

REVIEW ARTICLE

The Importance of Complying with Vaccination Protocols in Developed Countries: “Anti-Vax” Hysteria and the Spread of Severe Preventable Diseases

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Abstract: Background: Vaccines are very effective medical tools for disease prevention and life span increase. Controversies have raised concern about their safety, from autism to polio vaccine contamination with simian virus 40 (SV-40). Hysteria surrounding vaccine-associated risks has resulted in a declining number of vaccinations in developed countries. Outbreaks of vaccine-preventable diseases (e.g. measles) have occurred in Europe and North America, causing also some casualties.

Objectives: In this review, data on safety and efficacy of vaccines are discussed, showing that the benefits of vaccines far outweigh the risks and that it is important to comply with vaccination protocols, to avoid spreading of severe, preventable diseases.

Methods: Those opposed to vaccinations suggest that scientific literature supporting vaccines is influenced by pharmaceutical companies. In this review, studies on influenza produced by independent scientists and those authored by those who received some kind of benefit from the industry are discussed separately. All the chosen papers were selected through a MEDLINE research.

Results: Vaccination rates are decreasing, even though they are effective public health tools. Influenza, for example, is responsible for 250,000–500,000 deaths each year, according to the WHO. Yet, campaigns to extend influenza vaccine to all elderly subjects report little success, because of the vaccine scare and because not all patients develop immunity following vaccination.

Conclusions: This review proves that vaccine hysteria is detrimental because: 1) it causes an increased morbidity and mortality from preventable diseases; 2) it jeopardizes research for new vaccines; 3) patients are reluctant to accept any form of immune-therapy, commonly referred to as “vaccination”.

Keywords: Vaccines, vaccination, public health, influenza, prevention, anti-vax, immunosenescence.

1. INTRODUCTION

According to the WHO “vaccination has greatly reduced the burden of infectious diseases”. Only clean water, which is considered to be a “basic human right”,

has had a greater impact on human health worldwide. Disease control, achieved through elimination or eradication, can save huge amounts of money for communities and countries. In addition to their role in infectious diseases, vaccines also have a role in cancer prevention; vaccines have lowered the incidence of hepatocellular carcinoma and may eventually eradicate cervical cancer. The annual return on investment in vaccination has been calculated to be between 10 and 20% [1].

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The eradication of life-threatening diseases such as smallpox and polio are the most notable examples. Smallpox was globally eradicated in 1980, according to the WHO. Prior to its elimination, smallpox was a devastating human disease, accounting for an estimated 300-500 million deaths in the 20th century alone. Polio, once a disease resulting in countless deaths and permanent disabilities, has been eradicated in developed countries. However, it remains a devastating disease in countries where the vaccine is not available to the entire population.

Vaccination also prevents less devastating but still dangerous diseases such as measles, mumps and rubella (MMR). Although in Europe and the US measles is considered a relatively mild infection (even though deaths have been reported in Europe and the US in not vaccinated children), according to the UNICEF web site over 500,000 children died from this disease in 2003 alone worldwide, which is more than any other disease for which a vaccine is available. UNICEF states "The measles death toll in Africa is so high - every minute one child dies - that many mothers do not give children real names until they have survived the disease." http://www.unicef.org/immunization/index_why.html.

In developed countries vaccination against measles is available and recommended and has been extremely successful. The Centers for Disease Control and Prevention (CDC) declared measles eliminated in the United States in 2000. However, measles continues to enter the US from other countries, leading to a risk of new measles outbreaks. Indeed, as stated on a report released in April 2012 by the CDC "last year (2011) the U.S. reported the highest number of measles cases in 15 years, with over 220 cases and a 32% hospitalization rate". Although no deaths were reported in the 2011 outbreak, there were considerable health problems and economical costs. Eightyfive percent of the patients infected in this outbreak would have been eligible for measles-mumps-rubella (MMR) vaccination, but according to the report "[they] were not vaccinated because of a philosophic, religious or personal objection". According to the CDC a record was set in 2014 with over 600 cases; a new outbreak created an emergency situation in 2016 (<http://www.sciencealert.com/the-us-is-in-the-middle-of-its-biggest-measles-outbreak-this-year>); and in the first months of 2017 already 108 cases have been reported [2]. These reports reflect an alarming and dangerous trend.

Similarly, wide measles outbreaks have recently occurred in Europe in Switzerland, Austria and Italy [3].

In 2017, the European Union reported over 4,000 cases (<https://ecdc.europa.eu/en/epidemiological-update-measles-monitoring-european-outbreaks-170406>). In other words, developed countries where vaccination is available are facing the reappearance of diseases which had previously been all but eradicated.

The majority of the population regards vaccinations as safe and follows the recommendations coming from their local health authorities, both for the number and the frequency of compulsory vaccinations. 4 Yet, in spite of the remarkable success of vaccination programs throughout the world, vaccines are not yet available to all the vulnerable populations. Also, the struggle for safe and effective vaccines is ongoing for severe viral diseases such as hepatitis C and Ebola [5, 6].

The reluctance to undergo vaccinations in eligible groups with access to vaccines is a serious challenge with far reaching and devastating effects.. Several controversies, raised in the scientific and non-scientific literature, have taken hold in popular culture and have undermined the confidence of part of the population in the benefits of vaccinations.

2. THE AUTISM CONTROVERSY

The autism spectrum includes diseases with similar features, but probably different etiologies. Genetic predisposition to autism, for example, is a well-known mechanism and may involve ten or more genes, depending on the form of disease. Recent discoveries, such as the role of mast cells in the disease [7] are increasing our understanding, yet autism pathogenesis remains largely unknown.

In several cases the argument against the recommended MMR vaccination is related to the idea that the MMR vaccine causes autism. The idea that MMR vaccination could be related to the development of autism was originally postulated by Wakefield in 1999 in a Lancet paper [8], which was subsequently retracted under the accusation of fraud. The original Wakefield paper associated autism with a virus-related gastrointestinal disorder, which was suggested to be the result of MMR vaccination. Despite the retraction, the paper was followed by a great deal of controversy leading to legal actions as well as extensive press and web coverage [9]. Eventually, Wakefield was found guilty of committing fraud, using non-scientific and unethical methodologies and was struck off the medical register of the UK. Even so, this turmoil resulted in a MMR vaccination scare with a considerable number of children not being vaccinated. Vaccination rates decreased sharply in the UK and the Netherlands, followed by an

increase in the incidence of measles and mumps with associated deaths and permanent disabilities. In the Netherlands, during the 1999–2000 outbreak, over 3200 cases of measles were notified, and > 95% occurred in the unvaccinated population [10].

Several subsequent reports showed no association between MMR vaccine and autism [11], including a Danish study, by Madsen *et al.*, that evaluated over two million persons-per-year and is particularly remarkable. This retrospective cohort study of all children born in Denmark in the 8 years going from 1991 to 1998, was unable to find any association between vaccinations and development of autistic disorder [12]

A novel approach in investigating the relationship between MMR vaccine and autism was used by some Japanese researchers who took advantage of an exceptional event, i.e. the withdrawal of MMR vaccine in Yokohama (population approximately 300,000). The study showed no effects of MMR withdrawal on the incidence of autism [13]

The direct effects of MMR vaccine programs have been extensively studied. Marwick *et al.* reported that before the vaccine was introduced in 1963 there were 4 million cases of measles reported annually in the United States; in 1999 there were only 100 reported cases. Before 1963, complications from measles were common (>200,000), and included thousands of respiratory complications, otitis media, over 40,000 admissions to hospital, seizures, and encephalitis, with more than 4000 deaths annually [14]

Despite these reassuring data, suspicious attitudes towards vaccines persist in a small but significant part of the public opinion. Of course these concerns should be thoroughly investigated with an open mind, based on the concept, as old as the Hippocratic Oath, of *primum non nocere*.

Nevertheless, it is difficult to address the issue in a scientific way when the anti-vax movement claims against vaccines are often based on emotional more than scientific reasons. Moreover, controversial reports such as those by Geier *et al.* [15], which are flawed or erroneous are often used as scientific evidence supporting their stance. The Geier report has been dismissed by the American Academy of pediatrics, which states that: “this paper uses data from the Vaccine Adverse Event Reporting System (VAERS) inappropriately and contains numerous conceptual and scientific flaws, omissions of fact, inaccuracies, and misstatements.”

(<http://web.archive.org/web/20030604060812/http://aap.org/profed/thimaut-may03.htm>)

3. THE THIMEROSAL CONTROVERSY

The mercury-based vaccine preservative thimerosal (has also been claimed to have a possible causal role in autism. The main scientist claiming this link is again Andrew Wakefield but, even though he is no longer a licensed MD because of his false claims, his opinions still have a lot of supporters. Several studies showed the lack of association between thimerosal-preserved MMR vaccines and autism [16]

In any case, presently vaccines routinely recommended by CDC for children younger than 6 years of age have been thimerosal-free for years. However, thimerosal which is ethylmercury is contained in influenza vaccines (see below). According to CDC website “Three U.S. health agencies (The Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the National Institutes of Health (NIH)) have reviewed the published research on thimerosal and found it to be a safe product to use in vaccines. In addition, three additional independent organizations [The National Academy of Sciences’ Institute of Medicine, Advisory Committee on Immunization Practices (ACIP), and the American Academy of Pediatrics (AAP)] reviewed the published research and also found thimerosal to be a safe product to preserve vaccines. Thus, the medical community supports the use of thimerosal in influenza vaccines to protect against potential bacterial contamination of multi-dose vials.”

(<http://www.cdc.gov/flu/protect/vaccine/thimerosal.htm>)

Even though mercury’s [17] toxic effects are well-known and there is a call to eliminate thimerosal from vaccines aimed to children [18], there is no conclusive data on its dangerousness. Instead, it appears clear that the risks of under-vaccinating are far more consequential than the supposed side-effects of thimerosal [19]

4. THE SV40 CONTROVERSY

Simian virus 40 (SV40) is a polyomavirus that can infect both monkeys and humans. Starting from 1961, SV40 was found in cultures of monkey kidney cells used to produce polio vaccine. As a consequence, millions of subjects receiving the vaccine were infected by SV40 [20]. SV40 causes cancer in some animal models. Its role in human cancerogenesis remains debatable, but still raised reasonable concerns.

A meta-analysis of five published studies shows that it is unlikely that SV40 exposure increases the overall risk of cancer incidence or mortality [23]. Furthermore,

several nation-based large studies in Denmark [21], the USA [22] and Sweden [23] likewise found no increase in cancer rates in people who received contaminated vaccines. The Danish study is particularly well conducted and concluded that, after a follow-up of 19.5 million persons per year, incidence of all tumors combined was not associated with SV40 exposure. Despite these comforting data, media headlines ranged from “vaccinated with the virus of cancer” to “cancer inoculated in kids”.

The issue of SV40 contamination has been addressed and procedural changes made to prevent viral contamination from happening again. However manufacturers must be aware of the possibilities of other contaminations and act promptly, to protect the public from real health threats as well as the mistrust and hysteria which can follow from such mistakes.

5. THE INFLUENZA EMERGENCY: INFLUENZA VACCINES IN THE ELDERLY

Seasonal influenza is considered a common and relatively benign disease. Because of this, and in spite of an effective vaccine being available for most of the developed world, vaccination rates against influenza are disappointingly low. Influenza remains one of the major risks to human health worldwide, according to the WHO. It is estimated that seasonal influenza infection is associated with more than 35,000 deaths and nearly 300,000 hospitalizations in the United States every year [24]. Moreover influenza and its complications are leading causes of severe disabilities among the elderly [25]. Mortality rates are higher in older patients especially those affected with cardiovascular and pulmonary diseases. Worldwide, the number of people aged 65 or older is increasing and projected to be over one billion in 2050. This presents tremendous health and economic challenges particularly in the older populations of developed regions such as the EU and the USA. Infections, including influenza, in older adults are currently responsible for over 10% of all hospital admissions in the population 65-74 years of age. As a result, the oldest group (85+) consumes a huge amount of economical resources [26].

Older people are the main targets of vaccination programs, but they also have a lower rate of successful immunization [27]. Leaving them, like other immune suppressed patients, vulnerable to influenza infection. An ineffective immunization in an elderly patient is detrimental not only the patient, who succumbs to the potentially serious effects of influenza, but also to friends and relatives who will be discouraged from

complying themselves with influenza vaccination protocols. Such a decision further exposes vulnerable patients to the risk of contracting influenza.

For these reasons it is important to consider the challenges and progress developing effective vaccination in the aged and immunosuppressed.

The factors contributing to immune-senescence are complex and difficult to detangle. Bragstad *et al.* reported low influenza vaccine effectiveness among elderly people in Denmark. They summarize their results: “epidemiological data suggest a low vaccine efficacy against influenza A(H3N2) among elderly people in Denmark; this is in contrast with early vaccine efficacy estimates in the range of >45% reported from other studies including all age groups [28]. Supporting this finding, Goodwin *et al.*, in a meta-analysis, calculated that vaccine efficacy in the elderly was only 17-53% as compared to 70-90% in younger adults [29]. This phenomenon is usually referred to as immune-senescence and is the result of immunological impairment occurring in patients over 65 years of age, [30]. A decline of immune responses in the elderly is a complex process related to a reduced output of naïve T-cells and accumulation of memory T-cells. In addition, it has been shown that chronic Cytomegalovirus (CMV) infection can lead to a CMV-related accumulation of terminally-differentiated CD4 lymphocytes, which seems to correlate to a deficient humoral response to influenza [31]. However, the population of terminally-differentiated lymphocytes is very small and thus difficult to monitor. Further tests to predict deficient response to vaccine in the elderly would be beneficial.

Indeed one of the major problems related to unsuccessful immunization in the elderly is that at the moment it is virtually impossible to predict who will and who will not respond to influenza vaccination. Finding cheap and easy-to-evaluate markers to determine whether or not a patient will develop or not an immune response after the vaccination is very important.

One preliminary objective is to find an easy and inexpensive way to distinguish patients infected by the influenza virus from those with an influenza-like illness. Indeed, many people who undergo the influenza vaccination complain that they develop influenza, but it is difficult to establish how many actually develop it and how many develop a different disease with similar symptoms. It has been reported that the presence of high fever may help distinguishing patients with influenza from those with influenza-like illness. In patients with laboratory confirmed influenza (LCI) subjects who did not seroconvert to influenza infection, pre-

infection levels of the cytolytic mediator granzyme B correlated with fever and the IFN-gamma/IL-10 ratio [32]. The levels of these factors might be useful predictors of the protection afforded by vaccination. Another potentially useful predictor is IFN-gamma, low or late responses of which correlate with increased risk of infections in the elderly [33] and reduction in antibody responses [34].

Others confirm the central role of impaired cellular immunity in a decreased response to influenza vaccine in the elderly, probably due to an imbalance between the memory and effector CD4 T cells in the elderly, which seems to be related to an alteration in IL-7 levels. These findings raise the question on whether the vaccination strategy in the elderly should be modified to improve cellular mediated immune responses [35].

There is a great deal of ongoing studies to improve the immunogenicity of influenza vaccines with different strategies including: (1) making the vaccine more potent, for example through a double administration; (2) using adjuvants to enhance vaccine immunogenicity; (3) applying immune modulators or other interventions to improve host immunity. See review in [36].

It has been shown that two doses of adjuvated influenza vaccine are safe and induce a humoral response comparable to that triggered by natural infection in pharmacologically immune-suppressed patients after hematopoietic stem cell transplantation. In this study adult allogeneic hematopoietic stem cell transplantation recipients were vaccinated with two doses of influenza A/H1N1pdm09 vaccine, 3 weeks apart. They were compared with patients with proven influenza A/H1N1pdm09 infection. Antibody responses were measured by haemo-agglutination. The sero-protection rate observed 42 days after vaccination was not different from that observed in the patients with natural infection (66% and 60% respectively, $p = 0.78$) [37].

A commercial influenza vaccine specifically designed for use in the elderly entered clinical use in the 2010 influenza season. The main innovation was to use a specially designed injection system for easy intradermal delivery of a double dose of the regular three-component influenza vaccine. Though designed to better stimulate dendritic cells and Langherans cells, the evidence supporting a more powerful immunization in the aged through intradermal vaccines is weak [27].

Another strategy to try and improve vaccine, is combined intranasal inactivated virus. Treanor *et al.* showed that baculovirus expressing H5 HA can induce functional antibody in individuals who have not had

prior exposure to H5 viruses, but also suggested that further studies to improve the immunogenicity of vaccines are needed [38].

Promising results have been obtained with the usage of more potent adjuvants such as the oil-containing emulsions MF-59, also referred to as squalene, approved for use in Europe. Several studies have reported an increased immunogenicity of adjuvated *versus* non adjuvated vaccines in the elderly [24, 39]. In their study of over 400 elderly and non-elderly patients, Banzhoff *et al.* conclude that in the group receiving 15 mg of MF59, seroprotection rates among elderly and non-elderly adults increased from 25% and 62% after primary vaccination to 92% and 88% after booster vaccination, respectively [40].

Other groups have tried to boost the immune response by using higher doses, with modest results. Gross *et al.* employed two types of vaccines, split-product vaccine (SPV) and whole virus vaccine (WVV), at doses up to three times the standard dose. A dose-response effect was observed for the SPV recipients to the influenza A/Chile/83 (H1N1) strain [41].

It appears clearer and clearer that, in the over-50 population, standard vaccinations don't work as well as in the younger population [42] but yet they are extremely effective from a public health point of view [43]. However, as discussed below, people are reluctant to accept adjuvated or higher doses of vaccines, even though the safety evaluation of an adjuvated vaccine is ultimately based on the end product (adjuvant and antigen) [44].

In the future, the development and use of more effective markers of immune-senescence to identify patients who may have impaired responses to vaccination may help to reduce morbidity and mortality due to infections in the elderly by offering more potent vaccination protocols to elderly with impaired immune-response to vaccines.

6. THE GUILLAIN-BARRE' SYNDROME RISK

Guillain-Barre' syndrome (GBS) is a rare but serious disease, in which the immune system attacks nerve cells, which can lead to muscle weakness, paralysis and, in some cases, death. The causal mechanisms are not fully understood, but GBS may be triggered by infectious illnesses, especially gastrointestinal and upper respiratory tract infections, including influenza. Vaccinations have also been reported as potential triggers. The case of influenza is particularly intriguing as both the influenza infection and the anti -influenza vaccination are potential triggers for GBS

An increased rate of Guillain-Barre syndrome (GBS) was suspected during the 1976 swine flu vaccination campaign. Extensive epidemiological data showed that this consisted of only one additional case of GBS per 100,000 individuals vaccinated above background rates (532 cases in 45 million vaccines). The authors concluded that the attributable risk for acquiring GBS within six weeks after receiving swine Influenza vaccine was 11.70 cases per millions subjects vaccinated [45]. Others also reported a very low incidence of the syndrome: the excess cases of GBS during the first 6 weeks attributed to the vaccine were 8.6 per million vaccinations in Michigan and 9.7 per million vaccinations in Minnesota. No increase in relative risk for GBS was reported 6 weeks after vaccination [46].

A Norwegian study [47] reported that GBS was significantly higher during the influenza peak and was not influenced by vaccination.

Lehmann *et al.* reviewing the issue in 2010, concluded that influenza infection is a relevant trigger for GBS and therefore reducing the cases of influenza by vaccination should, logically, protect against GBS [48].

7. THE SQUALENE CONTROVERSY

Squalene is a natural compound, originally obtained from shark liver and used as an adjuvant in several vaccines and has been the target of a wider controversy regarding its possible toxicity and its relation to the Gulf War syndrome (GWS). Some data have linked the health problems of Gulf War veterans to the possible presence of squalene in vaccines the soldiers received. One published report suggested that some veterans who received anthrax vaccines developed anti-squalene antibodies and these antibodies caused disabilities [49].

On the other hand, a study of the "US Defense Center for Deployment Health Research" disagreed with this assessment. They examined the relationship between squalene antibodies and chronic symptoms reported by Navy construction workers (Seabees). Out of 579 Seabees 30.2% were deployed, 7.4% were defined as ill, and 43.5% were positive for squalene antibodies. They conclude: "we found no association between squalene antibody status and chronic multi-symptom illness" and "the etiology of Gulf War syndrome remains unknown, but should not include squalene antibody status." [50]. However it must be stressed that this well conducted study was performed by a military related Department and thus not independent.

7.1. Industry-sponsored Studies: Influenza Vaccines

To overcome the low immunogenicity of influenza vaccines, especially in the elderly population, potent

adjuvants such as MF-59 have been used with good results. Different formulations of such drugs have been proved to be efficient, safe and non-teratogenic. It is reported that: "The clinical trial database encompassing all Novartis vaccine studies from 1991 to 2009 was searched to compare pregnancy outcomes in subjects exposed to MF59-adjuvanted or non-adjuvanted influenza vaccines. Analysis of the clinical trial database found that the distribution of pregnancy outcomes (normal, abnormal, or ending in induced abortion) was similar in subjects exposed to MF59-adjuvanted and non-adjuvanted influenza vaccine at any time in pregnancy and also, specifically, in early pregnancy"[51]. MF59-adjuvanted vaccines against seasonal influenza and pandemic avian H5N1 influenza have been found effective and safe in both adults and the elderly [52].

One study, comparing plain and MF-59 adjuvanted vaccines against avian influenza concluded that only the MF-59 H5N1 vaccine induced high titers of neutralizing antibodies and a large pool of memory influenza-specific B lymphocytes. The CD4 positive response was dominated by a Th1 pattern of cytokine production. Remarkably, an increase in the frequency of virus-specific total CD4₊ T cells, predicted the rise of neutralizing antibodies after booster and their maintenance 6 months later. The authors suggested that CD4 positive T cell priming might be used as an early predictor of the immunogenicity of pre-pandemic vaccines [53]. However, this is not an easily performed test.

Ott *et al.* [54] showed that a MF-59 containing only the low toxicity components squalene, Tween 80 and Span 85 have been shown to enhance titers of anti-influenza antibodies from 5 to >200 times that achievable with vaccine alone.

In a vast trial in over 10000 elderly patients it has been shown that the addition of MF59 to subunit influenza vaccines significantly enhances the immune response in elderly subjects without causing clinically important changes in the safety profile of the flu vaccine [55].

One Italian study found that the adjuvanted vaccines, induced a higher antibody response than whole virus vaccine and adverse events were rare. [56] Others reported efficacy and safety of MF59 adjuvanted vaccines [57].

A randomized study of a small number of patients immunized against H5N1 virus showed that antibody response to adjuvanted vaccines was superior than the one to regular vaccine [58].

7.2. Non Industry-sponsored Studies: Influenza Vaccines

The independent studies on influenza vaccines and MF-59 were not all consistent in reporting an increased activity of the adjuvant vaccine compared to the non adjuvated form. Still no study reported any risk related to the adjuvant.

Two Italian studies reported safety and efficacy of influenza vaccines adjuvated with MF-59 in adults [59] and children [60]. A German multicenter study was carried out in elderly subjects to compare the immunogenicity and reactogenicity of a conventional influenza split vaccine (SpV) with an MF-59-adjuvanted subunit vaccine (aSuV) and a virosome-based subunit. This randomized trial concluded that 3 vaccines including one with MF-59 showed no serious adverse events related to vaccinations. The conclusions were that all three vaccines are highly immunogenic with an acceptable reactogenicity profile and that they are appropriate for use in elderly [61]. A Canadian study reported that MF-59 adjuvanted vaccines are able to assure better protection against influenza in the elderly [62].

Two Italian studies looked at the use of the MF-59 adjuvant in immune suppressed patients. They concluded that safety and tolerability appear to be good in all in adolescents with juvenile idiopathic arthritis and yet another Italian group studied the effect of such vaccinations in patients suffering from rheumatoid arthritis and reported positive results, in terms of immune response [63]. The magnitude of vaccine responses appeared to be dependent on the immunosuppressive treatment [64]. Such observation lead to the specific issue of influenza vaccination efficiency in immune-suppressed patients [65] and in ageing populations such as those of Europe and the US, as comorbidities treated with immunosuppressive drugs are frequent in elderly subjects. Two large studies confirmed efficiency and safety of influenza vaccines including the adjuvanted ones [66] in several conditions resulting in immune-suppression, such as recipients of transplants patient undergoing chemotherapy, patients in chronic haemodialysis, patients with rheumatic diseases [67] and in HIV disease where a randomized trial was conducted [68].

Other groups showed the efficiency of a MF-59 like adjuvant in influenza vaccines [69]. A Dutch study concluded that the MF-59-adjuvanted influenza vaccine showed better long-term immunogenicity in the elderly compared to the non adjuvanted vaccine. Others showed that an MF-59 adjuvanted vaccine provided im-

proved protection against influenza in the elderly as well as in children [70]. This group also showed no increased incidence of narcolepsy (another claimed side effect of vaccine) in patients receiving influenza vaccine [71]. On the other hand a study from the Netherlands showed no significant improvement of the MF-59 vaccine efficacy on influenza-related hospitalizations [72].

In the 2009 H1N1 pandemic season, an increase of narcolepsy was found to be associated with a particular brand of vaccine, Pandemrix, inducing an increased production of antibodies against the GM3 ganglioside.]

A recent report confirmed that vaccine efficacy in the 2013-2014 season in the US was estimated to be 62% against H1N1 virus infections and was similar across all tested age groups [73]. In contrast, others described that 3 vaccines including one with MF59 during the 2010 influenza season, had no differences in the risk of influenza hospitalization in subjects aged ≥ 65 years vaccinated with MF59-Trivalent influenza vaccine (TIV) compared with those vaccinated with virosomal- trivalent [74]. Yet, it is important to keep in mind that it is difficult to compare data from different influenza seasons because differently virulent viruses are present in different seasons.

A study from the Netherlands concluded that in their trial, virosomal vaccine had similar immunogenicity to MF-59-adjuvanted and conventional subunit vaccine and was considerably less reactogenic than the M-F59-adjuvanted vaccine in the aged population [75].

A meta-analysis of over 5700 studies confirmed that influenza vaccination can provide safe protection. They conclude that: "based on a track record of substantial safety and moderate efficacy in many seasons, the current influenza vaccines will continue to have a role in reduction of influenza morbidity until more effective interventions are available. However, evidence for consistent high-level protection is elusive for the present generation of vaccines, especially in individuals at risk of medical complications or those aged 65 years or older" [76].

It is reassuring that, overall, the industry-sponsored and non industry-sponsored data largely overlap and mostly confirm the idea that influenza vaccines are safe and efficient. This position is reinforced by top independent agencies such as the CDC and the WHO.

According to the WHO the most effective way to prevent the disease and/or severe outcomes from the illness is vaccination. Safe and effective vaccines are available and have been used for over 60 years. Among

healthy adults, influenza vaccine can provide reasonable protection. However among the elderly, influenza vaccine may be less effective in preventing illness, but it may be able reduce the severity of disease and incidence of complications and death.

Vaccination is especially important for people at higher risk of serious influenza complications and for people who live with (or care for) high risk individuals.

The WHO recommends annual vaccination for:

Pregnant women at any stage of pregnancy

Children aged 6 months to 5 years

Elderly individuals (≥ 65 years of age)

Individuals with chronic medical conditions

Health-care workers.

According to the WHO website: "Twenty-two million doses of influenza vaccine (Fluad) have been administered safely since 1997. This vaccine formulation contains about 10 mg of squalene per dose. No severe adverse events have been associated with the vaccine", although mild local reactogenicity may be present.

(http://www.who.int/vaccine_safety/committee/topics/adjuvants/squalene/questions_and_answers/en/)

8. CONSIDERATION OF THE VACCINATION SCHEDULE

Some concerns have been raised about the fact that there are 25 shots recommended in the first 15 months of life and up to six shots can be administered at one time. Many politicians around the world, including the actual President of the United States, Donald J. Trump, have expressed perplexities over the actual safety of multiple vaccine shots administered together (he tweeted: "Healthy young child goes to doctor, gets pumped with massive shot of many vaccines, doesn't feel good and changes - AUTISM. Many such cases!" on 05:35 - 28 mar 2014) and such statements have stirred up mixed feelings, leading to new studies, which examine the safety profile of hexavalent vaccinations [77].

In Oct. 2008, The American Association of Pediatrics released a web document "The Childhood immunization schedule; Why it is Like That?" defending the schedule and the necessity to have early protection.

Although children receive more vaccines now than ever before, the number of immunological components in vaccines has dramatically decreased to fewer than 130 proteins for the entire recommended schedule [78].

As immunologists, we have to point out that infants are colonized (by playing, eating and breathing) by trillions of bacteria each day and each bacterium contains thousand of antigens. Thus, the number of antigens in vaccines is minuscule when compared to what infants manage every day.

However, we recommend that the efficiency and safety of more diluted schedules should be tested by independent trials in order to address parents' concerns and improve educational intervention for vaccine-hesitant parents [79].

CONCLUSION

The recent controversy regarding the safety of vaccines has stemmed from small but significant segments of the population. This has led to the surge of previously controlled diseases within this population and also in individuals in the wider population who are vulnerable (for example infants too young to be vaccinated, the immuno-suppressed or compromised people).

No drug can be made 100%, safe, not even placebo pills. This is particularly true for biological drugs such as vaccines. However, a vast analysis of the available data supports the idea that the benefits of vaccination dramatically overcome the risk.

The anti-vax movement is driven by a small but vocal minority and can have a significant impact on the population, as the movement spreads. These behaviors are detrimental and can lead to severe consequences from preventable diseases. Focusing attention on aspects of vaccinations, which have been proven safe and that are accepted by the scientific community and indeed, the majority of the general population, is a distraction from real, serious problems with vaccination which need to be addressed, especially in vulnerable populations.

Vaccine hysteria may jeopardize future research in the development of new vaccines, such as anti cancer vaccines. In contrast to prophylactic vaccines that are administered to healthy individuals and designed to mount an immunological response when the subjects are exposed to infectious agents, therapeutic cancer vaccines are administered to cancer patients and are designed to eradicate cancer cells through enhancing the patients' own immune responses. The various immune effector mechanisms mobilized by therapeutic vaccination specifically attack and destroy cancer cells and spare normal cells. Thus, therapeutic cancer vaccines might be utilized to inhibit further growth of advanced cancer and/or relapse [80]

Concerns and hesitancy toward vaccines discussed in this paper are being echoed more and more frequently in newspapers and reported in the scientific literature.

Strategies to combat anti-vaccine messages cannot be developed by educated guesswork. Evidence-based approaches, that facilitate vaccination, are needed if we are to prevent diseases that can easily be avoided and fulfill the potential of modern vaccine research.

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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