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Development

Immunization

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Topic Editor:
David W. Scheifele, MD, University of British Columbia & Vaccine Evaluation Centre, Child and Family Research Institute, Canada

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Synthesis

How important is it?

The World Health Organization (WHO) and UNICEF estimate that 100 million children receive at least basic immunization, saving about 2.5 million lives each year. It is estimated that complete vaccine coverage of children could save an additional 2 million lives. Moreover, immunization reduces demands on health care systems and helps avoid neurological complications associated with diseases such as measles, mumps, rubella, and even chickenpox. Vaccines are given to young children during a time of rapid developmental changes. It is also in early childhood that neurological defects and behavioural syndromes are detected. Because neurological disorders are often diagnosed a short time after children receive vaccines, many parents and health professionals fear that the vaccines could be the cause of these developmental problems. This and other concerns have led to a large amount of research on the possible side effects of vaccines and also on the other causes of neurological and behavioural problems in young children. Based on this ongoing research, the purported association between vaccine and autism is now considered refuted, and it is now known that almost all neurological disorders that used to be attributed to vaccines have in fact other causes. The scientific consensus today is that vaccines are among the safest pharmacological products, that their side effects are almost always mild, and that their benefits far outweigh their potential risks.

What do we know?

Consequences of vaccine-preventable diseases

In the absence of large-scale immunization, highly infectious diseases such as measles, mumps, rubella and chickenpox affect nearly all children. Although these infections are usually benign and resolve quickly without particular treatment, a significant number of infected children will develop complications requiring hospitalization. Complications often affect the central nervous system and include seizures and encephalitis, an acute inflammation of the brain that can result in permanent brain injuries. For example, 1 person out of 25-30 affected with measles will develop seizures, and 1 out of 1000 will suffer from acute encephalitis. In a population of millions of individuals, these numbers translate into thousands of children with residual brain injuries, developmental delays

and ongoing seizures. Mumps complications can cause deafness, and rubella has devastating consequences for babies born after being infected in the womb, like brain malformation, blindness, deafness and seizures. Chickenpox can also be complicated by injury of the central nervous system with lasting consequences. A number of viruses and bacteria can cause an inflammation of the meninges, the membrane that protects the brain, which is also a risk for permanent brain damage. Pertussis (whooping cough) can occasionally cause encephalopathy, probably because long bouts of coughing can affect brain oxygenation. Most of these illnesses have become rare in North America and Europe since vaccination has been widespread but remain frequent in much of the world, one plane flight away.

Can vaccines cause harm?

Some parents fear that vaccinating healthy children can harm them. Monitoring programs of reported adverse events following vaccination have been set up to answer this question. When an adverse event is reported following vaccination, it can have many causes (i.e., it can be caused by the vaccine, by an inappropriate use of the vaccine or by a completely independent cause). The most frequent side effects of vaccines are fever and febrile seizures. For example, about 5% of children will have fever after receiving the Measles-Mumps-Rubella (MMR) vaccine. The fever will be high enough to trigger febrile seizure in about 1/3000 children, especially children with a family history of seizures. Febrile seizures are scary to witness for parents but fortunately, they usually have no lasting effects. Some children with pre-existing immunodeficiency developed encephalitis after receiving the MMR vaccine, so children with a compromised immune system should not receive vaccines like MMR which contain live viruses.

Most neurological disorders previously attributed to vaccines are in fact explained by another cause. Some children who appeared to have developed a neurological disorder after pertussis vaccination were found to have a rare genetic mutation associated with a form of childhood epilepsy called Dravet syndrome. At most, the vaccine may have precipitated the unavoidable onset of the disease. Thus, we know that vaccine-preventable diseases frequently have severe consequences, while the consequences of vaccines are rare and almost always benign.

Science does not support the association between autism and MMR, which should reassure concerned parents. Scientific research also found no link between pertussis vaccines and encephalopathy. However, fear of the MMR and other vaccines remain present, and vaccine refusal recently led to measles outbreaks in the United States, affecting mostly unvaccinated

persons.

What can be done?

The severe complications caused by vaccine-preventable diseases are well-known to health professionals. However, since the incidence of these diseases has fallen sharply in many countries after the implementation of large-scale vaccination programs, today’s parents are not always familiar with their potential consequences. When diseases are prevalent, they are feared more than the vaccines that can prevent them; when the diseases are rare, parents tend to fear the potential side effects of the vaccines a lot more than the diseases themselves. Therefore, it is important to document the side effects of vaccines as well as their benefits, study their potential risks, and give parents of young children up-to-date, research-based, quality information about immunization.

Continuing efforts to ensure vaccine safety

All vaccines are extensively tested before they are administered to the public. Still, some side effects are so rare (affecting less than 1/10,000 patients) that no preliminary study can be large enough to detect them. For this reason, the medical authorities must maintain the structures necessary for vaccine pharmacovigilance: to ensure the safety of the vaccines, all adverse events following immunization should be recorded, compiled and investigated. The ongoing research on vaccine safety is also essential to establish guidelines for the management and administration of vaccines.

Knowing the true cause of illnesses appearing after vaccination should reassure the parents about continuing the vaccine program for their child and is essential to ensure that the child will receive the best possible care. Future research should aim to collect enough data to make sure that even the rarest adverse events are recorded. Research should also investigate factors, for example genetic factors, with potential to increase the risk of adverse reaction.

Childhood Immunization and Brain Health

David W. Scheifele, MD

University of British Columbia, Child & Family Research Institute, Canada

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Introduction and Subject

The benefits of routine childhood immunizations can be described from many perspectives, such as deaths avoided, health care costs saved and suffering spared, each of which is important. The World Health Organization (WHO) and UNICEF estimate that basic childhood immunizations (Table 1) are given to over 100 million children, save over 2.5 million lives annually and could save 2 million more lives if fully implemented.[1] Childhood immunizations either save money (e.g., measles vaccine) or represent good value (e.g., meningitis vaccines). Most of the infections targeted by vaccines can cause neurological injuries (Table 2) so disease control avoids those complications and preserves brain health. The objective of this paper is to describe briefly the most common neurological conditions that are avoidable with routine childhood immunizations, recognizing that not all of the vaccines described are used in all countries and that disease risks vary with geography and population health (e.g., prevalence of HIV infections). The information is meant to assist health care providers to understand and explain the principal advantages of vaccination.

Recent Research Results

1. Contagious Infections of Childhood

The highly contagious childhood infections associated with fever and rash (measles, rubella, chickenpox) or parotitis (mumps) are infrequent causes of neurological complications but because they affect nearly every child, the cumulative numbers of neurological injuries become significant.

1a. Measles

Measles infection causes particularly high fevers that trigger febrile convulsions in about 1/25-30 cases. While seizures are frightening for parents, most simple febrile seizures are without consequences. However, some atypical febrile seizures can be prolonged (status epilepticus) and

without prompt medical attention and effective airway care can pose a risk of *hypoxic brain injury*.

Measles is complicated by acute *encephalitis* in about 1/1,000 cases. In a country with a birth rate of 100,000 children per year, that means ~100 children will suffer from measles encephalitis annually and cumulatively ~1,500 children will be affected by age 15 years. Measles encephalitis is typically severe, with a high rate of subsequent brain injury, developmental delay and ongoing seizures among survivors.[2] A post-infectious *encephalomyelitis* also occurs, with autoimmunity to *myelin basic protein (MBP)*.[3]

Measles infection can also initiate slowly progressive encephalitis. In immunocompromised children, measles inclusion body encephalitis develops after about six months. A slower infection, known as *subacutesclerosing panencephalitis (SSPE)*, affects previously healthy children seven to 10 years after their measles illness and progresses to a vegetative state and death within two to three years of becoming evident.[4] It is fortunately rare, affecting about one per million children.

With measles vaccination, both acute and chronic forms of encephalitis are avoided and the risk of febrile convulsions is markedly reduced. Vaccination causes fever in ~5% of first-time vaccinees and is occasionally high enough to trigger seizures in prone individuals. The estimated rate of febrile seizures after measles-mumps-rubella (MMR) vaccination in the USA was about 1/3,000, a rate 100-fold lower than after measles infection.[5]

1b. Mumps

Mumps infection is ordinarily benign but results in central nervous system (CNS) infections with surprising frequency. As many as 1/10 cases will have meningeal inflammation, potentially presenting with severe headache and neck stiffness, with cerebrospinal fluid (CSF) *pleocytosis*. This is typically self-limiting, resolving within a week. About 10% of CNS cases (1/1,000 children) will be more severe, presenting with encephalitis and/or nerve deafness. In the absence of vaccination programs, mumps is a significant contributor to acquired deafness. Mumps encephalitis is typically severe and prolonged and can result in permanent brain injury with *hydrocephalus*, developmental delay and ongoing seizures.[6]

Mumps vaccines are well tolerated but occasionally cause mild *aseptic meningitis*. Rates vary by vaccine virus.[7] Outcomes are generally benign, with symptoms resolving within a few days.

1c. Rubella

Acute rubella infection is generally benign for healthy children, posing a low risk of acute encephalitis. However, children with severe immunodeficiency can develop a chronic, progressive form of rubella encephalitis. Of greatest concern, however, is the occurrence of congenital rubella syndrome (CRS) following infection in utero.[8] This typically results in severe neurological damage, including microcephaly, cortical malformations, blindness, deafness, hydrocephalus and persistent seizures. The WHO recommends administration of combined rubella and measles vaccines to young children, whenever feasible, to prevent CRS. Rubella immunization of adolescent girls and susceptible women contemplating pregnancy are additional control strategies. Universal vaccination of young children and selective vaccination of susceptible women quickly resulted in the elimination of CRS cases in the U.S.[9] and the Americas.[10] Modern rubella vaccines have an excellent safety record when given to infants and young children.

1d. Varicella (Chickenpox)

About 1% of children with chickenpox suffer a significant complication requiring medical attention, with CNS complications prominent among them.[11,12] The latter can include febrile seizures, aseptic meningitis, cerebellitis, encephalitis and transverse myelitis. A distinctive CNS complication is cerebellitis, a focal encephalitis that presents with dizziness and *ataxia*, but from which patients generally recover well. [13] Reye's syndrome, a life-threatening disorder which almost always follows a viral illness such as chickenpox or a cold, is even more of a risk *ASA* exposure. Hemiparesis or hemiplegia may occur abruptly weeks or months after the rash illness as a result of stroke secondary to cerebral arteritis.[14] Varicella causes persistent infection of *paraspinal ganglia* so that later in life about 25% of infected individuals will experience reactivation of the latent virus, causing the vesicular, dermatomal rash of *zoster*. Zoster complications include *neuralgia*, which can be excruciating and persist for months, meningeal inflammation (aseptic meningitis) and, less commonly, transverse myelitis.

Varicella vaccination prevents neurologic complications and, later, zoster. The attenuated vaccine virus can also persist in ganglia but the rate of post-vaccination zoster is lower than with wild infection and the illness is much milder, with minimal neuralgia.

2. Neurotropic viruses

This category includes poliomyelitis, rabies, Japanese encephalitis and tick-borne encephalitis, each of which is neurotropic and vaccine preventable.

2a. Poliomyelitis

Polioviruses replicate in and spread from the gastrointestinal tract, making them highly contagious. Most infected persons are asymptomatic or mildly ill with fever but about 1% experience multi-focal infection of spinal motor neurons, with abrupt onset of weakness or paralysis. Brain stem involvement (bulbar polio) compromises respiration, necessitating assisted ventilation. With limited loss of motor neurons, recovery of function is possible. With greater losses, paralysis or weakness is permanent, with further risk of joint contractures and limb deformity in the absence of good physical therapy. The disease is epidemic at times but is otherwise endemic, causing sporadic cases.

Extensive global vaccination programs have eliminated circulation of wild polio viruses from most of the world. Mass vaccination programs aimed at eliminating the disease altogether have been highly successful: in 2011 disease activity was confined to just four remaining endemic areas (Nigeria, India, Pakistan and Afghanistan), where eradication efforts continue.[15]

3. Invasive Bacterial Infections

During first encounters with certain encapsulated bacteria, young children are at increased risk of bloodstream invasion, with spread of the pathogen to the meninges. Without prompt recognition and antibiotic treatment, meningitis can result in permanent brain injury. The leading pathogens have been the targets of vaccine development and subsequent disease control programs.

3a. Haemophilus influenzae type b

Once the leading cause of invasive bacterial infection in children, H. influenzae b (Hib) was estimated to affect 1/200 American children by 5 years of age.[16] About half of Hib infections involved purulent meningitis, complications of which included deafness (unilateral or bilateral, in 20% of survivors) and neurological sequelae (in 15%) that included developmental delay, hydrocephalus, seizure disorder, blindness, and motor impairments.[17] Injury resulted primarily from damage to cerebral vessels entrapped in the inflammatory process. Direct invasion of brain tissue was rare without antecedent focal hypoxic damage (*cerebritis*) but this mechanism could lead to cortical abscess formation. Hib meningitis was the leading cause of acquired deafness among children and the leading post-natal cause of developmental delay.

Where routine use of Hib conjugate vaccines has been well implemented, disease rates have fallen sharply, reducing case numbers by 99% or more.[18] In 2009, 82% of WHO-registered countries supplied Hib vaccines, affording protection to about 45% of young children globally.[19] Hib vaccines have an excellent safety record.

3b. Invasive Pneumococcal Infections

Second to Hib in causing invasive infections in children, Streptococcus pneumoniae bacteria less often infect the meninges: about 15% of cases involve purulent meningitis.[20] The outcome of meningitis cases is similar after either infection, with deafness occurring in 30% of pneumococcal cases in one series[21] and cortical damage in 15%.

The cumulative risk of pneumococcal invasive disease (IPD) for children <5 years of age in Canada[22] was estimated at one in 330 children with the risk of meningitis being about one-tenth of that. Estimated IPD incidence rates in the developing world are much higher,[23] even allowing for under-diagnosis, with meningitis accounting for a larger proportion of recognized cases.

The availability of multivalent pneumococcal conjugate vaccines has provided a means to substantially reduce the frequency of invasive pneumococcal infections, including meningitis.[23] These vaccines have not been associated with neurologic adverse events apart from occasional febrile seizures.

3c. Meningococcal Infections

Invasive meningococcal infections are feared for their abrupt onset and severity but are fortunately uncommon in developed countries, with incidence rates <1 per 100,000 population per year. Nevertheless children <2 years of age and adolescents have the highest incidence rates. About 50% of cases involve meningitis,[24] with the same range of potential complications as with Hib and pneumococcal meningitis, including deafness in about 10% of survivors.[25,26]

Immunization programs with serogroup C and/or tetravalent (ACYW135) conjugate vaccines have been effective, reducing rates of invasive and meningeal infections.[27] However, serogroup B meningococci are not yet vaccine preventable and account for a substantial proportion of remaining meningitis cases.

3d. Tuberculous meningitis

Tuberculous meningitis occurs as a complication of primary pulmonary tuberculosis, typically among young children. Failure to confine infection to the lungs results in seeding of the *meninges*, which initiates an inflammatory response particularly around the brain stem. Injury to cerebral vessels leads to*ischemic brain* stem and cortical injury. Outcome of modern multi-drug treatment is often poor, especially when children present in coma. Sequelae are frequent among survivors. Primary prevention with BCG vaccine is a better option. Currently available BCG vaccines are about 50% effective in preventing pulmonary infection but are ~64% effective in reducing progression to meningitis.[28,29]

4. Other Infections Occasionally Causing Brain Injury

In this category are preventable infections of childhood that can indirectly result in neurological injury, such as pertussis, influenza and tetanus.

4a. Pertussis

Seizures and encephalopathy are uncommon complications of pertussis, reported in about 2.5 and 0.5% of hospitalized cases, respectively.[30] Encephalopathy is believed to result from hypoxic injury suffered during lengthy bouts of coughing or apnea. *Petechial hemorrhages* may also occur in brain tissue during heavy, prolonged coughing, contributing to seizures and encephalopathy. About half of survivors of encephalopathy have permanent brain damage.

Immunization with whole cell or acellular pertussis vaccines has markedly reduced neurological injuries from pertussis. Vaccines are about 80% effective in preventing infection for periods of 5-10 years and reduce the risk of hospitalization and death among cases that occur despite vaccination.

Conclusion

Most of the infections targeted by childhood vaccines have the potential to cause neurologic complications and subsequent disability. Taken together, the burden for parents and society in caring for affected children is substantial. Fortunately, childhood vaccinations are effective in preventing infections and their neurologic complications. When well used, vaccines contribute significantly to the preservation of brain health in children.

TABLE 1

WHO Recommended Vaccines for All Children (11/2012)

Antigen	Comment
BCG tuberculosis	For infants in high-risk countries or households, except those with HIV infection
Hepatitis B	Starting as soon after birth as possible
Polio	3 infant doses of OPV recommended in polio-endemic countries; IPV used in polio-free countries
DPT	3-dose series in infancy, whole cell or acellular pertussis vaccine, with booster dose at 1-6 years of age
H. influenzae b	3-dose series in infancy, combination vaccine preferred where available or with concurrent DTP
Pneumococcal conjugate	3- dose series in infancy, 2 alternative schedules
Rotavirus	2- or 3- dose series in early infancy, depending upon product
Measles	1st dose given at 9 or 12 months; 2nd dose at 15-18 months
Rubella	1 dose minimum; ideally given in combined vaccine with measles, i.e. Measles-Rubella (MR) or Measles-Mumps-Rubella (MMR)
HPV	Females before onset of sexual activity; 3-dose series

Refer to http://www.who.int/immunization/documents/positionpapers/ for most recent schedule and details for use of these and other vaccines recommended for certain regions, some high-risk populations and immunization programs with certain characteristics.

TABLE 2

Infection-related Neurological Injuries Avoidable with Childhood Immunization

Infection	Meningitis	Encephalitis	Myelitis	Deafness	Neuropathy	Brain injury	Seizures
Measles		√[1]				√	√
Mumps	√	√		√		√	√
Rubella		√[2]				√	√
Varicella		√[3]				√	√
Zoster	√				√		
Polio	√	√	√		√[4]	√	
H. influenzae b	√			√		√[5]	√
Pneumococcus	√			√		√[5]	√
Meningococcus	√			√		√[5]	√
Pertussis		√[6]				√	√
Diphtheria					√		
Tetanus					√	√[7]	√[7]
Influenza		√	√			√	√
Tuberculosis	✓	✓		✓		✓	✓

[1] **Measles – includes subacute sclerosing panencephalitis in previously healthy children**

[2] **Rubella – includes chronic encephalitis in immunocompromised children**

[3] **Varicella – includes acute cerebellitis and vascular stroke**

[4] **Polio – neuropathy as post-polio syndrome**

[5] **Brain injury with meningitis mediated mainly through cerebrovascular injury; also subsequent hydrocephalus**

[6] **Pertussis encephalopathy is hypoxia-related**

[7] **Tetanus brain injury is hypoxia-related**

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Neurological Adverse Events After Vaccination

Barbara Law, MD, (FRCPC)

Public Health Agency of Canada, Canada

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Introduction

The first five years of a child's life are filled with developmental milestones. It is also a time for health promotion including scheduled immunizations to prevent up to 14 infections (Table 1) that were once common causes of childhood injury and death. Finally it may be a time when health problems first appear, as a result of genetic inheritance or injuries before, during or after birth.

For parents it is an exceptionally busy time full of wonder, joy, fatigue and fear as they strive to be the best possible caretakers and make good choices for their children to ensure health and avoid injury. Given the safety and benefit of vaccines, immunization is an excellent choice.[1] Still there are understandable concerns that immunizing an apparently healthy child may cause harm. Decisions should be based on the best available evidence.

Subject

This article summarizes the type and frequency of neurologic events proven to be caused by vaccines. Fortunately the list is short and easily summarized (Table 2). It also covers how vaccines are assessed before and after a product is marketed and some of the special challenges related to monitoring safety during early childhood.

Problems

It was once thought that all aspects of safety could be learned prior to product approval by regulatory authorities. The thalidomide disaster midway through the 20th century changed that. Thalidomide was a product given to pregnant women to prevent morning sickness. Pre-licensure studies failed to identify a significant side effect – notably limb shortening that occurred during intrauterine development of infants whose mothers took the drug. This led to a global declaration by the World Health Assembly in 1963 and the modern era *pharmacovigilance* was born.[2]

Vaccine pharmacovigilance is defined as the science and activities relating to the detection, assessment, understanding, prevention and communication of adverse events following immunization, or of any other vaccine-or immunization-related issues.[3]

Research Context

Currently, vaccines are among the safest of marketed products thanks to stringent regulatory standards and continuous product testing and monitoring before and after licensure.[4] Regulators such as Health Canada only approve a vaccine if it is shown that the product works as intended ("efficacious") and is safe. From the time of vaccine discovery throughout the life of a product, vaccine manufacturers must follow a set of international quality management standards ("good practices" related to laboratory, clinical study and manufacturing processes) to ensure the validity of studies used to support their claims for product safety and efficacy as well as the ongoing consistency and quality of the manufacturing process.

Much is learned about the safety profile of the vaccine during these studies including the frequency and severity of common side effects (affecting more than 1% of vaccine recipients) like injection site reactions and fever.[5] The presence or absence of rare side effects (affecting from 1 in 1,000 to 1 in 10,000 vaccine recipients) may also be confirmed.

Still, it is impossible to know everything about a vaccine before it is used in large populations. Very rare events (less than once for every 10,000 doses) can't be identified because of study size limitations. Seldom are there data on the safety profile in sub-populations such as premature infants or those with chronic disease. Thus additional studies as well as ongoing monitoring are needed to answer remaining questions concerning a vaccine product safety profile. These may require special techniques since once a vaccine is proven effective as it may be unethical to use unimmunized controls.[6-9]

Key Research Questions

There are three key questions to ask regarding vaccine administration and a subsequent adverse effect:[10]

1. Can it? The answer to this comes from well designed studies that seek to confirm or reject the hypothesis that a vaccine can cause an effect ("causal association"). If there is an association, even if rare, one can usually prove it, provided a large enough group is studied using appropriate

methods. Live vaccines have the potential to cause the same adverse effects as the wild target viruses but, because they are attenuated, do so at much reduced frequency.

2. Will it? This is the question most relevant to parents because it addresses the likelihood that an event will follow immunization. It would be good to have an absolute “yes or no” answer to the question, but that is no more possible than predicting any future event. Having the answer to Can it? is an essential part of considering Will it?, especially if an answer for How often can it? is also known.

3. Did it? This is the hardest question to answer and the one that is most poorly understood. What is actually being asked is:If the vaccine hadn’t been given, would the event still have happened?

Reporting systems for adverse events following immunization (AEFI) are intended to identify possible signals of a vaccine safety problem.[5] A signal could be increased frequency and/or severity of a known side effect or a previously unrecognized adverse event. The signal is a flag of a possible concern but it is still necessary to address the Can it? question with appropriately-designed studies. Depending on the seriousness of the concern, regulators may stop or limit use of a particular vaccine lot or product until the question can be answered.

Some AEFI reporting systems, such as VAERS (Vaccine Adverse Event Reporting System) in the U.S. are publicly accessible.[11] To interpret VAERS and similar data it is essential to understand what an AEFI is and what it is not. In the most general sense an AEFI is “Any untoward medical occurrence which follows immunization and which does not necessarily have a causal relationship with the usage of the vaccine. The AE may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.”[3] The AEFI reporter need only suspect that the vaccine could have caused the event to submit a report. However, a report is not proof that the vaccine caused the event. Rather there are five different possibilities that could have resulted in the adverse events (AE) of which four are related to vaccine and/or immunization and one is not:[3]

i. Vaccine product-related reaction: An AEFI that is caused or precipitated by a vaccine due to one or more of the inherent properties of the vaccine product.

> Example: febrile seizure occurring six to 14 days after measles-mumps-rubella (MMR) vaccine.[8]

ii. Vaccine quality defect-related reaction: An AEFI that is caused or precipitated by a vaccine, due to one or more quality defects of the vaccine product including its administration device as

provided by the manufacturer.

> Example: shortly after licensure of the Salk inactivated polio vaccine in 1955, some lots prepared by one manufacturer (Cutter laboratory) contained incompletely inactivated poliovirus, resulting in paralytic polio in several recipients. The Cutter vaccine was taken off the market but vaccine from other manufacturers' was safe for use and epidemic polio became a distant memory.[12] Additionally the incident led to more effective regulatory control of vaccines.

iii. Immunization error-related reaction: An AEFI that is caused by inappropriate vaccine handling, prescribing or administration and thus by its nature is preventable.

> Example: the live attenuated measles vaccine can cause fatal *encephalitis* if given to individuals whose immune system is weak or not working due to genetic or acquired disease or immune suppression therapy.[13] Live vaccines like MMR are contraindicated in such individuals. Failure to adhere to such contraindications is an example of this type of AEFI.

iv. Immunization anxiety-related reaction: An AEFI arising from anxiety about the immunization.

> Example: fainting episode shortly after immunization, sometimes, accompanied by jerking of the limbs which can be mistaken for a seizure, by onlookers. This is uncommon in preschool-aged children.[14]

v. Coincidental event: An AEFI that is caused by something other than the vaccine product, immunization error or immunization anxiety."

> Example 1: underlying disease – as pointed out above, the first five years of life is a time when genetic diseases or unrecognized injuries acquired before, during or after birth may first become apparent. When the first onset follows soon after immunization it is an AEFI – associated in time but not caused by the vaccine – it would have happened whether the vaccine was given or not.

> Example 2: early childhood is also a time of frequent infections which are usually fairly benign causing colds, ear infections, stomach upset or diarrhoea but which sometimes cause more serious complications including meningitis or encephalitis. Side effects can also be due to the drugs used to cure or relieve symptoms of such infections.

Given the fact that “coincidental events” may present as an AEFI, another important research question is: What is the incidence of neurological adverse effects in child populations in the absence of vaccination (commonly referred to as “background rate”), including any variations that depend on geographic location or seasonal variation as well as subgroups with increased risk.[15] Knowing the expected rates of events helps in monitoring vaccine safety where the goal is to detect any unexpected increased frequency when a new vaccine is introduced.

Recent Research Results

Table 2 summarizes the proven links between vaccine and neurologic adverse events as reviewed by the Institute of Medicine (IOM).[10,13,16-20] While only MMR, MMR-varicella and diphtheria-tetanus-acellular pertussis (DTaP) vaccines are listed as causes of febrile seizure, it is likely that any vaccine that causes fever could also induce a febrile seizure, especially in those with a personal or family history of such events. Note that the frequency of meningitis and encephalitis is much lower after the live viral vaccines than after infection with the wild viruses.

Research Gaps

In their exhaustive recent review of the evidence linking vaccines to serious adverse events[13] the Institute of Medicine concluded that “… some issues simply cannot be resolved with currently available epidemiologic data excellent as some of the collections and studies are. Particularly for rare events, we look to the day when electronic medical records truly are universal and when society reaches a broad-based consensus about how these records may be used to detect very rare adverse events from vaccines as well as other drugs and medical interventions.” The IOM report also noted that expert guidelines are needed regarding AEFI investigation in order to rule out coincidental events. Finally, a better understanding is needed of genetic and other factors that may increase the risk of suffering an adverse reaction.[21]

Conclusions

Vaccines are among the safest and most effective products used today thanks to ongoing efforts to standardize research and manufacturing practices before and after licensure as well as constant monitoring for signal detection and subsequent investigations to test whether a vaccine truly causes a given adverse event.

Febrile seizures are the only neurologic reactions that occur with any frequency following infant and childhood immunizations, and even these are rare, occurring less than once for every thousand doses of vaccine given. While frightening to witness, they are benign and don't cause lasting harm nor do they go on to become epilepsy. Hypotonic hyporesponsive episodes (HHE) occur with a similar frequency as febrile seizures, predominantly in infants following immunization with pertussis containing combination vaccines. HHE episodes, in which an infant becomes pale, floppy like a rag doll and less responsive, may represent a type of fainting spell. They cause no lasting effect and infants having had one episode are at no increased risk for another.

Implications for Parents, Services and Policy

When parents choose to immunize their children according to recommended schedules, they are opting for effective and safe measures to maintain health by preventing disease. While no vaccine is 100% safe, the benefit greatly outweighs any potential harm. Still research has clearly linked certain events, like febrile seizures, to vaccines. It is essential that vaccine and other health care providers give accurate information regarding common and rare side effects along with advice on what to do should an adverse event occur. Trustworthy information can also be found at several websites.[22-25] It is equally important that all those concerned with immunization of young children remain vigilant to the possibility of AEFIs and that they not only report them but also investigate appropriately to ensure that vaccines and immunization programs remain as safe as they can be and also that coincidental events are properly diagnosed and treated.

TABLE 1. Diseases targeted by vaccines given during the first 5 years of life

Approximate timing to start immunization*	Diseases prevented
Birth	Hepatitis B
First 6 months	Rotavirus gastroenteritis
	Whooping cough (pertussis)
	Diphteria
	Tetanus
	Polio
	Invasive Haemophilus influenzae type b infections
	Invasive pneumococcal infections
	Invasive meningococcal infection
6 to 23 months	Influenza

Approximate timing to start immunization*	Diseases prevented
12 to 15 months	Measles
	Mumps
	Rubella
	Chickenpoz

***Immunization schedules vary from province to province and from one country to another. For specific information in a given area it is best to ask your healthcare provider or local public health.**

TABLE 2. Synthesized evidence regarding neurologic events proven to be caused by vaccine(s). The data summarized in the table are meant to give a general overview of what is known based on published data as reviewed by the US Institute of Medicine.[10,13,16-19] The listed vaccines are those currently available in North America unless otherwise specified.

Neurologic event	Vaccines that can cause the event	Approximate frequency of event following vaccine	Time to onset of event after vaccine
Febrile seizure	MMR	Once in 2500-4000 doses	6 to 14 days
	MMRV	Once in 1250 to 2500 doses	6 to 14 days
	DTaP combinations	Once in 2900 to 50,000 doses	0-48 hours
Meningitis	MMR	≤once in 800,000 doses	1 to 3 weeks
	VZV	Rare with only five cases reported cases where the varicella vaccine strain was demonstrated in CSF. At least 3 children were healthy whereas the others had evidence of underlying immune deficiency.	19 months to 8 years
Encephalitis	MMR	A few confirmed cases in children with severe immunodeficiency where measles strain virus demonstrated in brain biopsy. For healthy children, if encephalitis occurs it is ≤ once in a million doses which is below the background rate for encephalitis due to all causes and a 1000 fold less frequent that after natural measles.	4 months to 9 months
	VZV	One proven case in a 3 year old healthy girl. Mild illness.	20 months
Brachial Neuritis	T, DT or dT given in the arm	≤ once for every 100,000 doses given (mainly in adults)	Few days to a month
Paralytic polio	Oral Polio Vaccine*	Once in 520,000 first doses; Once in 12.3 million subsequent doses	1 to 3 weeks
Hypotonic hyporesponsive episode	Acellular pertussis containing vaccines	Once in 2000 to 4000 doses	0 to 24 hours

*** Oral polio vaccine is not currently used in North America but may be used in other countries.**

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“What Else Could It Be?” When Neurologic Disorders Follow Immunization

David W. Scheifele, MD

University of British Columbia, Child & Family Research Institute, Canada

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Introduction and Subject

When brain disorders such as seizures or *encephalopathy* occur after an immunization, people (including many doctors) have a strong natural tendency to blame the vaccine. This is especially so when the interval between immunization and symptom onset was short and the child was considered normal beforehand. Without an obvious alternative cause such as trauma or intercurrent infection, immunization may be considered guilty by default: what else could the cause have been? Studies in recent years using increasingly sophisticated diagnostic tools have revealed a substantial number of alternative causes that may not be evident unless looked for. In fact, alternative causes exist for almost all of the severe neurologic disorders that follow infant vaccinations.

Recent Research Results

Post-immunization seizures

Fever is a recognized link between infant immunizations and seizures. Fever typically occurs in ~15% of infants given acellular pertussis-containing (DTaP) vaccines and in ~45% of those given whole cell pertussis-containing vaccines. Most fevers occur within 1-2 days after vaccination and are well tolerated. High fevers occasionally occur and may trigger seizures although the observed rate of febrile seizures after DTaP-type vaccines did not exceed baseline rates for U.S. infants in a large study.[1] Most instances occur in infants with a familial predisposition to febrile convulsions in early childhood, a trait present in 2-5% of some populations.[2] If vaccination is the first stimulus for fever in a young infant it may reveal this predisposition for seizures. Fortunately, familial seizures usually have a benign outcome, with no influence on later development.[2] If an *electroencephalogram (EEG)* is obtained after the seizure episode, the brain wave pattern is normal.

Fever after vaccination can also trigger seizures with less benign conditions not previously recognized in an infant, such as brain malformations or scarring from injuries in utero caused by vascular events, congenital infection or toxic drugs. Birth-related injuries or those associated with prematurity can predispose to later seizures. Here too, immunization may be the first cause of fever to trigger seizures. The nature of the underlying problem may be revealed by investigations including brain imaging studies, EEG, *cerebrospinal fluid (CSF)* analysis and others, depending upon the individual context.

Post-immunization encephalopathy

"Encephalopathy" broadly encompasses acute neurologic conditions with diminished level of consciousness and/or altered mental functions, with or without seizures. Conditions with prominent inflammation in CSF are called *encephalitis* or meningoencephalitis.

Infants are at higher risk of encephalitis with certain viral infections than are older age groups, so some instances will follow immunization purely by chance. Viruses commonly responsible for encephalitis in infants include herpes simplex, enteroviruses and human herpes virus type 6. Inflammatory changes in CSF (increased leukocytes, protein concentration) are an important clue to the presence of a viral infection of the central nervous system. A newly-recognized cause of encephalitis in infants is *parechovirus*, previously overlooked because it typically causes minimal abnormalities in the CSF of affected infants.[3] Testing CSF with *polymerase chain reaction (PCR)* assays for the common agents of encephalitis is the optimal diagnostic approach as most of these viruses are difficult or impossible to grow from CSF.

The most alarming situation for parents and health professionals is the occurrence after vaccination of acute encephalopathy that results in persistent seizures and developmental delay or reversal. This rare situation typically follows one of the first vaccinations in early infancy. Since those "baby shots" contain pertussis vaccine, the syndrome was labeled "pertussis vaccine encephalopathy" by some authors[4] although here was no direct evidence implicating pertussis vaccine as the cause. However, after brain malformation, injury, infection etc. were ruled out in individual cases, pertussis vaccine was the alleged cause ("What else could it be?" was the rationale at the time). Fortunately, that question now has answers.

A team of neurologists in Australia, led by Dr. Samuel Berkovic, has provided an alternate explanation for alleged "vaccine encephalopathy." They investigated 14 patients in Australia and

New Zealand who were considered to have chronic encephalopathy from vaccination.[5] Each had a first seizure within 72 hours after vaccination in infancy, with a pertussis-containing vaccine. Each had epileptic encephalopathy with refractory seizures and developmental slowing or regression, after previously normal development. Less than half had fever noted at seizure onset. None of the parents had a history of seizures. Patients had a variety of seizure syndromes and none had evidence at onset of brain inflammation or damage. The noteworthy insight was that 11 of the 14 patients had mutations in the sodium channel (SCN1A) gene on molecular genetic analysis. These appeared to be de novo, or new, mutations as they were absent in the parents. A number of different mutations existed, perhaps explaining the variety of seizure syndromes. This genetic defect was discovered relatively recently as the basis for most instances of severe myoclonic epilepsy of infancy, also known as Dravet syndrome.[6-9] The authors recommend testing for SCN1A mutations in cases of encephalopathy after vaccination that lack other identified causes because "correct diagnosis will reassure the family as to the true cause, remove the blame for having vaccinated the child, direct appropriate treatment and allow realistic planning for prognosis." [5]

The Australian team subsequently studied 40 patients with mutations in SCN1A regarding the relationship between seizure onset and vaccination.[10] Twelve patients had onset within 2 days after vaccination, at a mean age of 18.4 weeks, and 28 had greater separation between vaccination and seizure onset, which occurred at a mean age of 26.2 weeks. The authors' interpretation was that vaccination may have precipitated onset of some cases, although all were destined to be affected. Those with onset soon after vaccination had the same subsequent course of illness as the other patients, both groups having similar intellectual outcomes and seizure types as well SCN1A mutations. Onset of seizures soon after vaccination followed any one of the three scheduled infant vaccinations, with whole cell or acellular pertussis-containing vaccines and with or without fever. Vaccinations given after the onset of seizures did not affect intellectual outcome. The authors described the situation as a "gene-environment interaction," with vaccination being one of many potential triggers in a child's early life to reveal the underlying disorder. In retrospect, it is easy to understand why infant vaccinations appeared to cause this rare but severe condition as affected children appeared to be normal beforehand but it is gratifying to see "science prevail over speculation."[11]

Conclusion

Vaccine safety perspective

Experience from a Canadian vaccine safety surveillance network of pediatric hospitals illustrates the rarity of encephalopathy after infant vaccinations and the importance of investigating the true cause.[12] The 12 participating surveillance hospitals account for over 90% of the country's specialized pediatric beds and admit children with serious conditions from wide referral areas. During 10 years of active surveillance, Canadian children received approximately 6 million doses of vaccines containing whole cell pertussis and 7 million doses containing acellular pertussis. During this same period, nurse monitors at those hospitals reviewed every acute neurologic admission (>12,000) and found 7 cases of acute encephalopathy with onset within 7 days after pertussis-containing vaccination. Brain imaging and CSF studies revealed an alternate cause in every instance, including a previously unrecognized metabolic disorder and acute viral infections including herpes simplex and influenza. Presently, PCR testing of CSF is being expanded to detect parechovirus, given its newly recognized importance as a cause of encephalitis in infancy.[3] In selected infants with epileptogenic encephalopathy, testing for SCN1A mutations is arranged. Clearly, this is a dynamic situation that requires expanded testing as more causes of encephalopathies of early childhood are identified. For cases that occur soon after vaccination, every reasonable effort should be made to identify the actual cause and avoid incorrectly blaming the vaccine. For the earlier question of "What else could it be?," many answers are possible with appropriate investigations. It is increasingly unlikely that "vaccine encephalopathy" exists at all following the inactivated vaccines such as DTP or DTaP given to infants.

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The Myth of MMR and Autism Debunked

Michael J. Smith, MD, MSCE

University of Louisville, School of Medicine, USA

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Introduction

In 1998, Andrew Wakefield and colleagues published a brief report, entitled “Ileal-lymphoid nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children,” in the prestigious medical journal The Lancet.[1] This series of 12 children with developmental disorders and gastrointestinal (GI) problems included nine children with autism. According to their parents, eight of the 12 children had received the combined measles-mumps-rubella (MMR) vaccine prior to developing symptoms. Although the authors wrote “We did not prove an association between [MMR] vaccine and the syndrome described,” Dr. Wakefield suggested in a press release that parents separate the three components of the vaccine until further research could be performed. This study received significant media attention worldwide and many parents began to doubt the safety of the MMR vaccine.

Subject

Because of the concern about MMR and autism, an increasing number of parents have requested to delay or refused this vaccine.[2,3] These include first-time parents as well as those with older children who have been diagnosed with autism.

Problems

Measles is a highly contagious pathogen and vaccine refusal has been associated with disease outbreaks. During the 2008 outbreak in the United States, 91% of cases occurred in unvaccinated individuals, two-thirds of whom had no medical contraindication to vaccination.[4] A smaller outbreak in Indiana affected 34 people, 32 of whom were unvaccinated.[5] Similar outbreaks have occurred in other communities with high levels of susceptible individuals. In the United Kingdom measles was eliminated but with decreased vaccination rates post-Wakefield, is once again endemic, meaning there is sustained person-to-person spread over a 12-month period.[6]

Research Context

The original Wakefield paper was a small case series that included 12 children. Such studies cannot prove that one thing causes another. They may be used to generate hypotheses that may be tested in larger and more rigorous epidemiologic studies.

Key Research Questions

1. Have Wakefield's findings been replicated?
2. At the population level, is receipt of MMR vaccine associated with the development of autism?

Recent Research Results

1. Key Research Question 1: Wakefield postulated that the measles virus in the MMR vaccine traveled to the intestine where it caused inflammation, allowing proteins from the GI tract to enter the bloodstream, travel to the brain and cause autism. This theory has never been proven. In 2008, Hornig and colleagues[7] searched for the presence of measles virus in biopsy samples taken from children with GI disturbances undergoing colonoscopy procedures. Biopsy specimens were taken from the intestines of 25 children with autism and 12 without. The measles virus was not detected more often in the children with autism as compared to those with GI symptoms alone.
2. Key Research Question 2: To date, at least 13 epidemiologic studies have failed to support an association between MMR vaccine and autism.[8] Many of these were ecologic studies that demonstrated that national trends of MMR vaccination were not directly associated with national trends in the diagnosis of autism. For example, Japan suspended the use of MMR vaccine in 1993, but rates of autism continued to increase.[9] Additional studies have compared the risk of autism in individual children who did and did not receive the MMR vaccine. The largest and most compelling of these assessed 537,303 Danish children born between 1991 and 1998.[10] This study took advantage of the Danish Civil Registration system, which captures information from all medical encounters for all citizens. These researchers found no difference in rates of autism or other autism-spectrum disorders between vaccinated and unvaccinated children. Other population-based studies from across the world have reached similar conclusions.
3. Other Relevant Information: In addition to these scientific questions there are significant ethical considerations surrounding the MMR-autism myth. In 2010, The Lancet formally

retracted the original 1998 paper, citing issues of ethical misconduct on the part of Dr. Wakefield.[11] Specifically, he never obtained approval from the hospital ethics committee for his research and the children in the study were not "consecutively referred" as described in the paper, but were hand-selected. Even more worrisome is that Dr. Wakefield received compensation from attorneys who were representing several of the study subjects in a lawsuit against vaccine manufacturers and he held a patent for a new measles vaccine.[12] These financial conflicts of interest were not disclosed at the time of publication. Finally, recent allegations have been made that Dr. Wakefield may have falsified some of the data from this study.[13]

Research Gaps

As outlined above, there is no scientific evidence that the MMR vaccine causes autism. However, for many parents vaccine safety is not a scientific issue, but rather an emotional one. In this context, the key research question has shifted from "Does MMR cause autism?" to "What resources and communication strategies are most useful when discussing vaccine safety with parents who are concerned that vaccines may cause autism?" This line of questioning will require collaboration between medical and risk communication researchers. It is also important to better understand the role of the media in the dissemination of the MMR-autism myth, so future vaccine safety crises may be avoided.

Conclusions

The theory that MMR vaccine causes autism was based on a small case series that included only 12 children. Such a study may be used to generate a hypothesis, but does not establish causation. Because autism is diagnosed around the same time the MMR vaccine is administered, it is not surprising that parents would suspect an association between the two events. However, multiple microbiologic and epidemiologic studies over the past 14 years have failed to support this theory. We can now conclusively say that the science does not support an association between MMR vaccine and autism. Furthermore, it is clear that there were significant ethical concerns surrounding the initial study, resulting in the retraction of the paper and the revocation of Dr. Wakefield's medical license in 2010. Parents who are concerned about the putative connection between MMR and autism may be reassured by these facts.

Implications for Parents, Services and Policy

The implication for parents is clear; MMR vaccine does not cause autism. Although measles is still not as common as it was in the pre-vaccine era, it is only a plane flight away. As there are negative consequences of remaining unvaccinated, healthcare providers should reinforce this message with parents. From the perspective of policy and services it is time to put the putative connection between MMR and autism to rest. Future research funding and energy should be invested into other etiologies and potential treatments for autism.

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Immunization: Comments on Scheifele, Law and Smith

Philippe Duclos, PhD

World Health Organization, Switzerland

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Introduction

The four linked papers by Scheifele (two papers),[1,2] Law,[3] and Smith[4] provide an overview of the neurological aspects of vaccination and vaccine safety from three internationally-recognized authors with a strong clinical and academic background and who bring extensive experience not only in pediatrics and immunization but also importantly in the investigation and monitoring of the safety of vaccines.

Although those four papers focus only on the neurological aspect of the risks and benefits of vaccines, this narrow focus is quite appropriate and allows the authors to be more specific about their presentation of the evidence than if they were covering a wider set of aspects. Preventing neurological complications of vaccine preventable diseases and neurological risks of vaccines is indeed among the most important considerations in the choice of vaccines, and most of the lessons derived from these papers are relevant to the wider picture. The papers bring together a number of facts and considerations that may not be obvious or easily accessible to those clinicians who advise parents and those who may be confronted with managing neurologic events following immunizations, nor to parents themselves who are concerned with making the best choices for their children's health. Although the focus of the authors is slightly more relevant to a North American audience, there is no doubt that the content of the papers is relevant globally.

In times of high disease prevalence, fear of diseases prevails. As vaccine-preventable diseases become controlled through extensive vaccination, fears over the safety of vaccines surpass the fears of the diseases that vaccines are intended to prevent. A series of articles focusing on the risks in absence of vaccination and risks of vaccines is therefore important and perfectly timed in the context of both stalling vaccination coverage at the global level[5] and endorsement of the Global Vaccine Action Plan of the Decade of Vaccine at the May 2012 World Health Assembly.[6,7] One of the essential recommended actions to achieve the second strategic objective of the Global

Vaccine Action Plan (i.e., “individuals and communities understand the value of vaccines and demand immunization as both their right and responsibility.”) is to engage in a dialogue with those individuals and communities that transmit information and respond to people’s concerns and fears. Continuously informing and updating the knowledge base of physicians and health care personnel on immunization is essential to these efforts.

Research and Conclusions

“Childhood immunization and brain health” by David Scheifele[1] provides an excellent overview of a long list of the most common neurological complications and their potential dramatic consequences both for the affected children and their families. Those conditions are potentially avoidable with routine childhood immunizations. The author rightly recognizes that not all of the vaccines described are used in all countries, however, and that disease risks vary with geography and population health.

Scheifele also highlights the dramatic impact that vaccination programs have had or could have and gives a fair view of the limits of the effectiveness and/or protection afforded by some vaccines (e.g., the fact that some of the serogroups of meningococcal meningitis are not yet vaccine preventable).[8-11] From a global perspective, one could have added that the African region celebrated the vaccination of 100 million persons against meningococcal meningitis A in the so-called meningitis belt with a custom-designed conjugate vaccine.[5] Not a single case of meningococcal meningitis A was reported in vaccinated individuals. The elimination of rubella and congenital rubella syndrome from the region of the Americas and its dreadful neurological consequences is also worth flagging as a major achievement.[5]

In contrast “Neurological adverse events after vaccinations” by Barbara Law[3] presents the comparatively short list of neurologic events proven to be or possibly caused by vaccines. It highlights that fortunately the only neurologic reactions that occur with any, albeit rare, frequency are febrile seizures. The article also covers how vaccines are assessed before and after a product is marketed and some of the special challenges related to monitoring the safety of vaccines during early childhood, and particularly that of determining whether or not an event observed after vaccination is caused by the administration of the vaccine. This determination is rather difficult in view of the large number of vaccine doses administered at an age when health problems first appear. Law also refers to several useful websites and the Vaccine Safety Net, a network of websites that provide information on vaccine safety and that adhere to good

information practices, which can help practitioners and parents access trustworthy information.[12-15]

Drawing on the most publicized example of a false allegation, the third paper, “Autism and MMR association debunked” by Michael Smith,[4] clearly makes the case that MMR vaccine does not cause autism and highlights the dramatic negative consequences that such unfounded allegations and inappropriate communications have had and may continue to have in the future. Not only did this situation cause serious concern and inappropriate fear of vaccination but it also took enormous resources away that could instead have been used to investigate other vaccine safety concerns.

The final paper of the series, “What Else Could It Be? When neurologic disorders follow immunization,” again authored by Scheifele,[2] reviews the etiologies of neurological events that follow immunization, with emphasis on Dravet syndrome and sodium channel mutations.[16-19] Scheifele stresses that the most alarming situation for parents and health professionals is the occurrence after vaccination of acute encephalopathy that results in persistent seizures and developmental delay or reversal. This rare situation typically follows one of the first vaccinations in early infancy. Since those vaccinations contain pertussis vaccine, the syndrome was labeled “pertussis vaccine encephalopathy,” although there was no direct evidence that the vaccine was the cause. Scheifele rightly stresses that when brain disorders such as seizures or encephalopathy occur after an immunization, people (including many physicians) have a strong natural tendency to blame the vaccine. Without an obvious alternative cause such as trauma or intercurrent infection, immunization may be considered guilty by default. Scheifele indicates how in recent years increasingly sophisticated diagnostic tools have revealed a substantial number of alternative causes that may not be evident unless looked for and that, in fact, alternative causes exist for almost all of the severe neurologic disorders that follow infant vaccinations, including Dravet syndrome. Thorough investigation and correct diagnosis will reassure the family as to the true cause, remove the blame for having vaccinated the child, direct appropriate treatment and allow realistic planning for prognosis.

However, what the article does not say is that the saga of pertussis and encephalopathy has much in common with that of MMR and autism. The National Childhood Encephalopathy Study in the U.K. long ago concluded that a potential rare association existed between encephalopathy and administration of whole cell pertussis vaccine. Although upon reanalysis it was shown that there was actually no association between pertussis vaccine and encephalopathy,[20] the two continued to be linked for many years including in pediatric textbooks that were not updated or as informed as

they should have been. Since textbooks are supposed to represent medical truth, many cases of encephalopathy detected post-vaccination were unfortunately too quickly labeled post-pertussis encephalopathy and deprived of proper investigation and, even more tragically, of the appropriate treatment. In 1999 a cluster of deaths occurring among infants 2 months of age post vaccination was reported in Egypt.[21] A thorough international investigation revealed that the deaths were not due to the vaccine itself but to the application at the injection site of methanol impregnated compresses. Unfortunately clinicians labeled the deaths as post-immunization encephalopathy and fell short of ensuring the proper clinical investigations. As a result children died for not receiving the appropriate antidote that would have saved them.

Yet Dravet syndrome and its potential to be confused for a vaccine-related condition is not well known and by publicizing this potential confusion, Scheifele and the Encyclopedia lead the way forward.

Implications

It is essential that vaccinators and other health care providers give accurate information regarding common and rare vaccine side effects along with advice on what to do should an adverse event occur. It is equally important that parents and physicians alike be reminded of the dramatic consequences of vaccine-preventable diseases that would occur without vaccination. In a population with high vaccine coverage, disease risks are not equally distributed and they remain high for those not vaccinated. This was illustrated recently with the occurrence of serious cases of measles and related neurological complications in France and other European countries.[22]

This series of papers makes the case for early and timely vaccination of infants and vaccination of the mother prior to or during pregnancy in order to prevent the serious neurological complications of vaccine preventable diseases.

All those concerned with immunization and medical care of young children should remain vigilant to the possibility of adverse events following immunization and not only report them but also investigate them thoroughly to ensure that immunization programs remain as safe as possible and to ensure appropriate diagnosis and treatment. There are new possibilities to discriminate vaccine from non-vaccine related causes of neurological disorders and it is essential that one uses those possibilities to the extent possible particularly in countries where such diagnostic tools are readily available.

Following a legitimate suspicion and hypothesis that a medical condition might be caused by a vaccine, there is a need for prompt scientific investigations. The work by far does not stop with the conclusion of this investigation. It needs to go on to ensure that these conclusions are promptly and widely communicated to all who should know. There is a duty for pediatric textbooks to be up-to-date on vaccine safety issues. When updated versions cannot be produced quickly enough, critical information should be proactively disseminated to readers relying on those textbooks as a credible source of information. In view of the body of evidence and speed with which research can generate valuable information, there is also a duty for health providers to proactively and regularly update and inform themselves. Hopefully all modern textbooks will be accompanied by necessary brief web updates. Readers are encouraged to regularly access the WHO website and Vaccine Safety Net for regular updates reflected through vaccine position papers or statements from the Global Advisory Committee on Vaccine Safety.[23-24]

In view to contribute information into the potential association or lack of between various pediatric conditions and various immunizations, and considering the paucity of such systems around the world, it is a Canadian duty to maintain the Canadian vaccine safety surveillance network of pediatric hospitals first for the sake of Canadian children but beyond as an essential element of the global investigative capacity.[25]

The author is a World Health Organization staff member. The opinions expressed in this article are those of the author and do not necessarily represent the decisions, official policy or opinions of the World Health Organization.

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