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Vaccine Hesitancy: Drivers and How the Allergy Community Can Help



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Vaccine hesitancy—defined by the World Health Organization (WHO) as a “delay in acceptance or refusal of vaccines despite availability of vaccination services”—is not a recent phenomenon. Historical records indicate that vaccine hesitancy existed by the 18th century in Europe and even resulted in violent riots. The drivers of vaccine hesitancy have evolved over the last 200 years but not, perhaps, as much as one might expect. More problematic are the means by which concerns over vaccine hesitancy are communicated by a new landscape of digital communication, generating what has been described as an “infodemic” in which an overabundance of information—both factual and misinformation—contributes to hesitancy. In this review, we discuss the background and current drivers of vaccine hesitancy and the evidence base for strategies to combat this. We highlight the important role the allergy/immunology community could have in working to mitigate vaccine hesitancy, particularly with respect to the current coronavirus disease 2019 (COVID-19) pandemic. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;9:3568-74)

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Immunization has been a key part of global infection control since the 19th century. Although Edward Jenner is widely considered the founding father of immunization following the use of vaccinia virus (cowpox) to induce immunity to smallpox (resulting in its eradication in 1979), the inoculation of skin tears with cowpox (presumably against smallpox) was already practiced in China by the 17th century. New technologies have allowed the rapid implementation of a new generation of vaccines, for instance, against coronavirus disease 2019 (COVID-19), which deliver genetic material to instruct the body to produce proteins that stimulate an immune response.

Vaccine hesitancy—defined by the World Health Organization (WHO) as a “delay in acceptance or refusal of vaccines despite availability of vaccination services”¹—is not a recent phenomenon, although the term itself is relatively new. Historical records indicate that vaccine hesitancy almost certainly contributed to the smallpox epidemic in Stockholm in 1873 to 1874, predominantly driven by the clergy; a Swedish translation of a French provaccination leaflet has been found, dating from 1756.² Opposition to vaccination in Europe is mentioned in an annual report to the London Vaccine Institution in May 1818.² In the United Kingdom, the Vaccination Acts of 1840 and 1853 introduced compulsory vaccination and resulted in violent riots in several towns and the formation of the Anti-Vaccination League in London.³

Thus, vaccine delays and refusals have contributed to outbreaks of vaccine-preventable diseases since vaccines were first used as a public health measure. More recently, the impact of vaccine hesitancy has become of greater concern, particularly with the use of social media to propagate misinformation. This had led to the realization that the success of immunization programs cannot be taken for granted.⁴

The drivers of vaccine hesitancy have evolved over the last 200 years but not, perhaps, as much as one might expect. More problematic are the means by which concerns over vaccine hesitancy are communicated by a new landscape of digital communication, generating what has been described as an “infodemic” in which an overabundance of information—both factual and misinformation—contributes to hesitancy.⁵ In this review, we discuss the background and current drivers of vaccine hesitancy and the evidence base for strategies to combat this. We highlight the important role the allergy/immunology community could have in working to mitigate vaccine hesitancy, particularly with respect to the current COVID-19 pandemic.

VACCINE HESITANCY AS A CONTINUUM AND ITS DRIVERS

In 2012, the WHO Strategic Advisory Group of Experts appointed a Working Group on Vaccine Hesitancy.⁶ In 2014,

Abbreviations used

aP- Acellular pertussis vaccine

COVID-19- Current coronavirus disease 2019

HPV- Human papillomavirus

MMR- Measles-mumps-rubella

WHO- World Health Organization

wP- Whole cell pertussis vaccine

their definition was officially endorsed by WHO. The working group defined vaccine hesitancy as “delay in acceptance or refusal of vaccines despite availability of vaccination services. Vaccine hesitancy is complex and context-specific, varying across time, place and vaccines. It is influenced by factors such as complacency, convenience and confidence.”¹ Since then, the concept gained more and more traction and encouraged reflection in public health and scientific discourses around the drivers and a continuum of hesitancy sitting between vaccine acceptance and refusal (Figure 1).⁷ In 2019, the WHO declared that vaccine hesitancy was 1 of the top 10 threats to global health.⁸

The concept of vaccine hesitancy has been criticized as being ambiguous and without sufficient theoretical background⁹ and seen as not putting enough emphasis on the practical (or access) barriers to vaccine uptake.¹⁰ However, vaccine hesitancy has prompted more attention to the fact that, as for all behaviors, vaccination attitudes and decisions should be seen on a continuum, ranging from a small minority of activists against vaccination to the majority who accept to be vaccinated.¹¹ Vaccine hesitancy also highlights that vaccination decisions are complex and multifactorial (Table 1). Reasons why a nurse hesitates to be vaccinated against influenza are likely to be very different from the reasons why a pregnant person is unsure about pertussis vaccination during pregnancy.¹² Whereas most of the research on vaccine hesitancy has focused on childhood vaccination, vaccine hesitancy is not limited to parents making the decision for their children’s vaccination but exists across the life span and also among health care workers.^{13,14} In addition, there has been a surge in attention to vaccine hesitancy in the context of COVID-19 and other outbreaks of diseases such as Ebola.

At the individual level, the complex and interrelated factors influencing vaccine hesitancy and acceptance have been summarized under the 5Cs model (Figure 2).¹⁵ This model includes complacency (ie, low perceived risks of vaccine-preventable diseases and vaccination not perceived as a priority); confidence (ie, trust in safety and efficacy of vaccines, in the delivery system, and in the authorities that have issued recommendations); convenience and constraints (ie, quality of vaccination services that can impact acceptance and perceived self-efficacy to be vaccinated); collective responsibility (ie, willingness to protect others); and calculation (ie, extensive information gathering before making vaccination decisions).¹⁰ Acceptance and refusal of vaccines are also highly context-dependent: social, cultural/religious, historical, and political factors influence how people feel and decide about vaccination.¹⁶⁻¹⁸ Vaccine hesitancy can be a legitimate viewpoint, underscoring a failure or lack of effective public health messaging.¹⁹ It should not be conflated with being antisience or irrational, but seen, rather, as reflecting legitimate doubts and concerns about vaccines or a transitional state in the decision-making process about vaccines.

Finally, although vaccine hesitancy and acceptance are important determinants of vaccine uptake (ie, the proportion of a population that has received a specific vaccine), access to vaccines and vaccination services (ie, the supply-side) is crucial to understanding why people are not receiving recommended vaccines. Thomson et al²⁰ have summarized the different factors influencing vaccine uptake under a practical taxonomy called the 5 A’s for access (ie, the ability of individuals to be reached by, or to reach, recommended vaccines), affordability (ie, the ability of individuals to afford vaccination, in terms of both financial and nonfinancial costs), awareness (ie, the degree to which individuals have knowledge of the need for, and availability of, recommended vaccines and their objective benefits and risks), acceptance (ie, the degree to which individuals accept, question, or refuse vaccination), and activation (ie, the degree to which individuals are nudged toward vaccination uptake).

HOW COMMON IS VACCINE HESITANCY?

In high-income countries, it is estimated that between one-quarter and one-third of the population could be labeled as vaccine-hesitant.²¹ In 2016, Larson and collaborators²² surveyed over 65,000 respondents across 67 countries and found that confidence in vaccination was high overall, but with wide variation across countries and regions. Countries with high levels of education and good access to health services were associated with higher levels of negative sentiment regarding vaccination. Europe had the lowest confidence in vaccine safety, with France the least confident globally. A survey conducted by the Wellcome Trust in 2018 in 140 countries reached similar conclusions.²³ Using the results of the 2015 to 2017 WHO and United Nations Children’s Emergency Fund (UNICEF) Joint Reporting Forms on immunization, Lane et al²⁴ showed the vaccine hesitancy was common and reported by 90% of countries. In 2020, de Figueiredo et al²⁵ published a global mapping of vaccine confidence over time (2015-2019) across 149 countries, analyzing data collected with their Vaccine Confidence Index. The mapping over time revealed the volatility of vaccine confidence, with some countries becoming more confident over time and others more hesitant.²⁵

RUMORS AND MISINFORMATION AROUND VACCINATION

In the broader realm of influences on vaccine decisions—from confidence in the safety and effectiveness of vaccines to issues of access and trust in the institutions that deliver them—the age-old issues of rumors and misinformation can now have a greater impact owing to the phenomenon of digitally driven infodemics (ie, an overabundance of information, accurate or not). This has become particularly acute during the COVID-19 pandemic, prompting the WHO Director General to call out that “we’re not just fighting a pandemic; we’re fighting an infodemic.”²⁶

Whereas the reach and rapid spread of misinformation have accelerated in recent years (and are not unique to vaccines), the underlying beliefs and emotions—from fears to hopes—that drive vaccine rumors have existed since the first smallpox vaccine.²⁷ Then, rumors included the assertion that the smallpox vaccine (derived from cowpox) would turn people into cows—not so different from current claims that 1 of the COVID-19 vaccines, using a viral vector derived from chimp adenovirus, would turn people into monkeys²⁸ or the suggestion by some

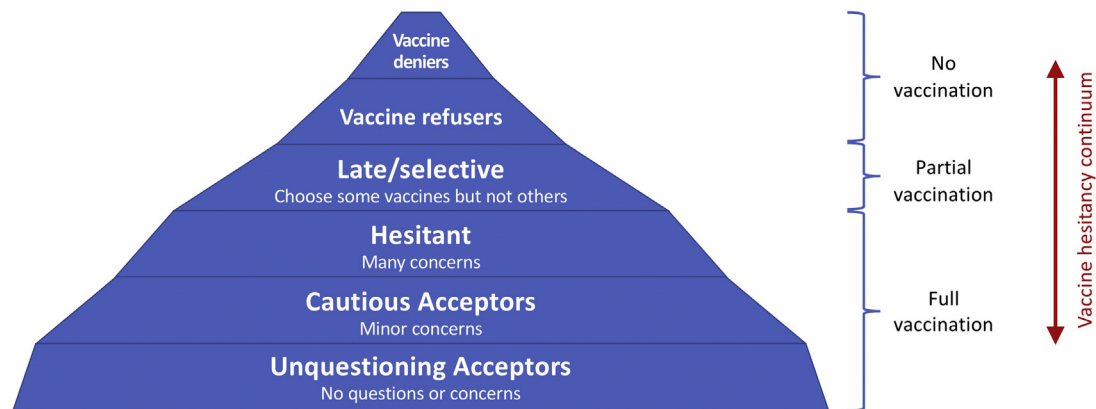


FIGURE 1. Continuum of vaccine hesitancy. Individuals may move between categories over time owing to variable influences such as (mis)information or the perceived need for vaccination (eg, pandemic response, requirement for vaccination in order for travel).⁷

TABLE I. Possible reasons for vaccine hesitancy

Factors that contribute to vaccine hesitancy	Reasons specific to COVID-19 vaccines
<ul style="list-style-type: none"> • Concerns over safety • Previous experiences with respect to vaccination 	<ul style="list-style-type: none"> • New technology and speed of vaccine development • (Perceived) lack of safety data, particularly with respect to longer-term safety
<ul style="list-style-type: none"> • Prior interactions with (and trust in) health care providers • Mistrust of doctors/health services/government/“big” pharma • Complacency over a perceived low risk of illness/lack of familiarity with vaccine-preventable diseases/concerns over low vaccine efficacy • (Mis-)information 	<ul style="list-style-type: none"> • Denial of COVID-19 as a problem by some politicians/leaders • Concern over safety scares as the vaccine program is rapidly rolled out • Lack of perceived need in those countries in which other public health measures have been successful in curbing infections (eg, Australia) • Lack of perceived need to for vaccination following SARS-CoV-2 infection
<ul style="list-style-type: none"> • Religious beliefs (eg, over use of aborted fetuses to generate cell lines which might be used in vaccine development; dietary restrictions) • Historical concerns over the use of vaccines in specific ethnic/minority groups • Preference toward a particular lifestyle (eg, natural medicine, veganism) • Peer pressure/perception of vaccination by peers • Needlephobia • Inconvenience • Cost of vaccine (both direct and indirect costs—eg, time off work) 	<ul style="list-style-type: none"> • Concerns over commercial interests driving vaccination • Lack of data over persistence of immunity • Long-COVID syndrome

SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2.

political leaders that the mRNA vaccine could turn someone into a crocodile.²⁹

The medical community has often focused on correcting such misinformation, rather than understanding and trying to address the underlying issues with emotions, beliefs, and trust that create the fertile ground for these rumors to take hold and multiply. The archetypal “vaccines cause autism” myth, provoked by a scientific hypothesis that Andrew Wakefield published in 1998—later retracted, and debunked by many other studies since—lives on and has gained significant traction around the world. This 3-word, tweetable meme has given many parents a plausible explanation for their burning question, “Why are more children getting autism” or an even more impassioned “Why did my child develop autism.” Wakefield had an answer, clear and simple, and lost his medical credentials standing by his hypothesis against the scientific consensus. He has become a martyr of sorts for those who believe in him, sharing with parents the feeling that he—like they—have been snubbed by the scientific community and rejected for speaking their “truth.”³⁰

Other persisting rumors relate to deeper historical abuses or marginalization that undermine trust and fuel hesitancy. Correcting misinformation is not enough for those who have deep beliefs compounded with distrust in authorities. Instead, trust-building efforts that engage local community members are needed. The Global Polio Eradication Initiative has generated multiple learnings in terms of how to effectively engage with local communities and build trust.³¹ And, in the context of Ebola vaccine trials and roll-out in Africa during the West Africa outbreak,³² trust building was key to mitigating vaccine hesitancy around the new Ebola vaccines.³³

Sometimes, it is not a local community that is hesitant, but other like-minded groups. Anxiety and rumors around adverse events reported to the human papillomavirus (HPV) vaccine, for example, were communicated globally by groups of teenage girls from Japan to Denmark to Colombia, sharing multiple symptoms of fainting, nausea, mobility issues, and chronic fatigue following vaccination—a constellation of symptoms now characterized by WHO as “immunization stress related responses.”³⁴ Despite this,

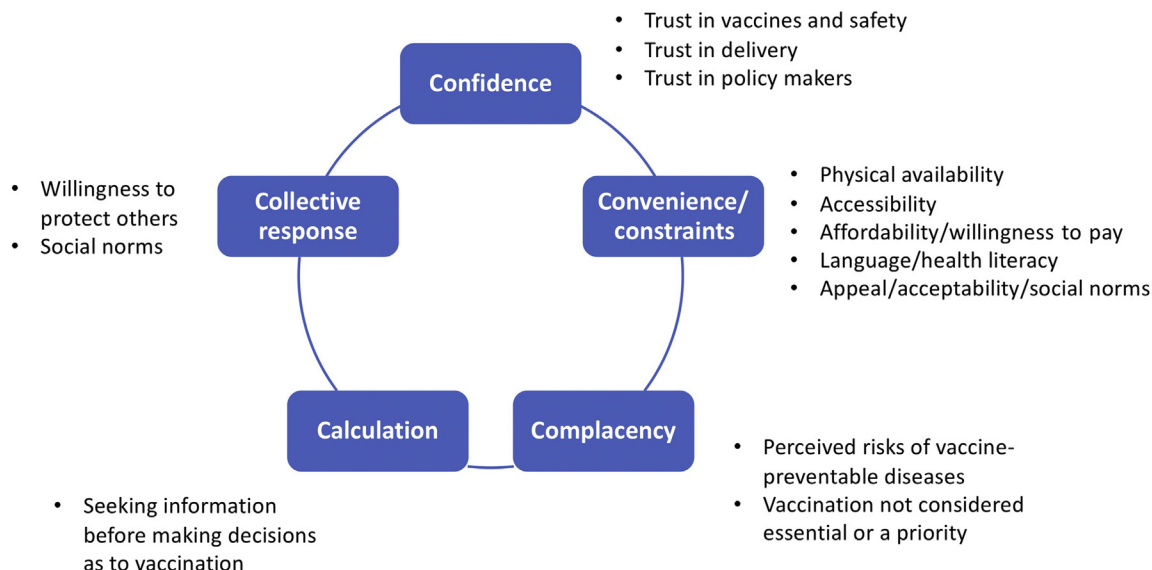


FIGURE 2. The 5C model of factors influencing vaccine hesitancy and acceptance.¹⁵

many remain convinced that the vaccine itself is the cause of these symptoms. This has created considerable anxiety over HPV vaccination in both teenagers and their parents, which in turn impacts politicians and policymakers: in Japan, the government suspended their proactive recommendation for HPV vaccination in 2013 owing to pressure from parents; the suspension persists 8 years later, despite the scientific consensus that HPV vaccination is safe.³⁵ Denmark developed one effective strategy to rebuild trust and overcome hesitancy: they brought together girls of HPV-vaccination age with the health authorities, to codesign a social media strategy to reach their female peers.³⁶

ALLERGY AND VACCINE HESITANCY

Although underreported in the medical literature, vaccine hesitancy among parents may be linked to concerns over the potential of vaccines to increase the risk of atopic disease.³⁷ Several large and well-conducted interventional or epidemiological studies have failed to find a link between vaccination and a risk of asthma and other atopic diseases.³⁸⁻⁴² These data must be considered distinct to the possibility that some vaccines may be protective against atopic disease. For example, in many countries, the switch around 20 years ago from whole cell (wP) to acellular pertussis (aP) vaccine (to reduce the incidence of nonallergic adverse events following immunization, which is higher with wP) coincided with increasing rates of food allergy. The aP vaccine is associated with a Th2-like immune response and it has been suggested that this might predispose to atopic disease.⁴³ Estcourt et al⁴⁴ recently reported results from a nested case-control study in Australia, which found a lower odds ratio (0.77; 95% confidence interval [95% CI] 0.62-0.95) in infants receiving a first dose of wP (rather than aP) among cases of food allergy. An adaptive randomized controlled trial of a mixed wP/aP vaccine schedule is now under way to further investigate this.⁴⁵ Thus, although there is no evidence to suggest that vaccines cause atopy, it is possible that some vaccines, compared with others, may be protective against the development of atopy.

Anaphylaxis as an adverse event following immunization is rare, with an incidence of less than 1 per million doses for most

vaccines.^{46,47} Most allergic reactions are due to vaccine excipients; in some vaccines, these are derived from food proteins. For instance, most influenza vaccines are produced using an egg-based manufacturing process; thus, vaccines can contain very small residual amounts of egg protein. However, there is now international consensus that influenza vaccines with very low ovalbumin content can be safely given to individuals with allergy, even those with a history of prior anaphylaxis, without concern.⁴⁸

Vaccine hesitancy driven by a fear of allergic reaction has persisted with respect to the measles-mumps-rubella (MMR) vaccine. The MMR vaccine is produced in chick embryo fibroblasts rather than in eggs *per se*, and does not, therefore, contain significant residual egg protein.⁴⁹ Despite this, at least in the United Kingdom, reluctance to vaccinate egg-allergic children with MMR in primary care persists.⁵⁰ In both cases, rather than provide reassurance to parents and proceed with vaccination in the community, children are instead referred to hospital for vaccination, which reinforces the myth that such a measure is required. These examples demonstrate the role allergists need to have in educating not only the public but also other health care professionals to avoid a possible driver of vaccine hesitancy.

More recently, concern over allergic reactions to vaccines against COVID-19 have also caused vaccine hesitancy. The United Kingdom was the first country to issue approval for use of the Pfizer-BioNTech BNT162b2 vaccine against COVID-19 in 2020. However, on the first day of roll-out, 2 cases of anaphylaxis were reported in individuals with a history of prior anaphylaxis. As a result, the U.K.'s Medicines and Healthcare products Regulatory Agency (MHRA) issued a warning that individuals with prior anaphylaxis to a vaccine, medicine, or food should not receive the vaccine.⁵¹ This advice was subsequently reversed 3 weeks later, following further review of data.⁵² Other major regulatory authorities including the U.S. Food and Drug Administration were not tempted to issue such a blanket warning. Despite this, and the fact that the concern over a higher rate of anaphylaxis was limited to just the Pfizer-BioNTech COVID-19 vaccine, advice issued by Ministry of Health and Family Welfare of the Government of India on January 14, 2021 lists "Immediate or delayed-onset

anaphylaxis or allergic reaction to vaccines or injectable therapies, pharmaceutical products or food items” as a contraindication to *any* COVID-19 vaccine.⁵³ Under the current circumstances, such a stipulation is not only without foundation but potentially dangerous. Health care professionals and regulatory bodies must take precautions not to inadvertently generate misinformation that can cause vaccine hesitancy.⁵⁴

ADDRESSING VACCINE HESITANCY

Although researchers have developed many tools for understanding the prevalence of vaccine hesitancy and the factors that drive it,⁵⁵ moving toward effective and scalable strategies to build confidence in vaccines is more complex. This is understandable, given that vaccine decisions are made across the lifespan, can change over time, are highly individual, and often take place within the context of limited personal experience with vaccine-preventable diseases. Still, there are promising frameworks for thinking holistically about how we address hesitancy and build confidence in vaccines. For example, the P3 model uses constructs from multiple behavioral theories to describe interventions at the provider, practice, and patient level that together can begin to address preventive care challenges, including vaccine hesitancy,⁵⁶ an approach not dissimilar to those based on the application of psychological science.⁵⁷ Recent reviews also identify multiple interventions that have shown success in addressing hesitancy directly with patients or indirectly through support of clinicians.^{58,59} Many of these interventions and strategies focus on supporting successful provider-patient communication about vaccines and building a culture of immunization support through practice-level activities and systems.⁶⁰

One common thread across the lifespan is the role of the individual clinician as a trusted source of vaccine information and advice for patients or their parents. This holds true, even for parents who express vaccine hesitancy or who do not plan to follow vaccine recommendations.⁶¹ Health care provider recommendations are cited as a top reason for acceptance of vaccines for HPV,⁶² seasonal influenza,⁶³ and vaccination during pregnancy.⁶⁴ Given the potential positive (or negative) impact of a health care provider’s advice, educational interventions aimed at supporting clinicians in their direct communication with patients have a central role to play.

One such intervention is the use of a presumptive or announcement approach to begin communication over vaccination. In 1 study testing this approach,⁶⁵ vaccine acceptance in a pediatric clinic was higher when the clinician began discussions with a presumptive choice (such as by saying “your child is due for vaccines today”) compared with a participatory approach (eg, “what do you want to do about vaccines today?”). The same study also found that, even when parents were initially unsure about vaccination, a brief follow-up reaffirming the physician’s recommendation in favor of vaccination led to acceptance in many cases. A similar approach has been successful in facilitating HPV vaccine uptake among adolescents.⁶⁶ For patients who are unsure or hesitant about vaccines even after a clear provider recommendation, techniques of motivational interviewing—including open-ended questioning to elicit specific concerns, expressing empathy with and affirming concerns—may be effective in addressing sources of hesitancy in greater depth at an individual level.⁶⁷

Practice-level interventions can address issues such as complacency and access, which may contribute to undervaccination.¹⁰ Mbaeyi et al⁶⁰ demonstrated the importance of vaccination to

patients by creating a practice culture that values on-time vaccination, contributing to positive social norms around vaccination. Practice-level interventions include strategies like assessment and feedback,⁶⁸ so that providers are aware of their practice-level vaccination rates and can focus their attention on areas of low coverage, reminder-recall systems to prompt patients to return for due or missed vaccines,⁶⁹ and standing orders to maximize opportunistic vaccination.⁷⁰ Other strategies, such as making vaccine information easy to find at the health care facility or proactively sharing the clinic’s policy on vaccination, can help foster a culture of immunization support that reinforces the importance of vaccination to all.⁶⁰

Hesitancy over COVID-19 vaccination brings additional challenges that have not occurred with other vaccines (Table I). The need to implement rapid global vaccination, using novel vaccine technology, is unprecedented. Political interference has further complicated both the impact of COVID-19 and the potential implementation and success of a vaccine program to mitigate against it. Certain demographic groups, who have historically experienced health disparities, discrimination, and structural injustice, appear to be at higher risk of severe outcomes following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, and yet exhibit the highest levels of vaccine hesitancy.⁷¹ A more open and personalized approach, employing shared decision making with patients, may be a better strategy to address this.⁷¹

CONCLUSIONS

The COVID-19 has brought unique challenges to the issue of vaccine hesitancy, which vary considerably from country to country. With the rapid development and roll-out of multiple vaccines, there are no current data to demonstrate and reaffirm longer-term vaccine safety. Not only can this cause anxiety that is easily amplified on social media, but the cautious response of regulatory agencies to emerging issues of vaccine safety with a newly developed vaccine can also impact adversely on public trust.

Given the current pandemic, health care providers have an even more crucial role to play in helping address reasons for nonvaccination, tailoring interventions to the position of individual patients on the vaccine acceptance continuum. As a community, we must also address vaccine hesitancy among health care workers, providing tailored information and reassurance to both individuals and groups of individuals who may have understandable concerns. Finally, the allergy and clinical immunology community has a crucial role in not overstating the problem: the response to the potential for allergic reactions to vaccination must be reasoned and proportionate. The risk of allergic reactions to vaccines must not be exaggerated because the demonstrated risk is minimal compared with the risks posed by COVID-19 infection. It is part of our role to help facilitate the ability of every individual to safely receive vaccines, against both COVID-19 and other vaccine-preventable diseases.

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