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Delayed harmful effects of vaccination

PERSPECTIVES

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The author has completed the ICMJE form and reports the following conflict of interest: He has served as a medical expert in several court cases involving sequelae following vaccination.

Since the mass vaccination against swine flu in 2009, new knowledge has changed the basis for the assessment of injury compensation and for further research on delayed sequelae following vaccination.

Vaccination is considered to be a safe medical procedure. Except for reactions around the injection site and mild systemic symptoms, vaccination rarely results in injury. Of the 824 500 vaccine doses administered in 2017, 68 cases of possible severe adverse effects were reported (1). Since some reported injuries have causes other than vaccination, and since not all vaccine injuries are thought to be reported, the low number of injuries should be regarded more as an indicator of the scope of injuries rather than as a scientific finding.

In Norway, two vaccines in particular have resulted in claims for injury compensation: the meningococcal B vaccine, which was tested on 292 000 military recruits and lower secondary school pupils in 1988–1994, and Pandemrix, which was given to 1.9 million Norwegians during the swine flu pandemic in 2009–2010 (2). By the end of 2018, the Norwegian System of Patient Injury Compensation had received 383 compensation claims regarding the meningococcal B vaccine and 769 claims related to Pandemrix. While both vaccines were associated with chronic fatigue syndrome, Pandemrix was also linked to the development of narcolepsy and Guillain-Barré Syndrome.

Sequelae

Even if a patient develops narcolepsy or Guillain-Barré Syndrome following a vaccination, the condition is not necessarily a sequela. In addition, there must be a causal relationship between the events. Causal relationships are difficult to prove in individual patients, partly because inflammatory conditions such as narcolepsy and Guillain-Barré Syndrome have an unclear aetiology, and partly because important questions about the incidence and pathogenesis of sequelae remain unanswered. At a more fundamental level and, it could be argued, as a consequence of insufficient knowledge about injury mechanisms, it is uncertain whether the term 'sequela' has a consistent pathophysiological correlate.

> ***«Their belief in a causal relationship between vaccines and health problems is bolstered by media reports about patients whose lives have been turned upside down after receiving a vaccine»***

The general population, however, does not seem to harbour the same doubt. Their belief in a causal relationship between vaccines and health problems is bolstered by media reports about patients whose lives have been turned upside down after receiving a vaccine (3, 4). Many of these cases have been thoroughly reviewed in the legal system, and some judgments in favour of patients have had to go all the way to the Supreme Court to be legally enforced. Such reports generate fear, give vaccines a bad reputation, make people less willing to get vaccinated, and highlight the need for further research on the incidence and pathophysiology of sequelae.

Attribution of cause – law and medicine

That patients succeed in the courtroom can give the impression that lawyers are taking liberties with the field of medicine and 'play fast and loose' with issues of medical causality. But this impression does not tell the whole story, for while doctors base their causal assessments on empirical data and theory, lawyers take their point of departure in criteria established in the Patient Injury Act (5). Rules of law are designed to ensure that the state will rule in favour of the patient if a medical expert can establish a probable causal relationship between the vaccination and any sequelae, and if the state cannot provide evidence of another and more likely cause of the patient's condition (6). In 2015, the Supreme Court clarified the standard of proof in vaccine injury cases by stating that 'there must be a cause that cannot only be explained in theory, but that has the practical potential of being realised. This means that the properties of the vaccine and medical knowledge must support the causal finding' ((7), para. 47).

Mechanistic and statistical explanations

To explain a phenomenon means to establish an attribution of cause. In sequelae cases, medical experts use two types of explanations: mechanistic explanations, which intend to show that a postulated cause results in a given effect in an individual patient, and statistical explanations, which entail that a postulated cause results in different effects between groups (8). The two types of explanations correspond with the court's emphasis on balance between theory and practice.

Results from mechanistic and statistical studies will often reinforce each other, but not always. There may be mechanistic causal relationships at the individual level that cannot be reproduced at the statistical level, such as rare injuries with only one or few realisations. And vice versa – it is possible to find a statistical relationship that is not relevant at the individual level, for example if pathophysiological mechanisms cannot be established. In these cases, it cannot be ruled out that the statistical relationships are spurious.

> ***«The potential for sequelae to occur should therefore be systematically studied as soon as a new vaccine has been introduced»***

Disagreement between medical experts is often due to differing emphasis on statistical and mechanistic explanations and to the fact that information contained in patients' medical records is often too vague and unsystematic to guide the experts in their assessments. Moreover, sequelae are complex conditions with a high degree of uncertainty related to aetiological and pathological factors. This leaves the data wide open to alternative interpretations.

Time criterion

It is obvious that the cause must occur before the effect, but there is no similarly evident answer to the question of how much time it takes to develop a sequela. Experimental animal models have shown that vaccines can induce tolerance breakdown and improper functioning of the immune system (9, 10), and analogies suggest that the same mechanisms can be applied to sequelae in humans.

Such injuries may take a long time to develop, and it is therefore difficult to have confidence in assertions that only injuries arising between five days and eight weeks following vaccination can be considered to be triggered by vaccination (11). The argument – which lacks research-based support – was thoroughly falsified following the Pandemrix vaccination against swine flu. While 12 of the children injured by the vaccine developed narcolepsy within six

weeks of receiving the vaccine, 30 other children developed narcolepsy from six weeks to six months following vaccination, and an additional 11 children had the same outcome from six months to two years (12).

Research on sequelae

Experts or expert panels regularly clarify issues related to the development of sequelae following vaccination. They conduct thorough, systematic assessments of the patient's medical history and compare patient information with research-based knowledge about the relevant vaccine's potential to cause injury (13). Their approach seems to be logical and correct, but because of insufficient knowledge about sequelae, it has turned out to be unreliable and fallible (14, 15). The lack of adequate knowledge suggests that more research is needed.

For established vaccines, research becomes difficult if the entire population has been vaccinated and thus homogenous with regard to the vaccine as a risk factor. In this case, the frequency of any sequelae will be concealed within the background incidence of the condition in question. Studies of the potential of new vaccines to cause injury will not be limited in the same way, and the potential for sequelae should therefore be systematically studied as soon as a new vaccine has been introduced.

Ideally, a randomised controlled trial should be conducted over several years, preferably as an extension of the phase III studies in which the efficacy and short-term adverse effects of new vaccines are studied. Using this approach, the incidence and type of sequelae in vaccinated individuals could be compared with the incidence of the same sequelae in unvaccinated individuals. However, withholding an approved vaccine from a person in a high-risk group for the disease, and who just happened to end up in the control group, presents an ethical dilemma. And moreover – it is nearly impossible to follow up the large number of people needed to conduct a study over many years. To search for narcolepsy in children, who have an incidence of 0.5–1/100 000 per year (12), 1 570 208 people would be needed to achieve sufficient statistical power to detect a three-fold increase in relative risk, and 588 822 people to find a five-fold increase (16).

> ***«One approach that would avoid the pitfalls of adverse effect registers would be to review national health registers on a regular basis to identify signs of incidence changes»***

To compensate for a lack of high-quality data, the authorities in many countries have established adverse effect registers where health personnel or patients can report injuries. However, these registers are less useful for sequelae. A sequela does not announce itself with the label *sequela*; someone must suspect it. And for conditions not previously registered as sequelae – such as narcolepsy following the swine flu vaccination – the connection could remain undetected unless coincidental events cause someone to suspect a connection (17).

One approach that would avoid the pitfalls of adverse effect registers would be to review national health registers on a regular basis to identify signs of incidence changes – whether this be an increasing or decreasing incidence of conditions that can be associated with sequelae. As long as there are good patient registers for various conditions, the vaccine's sequelae potential could be monitored almost in real-time. This approach would not work, though, for conditions that are not systematically registered.

To generate more knowledge about the mechanisms that trigger sequelae, it would be helpful to register as much information as possible about the development of injury in individual patients. In many of the reported cases of sequelae, the patients state that they experienced adverse effects soon after the vaccination. In the meningococcal B vaccine injury cases, it came to light that the participants had been told it was not necessary to see a doctor to have any early adverse effects assessed. This advice turned out to be disastrous in terms of injury assessment. To avoid similar situations and to encourage good research, vaccinated individuals who report reactions should be advised to see a doctor as soon as possible so that any symptoms can be registered and monitored. In addition, blood samples should be taken and securely stored in a biobank. Even though the injuries tend to develop in complex, non-linear patterns (18), and although it is not possible at this time to diagnose or predict sequelae, new and expanding knowledge about how the immune system functions suggests that mechanistic studies may be able to chart tolerance breakdown in the future (19).

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