

Combating Vaccine Hesitancy Requires Knowledge of Misfortunes and Controversies

Combater a Hesitação Vacinal Requer Conhecimento de Infortúnios e Controvérsias

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The story of anti-vaccination: a *déjà-vu*

Before the advent of safe vaccines, smallpox was a dreadful condition that occurred in epidemic waves with case-fatality rates around 30% (variola major).^{1,2} In the 10th century, Chinese and Indian physicians rubbed the fluid from smallpox pustules into a scratch on the arm of healthy individuals. This process was called variolation: the inoculation with low doses of smallpox aimed to induce a mild infection that would lead to immunity against the disease. However, variolation could cause disease and even death (1% - 2%) and was also related to outbreaks.² In the 18th century, this practice spread throughout Europe, although many physicians considered it ineffective and were afraid to adopt it. The first movements of vaccine hesitancy appeared due to fear of the side effects of variolation (including possible death). More organized anti-vaccine sentiments were often based on religious antagonism, considering it a violation of divine providence.^{1,3}

Variolation was replaced by the much safer vaccination process, which Jenner developed from 1796 to 1798, and self-published (*Variolae vaccinae*).^{2,3} Between 1840 and 1853, pro-vaccination laws were enacted, for example, the English government made vaccination compulsory for children and the poor and determined fines and prison for heads of families refusing to vaccinate their offspring.^{2,3} This situation generated a widespread antagonistic reaction from the population. While the main concern was the perceived infringement of individual freedom and the fear of establishing medical tyranny, social and economic aspects caused by the fines and imprisonment were also rife. All this led to the creation of the anti-vaccination league and in 1867 a new law was passed giving freedom to parents to take responsibility for not vaccinating their children (which is when the term 'conscientious objector' originated).^{1,3}

Spectrum of vaccine hesitancy: from bizarre ideas to plausible economic concerns

Vaccine hesitancy is often detached from scientific reasoning and a rational risk assessment of efficacy and possible side effects. Many reasons, reminiscent of the historical anti-vaccination movements, are subjectively important concerns of a religious, social, cultural, or political nature; frequently disguised as fear of persecution of minorities. In the shape of rumours, where central aspects are often factually incorrect, they may spread widely and rapidly.⁴ One example is the fear of population control, such as alleged sterilization or intentional decimation with an infectious disease: the 'North', ex-colonizers *versus* African populations (i.e.: tetanus vaccination in Kenya) or Western civilization *versus* Muslims (i.e.: polio-vaccination in Pakistan).⁴ Potentially more rational reasons of an economic nature may be important as the whole-cell pertussis vaccine scare during the 1970s in the United Kingdom (UK) may illustrate. Media reports abounded about an increase in alleged severe neurological sequela after vaccination, which epidemiological studies could not confirm. However, a large aspect of this was the perceived lack of social support to those potentially affected which led to a considerable drop in vaccination rates. The UK government passed the Vaccine Damage Payments Act, with a payment of £10 000 to those affected, to restore trust.⁵

The bumpy road of vaccine development: genuine misfortunes

Vaccines are arguably the biggest success story in medicine, with huge reductions in cases and associated mortality.² Healthcare workers (HCW) may often be unaware that the development was a bumpy road with several high-profile misfortunes or accidents (Table 1).^{2,6,7} Undoubtedly, when comparing the dimension of these incidents with the overall beneficial public-health effects of these vaccines,

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Table 1 – Notable misfortunes and accidents in the history of vaccines

Designation/disease	Year	Comment/description
Lübeck disaster/Tuberculosis	1929 - 1933	BCG vaccine contaminated with <i>M. tuberculosis</i> : 173 developed disease and 72 died
Kolmer's Vaccine trial/Polio	1932	Poorly designed trial with 10 children developing polio and five deaths ^a
Cutter Incident/Polio	1955	120 000 doses contained live virus: 40 000 abortive polio cases, 250 paralytic polio cases, and 10 people died ^b
Simian virus 40/Polio	1955 - 1963	Polio vaccine contaminated with the SV40 (monkey virus) was potentially associated with an increased risk of cancer. Studies found no evidence for cancer in millions of vaccine recipients.
Swine Flu Vaccine/Influenza	1976	Slight increased risk of Guillain Barré syndrome (1 additional case/100 000)
Rotavirus Vaccine/Diarrhoea	1998 - 1999	RotaShield vaccine was associated with an increased risk of intussusception – withdrawn from the market ^c
H1N1 Flu Vaccine/Influenza	2009 - 2010	Pandemrix (monovalent H1N1 pandemic strain) was associated with an increased risk of narcolepsy in Europe (Finland/Sweden)

^a: Brodie's trial at the same time with an inactivated vaccine also produced two polio cases and one death.

^b: including secondary cases because of spread in families/community.

^c: total number of cases observed in the US is very small; newer vaccines still carry a small risk of intussusception.

Based on information in references^{2,6,7}

the administration of vaccines largely outweighs any damages caused, as the example of the polio vaccine illustrates particularly well (Table 1). Despite some misfortunes, like the polio cases and even deaths that occurred during the Cutter incident (Table 1), millions of cases of paralytic polio were prevented. Moreover, in the WHO African region, wild poliovirus is considered eliminated (Table 2). Nowadays, highly efficient security protocols are in place during vaccine development and administration to monitor for even rare adverse events and thus make vaccines safe.⁶ However, HCW should be familiar with these misfortunes (and their dimensions) to be able to put them into perspective, which can allay the fears of vaccine-hesitant individuals who are aware of these incidents.

Controversies in vaccinology: measles and beyond

The measles vaccine also illustrates well the spectrum of arguments, from the ludicrous (scientifically disproved) to scientifically valid findings (even if controversial). Incorrect and fabricated results from 12 children published in *The Lancet* in 1998 by Wakefield and colleagues (retracted in 2010) caused the autism scare.^{6,8} Yet, the association between measles vaccination and autism has been extensively refuted.⁶ Similarly, no evidence was found that thiomersal, an ethylmercury preservative in vaccines is toxic (contrary to methylmercury which is toxic), or that thiomersal is associated with autism.⁶ Unfortunately, the anti-vaccine movements are often enthralled by these myths, although the whole story, which includes vested financial interests and fraud, Wakefield being struck off the UK medical register, the making and contents of the movie "Vaxxed", or the involvement of celebrities, like Robert Kennedy Jr., seems more like something out of a blockbuster thriller.⁴

However, it is often ignored that, on a few occasions,

vaccines and vaccination schemes may have been associated with poor outcomes, although the absolute effects were usually small, especially when compared to the overall beneficial effects the respective vaccine had (Table 2). For example, in Africa (Guinea-Bissau, Senegal, Zaire, Rwanda) the high dose Edmonton-Zagreb measles live vaccine was reported to have been associated with increased overall mortality in girls compared to the standard vaccine (1989 - 1992).^{6,9} Although no satisfactory reason for the observation has been found yet, in 1992 the WHO suspended this recommended practice.¹⁰ The administration of an inactivated measles vaccine to almost one million children during the 1960s resulted in short-lived protection, and worse, it led to atypical measles (a more severe form of the disease) and possibly some associated deaths.^{6,9} A Danish group led extensive vaccination campaigns, focusing on measles, in post-independence Guinea-Bissau, which led to the creation of the Bandim research center. They reported that live vaccines (BCG, measles, etc.) seem to provide an additional non-specific, beneficial effect, and are associated with decreased mortality beyond the rate expected due to the decrease in the vaccine-targeted disease.¹¹ However, this was offset by their findings that the administration of inactivated vaccines only (especially diphtheria-pertussis-tetanus – but also others), seemed to be associated with increased childhood mortality, with a significant preponderance for girls.¹¹ It has also been observed that the administration of a live vaccine with or after administration of an inactivated vaccine seems to abolish this phenomenon.¹¹

Combating vaccine hesitancy requires awareness of misfortunes and controversies

Certainly, vaccination is a crucial strategy to achieve better health outcomes for many infections. Even some

Table 2 – Conceivable factual origin of anti-vaccine arguments

Anti-vaccine argument	Possible factual origin ^a
Vaccines cause death/increase mortality	Misfortunes/accidents: Lübeck, Cutter ^b High titre measles vaccine in Africa was associated with increased risk of death ^c Increased risk of death after inactivated vaccines ^c
Vaccines cause the disease they should prevent	Oral polio-vaccine (OPV) strains, especially OPV 2, reverted (became pathogenic) and cause most polio cases in Africa now ^{d,e} Dengvaxia (dengue) vaccine may be associated with an increased risk of severe disease if there is no prior infection before the first vaccine dose (antibody-dependent enhancement) ^d Inactivated measles vaccine may cause atypical (more severe) measles ^c Varicella vaccine strain can become latent and cause herpes zoster (HZ), although HZ rates are lower in vaccinated than unvaccinated ^d
Vaccines cause (severe) side-effects/disease	Increased risk of Guillain-Barré syndrome – swine flu vaccine 1976 ^b Increased risk of narcolepsy after H1N1 pandemic flu vaccine in 2009 ^b Increase in risk of intussusception after rotavirus vaccine ^b

^a: it should be noted that most of the reported absolute risks are very small, especially when compared to the overall beneficial effects the respective vaccine has/had.

^b: see Table 1 for a description.

^c: see text for description and reference.

^d: see references^{2,6,7,8,10}

^e: Wild poliovirus is considered eliminated in Africa since 2020 and sporadic cases are imported. WHO reports less than 1000 vaccine derived cases per year in 2020-2023.¹²

cancers, which represent a significant cause of morbidity and mortality worldwide, are now preventable through vaccination. While the minority (thought to be less than 10%) with extreme anti-vaccine views may not be swayed by these achievements or scientific arguments, most vaccine-hesitant people (‘fence sitters’) are usually open to discussion. Certainly, subjective concerns of a religious, cultural, or societal nature must be carefully respected to maintain the population’s trust in HCW.

It should be noted that some common anti-vaccine arguments (Table 2) have hinged on a historically true incident or a factually correct misfortune, even if the dimension of any occurred damages or risks was very small when compared to all the beneficial effects of the respective vaccination. Considering that extensive literature suggests that humans often lack a solid understanding of the statistically correct dimension of risks, vaccine-hesitant people may lack the scientific literacy to realistically assess and understand the risk/benefit ratio and consequently be fearful, knowing that some anti-vaccine arguments might refer to some historically true incident or some factual controversy.

What could happen if HCW are not so aware of occurred misfortunes and current controversies? They may be more likely to rebuff vaccine doubters and reject any criticism as fake or untrue and provide ‘generic information’ that all vaccines are 100% safe, which may be perceived as patronizing and incorrect. This can easily erode the much-needed trust necessary to persuade vaccine-doubters to see the scientific evidence favouring vaccines for personal protection and as a public health good. As everything else in medicine, it is sound knowledge which allows one to respond

best to vaccine-hesitancy, not only the capacity to debunk bizarre myths but especially the ability to explain the scientific facts (even the ‘bad ones’) in a convincing way.

AUTHOR CONTRIBUTIONS

VLPJ, EV: Conception and writing of the manuscript.

TH: Conception, writing, and critical review of the manuscript.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in 2013.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients’ data publication.

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