Disparities in accessibility are also widespread between countries, both with respect to the types of vaccines used as well as with how and by whom they are delivered. Additional important challenges include phobias of conventional injections, as well as the challenge of cold-storing vaccines in remote areas of many developing countries (also known as the cold chain).[1] Vaccines are also not always effectively distributed to those who are in most need. The World Health Organization (WHO) has projected improving global vaccine distribution could save an additional 1.5 million lives each year (World Health Organization, *World Immunization Week 2016*).

Government involvement with vaccine distribution is different in each country. In most developed countries, distribution of a specific vaccine formulation depends on licensure of the vaccine, which can either occur directly in the country of use given sufficiently developed regulatory authorities, or in the manufacturing country, in which case the country of use will review and approve it (Smith et al.). For developing countries that may not have adequate licensing/regulatory authorities, vaccines are often obtained by United Nations agencies and their partners, such as Gavi, the Vaccine Alliance (Gavi), who ensure that the vaccine meets WHO pre-qualification standards (Smith et al.). However, there remains inadequate access to essential vaccines (Oyston and Robinson). The WHO estimates that nearly 1 in every 5 children worldwide lacks a routine immunization that could prevent diseases such as diphtheria, pertussis, and tetanus. Furthermore, while 160 vaccine introductions have been made in 99 countries between 2010 and 2015, global vaccination coverage has only increased by a mere 1% (Strategic Advisory Group of Experts on Immunization). Manufacturing capacities insufficient to satisfy global vaccine demand and the absence of specific purchasing and supply agreements for new vaccines leave novel products inaccessible to many people in developing countries for at least another 20 to 30 years (Smith et al.).

Barriers to vaccine accessibility in developing countries include relatively weaker health systems, overloaded infrastructure, limited logistical support systems, and insufficient understanding about the importance of vaccines (Maurice and Davey). In developed countries, vaccines are usually accessible via primary-care physicians, pharmacists, or community health clinics who either order them directly from a distributor or are supplied by a local public health agency (Smith et al.; Hattingh et al.). Developed countries are usually better able to provide vaccine access to at-risk groups through social insurance and/or subsidization, resulting in more comprehensive vaccination coverage. Frequently, there are routine vaccine programs for both children and adolescents (Centers for Disease Control and Prevention, *National Center for Health Statistics*). Unlike most medicines, it is particularly important to achieve high vaccine uptake rates for the purpose of herd immunity, the phenomenon by which non-immune persons are awarded

some form of protection from a disease as a result of a large proportion of the population being vaccinated against that disease (Fine et al.). This effect indirectly controls and mitigates disease outbreaks, as vaccinated individuals will act as barriers to the spread of disease, resulting in the gradual elimination of the disease from a population after a high uptake threshold is achieved (Merrill; Somerville et al.). Achieving herd immunity is of particular importance for the many people who cannot get vaccinated themselves, including those who are pregnant, immunodeficient, or allergic to vaccines, and for those who lack access to vaccines for reasons such as poverty (Centers for Disease Control and Prevention, *Who Should Not Get Vaccinated*).

While there are challenges to vaccine accessibility at the systems level, there are also delivery challenges at the individual level. The pain and anxiety commonly associated with needle injections act as significant uptake barriers, as they are often a source of distress for children, their parents, and even those administering the injections (Taddio et al.). If not addressed early on, studies have shown that this pain can lead to much pre-procedural anxiety (Taddio et al.). In fact, up to 25% of adults report a fear of needles—most of which develop in childhood—and 10% of the population avoids needles and needle-related procedures as a result (Taddio et al.). Novel vaccine delivery systems are being developed in the hopes of bolstering vaccine distribution and uptake. Potential delivery substitutes that can address these issues include aerosol formulations that are sprayed through the nose (such as those already available for the influenza vaccine), as well as adhesive patches, drops under the tongue, and oral pills, all of which are being investigated (Maurice and Davey). These alternatives show additional promise as they are likely to not require specialized cold-chain storage, in turn increasing their cost effectiveness (Birkhoff et al.).

Paradoxically, a significant problem facing vaccine distribution in developed countries is overstock in supply. Overstocking of vaccines increases cold-storage costs and generates waste, both of which are further exacerbated when volume flow increases, as it has since 2000 (World Health Organization, "Vaccination"). The cold chain is a method of storing and transporting vaccines whereby vaccines are kept between 2° and 8°C, which is costly and logistically challenging

to maintain, particularly in difficult to access areas (World Health Organization, "Controlled Temperature Chain"). While new vaccines are often in single- or two-dose packages, they also cost more per dosage and require up to five times more cold-chain space per dose when compared with the traditional Expanded Program on Immunization (EPI) vaccines that come in 10 and 20-dose vials (World Health Organization, "Vaccination"). Some countries are forced to postpone the introduction of certain vaccines because they do not have the capacity to store them (World Health Organization, "Vaccination"). Alternatives to cold-chain storage are being investigated to address these concerns, such as the controlled temperature chain method, which allows specified vaccines to be transported at temperatures up to 40°C for a number of days (World Health Organization, "Controlled Temperature Chain"). Research studying the implementation of this technique for the meningitis A vaccine has shown low vaccine waste as well as high satisfaction and desire for increased implementation among vaccinators (Zipursky et al.). While promising, the controlled temperature chain remains in the early stages of implementation, and research is required to determine its viability and benefits for different vaccines.

Given the large disparities in access between developed and developing countries, as well as the lack of market incentives for companies to develop vaccines against diseases that primarily affect marginalized populations, it is important to consider whether global society is effectively distributing limited vaccine resources to those most in need. Various theoretical, ethical, and mathematical models have been created with the goal of ethically distributing vaccines for specific diseases under the egalitarian principle of equity, which prioritizes vaccination of the most vulnerable sectors of the population (e.g., children, homeless, low socioeconomic status) (Buccieri and Gaetz; Moodley et al.). However, these equitable models often conflict with more utilitarian approaches, wherein the goal is to maximize the total benefit to society, such as vaccinating easy-to-reach populations and frontline health care workers (Moodley et al.). These questions are particularly important for novel vaccine distribution during pandemics when limited supply and high need force difficult choices.

AFFORDABILITY

Affordability in the context of vaccines primarily involves questions of cost—both to investors and funding agencies, who decide which diseases warrant the most research, as well as to consumers, who decide how much they are willing to pay for protection against diseases and who often depend on third-party coverage to pay for the life-saving technology. Yet the word "affordable" has different meanings in different settings and has often been used as a convenient defence for inaction when it comes to funding the distribution of vaccines in developing countries (Heymann). While some middle-income countries have accepted the challenge of providing medicines from their own national government budgets, others—some of which have the resources to purchase these medications—have pointed to vaccine unaffordability as a defence and justification to wait for financial assistance from international development agencies (Heymann). As such, defining "affordability" in the context of vaccine distribution is challenging, as no simple solution can be found in different pricing for different markets in response to a flexible application of intellectual property and trade agreements (Heymann). As with most vaccine-related challenges, the issue is both nuanced and complex, and has many normative and ethical considerations, such as determining who should be paying for vaccines. Regardless, profits unfortunately depend on consumers' ability to pay high prices, which is not possible for diseases that primarily affect the world's poorest people.

At ground level, the cost of vaccination per fully immunized child varies according to the delivery strategy, the cost of key inputs such as personnel and transportation, and the scale of the program (Levin et al.). In addition, cost variation reflects several contextual factors, such as national income, public health infrastructure, health system policies, and the resources available (Levin et al.). For developing countries that qualify for support from Gavi, the Vaccine Alliance, bulk purchasing of vaccines allows for long-term agreements that ensures a smooth and constant flow of high-quality vaccines and necessary supplies at affordable prices (Smith et al.). Another notable organiza-

tion is UNICEF, which provided 2.7 billion vaccine doses in 2014 for US$1.5 billion, corresponding to a 97% average price reduction (Hill et al.).

The human papillomavirus (HPV) vaccine serves as a good example for how costs and associated challenges vary across countries and income economies. This vaccine, important for preventing cervical cancer and recommended by WHO, costs more than US$100 per dose in the United States, or US$300 for the three-dose series (Levin et al.). In developing countries, Gavi has been able to obtain significant discounts from major manufactures, with one distributor even offering the quadrivalent HPV vaccine at US$5 per dose for use in eligible countries (Levin et al.; Butler). Furthermore, Gavi's pledging conference in January 2015 raised over US$4.3 billion, which, when accompanied with the lower pricing, promises progress in achieving more affordable vaccines to people in developing countries (Nguyen et al.). Nonetheless, countries that apply for vaccine support through Gavi have to commit to a co-financing policy, whereby each country's income determines the proportion of co-financing the country must commit (Gavi, the Vaccine Alliance). While this stipulation may be challenging for some countries to satisfy, the policy remains beneficial, as it requires the country to play an active role in financing its vaccination programs, thus improving sustainability as countries' economies grow and governments transition out of Gavi funding (Gavi, the Vaccine Alliance). Despite being ineligible for Gavi's discounted prices, low- and middle-income countries in Latin America can still purchase the HPV vaccine for only US$10 to $15 per dose through the Revolving Fund of the Pan American Health Organization (Levin et al.). For such vaccines, there has been significant progress towards achieving affordability in developing countries; however, there is much work to be done to ensure that this is the case for all people and for all needed vaccines.

In relation to affordability, there have been several international intellectual property (IP) policy challenges associated with developing and manufacturing vaccines and their impact on public health. The Indonesian government's stance on the avian flu well illustrates the intricacies and challenges involved in creating IP that has the potential for

global, and not merely state, benefit. In the mid-2000s, Indonesia was most affected by the evolving avian influenza virus and was asked by the international community to supply samples of the avian influenza virus for free to university researchers and pharmaceutical companies as per WHO's recommendation. The Indonesian government, however, was reluctant to freely supply these samples in fear that they would be used to develop patented vaccines targeted for use in developed countries, and in the process, become unaffordable to developing countries such as itself (Gerhardsen).

Affordability is far less of a concern in developed countries, where governments often subsidize or completely pay for certain vaccinations, especially those aimed at children. The United States, for example, has passed the Vaccination Assistance Act, which aims to support childhood vaccination, and introduced the Vaccines for Children Program, which provides additional support (Hinman et al.). However, most adult vaccines are obtained through the private sector. More comprehensively, the provincial governments of Canada each offer publicly funded immunization schedules for children, as well as vaccinations against specific diseases for adults, although the schedules and qualifying diseases vary across provinces (Public Health Agency of Canada, "Immunization Schedules").

APPROPRIATENESS

The question of *appropriateness* concerns the correctness of the service provided for the prevention of a disease (Jackson). In terms of vaccines, screening and assessment tools can be utilized to ensure that the target population for a particular vaccine will result in the most effective protection and the most cost-efficient use of resources. Determining the appropriateness of vaccines as a preventive measure involves an analysis of benefits, costs, and potential harms. Additional challenges also arise when considering vaccinating children versus vaccinating adolescents.

To determine the appropriateness of vaccines, we observe that vaccines constitute the intervention performed, and that the intended out-

come is of preventing a specific disease. In these terms, it seems that vaccines are indeed effective at preventing their target diseases: estimates suggest that childhood vaccinations prevented more than 100 million cases of serious disease between 1924 and 2012 (Gostin). On an individual level, virtually all persons who receive a vaccine will react to the formulation and develop antibodies, resulting in long-term, and most likely lifelong, vaccine-induced immunity to the target disease (Atkinson et al.). On a population level, immunization schedules are crucial for containing and controlling potential infectious diseases, preventing them from escalating into serious public health risks. In this capacity, they are highly cost-effective, as the diseases they prevent pose significant costs to individuals, health systems, and society in the form of increased health care burdens (e.g., visits to health care providers, hospitalization), premature deaths, and overall loss of productivity due to sickness (Public Health Agency of Canada, *Benefits of Immunization*). It is thus much more beneficial, both to the individual and for society as a whole, to implement an immunization schedule than to treat cases of the disease that may have arisen without such a program (Public Health Agency of Canada, *Benefits of Immunization*). However, it is important to note that not all research shows equally strong support. A systematic review analyzing the efficacy of influenza vaccines found them to be only moderately effective, with the highest relative efficacy noted in children (Osterholm et al.).

Vaccines are generally regarded as highly appropriate with respect to safety, but they may result in minor side effects, which can include reactions at the injection site, mild fevers, headaches, and muscle and joint pain (Centers for Disease Control and Prevention, *Vaccines*). Vaccinations may also pose additional risks to certain vulnerable populations, such as the immune-compromised, who may not be able to mount a sufficient immune response to the vaccination (Centers for Disease Control and Prevention, *Who Should Not Get Vaccinated*; Shepherd and Grabenstein). In the immune-compromised, a live vaccine (i.e., one that includes a live attenuated virus) could cause complications, including infections. This can be avoided, for the most part, by administering inactive DNA or component vaccines to these select populations, although the effectiveness of these alternatives

varies (Shepherd and Grabenstein; World Health Organization, "WHO | DNA Vaccines"; Centers for Disease Control and Prevention, *Who Should Not Get Vaccinated*). For the majority of the population, it is clear that the benefits of vaccines far outweigh the risk.

Safety, effectiveness, and age at immunization are all considered when developing vaccine schedules and guidelines for appropriateness (Smith). While most vaccines are offered during early childhood, rates of vaccine delivery to adolescents have recently been measured as substantially lower than for young people—below the Healthy People 2010 goals (Ford et al.). Vaccines that target young people between 9 and 25 years of age are met with unique considerations, including variation in parent-child relationships, cognitive development, autonomy, time spent in school, legal status, and the likelihood of having insurance (Ford et al.). As a result, traditional strategies to increase vaccination rates among young children may not effectively reach all adolescent groups (Ford et al.). These considerations are important to keep in mind when determining the appropriateness of immunization schedules to specific target groups, be it young children or young adults.

Perceptions of appropriateness have a large role in informing acceptability. Some have speculated that one of the barriers to the support of vaccines is that they are administered to healthy individuals and provide disease protection in the long term with no immediate or tangible benefit to recipients. Additionally, thanks to the effectiveness of vaccines, citizens have the privilege of forgetting the physiological, economic, and social impacts of the diseases that vaccines prevent (Taylor, Miller, Farrington, et al.). Lower rates of vaccine-preventable disease in developed countries may offer a false sense that vaccines are not an appropriate or necessary measure. The nature of vaccines as a preventative measure that works in healthy individuals is an inherent benefit; unfortunately, misperceptions of this quality set vaccines up for mistrust and decreased support.

ACCEPTABILITY

Acceptability is the degree to which vaccines are congruent with cultural beliefs, values, and worldview, from the perspective of the recipient (Jackson). This can also be applied to relevant stakeholders including the public, the government, and associated organizations. For the most part, governments of both developing and developed countries have recognized the importance and value of vaccinations, and have sought to develop and sustain national immunization programs. Associated organizations, including the WHO and Gavi, have similarly supported vaccinations and have sought to advocate and supply them to developing countries. The public, however, has been divided. In developed countries, vaccines have been a hotly debated topic in the public sphere, with both pro- and anti-vaccination advocates expressing polarized views on the benefits and risks of vaccinations.[2] In addition to concerns about health risks, vaccine acceptability concerns can arise from religious, philosophical, or personal beliefs, as well as from misinformation about risks and diseases, mistrust of healthcare professionals and government, and fear of the pharmaceutical industry (Offit and Moser; Siddiqui et al.).

Vaccine use and related acceptability concerns are shaped by social, economic, political, and religious contexts, which differ between developing and developed countries. To understand acceptability, it is important to consider how vaccines play different roles in different countries. In many developed countries, vaccines are one part of a comprehensive preventative strategy to combat disease, serving to complement regular check-ups, screening for at-risk populations, and medical care when disease occurs. This presents the possibility of alternative vaccine schedules and contributes to lower perceived risks of vaccine-preventable diseases. Developed countries can take advantage of existing infrastructure, such as the internet and other media, to organize and publicize opposition to vaccines. So, while the existence of acceptability concerns is common to developing and developed countries, the anti-vaccine movement is primarily associated with developed countries. In contrast, developing countries often have relatively weaker health systems in which vaccines represent an important

measure against infectious disease, and sometimes the only available measure. Reduced health care accessibility and infrastructure make the acceptability concerns of developed countries less prevalent. Instead, prevailing cultural and societal issues raise unique acceptability challenges in developing countries. Briefly, these additional obstacles can stem from poverty, illiteracy, religious influence, taboos, and superstition (Pang). These contextual factors can cause health illiteracy and misinformation, leaving people both unaware of the importance of vaccines and afraid of their use. Prevailing false perceptions include the belief that vaccines are curative, not preventative, which leads to the conclusion that healthy children do not need to be vaccinated (Pang). Religious influence and tradition can also propel fears, as some may believe that disease is deliberately created by the supernatural, leading to the idea that immunization against disease will anger these entities. Others fear that vaccinating children will lead them to become too dependent on Western medicine and reduce their fertility as they grow older (Pang). Similar to the anti-vaccine movement in developed countries, many parents in developing countries remain insufficiently educated about vaccines and hold various concerns about their safety, both of which can unfortunately affect their decision to vaccinate (Wakefield et al.). Historically, as with the example of the British colonization of India, some opposed vaccine programs as an intrusion of the colonial state (Streefland). Parents in both developing and developed countries, either out of mistrust of the government officials, health workers, or pharmaceutical countries, may also perceive mass vaccinations as unsafe under the belief that they have been deliberately contaminated. These issues pertaining to trusting the supplier or provider can affect uptake, as it has been found that American anti-vaccination advocates often do not trust their government (Grabmeier).

In light of a series of vaccine controversies in the mainstream media, it may be the case that the anti-vaccine movement is gaining popularity. The movement was largely fuelled by the retracted *Lancet* study that reported a correlation between the measles, mumps, rubella (MMR) vaccine and autism, based on fraudulent data (Wakefield et al.). Despite the large ensuing body of evidence failing to find any

such correlation, claims of causation persisted where none were warranted, and anti-vaccine hysteria spread rapidly in part due to media sensationalization of the original *Lancet* study (Taylor, Miller, Farrington, et al.; Taylor, Miller, Lingam, et al.; Honda et al.; Institute of Medicine (US) Immunization Safety Review Committee; Madsen et al.). Several other similar hypotheses have since been perpetuated by "anti-vaxxers," with one of the more notorious asserting a correlation between the mercury-based thimerosal component of vaccines and autism (Kennedy). The movement has also garnered widespread attention, support, and advocacy from celebrities and public figures with the ability to significantly influence public attitudes and opinions against vaccines (Kennedy). Currently, the anti-vaccination movement is predominantly internet-based, with websites that promote a general distrust of science and that rely on strong emotional appeals for their arguments (Ernst and Jacobs). These sites even include "how-to" guides for obtaining vaccination exemptions easily, contributing to the increase of philosophical and personal belief exemption utilization in the United States (Ernst and Jacobs). These websites seem to have tangible effects on the decision-making of parents who choose not to vaccinate their children. For example, it was found that parents of children who received exemptions for school vaccinations were more likely than parents of vaccinated children to obtain information from the internet and have providers who offer complementary or alternative health care (Omer et al.).

Of course, the anti-vaccine movement's activities pose significant public health risks. Vaccines work best through herd immunity,[3] which occurs when the vast majority of the population is vaccinated against a certain disease (National Institute of Allergy and Infectious Diseases). Interestingly, some anti-vaccine promoters acknowledge the validity of herd immunity as protecting communities from vaccine-preventable diseases, but instead of strengthening and supporting this phenomenon by vaccinating, they suggest taking advantage of herd immunity's benefits while simultaneously undermining its effectiveness (Offit and Moser). That is, some anti-vaccine promoters say that you don't need to risk vaccine-related adverse events when you can profit from herd immunity to protect you from disease instead (Offit

and Moser). This and other mentalities in the anti-vaccine movement are flawed because when vaccination rates decrease—as we have seen occurring with the rise of the anti-vaccination movement—the likelihood of an outbreak increases, and this can have devastating effects for entire communities.

The unsubstantiated perceptions and beliefs held by the anti-vaccine movement about the dangers of vaccinations have contributed to vaccine hesitancy—the reluctance or refusal to vaccinate when vaccinations are available (World Health Organization, *Ten Threats to Global Health*). Those who are vaccine hesitant may not refuse vaccines entirely; individuals in this group may accept the role of vaccines but experience a reluctance to embrace the established approach to vaccination. They may agree to receive some vaccines, while refusing others; delay the recommended vaccination schedule; or feel unsure about vaccinating themselves and their children (Larson et al.). Aside from the influence of the anti-vaccination movement, there are many additional factors that may contribute to vaccine hesitancy, which include unfamiliarity with vaccine-preventable diseases, the lack of trust in public health agencies and corporations, fear of adverse health outcomes, and the compulsory nature of vaccines (Salmon et al.).

Instead of refusing vaccines, some vaccine-hesitant parents choose to delay vaccination of their children or follow a novel vaccine schedule proposed by individual physicians, as opposed to those developed by expert committees (Omer et al.). Most novel schedules involve administering vaccines over a longer period than that recommended by the Advisory Committee on Immunization Practices, the American Academy of Pediatrics, the Centers for Disease Control and Prevention, the American Academy of Family Physicians, and similar organizations in other countries (Omer et al.; Offit and Moser). Some alternative schedules recommend delaying some vaccines and avoiding others altogether (Dempsey et al.). Although the individual consequences of delayed vaccination schedules have not been studied in detail, it is well known that under-immunization presents serious risks of vaccine-preventable diseases (Dempsey et al.). Vaccine delays are of particular concern as the risk of vaccine-preventable diseases are not constant throughout childhood, with younger children at an increased risk for

illness and death related to infectious disease (Song). Novel vaccine schedules that recommend administering vaccinations over a longer period of time may also exacerbate health inequalities, as parents of higher socioeconomic status may be more capable of making the extra medical visits required by the alternative schedule (Omer et al.). Furthermore, the distaste that is sometimes seen among anti-vaccine advocates against science generates skepticism and disapproval of health care professionals and the scientific process in general, which itself can be harmful.

Beyond the anti-vaccine movement and those who are vaccine-hesitant, there are more substantive objections to vaccines; these include objections on religious, cultural, ethical, and moral grounds. Although all 50 American states recommend that children be vaccinated before attending school, various exemptions are also allowed (Song). Religious exemptions are permitted in all states except for Mississippi and West Virginia, and roughly 20 states also grant exemptions for philosophical reasons (Song). Refusal can also be based on ethical objections to state laws that mandate vaccinations, on the grounds that they violate personal autonomy (Sadaf et al.).

The ethical dilemma for individuals who choose not to vaccinate themselves or their children is whether an individual's right to personal autonomy overrides the unrealized health benefits to the entire vulnerable population (Amin et al.). While this ethical dilemma is difficult to resolve, one can begin by analyzing the scenario through the utilitarian principle of "producing the maximal balance of benefits over harm or other costs" (Amin et al.). Given that we can view unvaccinated persons as a "harm" to the community at large (Diekema and Marcuse), any individuals failing to vaccinate themselves and/or their children put everyone else at risk. In other words, the total harm that an individual failing to vaccinate will create—whether via initiating or propagating an outbreak or increasing burdens on the health care system—will likely be greater than the benefit that the individual will receive by retaining autonomy. This line of reasoning presents strong ethical grounds for enacting and enforcing mandatory vaccination laws. Of course, the same ethical dilemma could be considered

under other principles—like libertarian ones—leading to possibly different conclusions.

As a result of the various objections previously mentioned, non-medical exemptions (NME), such as religious and philosophical beliefs, have recently been on the rise in many American states (Olive et al.). The most common reason given by parents seeking exemptions from school vaccination requirements is a concern that the vaccine will cause their children harm (Diekema). Studies have shown that geographical NME clusters are associated with high socioeconomic status, lower population density, lower average family size, lower percentage of racial or ethnic minorities, and higher median household income (Atwell et al.). The process for acquiring an NME varies in rigour by state, with some requiring as little as a signature on a preprinted form (Gostin). State exemption processes significantly influence vaccination rates and incidences of vaccine-preventable illness. In fact, in 2012, researchers reported NME rates 2.3 times higher in states with easy administrative policies as compared to those with more difficult policies (Gostin).

Ultimately, many factors filter into and reinforce societal and cultural attitudes towards vaccinations, thereby affecting acceptability. It seems that a lack of effective communication between health care providers and parents regarding the types of vaccines administered, the importance of vaccines, and the possible adverse effects are facilitating many of these misconceptions (Asiimwe et al.).

CONCLUSION

This overview has outlined some of the key legal, political, and social issues related to vaccination efforts worldwide. Although vaccination uptake has increased substantially over the last hundred years, it is clear that there is still more work to be done. Global vaccination uptake not only requires the support of many stakeholders, it needs funding, research and development, storage facilities, partnerships, proper delivery systems, and public support. Harnessing the promise of vaccines depends on their availability, ac-

cessibility, affordability, appropriateness, and acceptability. Without these requirements, the goal of universal vaccination will be difficult to achieve.

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NOTES

1. Editor's note: Jesper Alvaer's work for the <*Immune Nations*> exhibition addresses the challenge of cold-storing vaccines in remote areas of developing countries. See Alvaer, "*Upstreaming the Cold Chain*," this volume. Hou and Mahon also mention the cold chain in their dialogue, "Reflecting on the Genesis and Realization of *Design for a Dissemunization Station*," in this volume.↵

2. Editor's note: On this, see Kaisu Koski and Johan Holst's contribution to this volume. See also Koski, K., and J. Holst, "Interdisciplinary Dialogue on Vaccine Hesitancy: Developing Trust and Shifting Stereotypes," *Journal of Clinical Research & Bioethics*, vol. 9, no. 1, 2018, doi: 10.4172/2155-9627.1000320; and Koski, K., and J. Holst, "Exploring Vaccine Hesitancy through an Artist-Scientist Collaboration: Visualizing Vaccine-Critical Parents' Health Beliefs," *Journal of Bioethical Inquiry*, vol. 14, no. 3, 2017, pp. 411–26, http://rdcu.be/u213.

3. Editor's note: Herd immunity is addressed by *Shadowpox*, one of the works in <*Immune Nations*> and discussed by collaborators Alison Humphrey, Caitlin Fisher, and Steven Hoffman in "*Shadowpox: The Antibody Politic* – Thoughts and Reflections," in the Reports and Dialogues section of this volume.