

The “urban myth” of the association between neurological disorders and vaccinations

R. GASPARINI, D. PANATTO, P.L. LAI, D. AMICIZIA
Department of Health Sciences, University of Genoa, Italy

Key words

Vaccine • Vaccinations • Neurological disorders

Summary

In modern society, a potentially serious adverse event attributed to a vaccination is likely to be snapped up by the media, particularly newspapers and television, as it appeals to the emotions of the public. The widespread news of the alleged adverse events of vaccination has helped to create the “urban myth” that vaccines cause serious neurological disorders and has boosted anti-vaccination associations. This speculation is linked to the fact that the true causes of many neurological diseases are largely

unknown. The relationship between vaccinations and the onset of serious neuropsychiatric diseases is certainly one of coincidence rather than causality. This claim results from controlled studies that have excluded the association between vaccines and severe neurological diseases, therefore it can be said, with little risk of error, that the association between modern vaccinations and serious neurological disorders is a true “urban myth”.

Introduction

Many severe neuropsychiatric diseases, such as Alzheimer’s disease, multiple sclerosis, autism, epilepsy, schizophrenia, encephalomyelitis, encephalopathies, transverse myelitis and optic neuritis, do not yet have a well-defined etiopathogenesis, although important progress has been made on their causes. Several studies have shown that these diseases are due both to genetic factors (intrinsic factors) and environmental factors (extrinsic factors). With regard to autism spectrum disorders, for example, as early as 1977 Folstein and Rutter published the first study of twins and autism focusing on genetic aspects, which showed that the concordance rate in monozygotic twins was much higher than in fraternal twins [1]. Incomplete understanding of the causes of the above diseases has sometimes led to the belief that they are caused by vaccinations; in reality, however, the relationship between vaccinations and the onset of serious neuropsychiatric diseases is certainly one of coincidence rather than causality. In modern society, a potentially serious adverse event attributed to a vaccination is likely to be snapped up by the media, particularly newspapers and television, as it appeals to the emotions of the public. Indeed, a “good” item of news is one that arouses fear or hope. Thus, for example, considerable attention was devoted to the publication of Andrew Wakefield’s article, which linked measles vaccination to pervasive developmental disorders and non-specific colitis [2], and to the case of Heather Whitestone, who was elected Miss America despite her deafness, which had erroneously been attributed to the diphtheria, tetanus and pertussis vaccine [3]. The widespread news of the alleged adverse events of

vaccination has helped to create the “urban myth” that vaccines cause serious neurological disorders and has boosted anti-vaccination associations. These associations can be traced back to the nineteenth century, with the foundation of the National Anti-Vaccination League in 1896 in Britain and the Anti-Vaccination Society of America in 1879 in the US [4]. By the end of the twentieth century, opposition to vaccinations had strengthened in most developed countries because diseases preventable by vaccinations had become increasingly rare. Thus, with regard to the subject of vaccinations, the ethical, social, religious and legal issues cannot be ignored.

Neurological diseases without a well-defined etiopathogenesis

a) *Alzheimer’s disease.* Alzheimer’s disease (AD) is the most common form of dementia among older people. AD begins slowly, first involving those parts of the brain that control thought, memory and language. People with AD may have trouble remembering things that happened recently or the names of people they know. Over time, the symptoms worsen; sufferers may no longer recognize family members or have difficulty speaking, reading or writing. Subsequently, they may become anxious or aggressive, or wander away from home. Eventually, they need total care [5]. Scientists do not yet fully understand what causes Alzheimer’s disease, but it has become increasingly clear that it develops because of a complex series of events that take place in the brain over a long period of time.

It is likely that the causes include some mix of genetic, environmental and lifestyle factors [6].

- b) *Autism*. The autism spectrum disorders are developmental disabilities, which debut during childhood. Their clinical presentation is characterized by disorders in social and communication relationships with others and by repetitive, stereotyped behaviors [7]. Although the causes of autism are not yet fully understood, it is certain that genetic factors are involved. However, the genetics of the disorder is extremely complex; indeed, a recent study has shown that at least 127 genes are involved [8]. Moreover, extrinsic causes would act only during pregnancy [9].
- c) *Encephalomyelitis*. Acute disseminated encephalomyelitis (ADEM) is an immune-mediated inflammatory demyelinating state, which mainly affects the white substance of the neuraxis. The disease manifests itself as an acute onset encephalopathy combined with multiple neurological deficits, and is typically self-limiting [10-12]. ADEM usually develops after viral or bacterial infection and, in the past, it could develop after vaccination against rabies or smallpox; in some patients, however, the cause remains unknown. Many infectious agents have been linked to ADEM, including chickenpox, mumps, measles, rubella, influenza, coxsackievirus B, herpes simplex virus, *Legionella*, *Campylobacter*, *Borrelia burgdorferi*, *Salmonella typhi*, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, etc. [13].
- d) *Encephalopathies*. The term encephalopathy indicates any widespread disease of the brain that alters the function or structure of the brain. Encephalopathy can be caused by an infectious agent (bacteria, viruses, or prions), by a mitochondrial or metabolic dysfunction, brain tumors or increased pressure in the skull, prolonged exposure to toxic elements (including solvents, drugs, radiation, paints, industrial chemicals and certain metals), chronic trauma, poor nutrition, or lack of oxygen or blood flow to the brain. The hallmark of encephalopathy is an altered mental state. Depending on the type and severity of the encephalopathy, the most common neurological symptoms are progressive memory loss and the deterioration of cognitive abilities, inability to concentrate, lethargy, and the gradual loss of consciousness [14].
- e) *Epilepsy*. Epilepsy is a disorder of the central nervous system in which the activity of nerve cells in the brain is interrupted, causing seizures or periods of unusual behavior, strange sensations and sometimes loss of consciousness. Symptoms may include confusion, temporary absence and involuntary movements of the arms and legs. These symptoms may be associated to psychological symptoms. In about half of cases, epilepsy does not have an identifiable cause; in the other half, the condition can be attributed to various factors. The genetic influence seems to be very important. Indeed, some researchers have estimated that in 70% of cases there is a genetic influence, and that more than 500 genes may be linked to the condition [15]. Head trauma, brain tumors, stroke and some infectious diseases,

such as AIDS, can cause epilepsy. Even prenatal injury, caused by an infection in the mother, malnutrition or oxygen deficiency, for example, may be involved. Epilepsy can sometimes be associated to developmental disorders, such as autism and neurofibromatosis.

- f) *Optic neuritis*. Optic neuritis is a condition characterized by inflammation of the optic nerve. While it may be associated to a variety of systemic autoimmune diseases, the most common form is best known for its association to multiple sclerosis [16]. Recurrence of optic neuritis after a single, isolated incident is not uncommon [17]. Patients report sub-acute visual loss and difficulty in seeing colors, especially red, which appears faded. Pain on eye movement is often present. Visual loss is usually monocular, but may involve both eyes, and generally reaches its peak within hours or days. The majority of patients recover their visual acuity.
- g) *Schizophrenia*. Schizophrenia is a debilitating mental illness that affects 1% of the population worldwide. Schizophrenia is characterized by positive and negative symptoms. The former include hallucinations and voices that speak to the patient; the latter include loss of the sense of pleasure, loss of will and social isolation [18]. A family history of schizophrenia is the main risk factor [19]. Other hypothetical risk factors include: the season and place of birth, socioeconomic status and maternal infections [20]. Schizophrenia appears to be a polygenic disorder which can be influenced by environmental factors [21].
- h) *Transverse myelitis*. Transverse myelitis is a neurological disorder caused by bilateral inflammation of a level, or segment, of the spinal cord. This inflammation damages myelin, disrupting communications between the nerves of the spinal cord and the rest of the body. The symptoms of transverse myelitis include a loss of spinal cord function for several days or weeks. The onset is characterized by a sudden back pain, muscle weakness, or abnormal sensations in the fingers and toes. The disease can rapidly progress, causing more severe symptoms, including paralysis, urinary retention and loss of sphincter control. Although some patients recover and are left with minor damage or no residual problems, others suffer permanent disabilities that affect their capacity to perform normal everyday activities. Researchers are uncertain of the exact causes of transverse myelitis. The inflammation which causes such extensive damage to the nerve fibers of the spinal cord can result from viral infections or abnormal immune reactions. Transverse myelitis may also occur as a complication of syphilis, measles and Lyme disease [22].

Causality or casualness?

ALZHEIMER'S DISEASE

An "urban myth" concerning the association between influenza vaccination and Alzheimer's disease was created in 2005 after an episode of the television show "Larry

King Live” in which Bill Maher was being interviewed by Larry King. Maher argued that “if you have a flu shot for more than five years in a row, there’s ten times the likelihood that you’ll get Alzheimer’s disease” [23]. Dr. Maher was referring to Dr. Hugh Fudenberg’s speech during the 1st annual International Public Conference on Vaccination, held by the National Vaccine Information Center in Arlington, Virginia in 1997 [24]. However, a study conducted by Verreault et al. in 2001 refuted Maher’s claim. Indeed, by means of a prospective study – the “Canadian Study on Health and Aging”, a cohort Study on dementia – Verreault et al. had shown that increased exposure to vaccines against diphtheria, tetanus, polio and flu not only was not a risk of contracting Alzheimer’s, but could actually protect against the disease [25].

AUTISM

Regarding Mumps/Measles/Rubella (MMR) vaccines, the *British Medical Journal* [26] defined the main study that linked these vaccines to autism as a “deliberate fraud”. This conclusion resulted from an investigation conducted by the investigative journalist Brian Deer into the research originally published in 1998 by the journal the *Lancet*, before being withdrawn in February 2010 [2]. The paper had associated the administration of MMR vaccine with a new syndrome characterized by autism and ileal lymphoid hyperplasia associated to non-specific colitis. According to Fiona Godlee, the editor in chief of the *BMJ*, the article by Wakefield “was based not on bad science but on a deliberate fraud” [26]. In her editorial, published in 2011, Godlee pointed out that in Wakefield’s research:

- only one of the nine children who allegedly had autism really did;
- five of the children had developmental difficulties before vaccination, although the article claimed that all were in good health before vaccination.
- Although the paper claimed that a mean time of 6.3 days elapsed between vaccination and the onset of symptoms, some children who had their first symptoms months after vaccination. Furthermore, many studies carried out after the publication of the paper by Wakefield et al. demonstrated without any doubt that MMR vaccines do not engender a higher risk of autism or colitis [27-30]. The US Institute of Medicine (IOM) also concluded that “The evidence favors rejection of a causal relationship between MMR vaccine and autism” [31].

ACUTE DISSEMINATED ENCEPHALOMYELITIS (ADEM), ENCEPHALITIS AND ENCEPHALOPATHIES

With regard to encephalitis, it is necessary to distinguish between acute disseminated encephalomyelitis (ADEM), encephalitis and encephalopathy. Some neurology texts state that ADEM may be caused by vaccines. Actually, this association is linked mainly to the fact that the old vaccines against rabies, which were derived from animal nerve tissue (NTV), namely Fermi and Semple vaccines, could lead to sensitization, not least because of the high number of doses required for post-exposure prophylaxis.

However, these vaccines have not been used in industrialized countries since the 1970s, and the World Health Organization (WHO) effectively banned them in 1992. The incidence of neurological Serious Adverse Events (SAE) after administration of rabies NTV varied widely: from 1 per 230 to 1 per 6,000 vaccinations [32]. In the case of smallpox vaccines, too, post-vaccination encephalopathies and encephalitis were well-known, albeit very rare, adverse events (about 1 case per 665,000 vaccinees in the US and 1 case per 345,000 in Italy) [33]. However, as smallpox has been eradicated, smallpox vaccines are no longer used. Subsequently, neurological SAE were attributed to several vaccines, namely: MMR, varicella, influenza, hepatitis A and B, papillomavirus, diphtheria-tetanus-pertussis and menC conjugate vaccines. Regarding the hypothesis that MMR vaccine causes a risk of encephalitis, Duclos et al. estimated an incidence of 1 case per million recipients [34], and studies conducted in Albania [35], Finland [36], the US [37], Great Britain and Ireland [38] suggested that there was no link between MMR vaccine and encephalitis. Indeed, in 2011 the Institute of Medicine concluded that “The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and encephalitis” [31]. In addition, adverse events such as encephalitis and encephalopathy have been reported after the administration of influenza vaccines. Although there are reports (case reports) of encephalitis or encephalopathy after the administration of flu vaccines [39, 40], the controlled studies reported in the literature do not demonstrate a causal association with either inactivated vaccines (TIV) or live attenuated vaccines [41-43]. In this regard, Lee et al. conducted a study on the safety of both the monovalent pandemic vaccine containing the virus H1N1pdm09 and the seasonal vaccine administered separately in the 2009-10 flu season. Having investigated over 1,345,663 individuals who had received the monovalent inactivated pandemic vaccine; 267,715 individuals who had been vaccinated with the live attenuated pandemic vaccine; 2,741,150 subjects vaccinated with the seasonal inactivated vaccine, and 157,838 recipients of the seasonal live attenuated vaccine, the authors found non-significant associations between the vaccines and Guillain-Barré syndrome and other major neurological diseases [44]. With regard to the possible association between the vaccine against hepatitis B and encephalitis or encephalopathy, after analyzing the literature the IOM concluded that, from the epidemiological standpoint, there was no evidence of a possible causal association [45, 46].

As for the hypothetical association between encephalitis / encephalopathy and the Tdap vaccine, the only two controlled studies considered by the IOM reached conflicting conclusions, but both displayed methodological limitations. Moreover, a study conducted in Italy by Greco et al. [47] was refuted by later research [48]. In addition, a study conducted by Yih et al. [49] on 660,000 patients, within the network of the Vaccine Safety Datalink, found a lower risk of encephalopathy (0.84) in patients who received the Tdap vaccine than in the control group. Another study by Ray et al. found a lack of evi-

dence of an association between Tdap vaccine or MMR vaccine and encephalitis or encephalopathy [50].

It has also been speculated that the conjugate vaccine against meningitis C could cause encephalitis or encephalopathy. However, a controlled study conducted by Ward et al. [51] found no causal association between this vaccine and any type of encephalopathy. Safety indications, which also exclude associations between the meningococcal tetravalent conjugate vaccine and encephalopathies, were suggested by large studies [52-54]. In 2000, Creutzfeldt Jacobs Disease (CJD), a progressive degenerative disease of the central nervous system, was diagnosed in 73 subjects in England. This disease is caused by infectious proteins, called prions, and can be acquired by consuming the meat of animals affected by "mad cow disease". Since small amounts of bovine serum and gelatin were used to prepare the vaccines obtained from cell culture, it was erroneously assumed that these vaccines were capable of transmitting CJD. However, the probability that the vaccines contained prions was, in fact, nil. Indeed, prions have never been found in the serum or connective tissue of cattle with bovine spongiform encephalopathy (BSE); bovine serum is present in low concentrations in the cell cultures used to prepare vaccines; prions do not multiply in cell cultures *in vitro* and, finally, CJD is transmitted to humans only by eating meat contaminated with prions [32].

MULTIPLE SCLEROSIS

In 1991, an article by Herroelen et al. [55] published in the *Lancet* reported the onset of multiple sclerosis six weeks after the administration of DNA-recombinant vaccine against hepatitis B. Although subsequent studies found no association between the vaccine and multiple sclerosis [56], the report aroused considerable mistrust of this vaccine in France, where vaccination coverage (86%) at the age of 6 months is still insufficient [57]. By contrast, in Italy, where vaccination is mandatory for all new-borns, coverage with 3 doses at 24 months stands at 95.3% [58].

EPILEPSY

In 1974, Kulenkampff et al. published a study on an uncontrolled case series which reported mental retardation and epilepsy in children who had received the whole-cell whooping cough vaccine [59]. This study was widely publicized by the mass media, resulting in widespread mistrust of the pertussis vaccine in Britain; subsequently, coverage fell drastically from 83% to 31%. As a result, more than 100,000 cases of pertussis and 36 avoidable deaths occurred in Britain [60]. Similarly, decreased immunization rates and increased deaths due to pertussis were also seen in Japan, where pertussis vaccination was temporarily suspended. In this country, the proportion of children immunized dropped from 70% to 20%, while cases of pertussis increased from 393 (0 deaths) in 1974 to 13,000 (41 deaths) in 1979 [61]. Subsequently, excellent well-controlled studies demonstrated that there was no difference in the rates of mental retardation and epi-

lepsy between children who had been vaccinated against pertussis and those who had not [45, 62].

As for the hypothesis that vaccinations, or some of them at least, may increase the risk of epilepsy, it should be pointed out that only the vaccine against MMR induces a statistically significant increased risk of febrile seizures [63, 64]. With regard to varicella, hepatitis, diphtheria, tetanus and pertussis, there is no evidence of a correlation between vaccines and febrile seizures [31]. Moreover, the literature suggests that there is no epidemiological evidence of an association between flu vaccines and febrile seizures [41, 42, 65]. However, the risk of febrile seizures is not associated with a major risk of epilepsy [31]. As for the association between MMR vaccines and afebrile seizures, there is evidence of a null association [31].

The hypothesis of a potential link between MMR vaccine and epilepsy was investigated in 2004 by Vestergaard et al. [66], who considered a sample of 439,251 Danish children. They concluded that there was no evidence of an increased risk of epilepsy in children vaccinated with MMR, since their study, which had involved a large sample of subjects, did not find any difference in the incidence of epilepsy between vaccinated and unvaccinated children. Furthermore, next-generation sequencing technologies have markedly increased the speed of gene discovery in monogenic epilepsies, allowing us to recognize a genetic cause of the disease in a growing number of patients and improving our understanding of its underlying pathophysiology [67].

Advances in the field of genetics have revealed how misguided it is to attribute serious neurological adverse events to vaccinations. In this perspective, Reyes et al. published a very enlightening article entitled: "Alleged cases of vaccine encephalopathy re-diagnosed years later as Dravet Syndrome". In this paper, the authors reported that, in five subjects with encephalopathy previously attributed to the pertussis vaccine, subsequent genetic investigations revealed Dravet's syndrome, a rare epileptic encephalopathy known to be linked to mutations in the SCN1A (neuronal sodium channel alpha subunit) [68].

OPTIC NEURITIS

- MMR, influenza, hepatitis B and DTap vaccines have been suspected of involvement in optic neuritis. With regard to the association of MMR vaccination with optic neuritis, only one paper on a controlled study has been published [69]. In this study, the authors compared 108 cases from three HMOs participating in the VSD (Vaccine Safety datalink) with 228 controls. The conclusion was that MMR vaccination did not increase the risk of optic neuritis. Having examined this study and also considering its limitations, the IOM concluded that: "The evidence is inadequate to accept or reject a causal relationship between MMR vaccine and optic neuritis" [31]. Regarding influenza vaccination and optic neuritis risk, several papers have reported single cases of the disorder after vaccine administration [70-74]. Howev-

er, while case-reports must be regarded as an alarm signal, they do not scientifically demonstrate a correlation. The IOM also evaluated 2 controlled studies [69, 75]; these did not reveal a higher risk among recipients of influenza vaccine than among controls. However, after considering the limitations of these studies, the IOM concluded that: “The evidence is inadequate to accept or reject a causal relationship between influenza vaccine and optic neuritis” [31]. Furthermore, a survey carried out in China after the administration of 89.6 million doses of influenza A H1N1pdm09 vaccine during September 2009 and March 2010 recorded only 3 cases of optic neuritis; the corresponding morbidity rate was 0.003 cases per 100,000 inhabitants, while the morbidity of optic neuritis in Singapore in 2009 was 0.89 per 100,000 people [76]. In addition, no cases of optic neuritis were reported to the US passive surveillance system (VAERS) in the period 2009-10 [77].

- Concerning the risk of optic neuritis in adults after the administration of hepatitis B vaccine, the literature reports two controlled studies: one by DeStefano [69] and one by Payne [75]. The conclusions of both studies were that hepatitis B vaccination did not appear to be associated with an increased risk of optic neuritis in adults. Regarding mechanistic evidence, several case-report studies are available in the literature; for the most part, however, these provided only temporal evidence [78-80].
- A study conducted by Roussat et al. in children found that a presumed trigger for optic neuritis could be suspected in 7 of the 20 children studied: five viral infections and two recent administrations of recombinant hepatitis B vaccine. However, the authors concluded that it was very difficult to establish a causal association between the vaccinations and optic neuritis in infants [81]. With regard to the hypothesized association between optic neuritis and vaccines containing diphtheria and tetanus toxoids or antigens of *Bordetella pertussis*, in 2011 the IOM concluded, on the basis of a single controlled study [69] and a single case report [82], that: “The evidence was inadequate to accept or reject a causal relationship between diphtheria and tetanus toxoid-, or acellular pertussis-containing vaccine and optic neuritis” [31].

SCHIZOPHRENIA

On the relationship between vaccines and schizophrenia, some scholars have speculated that vaccines administered during pregnancy may pose a risk for the unborn child. Although no epidemiological studies have shown the existence of a causal link, some authors, such as Russell Blaylock, have described a theoretical risk. He claims that immune cytokines (IL-1, IL-2, IL-8, IL-6 and TNF-alpha) can cause injury to the baby’s developing brain, and that excessive immune stimulation during pregnancy could give rise to autism and other pervasive neurological disorders, including schizophrenia [83-85]. Although experiments on animal models have documented problems of brain development in baby mice

born to mothers infected with influenza viruses, this does not demonstrate an association with flu vaccination. Moreover, in a paper entitled “Pregnancy, Immunity, Schizophrenia and Autism”, Patterson underlines the fact that cytokines are not the only possible bridge from a mother’s infection to the developing fetal brain; indeed, during infections, changes occur in other soluble immunological substances, such as corticosteroids for instance. Furthermore, Patterson highlights the need to consider genetic components and how they act to modulate brain development [86]. In addition, Short et al. have demonstrated that babies born to rhesus monkeys infected with the flu virus during pregnancy have both significantly smaller brains than normal and other brain abnormalities seen in schizophrenia [87]. These results are consistent with the findings of Mednick et al. [88], who reported an increased risk of schizophrenia in persons who had been in the fetal stage in 1957 – the time of the pandemic known as the “Asian” pandemic – and with the study by Byrne et al. [89]. Vaccination should therefore be considered a valuable tool, particularly during pregnancy, in that it may also help to prevent schizophrenia. Indeed, the CDC recommends influenza vaccination in any period of gestation [90].

TRANSVERSE MYELITIS

Concerning transverse myelitis, a number of papers have reported the occurrence of this severe adverse event after the administration of different types of vaccines (against measles, varicella, influenza, hepatitis, etc.) [91-97]. However, these are only case reports which do not establish a causal link, as pointed out by the IOM with regard to vaccines against: MR / MMR, chickenpox, influenza, hepatitis A, hepatitis B, papillomavirus, diphtheria, tetanus, pertussis, and meningococcus [31].

Discussion

Since the 1970s, fears concerning vaccinations have periodically flared among populations. These fears have arisen from reports of individual cases of adverse events or from studies on groups of patients suffering from serious diseases, such as autism, mental retardation, epilepsy, etc.

In truth, vaccinations may elicit serious adverse reactions, such as anaphylactic shock, which is actually a very rare occurrence [98]. However, each vaccination centre must be appropriately equipped to treat this type of event promptly. It cannot be denied that the old vaccines against rabies and smallpox and the oral polio vaccine could cause serious, albeit rare, neurological reactions. However, by the early twentieth century enormous progress had been made in terms of the design, development and quality control of vaccines. Thus, in most cases, only mild and transient side effects can now be expected after vaccination. They are scientifically and rationally designed to stimulate the immune system. Indeed, vaccines stimulate a large number of cells to produce a variety of soluble substances, which interact with

each other in a process that enables lymphocytes and antibodies to be activated, produced, balanced and stored). The substances that are produced during the immune-response include compounds that induce the local symptoms (pain, redness and swelling) and general symptoms of inflammation (fever). Inflammation should therefore be regarded merely as the protective attempt of the organism to remove harmful stimuli, and is achieved by the increased movement of plasma and leukocytes (especially granulocytes) to initiate healing [99].

Unfortunately, however, a severe neurological disease may arise simply by chance after the administration of a vaccine. This has prompted speculation that such diseases may actually be caused by the vaccination, not least because the true causes of many neurological diseases are largely unknown. It is understandable that neurological disorders arouse fear. Indeed, they can cause severe disability, seriously impairing the individual's quality of life (dependence on others, inability to carry out intimate personal care, sexual difficulty, memory loss and impaired judgment, prejudice and social stigma, etc.). Such considerations have fuelled anti-vaccination associations, as in the cases of MMR vaccination and autism and influenza vaccination and Alzheimer's disease. On these issues, the mass media have often adopted a somewhat "sensational" stance, which has impacted negatively on public health in general and on the health of children in particular. In reality, it should be borne in mind that the case reports published in the literature have almost always shown only a temporal association between vaccination and neurological events, while controlled studies have either excluded such associations, as in the case of the MMR vaccine and autism, or have been unable to establish a causal link between the vaccine and severe neurological reactions, such as in the case of diphtheria, tetanus and pertussis vaccines and optic neuritis.

In conclusion, we can say, with little risk of error, that the association between modern vaccinations and serious neurological disorders is a true "urban myth".

References

- [1] Folstein S, Rutter M. *Infantile autism: a study of 21 twin pairs*. J Child Psychol Psychiatry 1977;18:297-321.
- [2] Wakefield AJ, Murch SH, Anthony A, et al. *Ileal lymphoid nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children [retracted]*. Lancet 1998;351:637-41.
- [3] Freed GL, Katz SL, Clark SJ. *Safety of Vaccinations: Miss America, the Media, and Public Health*. JAMA 1996;276:1869-72.
- [4] Kaufman M. *The American anti-vaccinationists and their arguments*. Bull Hist Med 1967;41:463-78.
- [5] US. National library of Medicine. *Alzheimer's disease*. Document available at: <http://www.nlm.nih.gov/medlineplus/alzheimersdisease.html>. Accessed on 14th January 2015.
- [6] NIH. *Alzheimer's Disease Fact Sheet*. Document available at: <http://www.nia.nih.gov/alzheimers/publication/alzheimers-disease-fact-sheet>. Accessed on 14th January 2015.
- [7] Szatmari T. *The causes of autism disorders*. BMC 2013;326:173-4.
- [8] Liu L, Lei J, Sanders SJ, et al. *DAWN: a framework to identify autism genes and subnetworks using gene expression and genetics*. Mol Autism 2014;5:22.
- [9] Persico A, Scattoni ML. *Alle origini dell'Autismo*. Document available at: <http://www.epicentro.iss.it/temi/vaccinazioni/originiAutismo.as>. Accessed on 23th January 2015.
- [10] Rust RS. *Multiple sclerosis, acute disseminated encephalomyelitis, and related conditions*. Semin Pediatr Neurol 2000;7:66-90.
- [11] Tenenbaum S, Chitnis T, Ness J, Hahn JS. *Acute disseminated encephalomyelitis*. Neurology 2007;68(suppl 2):S23-S36.
- [12] Dale RC. *Acute disseminated encephalomyelitis*. Semin Pediatr Infect Dis 2003;14:90-5.
- [13] Sacconi S, Salviati L, Merelli E. *Acute disseminated encephalomyelitis associated with hepatitis C virus infection*. Arch Neurol 2001;58:1679-81.
- [14] National Institute of Neurological Disorders and Stroke. *NINDS encephalopathy information page*. Document available at: <http://www.ninds.nih.gov/disorders/encephalopathy/encephalopathy.htm>. Accessed on January 23th 2015.
- [15] Weckhuysen S, Korff CM. *Epilepsy: old syndromes, new genes*. Curr Neurol Neurosci Rep 2014;14:447.
- [16] Balcer JL. *Optic neuritis*. NEJM 2006;354:1273-80.
- [17] Beck RW, Gal RL, Bhatti MT, et al. *Visual function more than 10 years after optic neuritis: experience of the optic neuritis trial treatment*. Am J Ophthalmol 2004;137:77-83.
- [18] Schultz SH, North SW, Shields CG. *Schizophrenia: a review*. Am Fam Physician 2007;75:1821-9.
- [19] Mortensen PB, Pedersen CB, Westergaard T, et al. *Effects of family history and place and season of birth on the risk of schizophrenia*. N Engl J Med 1999;340:603-8.
- [20] Wahlberg KE, Wynne LC, Hakko H, et al. *Interaction of genetic risk and adoptive parent communication deviance: longitudinal prediction of adoptee psychiatric disorders*. Psychol Med 2004;34:1531-41.
- [21] Lewis DA, Lieberman JA. *Catching up on schizophrenia: natural history and neurobiology*. Neuron 2000;28:325-34.
- [22] National Institute of Neurological Disorders and Stroke. *Transverse myelitis fact sheet*. Available at: http://www.ninds.nih.gov/disorders/transversemyelitis/detail_transversemyelitis.htm. Accessed on January 23th 2015.
- [23] CNN "Larry King Live Transcript". CNN. 15 December 2005. Available at: <http://transcripts.cnn.com/TRANSCRIPTS/0512/15/lkl.01.html>, accessed on 10th February 12 2015
- [24] Russ S. *According to the media, it's flu season again. Alzheimer's anyone?*. Available at: <http://www.doctorschierling.com/blog/its-flu-season-again-alzheimers-anyone>. Accessed on February 12th, 2015.
- [25] Verreault R, Laurin D, Lindsay J, et al. *Past exposure to vaccines and subsequent risk of Alzheimer's disease*. CMAJ 2001;165:1495-8.
- [26] Godlee F, Smith J, Marcovitch H. *Wakefield's article linking MMR vaccine and autism was fraudulent*. BMJ 2011;342:c7452.
- [27] Black C, Kaye JA, Jick H. *Relation of childhood gastrointestinal disorders to autism: nested casecontrol study using data from the UK General Practice Research Database*. BMJ 2002;325:419-21.
- [28] Taylor B, Miller E, Lingam R, et al. *Measles, mumps, and rubella vaccination and bowel problems or developmental regression in children with autism: population study*. BMJ 2002;324:393-6.
- [29] Madsen KM, Hviid A, Vestergaard M, et al. *A population-based study of measles, mumps, and rubella vaccination and autism*. N Engl J Med 2002;347:1477-82.
- [30] Honda H, Shimizu Y, Rutter M. *No effect of MMR withdrawal on the incidence of autism: a total population study*. J Child Psychol Psychiatry 2005;46:572-9.
- [31] IOM (Institute of Medicine). *Adverse effects of vaccines: evidence and causality*. Washington, DC: The National Academies Press 2011.

- [32] Plotkin SA, Orenstein WA, Offit PA. *Vaccines*. 6th edition. Philadelphia: Elsevier Health Sciences 2012.
- [33] Albano A, Salvaggio L. *Manuale di Igiene*. 2nd edition. Padova: Piccin 1987.
- [34] Duclos P, Ward BJ. *Measles vaccines: a review of adverse events*. Drug safety 1998;6:435-454.
- [35] Bino S, Kakarriqi E, Xibinaku M, et al. *Measles-rubella mass immunization campaign in Albania, November 2000*. J Infect Dis 2003;187(Suppl 1):S223-S229.
- [36] Makela A, Nuorti JP, Peltola H. *Neurologic disorders after measles-mumps-rubella vaccination*. Pediatrics 2002;110:957-63.
- [37] Ray P, Hayward J, Michelson M, et al. *Encephalopathy after whole-cell pertussis or measles vaccination: lack of evidence for a causal association in a retrospective case-control study*. Pediatr Infect Dis J 2006;25:768-73.
- [38] The Health Boards Executive. *The MMR discussion pack an information guide for health professionals and parents*. Produced by the National Disease Surveillance Centre and the Department of Public Health, Southern Health Board. Available at <https://www.hpsc.ie/A-Z/VaccinePreventable/Measles/Publications/File,1242,en.pdf> Accessed on 20th February 2015.
- [39] Shoamanesh A, Traboulsi A. *Acute disseminated encephalomyelitis following influenza vaccination*. Vaccine 2011;29:8182-5.
- [40] Machicado JD, Bhagya-Rao B, Davogusto G, et al. *Acute disseminated encephalomyelitis following seasonal influenza vaccination in an elderly patient*. Clin Vaccine Immunol 2013;20:1485-6.
- [41] France EK, Glanz JM, Xu S, et al. *Safety of the trivalent inactivated influenza vaccine among children: a population-based study*. Arch Pediatr Adolesc Med 2004;158:1031-6.
- [42] Goodman MJ, Nordin JD, Harper P, et al. *The safety of trivalent influenza vaccine among healthy children 6 to 24 months of age*. Pediatrics 2006;117(5):e821-e826.
- [43] Hambidge SJ, Glanz JM, France EK, et al. *Safety of trivalent inactivated influenza vaccine in children 6 to 23 months old*. JAMA 2006;296:1990-7.
- [44] Lee GM, Greene SK, Weintraub ES, et al. *Vaccine safety datalink project. H1N1 and seasonal influenza vaccine safety in the vaccine safety datalink project*. Am J Prev Med 2011;41:121-8.
- [45] Institute of Medicine (US) Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines. *Adverse effects of pertussis and rubella vaccines: a report of the Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines*. In: Howson CP, Howe CJ, Fineberg HV, eds. Washington (DC): National Academies Press 1991.
- [46] Stratton K, Gable A, Dhetty P, et al. *Immunization Safety Review Measles-Mumps-Rubella Vaccine and Autism*. Institute of Medicine. National Academy Press 2001.
- [47] Greco D. *Case-control study on encephalopathy associated with diphtheria-tetanus immunization in Campania, Italy*. Bulletin of The World Health Organization 1985;63:919-25.
- [48] Crovari P, Gasparini R, D'Aste E, et al. *Case-control study on the association of neurological syndromes and compulsory vaccinations in Liguria during the period January 1980-February 1983*. Boll Ist Sieroter Milan 1984;63:118-24.
- [49] Yih WK, Nordin JD, Kulldorff M, et al. *An assessment of the safety of adolescent and adult tetanus-diphtheria-acellular pertussis (Tdap) vaccine, using active surveillance for adverse events in the vaccine safety datalink*. Vaccine 2009;27:4257-62.
- [50] Ray P, Hayward J, Michelson D, et al. *Encephalopathy after whole-cell pertussis or measles vaccination: lack of evidence for a causal association in a retrospective case-control study*. Pediatr Infect Dis J 2006;25:768-73.
- [51] Ward KN, Bryant NJ, Andrews NJ, et al. *Risk of serious neurologic disease after immunization of young children in Britain and Ireland*. Pediatrics. 2007;120:314-21.
- [52] Tregnaghi M, Lopez P, Stamboulian D, et al. *Immunogenicity and safety of a quadrivalent meningococcal polysaccharide CRM conjugate vaccine in infants and toddlers*. Int J Infect Dis 2014;26:22-30.
- [53] Ilyina N, Kharit S, Namazova-Baranova L, et al. *Safety and immunogenicity of meningococcal ACWY CRM197-conjugate vaccine in children, adolescents and adults in Russia*. Hum Vaccin Immunother 2014;10:2471-81.
- [54] Lee HJ, Chung MH, Kim WJ, et al. *Immunogenicity and safety of a novel quadrivalent meningococcal conjugate vaccine (MenACWY-CRM) in healthy Korean adolescents and adults*. Int J Infect Dis 2014;28:204-10.
- [55] Herroelen L, de Keyser J, Ebinger G. *Central-nervous-system demyelination after immunisation with recombinant hepatitis B vaccine*. Lancet 1991;338:1174-5.
- [56] Ascherio A, Ahang SM, Hernan MA, et al. *Hepatitis B vaccination and the risk of multiple sclerosis*. N Engl J Med 2001;344:327-32.
- [57] Institut de Veille Sanitaire. *La couverture vaccinale en France*. Available at: <http://www.invs.sante.fr/Espace-presse/Communiqués-de-presse/2013/La-couverture-vaccinale-en-France>. Accessed on 25 January 2015).
- [58] Ministero della salute. *Vaccinazioni dell'età pediatrica*. Anno 2013. Document available at: http://www.salute.gov.it/imgs/C_17_pagineAree_811_listaFile_itemName_17_file.pdf; accessed on 25th January 2015.
- [59] Kulenkampff M, Schwartzman JS, Wilson J. *Neurological complications of pertussis inoculation*. Arch Dis Child 1974;49:46-9.
- [60] Koplan JP, Hinman AH. *Decision analysis, public policy, and pertussis: are they compatible?* Medical Decision Making 1987;7:72-3.
- [61] Coulter HL, Fisher BL. *DTP: a shot in the dark*. San Diego: Harcourt Brace Jovanovich 1985.
- [62] Institute of Medicine (US) Committee to Review the Adverse Consequences of Pertussis and Rubella Vaccines. *Consequences of Pertussis and Rubella Vaccines*. In: Howson CP, Howe CJ, Fineberg HV, eds. Washington (DC): National Academies Press 1991.
- [63] Farrington P, Pugh S, Colville A, et al. *A new method for active surveillance of adverse events from diphtheria/tetanus/pertussis and measles/mumps/rubella vaccines*. Lancet 1995;345:567-9.
- [64] Barlow WE, Davis RL, Glasser JW, et al. *The risk of seizures after receipt of whole-cell pertussis or measles, mumps, and rubella vaccine*. N Engl J Med 2001;345:656-61.
- [65] Miller E, Andrews N, Stowe J, et al. *Risks of convulsion and aseptic meningitis following measles-mumps-rubella vaccination in the United Kingdom*. Am J Epidemiol 2007;165:704-9.
- [66] Vestergaard M, Hviid A, Madsen KM, et al. *MMR vaccination and febrile seizures: evaluation of susceptible subgroups and long-term prognosis*. JAMA 2004;292:351-7.
- [67] Weckhuysen S, Korff CM. *Epilepsy: old syndromes, new genes*. Curr Neurol Neurosci Rep 2014;14:447.
- [68] Reyes IS, Hsieh DT, Laux LC, et al. *Alleged cases of vaccine encephalopathy rediagnosed years later as Dravet syndrome*. Pediatrics 2011;128:e699-702.
- [69] DeStefano F, Verstraeten T, Jackson LA, et al. *Vaccinations and risk of central nervous system demyelinating diseases in adults*. Arch Neurol 2003;60:504-9.
- [70] Ray CL, Dreizin IJ. *Bilateral optic neuropathy associated with influenza vaccination*. Journal of Neuro-Ophthalmology 1996;16:182-4.
- [71] Vilain S, Waterschoot MP, Mavroudakakis N. *Encephalomyelitis and bilateral optic perineuritis after influenza vaccination*. Bulletin de la Societe Belge d Ophtalmologie 2000;277:71-3.
- [72] Huynh W, Cordato DJ, Kehdi E, et al. *Post-vaccination encephalomyelitis: Literature review and illustrative case*. J Clin Neurosci 2008;15:1315-22.

- [73] Tan FU, Akarsu C, Gullu R, Kansu T. *Bilateral optic neuritis after influenza vaccination*. *Neuro-Ophthalmology* 2010;34:115-7.
- [74] Vellozzi C, Burwen DR, Dobardzic A, et al. *Safety of trivalent inactivated influenza vaccines in adults: background for pandemic influenza vaccine safety monitoring*. *Vaccine* 2009;27:2114-20.
- [75] Payne DC, Rose CE, Kerrison J, et al. *Anthrax vaccination and risk of optic neuritis in the United States military, 1998-2003*. *Arch Neurol* 2006;63:871-5.
- [76] Liang XF, Li L, Liu DW, et al. *Safety of influenza A (H1N1) vaccine in post-marketing surveillance in China*. *N Eng J Med* 2011;364:638-47.
- [77] Williams SE, Pahud BA, Vellozzi C, et al. *Causality assessment of serious neurologic adverse events following 2009 H1N1 vaccination*. *Vaccine* 2011;29:8302-8.
- [78] Albitar S, Bourgeon B, Genin R, et al. *Bilateral retrobulbar optic neuritis with hepatitis B vaccination*. *Nephrol Dial Transplant* 2007;12:2169-70.
- [79] Voigt U, Baum U, Behrendt W, et al. *Neuritis of the optic nerve after vaccinations against hepatitis A, hepatitis B and yellow fever*. *Klinische Monatsblätter für Augenheilkunde* 2001;218:688-90.
- [80] Erguven M, Guven S, Akyuz U, et al. *Optic neuritis following hepatitis B vaccination in a 9-year-old girl*. *J Chin Med Assoc* 2009;7:594-7.
- [81] Roussat B, Gohier P, Doummar D, et al. *Acute optic neuritis in children: clinical features and treatment. A study of 28 eyes in 20 children*. *J Fr Ophthalmol* 2001;24:36-44.
- [82] Quast U, Hennessen W, Widmark RM. *Mono- and polyneuritis after tetanus vaccination (1970-1977)*. *Dev Biol Stand* 1979;43:25-32.
- [83] Blaylock RL. *Immunology primer for neurosurgeons and neurologists part 2: innate brain immunity*. *Surg Neurol Int* 2013;4:118.
- [84] Blaylock RL. *The danger of excessive vaccination during brain development*. Available at <http://www.vaccineinfo4parents.co.uk/PDF/Mercola005.pdf>. Accessed on 7th February 2015.
- [85] Miranda LR. *Schizophrenia and Autism are the effects of vaccine stimulation in unborn children*. Available at: <http://real-agenda.com/2014/04/14/schizophrenia-and-autism-are-the-effects-of-vaccine-stimulation-in-unborn-children/> Accessed on 7th February 2015.
- [86] Patterson H. *Pregnancy, Immunity, Schizophrenia, and Autism*. *Engineering & Science* 2006;3:10-21.
- [87] Short SJ, Lubach GR, Karasin AI, et al. *Maternal influenza infection during pregnancy impacts postnatal brain development in the rhesus monkey*. *Biol Psychiatry* 2010;67:965-73.
- [88] Mednick SA, Machon RA, Huttunen MO, et al. *Adult schizophrenia following prenatal exposure to an influenza epidemic*. *Arch Gen Psychiatry* 1988;45:189-92.
- [89] Byrne M, Agerbo E, Bennedsen B, et al. *Obstetric conditions and risk of first admission with schizophrenia: a Danish national register based study*. *Schizophr Res* 2007;97:51-9.
- [90] CDC. *Prevention and control of seasonal influenza with vaccines. Recommendations of the Advisory Committee on Immunization Practices-United States, 2013-2014*. *MMWR* 2013;62:1-43.
- [91] Cizman M, Pokorn M, Osredkar D. *Re: transverse myelitis after measles and rubella vaccination*. *J Paediatr Child Health* 2005;41:460.
- [92] Joyce KA, Rees JE. *Transverse myelitis after measles, mumps, and rubella vaccine*. *BMJ* 1995;311:422.
- [93] Lim S, Park SM, Choi HS, et al. *Transverse myelitis after measles and rubella vaccination*. *J Paediatr Child Health* 2004;40:583-584.
- [94] LaRovere KL, Raju GP, Gorman MP. *Postvaricella acute transverse myelitis in a previously vaccinated child*. *Pediatric Neurology* 2008;38:370-2.
- [95] Bakshi R, Mazziotta JC. *Acute transverse myelitis after influenza vaccination: magnetic resonance imaging findings*. *J Neuroimaging* 1996;6:248-50.
- [96] Nakamura N, Nokura K, Zettsu T, et al. *Neurologic complications associated with influenza vaccination: two adult cases*. *Internal Medicine* 2003;42:191-4.
- [97] Tartaglino LM, Heiman-Patterson T, Friedman DP, et al. *MR imaging in a case of postvaccination myelitis*. *AJNR Am J Neuroradiol* 1995;16:581-2.
- [98] Government of Western Australia – Department of Health. *Vaccine side effects fact sheet, November 2005*. Available at: <http://www.public.health.wa.gov.au/cproot/432/2/fs%20vaccine%20side%20effects.pdf>. Accessed on February 21st 2015.
- [99] Ferrero-Miliani L, Nielsen OH, Andersen PS, et al. *Chronic inflammation: importance of NOD2 and NALP3 in interleukin-1beta generation*. *Clin Exp Immunol* 2007;147:227-35.

■ Received on February 12, 2015. Accepted on March 9, 2015.

■ Correspondence: Roberto Gasparini, Department of Health Sciences, via Pastore 1, 16132 Genoa, Italy - Tel. +39 010 3538527 - Fax +39 010 3538541 - E-mail: gasparini@unige.it