

Vaccine Hesitancy: Drivers and how the Allergy Community can help

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Abstract

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” where 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 COVID-19 pandemic.

Key words: anaphylaxis; COVID-19; vaccination; vaccine refusal; vaccine hesitancy.

Abbreviations

AEFI Adverse events following immunization

HPV Human Papillomavirus

MMR Measles/Mumps/Rubella

SAGE Strategic Advisory Group of Experts

WHO World Health Organization

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Immunization has been a key part of global infection control since the 19th century. While 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 COVID-19, which deliver genetic material to instruct body to produce proteins which 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 1873-4, predominantly driven by the clergy; a Swedish translation of a French pro-vaccination 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” where 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 (SAGE) appointed a Working Group on Vaccine Hesitancy.⁶ In 2014, 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 continuum of hesitancy sitting between vaccine acceptance and refusal (Figure 1). In 2019, the WHO declared that vaccine hesitancy was one of the top ten threats to global health.⁷

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 (see 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 While most of the research on vaccine hesitancy has focused on childhood vaccination, vaccine hesitancy is not limited to parents making 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 (i.e., low perceived risks of vaccine-preventable diseases and

vaccination not perceived as a priority); confidence (i.e., trust in safety and efficacy of vaccines, in the delivery system and in the authorities that have issued recommendations); convenience & constraints (i.e., quality of vaccination services that can impact acceptance and perceived self-efficacy to be vaccinated); collective responsibility (i.e., willingness to protect others) and calculation (i.e.; 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 “anti-science” or irrational, but seen 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 (i.e., the proportion of a population that has received a specific vaccine), access to vaccines and vaccination services (i.e. “the supply-side”) is crucial to understanding why people are not receiving recommended vaccines. Thomson et al 2016 have summarized the different factors influencing vaccine uptake under a practical taxonomy called the “5 A’s” for: access (i.e. the ability of individuals to be reached by, or to reach, recommended vaccines), affordability (i.e. the ability of individuals to afford vaccination, both in terms of financial and non-financial costs), awareness (i.e. the degree to which individuals have knowledge of the need for, and availability of, recommended vaccines and their objective benefits and risks), acceptance (i.e. the degree to which individuals accept, question or refuse vaccination) and activation (i.e. the degree to which individuals are nudged towards vaccination uptake).²⁰

How common is vaccine hesitancy?

In high-income countries, it is estimated that between a quarter to one third of the population could be labeled as vaccine-hesitant.²¹ In 2016, Larson and collaborators 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.²² 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 UNICEF Joint Reporting Forms (JRF) on immunization, Lane et al. showed vaccine hesitancy was common and reported by 90% of countries.²⁴ In 2020, de Figueiredo et al. published a global mapping of vaccine confidence over time (2015-2019) across 149 countries, analysing 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 due to the phenomenon of digitally-driven infodemics (i.e., 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

While the reach and rapid spread of misinformation has accelerated in recent years (and is not unique to vaccines), the underlying beliefs and emotions – from fears to hopes – which 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 one of the COVID-19 vaccines, using a viral vector derived from chimp adenovirus, would turn people into monkeys²⁸ or the suggestion by some 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 which 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 three-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 which 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 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 characterised by WHO as “immunization stress related responses.”³⁴ Despite this, 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 due 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 co-design 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 non-allergic adverse events following immunization (AEFI), 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 al recently reported results from a nested case-control study in Australia, which found a lower odds ratio (0.77, 95% CI 0.62 to 0.95) in infants receiving a first dose of wP (rather than aP) among cases of food allergy.⁴⁴ An adaptive randomized controlled trial of a mixed wP/aP vaccine schedule is now underway to further investigate this.⁴⁵ Thus, while there is no evidence to suggest that vaccines cause atopy, it is possible that some vaccines may be protective against the development of atopy, compared to others.

Anaphylaxis as an AEFI 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 UK, 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 healthcare 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 UK 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 UK'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 US 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 14 January 2021 lists "Immediate or delayed-onset anaphylaxis or allergic reaction to vaccines or injectable therapies, pharmaceutical products or food items" as a contra-indication to *any* COVID-19 vaccine.⁵³ Under the current circumstances, such a stipulation is not only without foundation but potentially dangerous. Healthcare professionals and regulatory bodies must take precautions not to inadvertently generate misinformation which can cause vaccine hesitancy.⁵⁴

Addressing vaccine hesitancy

While researchers have developed many tools for understanding the prevalence of vaccine hesitancy and the factors which drive it,⁵⁵ moving towards 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 Healthcare provider recommendations are cited as a top reason for acceptance of vaccines for HPV,⁶² seasonal influenza⁶³ and vaccination during pregnancy.⁶⁴ Given the potential positive (or negative) impact of a healthcare 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 one 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 to a participatory approach (e.g. "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 under-vaccination¹⁰. As discussed by Mbaeyi et al, they demonstrate the

importance of vaccination to patients by creating a practice culture that values on-time vaccination, contributing to positive social norms around vaccination.⁶⁰ 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 maximise opportunistic vaccination.⁷⁰ Other strategies, such as making vaccine information easy to find at the healthcare 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 which have not occurred with other vaccines (Table 1). 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 programme 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 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

Conclusion

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 re-affirm 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, healthcare providers have an even more crucial role to play in helping address reasons for non-vaccination, tailoring interventions to the position of individual patients on the vaccine acceptance continuum. As a community, we must also

351 address vaccine hesitancy amongst healthcare workers, providing tailored information and
352 reassurance to both individuals and groups of individuals who may have understandable
353 concerns. Finally, the Allergy and Clinical Immunology community have a crucial role in not
354 overstating the problem: the response to the potential for allergic reactions to vaccination
355 must be reasoned and proportionate. The risk of allergic reactions to vaccines must not be
356 exaggerated, as the demonstrated risk is minimal compared to the risks posed by COVID-19
357 infection. It is part of our role to help facilitate the ability of every individual to safely
358 receive vaccines, both against COVID-19 and other vaccine-preventable diseases.
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REFERENCES

1. MacDonald NE. Vaccine hesitancy: Definition, scope and determinants. *Vaccine*. 2015;33(34):4161-4.
2. Nelson MC, Rogers J. The right to die? Anti-vaccination activity and the 1874 smallpox epidemic in Stockholm. *Soc Hist Med*. 1992 Dec;5(3):369-88.
3. Wolfe R M, Sharp L K. Anti-vaccinationists past and present *BMJ* 2002; 325 :430
4. Larson HJ, Cooper LZ, Eskola J, Katz SL, Ratzan S. Addressing the vaccine confidence gap. *Lancet* (London, England). 2011;378(9790):526-35.
5. Royal Society and the British Academy. COVID-19 vaccine deployment: Behaviour, ethics, misinformation and policy strategies. Available at <https://royalsociety.org/-/media/policy/projects/set-c/set-c-vaccine-deployment.pdf> (accessed 21 May 2021)
6. World Health Organization. Report of the Sage Working Group on Vaccine Hesitancy 2014). Available from: https://www.who.int/immunization/sage/meetings/2014/october/1_Report_WORKING_GROUP_vaccine_hesitancy_final.pdf (accessed 21 May 2021)
7. World Health Organization. Ten threats to global health in 2019. Available from: <https://www.who.int/news-room/spotlight/ten-threats-to-global-health-in-2019> (accessed 21 May 2021)
8. Leask J. Improving communication about vaccination. (2015, May 12). Available at: <https://julieleask.wordpress.com/2015/05/12/improving-communication-about-vaccination-sarah/> (accessed 21 May 2021)
9. Peretti-Watel P, Larson HJ, Ward JK, Schulz WS, Verger P. Vaccine hesitancy: clarifying a theoretical framework for an ambiguous notion. *PLoS currents*. 2015;7.
10. Bedford H, Attwell K, Danchin M, Marshall H, Corben P, Leask J. Vaccine hesitancy, refusal and access barriers: The need for clarity in terminology. *Vaccine*. 2018;36(44):6556-8.
11. Hickler B, MacDonald NE, Senouci K, Schuh HB. Efforts to monitor Global progress on individual and community demand for immunization: Development of definitions and indicators for the Global Vaccine Action Plan Strategic Objective 2. *Vaccine*. 2017;35(28):3515-9.

12. Dubé E, Gagnon D, MacDonald N, Bocquier A, Peretti-Watel P, Verger P. Underlying factors impacting vaccine hesitancy in high income countries: a review of qualitative studies. *Expert Review of Vaccines*. 2018;17(11):989-1004.
13. Schmid, P., Rauber, D., Betsch, C., Lidolt, G., & Denker, M. L. (2017). Barriers of influenza vaccination intention and behavior—a systematic review of influenza vaccine hesitancy, 2005–2016. *PloS one*, 12(1), e0170550.
14. Verger, P., Fressard, L., Collange, F., Gautier, A., Jestin, C., Launay, O., ... & Peretti-Watel, P. (2015). Vaccine hesitancy among general practitioners and its determinants during controversies: a national cross-sectional survey in France. *EBioMedicine*, 2(8), 891-897.
15. Betsch C, Schmid P, Heinemeier D, Korn L, Holtmann C, Böhm R. Beyond confidence: Development of a measure assessing the 5C psychological antecedents of vaccination *PLoS ONE* 13(12): e0208601
16. Leach M, Fairhead J. Vaccine anxieties: global science, child health and society. London: Earthscan; 2007.
17. Reich J. *Calling the Shots: Why Parents Reject Vaccines*. 1st ed. New York: NYU Press; 2016.
18. Sobo EJ. Social Cultivation of Vaccine Refusal and Delay among Waldorf (Steiner) School Parents. *Medical anthropology quarterly*. 2015;29(3):381-99.
19. Razai M S, Osama T, McKechnie D G J, Majeed A. Covid-19 vaccine hesitancy among ethnic minority groups *BMJ* 2021; 372:n513
20. Thomson A, Robinson K, Vallée-Tourangeau G. The 5As: A practical taxonomy for the determinants of vaccine uptake. *Vaccine*. 2016;34(8):1018-24.
21. Yaqub, O., Castle-Clarke, S., Sevdalis, N., & Chataway, J. (2014). Attitudes to vaccination: a critical review. *Social science & medicine*, 112, 1-11
22. Larson HJ, de Figueiredo A, Xiahong Z, Schulz WS, Verger P, et al. 2016. The State of Vaccine Confidence 2016: Global Insights Through a 67-Country Survey. *EBioMedicine* 12:295-301
23. Wellcome Global Monitor. 2018. Wellcome Global Monitor 2018 : How does the world feel about science and health?
<https://wellcome.ac.uk/sites/default/files/wellcome-global-monitor-2018.pdf>.

24. Lane S, MacDonald NE, Marti M, Dumolard L. 2018. Vaccine hesitancy around the globe: Analysis of three years of WHO/UNICEF Joint Reporting Form data-2015-2017. *Vaccine* 36:3861-7
25. De Figueiredo A, Simas C, Karafillakis E, Paterson P, Larson HJ. Mapping global trends in vaccine confidence and investigating barriers to vaccine uptake: a large-scale retrospective temporal modelling study. *Lancet* 2020; 396 (10255): 898-908.
26. Lancet Editorial, The Covid-19 Infodemic. *The Lancet* 2020; 20(8):875.
27. Leask J. Vaccines – lessons from three centuries of protest. *Nature* 585, 499-501 (2020)
28. Rana M, O'Neill S. Coronavirus: fake news factories churning out lies over 'monkey' vaccine. *The Times (UK)* 16 October 2020
29. <https://www.businessinsider.com/bolsonaro-claims-covid-19-vaccines-could-turn-people-into-crocodiles-2020-12?r=US&IR=T>
30. Larson HJ. *Stuck: How Vaccine Rumors Start – and Why They Don't Go Away*. New York: Oxford University Press, 2020.
31. Andrus JK, Perry HB. Community Engagement, Ownership, and Civil Society Organizations in Polio Eradication. *Am J Trop Med Hyg.* 2019;101(4_Suppl):1-3.
32. Coltart CE, Lindsey B, Ghinai I, Johnson AM, Heymann DL. The Ebola outbreak, 2013-2016: old lessons for new epidemics. *Philos Trans R Soc Lond B Biol Sci.* 2017;372(1721):20160297.
33. Enria L, Lees S, Smout E. et al. Power, fairness and trust: understanding and engaging with vaccine trial participants and communities in the setting up the EBOVAC-Salone vaccine trial in Sierra Leone. *BMC Public Health* 16, 1140 (2016).
34. World Health Organization. Immunization stress-related response. A manual for program managers and health professionals to prevent, identify and respond to stress related responses following immunization. Geneva: World Health Organization; 2019.
35. Larson HJ. Japan's HPV vaccine crisis: act now to avert cervical cancer cases and deaths *The Lancet* 2020; 5(4):E184-E185.
36. Pedersen, Eva & Loft, Louise & Jacobsen, Stine & Søbørg, Bolette & Bigaard, Janne. Strategic health communication on social media: Insights from a Danish social media

- campaign to address HPV vaccination hesitancy. *Vaccine* 2020; 38. 10.1016/j.vaccine.2020.05.061.
37. Offit PA, Hackett CJ. Addressing parents' concerns: do vaccines cause allergic or autoimmune diseases? *Pediatrics*. 2003 Mar;111(3):653-9.
 38. Anderson HR, Poloniecki JD, Strachan DP, et al. Immunization and symptoms of atopic disease in children: results from the international study of asthma and allergies in children. *Am J Public Health*. 2001 Jul;91(7):1126-9.
 39. DeStefano F, Gu D, Kramarz P, et al. Childhood vaccinations and the risk of asthma. *Pediatr Infect Dis J*. 2002 Jun;21(6):498-504.
 40. Gruber C, Kulig M, Bergmann R, et al. Delayed hypersensitivity to tuberculin, total immunoglobulin E, specific sensitization, and atopic manifestations in longitudinally followed early Bacille Calmette-Guerin-vaccinated and nonvaccinated children. *Pediatrics*. 2001 Mar;107(3):E36.
 41. Koppen S, de Groot R, Neijens HJ, et al. No epidemiological evidence for infant vaccinations to cause allergic disease. *Vaccine*. 2004;22:3375-3385.
 42. Matheson MC, Haydn Walters E, Burgess JA, et al. Childhood immunization and atopic disease into middle-age — a prospective cohort study. *Pediatr Allergy Immunol*. 2010; 21:301-306.
 43. Venter C, Stowe J, Andrews NJ, Miller E, Turner PJ. No association between atopic outcomes and type of pertussis vaccine given in children born on the Isle of Wight 2001-2002. *J Allergy Clin Immunol Pract*. 2016 Nov-Dec;4(6):1248-1250.
 44. Estcourt MJ, Campbell DE, Gold MS, Richmond P, Allen KJ, Quinn HE, et al. Whole-Cell Pertussis Vaccination and Decreased Risk of IgE-Mediated Food Allergy: A Nested Case-Control Study. *J Allergy Clin Immunol Pract*. 2020 Jun;8(6):2004-2014.
 45. Perez Chacon G, Estcourt MJ, Totterdell J, Campbell DE, Perrett KP, Marsh JA, et al. OPTIMUM study protocol: an adaptive randomised controlled trial of a mixed whole-cell/acellular pertussis vaccine schedule. *BMJ Open*. 2020 Dec 17;10(12):e042838.
 46. Dreskin SC, Halsey NA, Kelso JM, et al. International Consensus (ICON): allergic reactions to vaccines. *World Allergy Organ J*. 2016;9(1):32.
 47. Su JR, Moro PL, Ng CS, Lewis PW, Said MA, Cano MV. Anaphylaxis after vaccination reported to the Vaccine Adverse Event Reporting System, 1990-2016. *J Allergy Clin Immunol*. 2019 Apr;143(4):1465-1473.

48. Greenhawt M, Turner PJ, Kelso JM. Administration of influenza vaccines to egg allergic recipients: A practice parameter update 2017. *Ann Allergy Asthma Immunol*. 2018 Jan;120(1):49-52.
49. Fasano MB, Wood RA, Cooke SK, Sampson HA. Egg hypersensitivity and adverse reactions to measles, mumps, and rubella vaccine. *J Pediatr*. 1992 Jun;120(6):878-81.
50. Bandi S, Macdougall C. MMR and egg allergy: to vaccinate or not to vaccinate? *Br J Gen Pract*. 2010 Sep;60(578):693-4.
51. Raine J. Confirmation of guidance to vaccination centres on managing allergic reactions following COVID-19 vaccination with the Pfizer/BioNTech vaccine (press release). Medicines and Healthcare products Regulatory Agency (MHRA), 9 December 2020. Available at: <https://www.gov.uk/government/news/confirmation-of-guidance-to-vaccination-centres-on-managing-allergic-reactions-following-covid-19-vaccination-with-the-pfizer-biontech-vaccine>
52. Medicines and Healthcare products Regulatory Agency (MHRA). Oxford University/AstraZeneca COVID-19 vaccine approved (press release). 30 December 2020. Available at: <https://www.gov.uk/government/news/oxford-universityastrazeneca-covid-19-vaccine-approved>
53. National Health Mission, Ministry of Health and Family Welfare of the Government of India. Precautions and contraindications for COVID-19 vaccination. Available at: <https://www.mohfw.gov.in/pdf/LetterfromAddlSecyMoHFWregContraindicationsandFactsheetforCOVID19vaccines.pdf>
54. Hourihane JO'B, Byrne AM, Blümchen K, Turner PJ, Greenhawt M. Ascertainment Bias in Anaphylaxis Safety Data of COVID-19 Vaccines. *J Allergy Clin Immunol Pract*. 2021 May 4. doi: 10.1016/j.jaip.2021.04.025. Epub ahead of print.
55. Dyda A, King C, Dey A, Leask J, Dunn AG. A systematic review of studies that measure parental vaccine attitudes and beliefs in childhood vaccination. *BMC Public Health*. 2020;20(1):1253.
56. Bednarczyk RA, Chamberlain A, Mathewson K, Salmon DA, Omer SB. Practice-, provider-, and patient-level interventions to improve preventive care: Development of the P3 model. *Prev Med Rep*. 2018;11:131-138.

57. Brewer NT, Chapman GB, Rothman AJ, Leask J, Kempe A. Increasing vaccination: Putting psychological science into action. *Psychological science in the public interest*. 2017;18(3):149-207.
58. Frew PW, Lutz CS. Interventions to increase pediatric vaccine uptake: An overview of recent findings. *Hum Vaccin Immunother*. 2017;13(11):2503-2511.
59. Cataldi JR, Kerns ME, O’Leary ST. Evidence-based strategies to increase vaccination uptake: a review. *Curr Opin Pediatr*. 2020;32(1):151-159.
60. Mbaeyi S, Fisher A, Cohn A. Strengthening vaccine confidence and acceptance in the pediatric provider office. *Pediatr Ann*. 2020;49(12):e523-e531.
61. National Academies of Sciences, Engineering, and Medicine 2021. The Critical Public Health Value of Vaccines: Tackling Issues of Access and Hesitancy: Proceedings of a Workshop. Washington, DC: The National Academies Press.
<https://doi.org/10.17226/26134>.
62. Oh NL, Biddell CB, Rhodes BE, Brewer NT. Provider communication and HPV vaccine uptake: A meta-analysis and systematic review. *Preventive Medicine*. 2021;148.
63. Villacorta R, Sood N. Determinants of healthcare provider recommendations for influenza vaccinations. *Preventive Medicine Reports*. 2015;2:355-370.
64. Myers KL. Predictors of maternal vaccination in the United States: An integrative review of the literature. *Vaccine*. 2016;34(34):3942-3949.
65. Opel DJ, Mangione-Smith R, Robinson JD, Heritage J, DeVere V, Salas HS, et al. The influence of provider communication behaviors on parental vaccine acceptance and visit experience. *Am J Public Health*. 2015; 105(10), 1998-2004.
66. Brewer NT, Hall ME, Malo TL, Gilkey MB, Quinn B, Lathren C. Announcements Versus Conversations to Improve HPV Vaccination Coverage: A Randomized Trial. *Pediatrics*. 2017;139(1) e20161764.
67. Gagneur A, Gosselin V, Dube E. Motivational interviewing: A promising tool to address vaccine hesitancy. *Vaccine*. 2018;36:6553-6555.
68. The Community Guide. Vaccination Programs: Provider assessment and feedback.
<https://www.thecommunityguide.org/findings/vaccination-programs-provider-assessment-and-feedback>. Accessed May 2, 2021.

- 544 69. The Community Guide. Vaccination programs: Client reminder and recall systems.
545 [https://www.thecommunityguide.org/findings/vaccination-programs-client-](https://www.thecommunityguide.org/findings/vaccination-programs-client-reminder-and-recall-systems)
546 [reminder-and-recall-systems](https://www.thecommunityguide.org/findings/vaccination-programs-client-reminder-and-recall-systems). Accessed May 2, 2021.
- 547 70. Tan LJ, Van Oss R, Ofstead CL, Wetzler HP. Maximizing the impact of, and sustaining
548 standing orders protocols for adult immunization in outpatient clinics. *American*
549 *Journal of Infection Control*. 2020;48(3):290-296.
- 550 71. Opel DJ, Lo B, Peek ME. Addressing Mistrust About COVID-19 Vaccines Among
551 Patients of Color. *Ann Intern Med*. 2021 May;174(5):698-700.
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Factors which contribute to vaccine hesitancy	Reasons specific to COVID-19 vaccines
• Concerns over safety • Previous experiences with respect to vaccination • Prior interactions with (and trust in) healthcare 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 • Religious beliefs e.g. over use of aborted fetuses or dietary restrictions • Historical concerns over the use of vaccines in specific ethnic/minority groups • Preference towards a particular lifestyle e.g. “natural” medicine, veganism • Peer pressure / perception of vaccination by peers • Needlephobia • Inconvenience • Cost of vaccine (both direct and indirect costs e.g. time off work)	• New technology and speed of vaccine development • (Perceived) lack of safety data, particularly with respect to longer-term safety • 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 where other public health measures have been successful in curbing infections e.g. Australia • Lack of perceived need to for vaccination following SARS-CoV-2 infection • Concerns over commercial interests driving vaccination • Lack of data over persistence of immunity • Long-COVID syndrome

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555 **Table 1:** Possible reasons for vaccine hesitancy

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FIGURE LEGENDS

Figure 1: Continuum of vaccine hesitancy. Individuals may move between categories over time due to variable influences such as (mis)information, or the perceived need for vaccination (e.g. pandemic response, requirement for vaccination in order for travel). Adapted from Leask, 2015.⁸

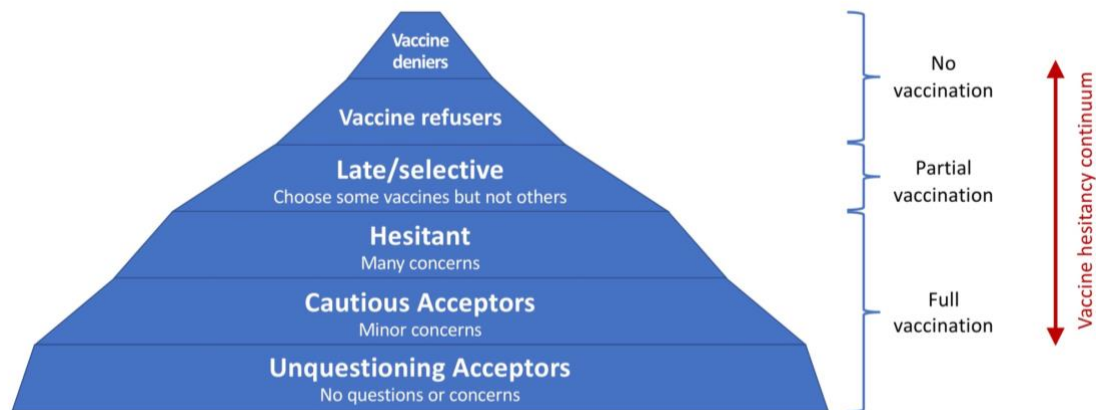


Figure 2: 5C model of factors influencing vaccine hesitancy and acceptance. Adapted from Betsch et al.¹⁵

