Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Immunization stress-related responses: Implications for vaccination hesitancy and vaccination processes during the COVID-19 pandemic

1. Introduction

Vaccination hesitancy is a widespread problem, representing one of the current top ten global health threats (WHO, 2019a). Most people do not adhere to vaccination recommendations during regular influenza season. For example, only about 30% of US adults routinely receive vaccination against seasonal influenza (Levi, Segal, Laurent, & Lieberman, 2010). Vaccination hesitancy is also a problem during pandemics, including past influenza pandemics and the COVID-19 pandemic. During the Swine flu pandemic in 2009, only 20–40% of people in Europe and North American sought, or intended to seek, vaccination (Taylor, 2019). Surveys in 2021 have reported that only 50–60% of respondents worldwide were willing to be vaccinated against COVID-19 (Razai, Chaudhry, Doerholt, Bauld, & Majeed, 2021), although these figures are likely to change as a result of shifts in the balance of vaccination incentives (e.g., vaccination passports, which permit access to social venues such as restaurants and sporting events) and disincentives (e.g., vaccine-related adverse events, especially those that are widely reported in the media; Clements, 2003).

A distinction can be drawn between two types of adverse reactions to vaccines, including (1) those attributable to the ingredients in the vaccine, and (2) those that are not due to the vaccine but, instead, represent stress reactions to the process of getting immunized. Vaccine-related adverse reactions are commonly misinterpreted in the news media and social media, with commentators mistakenly regarding immunization stress reactions as evidence for the harmfulness of vaccines. The purpose of this editorial is to highlight the importance of immunization stress-related adverse events in the context of vaccination hesitancy and the vaccination process and to discuss ways of addressing the problem.

2. Nocebo effect

Understanding the nocebo effect, which occurs when negative expectations about an intervention or treatment (e.g., a vaccination injection) cause the person to experience negative side effects (Kennedy, 1961), is essential for understanding adverse stress-related reactions to vaccination. Negative expectations may involve symptom misattribution, including the misattribution of stress reactions as an intervention or treatment side effect. Nocebo effects can be elicited for a range of symptoms, including localized pain at the injection site, nausea, headache, cardiovascular functioning, perception of cognitive abilities, sensory phenomena (e.g., numbness, tingling), and motoric responses (e.g., agitation, unsteadiness, twitching, tics, speech impairment) (Bagarić, Jokić-Begić, & Sangster Jokić, 2021).

Negative expectations about vaccinations can be acquired via various informational routes, including exposure to news media or social media, direct verbal suggestion, conditioned learning experiences (e.g., classical conditioning involving the association of injections with adverse effects), and observational learning of other people having adverse reactions (Bagarić et al., 2021; Colloca & Barsky, 2020). They can even be acquired when conditioning is implicit; that is, conditioning outside of awareness (Bajcar, Adamczyk, Wiercioch-Kuzianik, & Bąbel, 2020).

Negative expectations increase the awareness and reporting of adverse effects and they can also be generated by explicit warnings about specific side effects of a given drug or vaccine (Petrie & Rief, 2019). COVID-19 vaccines are ripe for nocebo reactions because: (1) coronavirus vaccines are novel, without a track record, and therefore there is uncertainty about their long-term effects, (2) the vaccines have been associated with rare but dramatic complications, as highlighted in the media, (3) people are told to expect intense side effects of the COVID-19 vaccine (e.g., flu-related symptoms), especially for the second dose of the two-dose vaccines, and these side effects have been widely reported in the media, (4) rumors, misinformation, and conspiracy theories about the COVID-19 vaccines have been widely disseminated in social media, fuelling concern or alarm, at least among some people, and (5) societal pressure to get vaccinated against SARSCoV-2 has been increasing, as illustrated by community announcements stating that the majority of COVID-19 outbreaks and infections during 2021 are among unvaccinated people.

Stronger nocebo effects are likely to occur for vaccines that have been criticized in the media (e.g., the AstraZeneca vaccine for COVID-19), as compared to other vaccines (e.g., Pfizer or Moderna vaccines for COVID-19). Nocebo reactions are more likely when a vaccination injection is painful (Colloca & Barsky, 2020) or, as in the case of oral vaccines, if the vaccine syrup has a bad taste. For example, in a case of mass psychogenic illness associated with an oral cholera vaccine, the disagreeable taste of the vaccine was thought to be a contributing factor for the mass outbreak (Khiem et al., 2003). The tendency to have nocebo reactions is also associated with high levels of negative emotionality (i.e., neuroticism), somatic preoccupation, fear of pain, and the tendency to misinterpret harmless bodily sensations as negative effects of a treatment (Bagarić et al., 2021). Nocebo effects tend to be most commonly reported by people with a history of anxiety disorders, mood disorders, or medically unexplained physical symptoms (Kern, Kramm, Witt, & Barth, 2020).

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3. Immunization stress-related responses

The WHO (2018) proposed that some adverse events following vaccination are forms of immunization stress-related responses (ISRRs), which are nocebo effects triggered by the process of vaccination but not caused by the components of the vaccine. Four overlapping groups of reactions are listed as ISRRs, including: (1) acute anxiety and stress responses, (2) vasovagal reactions, (3) mass psychogenic illness, and (4) functional neurological disorders. ISSRs may arise just prior, during, or after immunization. Here, immunization refers to the process of administering the vaccine, which includes psychosocial elements (e.g., lining up with other people, watching others getting vaccinated, seeing others in post-injection waiting areas). ISRRs tend to occur when new vaccines are introduced or when there are changes to an established vaccination program, such as a new age group or new vaccination setting (Loharikar et al., 2018).

3.1. Acute anxiety and stress responses

Common vaccination-related anxiety or stress reactions include palpitations, headache, dizziness, and faintness, and may be associated with stress-related hyperventilation (WHO, 2018). These reactions typically occur in schools or other closed, cohesive social settings (Loharikar et al., 2018). Anxiety- or stress-related adverse effects have occurred for vaccines for a range of diseases, including tetanus, hepatitis B, cholera, human papillomavirus, and influenza. In all cases the affected people, typically children or young adolescents, recovered quickly, although vaccine programs were disrupted and public trust in these programs was eroded (Loharikar et al., 2018).

3.2. Vasovagal reactions

Injection-related vasovagal reactions involve an initial increase in heartrate followed by bradycardia, faintness, and sometimes syncope. Such reactions can occur in isolated form or they may be a feature of blood-injury-injection phobia (American Psychiatric Association, 2013). If the person faints, it typically occurs rapidly after immunization and virtually all (98%) episodes of immunization-triggered syncope occur within 30 min after vaccination (WHO, 2018). Adolescents, especially if immunized in mass clinical settings, are more prone to have anxiety-related vasovagal reactions resulting in fainting, sometimes accompanied by pseudoseizures (WHO, 2018). The latter are tonic-clonic like movements that mimic epileptic seizures but with no neurologic origins and typically lacking in tongue-biting, urinary incontinence, cyanosis, and auras.

3.3. Mass psychogenic illness

Mass psychogenic illness (MPI) is the collective occurrence of a constellation of bodily reactions (or “symptoms”) suggestive of organic illness but without an identified cause in a group of people with shared beliefs about the cause of the symptoms (Clements, 2003). MPI typically occurs in closed, cohesive social settings, such as schools. MPI can be triggered by a range of factors, including noxious smells, the sight of sick people, and vaccination. Vaccine-related MPI is strikingly similar to other forms of MPI in terms of common symptoms, line-of-sight transmission, ripple effects, and demographics, with children and young adolescents being most affected (Clements, 2003). Common symptoms include headache, dizziness, weakness, nausea, trembling, and fainting, but can also involve functional neurological symptoms such as difficulty walking or speaking or pseudoseizures (Clements, 2003). MPI can spread rapidly and, once underway, is difficult to stop. It can be exacerbated by media coverage showing, for example, groups of afflicted school children being whisked away to hospital by ambulance as their parents anxiously look on. Recovery is typically rapid, typically within hours or days after receiving a medical evaluation and reassurance that they are not physically ill.

There have been many reported episodes of vaccine-triggered MPI for a range of different vaccines throughout the world, including those for influenza, tetanus, diphtheria, helminths parasites (i.e., worms), papillomavirus, cholera, and Japanese encephalitis (e.g., Clements, 2003; Dodoo, Adjei, Couper, Hugman, & Edwards, 2007; Huang, Hsu, Lee, & Chuang, 2010; Kharabsheh et al., 2001; Marchetti et al., 2020). Outbreaks have been largely confined to mass vaccination settings in schools, with sufferers being typically children or young adolescents. In each episode there was no evidence that the vaccine components caused the symptoms. Vaccine-related MPI, like MPI in general, tends to have an acute onset, rapid spread, and rapid resolution of symptoms, usually within hours or days after the sufferers (and their parents, in the case of children and adolescents) have been reassured.

The odds of MPI outbreaks are increased when there is a strong anti-government sentiment in the community, including media debate, about the safety of public health measures (Kharabsheh et al., 2001). These social conditions are present during COVID-19 in which there are vociferous protests from anti-vaxers about the supposed dangers of the COVID-19 vaccines. Rumors and misinformation, especially when circulated in the media, can aggravate outbreaks of MPI. To illustrate, MPI broke out during a mass deworming program in Ghana, in which school children were treated with mebendazole (Dodoo et al., 2007).

Within hours of the start of the programme, there were reports on local radio stations about deaths and serious side-effects affecting several children in three administrative regions. These reports led to considerable public disorder. In some instances, teachers were attacked [by irate parents or caregivers] and schools were shut. (Dodoo et al., 2007, p. 465).

In fact, there were no deaths and only scattered reports of mild gastrointestinal upset, which is a known side effect of mebendazole. Over 350 children were brought to hospital. They and their parents were reassured and the children were discharged.

3.4. Functional neurological disorders

Previously known as conversion disorders, functional neurological disorders (FNDs) are mental disorders characterized by one or more motor or sensory reactions resembling neurological symptoms but incompatible with known neurologic diseases (American Psychiatric Association, 2013). Common symptoms of FNDs include weakness, paralysis, movement disorders, speech impairment, and pseudoseizures. Acute physiological reactions to immunization, such as localized pain at the injection site, vasovagal responses, and flu-like symptoms, can trigger or evolve into FNDs (Butler et al., 2021). FNDs are assumed to arise involuntarily, although this can be difficult to establish in clinical practice. The diagnosis of FND is made through the identification of positive symptoms (i.e., positive indications of FND, such as tremors that abate when the person is distracted) rather than as a diagnosis of exclusion (Espay et al., 2018). FNDs can be transient or chronic. FND and MPI can overlap, as in cases of outbreak of pseudoseizures in school settings. However, MPI is more likely to be transient and affect groups of young people, especially children, whereas FND affects mainly adolescents or adults, tends to arise sporadically in single individuals rather than affecting groups of people, and can become chronic if untreated (Espay et al., 2018).

FND has been triggered by influenza inoculations, including those for season flu and Swine flu (e.g., Lin, Peng, Liu, & Chiu, 2011; Ryu & Baik, 2010). During COVID-19 there have been several cases of FND (e.g., Butler et al., 2021; Fasano & Daniele, 2021). The following illustrative example, reported by Butler et al. (2021), is summarized as follows and edited for brevity:

A 38-year-old female with no significant past medical history was administered the first dose of the Pfizer-BioNTech SARSCoV-2 vaccine to her left arm. Around 20 min postvaccination, she developed an odd sensation (which the patient described as “weakness”) around the left

ear, which in seconds spread to the mouth and then to the left arm and leg over the rest of the day. No headache or other symptom was noted. … On waking the next morning, the patient had difficulty moving the left side of her face, as well as heaviness in her left leg. … The patient's difficulty in moving her left arm and left leg, as well as her facial weakness, continued and peaked 2 days after the vaccine was administered. An MRI brain scan … was normal. … Two months post-vaccination, the patient was examined in a general neurology clinic by a neurologist. The only abnormality on neurological examination was mild weakness in the left lower limb with positive hip abductor and Hoover's sign. FND was diagnosed on the basis of positive neurological measures, including Hoover's sign, hip abduction test, and symptom variability. (Butler et al., 2021, pp. 1–2).

Expectations about vaccination, prior belief about vaccines in general, heightened body-focused attention, anxious arousal, and other factors may play a role in the pathophysiology of FND (Kim, Kung, & Perez, 2021). Research shows that FNDs tend to associated with heightened suggestibility (Wieder, Brown, Thompson, & Terhune, 2021); that is, an increased responsiveness to direct verbal suggestions. This raises the question of whether vaccine-related FNDs are dramatic types of nocebo reactions wherein one is led to expect dramatic negative side effects and then experiences them.

Fasono and Daniele (2021) underscored the importance of FNDs during the COVID-19 vaccination program: "In our view, FND following COVID-19 vaccination will not be a rare phenomenon and will be widely covered by the media, being interpreted as a direct consequence of the vaccine, as already seen in the past" (p. 1). Indeed, there have been a number of videos circulating on social media (e.g., YouTube), some garnering millions of views, purportedly showing neurological adverse effects of COVID-19 vaccines (Kim et al., 2021). In several instances, neurologists have reviewed the video materials and found evidence that the so-called neurological adverse effects were most likely FNDs and, therefore, unrelated to the contents of the vaccine (Kim et al., 2021). In such cases it was not even clear that the person in the video had even been vaccinated. Nevertheless, such negative publicity can undermine vaccination uptake in the community.

Treatment of FND involves education on the diagnosis, physical rehabilitation, and cognitive behavior therapy (Gutkin, McLean, Brown, & Kanaan, 2021; Kim et al., 2021). Here, patients are informed that the symptoms are real but the symptoms are caused by an aberration in brain circuitry rather than structural lesions.

4. Implications for vaccination hesitancy

The disruptive effects of ISRRs on vaccination programs have been described worldwide (Loharikar et al., 2018; WHO, 2018). At the time of writing this editorial, vaccines for SARSCoV-2 had not been approved for children. When that approval is obtained and mass vaccination programs are implemented in clinics and schools, three things are likely to occur: (1) anti-vaccination activists will become increasingly vocal, arguing that it is their civil right and moral duty to protect their children from "dangerous" vaccines, (2) outbreaks of MPI will occur at some immunization sites, most likely at school-based sites, with intense media coverage and widespread speculation that the outbreak was due to a "bad batch" of vaccine, and (3) vaccination hesitancy will worsen because many people in the community will misinterpret the outbreaks as evidence for the harmfulness of vaccines. Bad experiences with an initial round of COVID-19 vaccines, including the occurrence of ISRRs, is likely to increase vaccination hesitancy for booster shots.

Prompt management of ISRRs is important because reports of these adverse effects can spread rapidly in the news media and social media. Ideally, healthcare workers administering vaccines would be trained in recognizing ISRRs and in providing reassurance about the benign nature of the adverse effects. To this end, just prior to the COVID-19 pandemic the WHO (2019b) published a manual that details strategies designed to help guide health professionals in the prevention, identification, and management of ISRRs. Public health authorities should also be prepared to prevent or manage such reactions. This begins with public education about the way in which real but harmless adverse effects can occur during vaccination. The reactions should not be trivialized; rather, the public should be educated about how real, unpleasant, but harmless reactions such as dizziness, fainting, pain, and headache can be part of a stress reaction.

There are various ways of reducing nocebo effects, and thereby lowering the risk of ISRRs, while still providing patients with information necessary for informed consent (Petrie & Rief, 2019). Simply warning about nocebo effects can reduce those effects (Pan, Kinitz, Stapic, & Nestoriuc, 2019). Positive framing can also reduce nocebo effects; specifically, instead of informing patients that "a minority of patients experience side effects" the message could be reframed as "the majority of people don't experience side effects" (Mao et al., 2021). For the COVID-19 vaccines, unfortunately, there has been widespread media reporting of unpleasant side effects (e.g., soreness at the injection site along with mild flu-like symptoms), which likely primes the nocebo effect.

Organizers of vaccination clinics need to be aware that MPI could be triggered when groups of people, especially children and young adolescents, are vaccinated. The odds are that MPI can be reduced by administering the vaccine injection in a room or cubicle that shields the patient from the view of others, thereby eliminating line-of-sight transmission of psychogenic stress reactions. If there is an outbreak of MPI, healthcare providers need to conduct a thorough assessment rather than dismissing the outbreak as "hysteria". It would be critical that vaccine recipients and the public in general be reassured that due diligence has been followed to rule out the possibility that the adverse reactions were due to a "bad batch" of vaccine. Methods for reducing the risk of FNDs are less clear, given the difficulties in predicting who is at greatest risk of developing a vaccine-triggered FND.

Systematically informing the public that ISRRs are real experiences, but ones not caused by the vaccine ingredients, may help offset the negative effects that these reactions have on the willingness of people to be vaccination. This is important for initial COVID-19 vaccination shots, especially given the forthcoming approval and roll-out of SARSCoV-2 vaccines for children, and for future booster immunizations that may be needed across all ages. Notwithstanding, research is required to determine whether the provision of public information—at what stages, by whom, and in what formats—is an effective means of preventing and managing ISRRs and reducing vaccine hesitancy. Additional research is also needed to establish the psychological and social predictors of ISRRs, linkages between ISRRs and vaccine hesitancy, how ISRRs related to COVID stress syndrome (Taylor, Landry, Paluszek, Rachor, & Asmundson, 2020), and how to target public information campaigns to those most at risk.

Conflict of interest

None.

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