Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Vaccine-preventable diseases, vaccines and Guillain-Barre' syndrome

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ARTICLE INFO

Article history:
Received 15 January 2018
Received in revised form 27 May 2018
Accepted 28 May 2018
Available online xxxx

Keywords:
Guillain-Barrè syndrome
Human papillomavirus vaccine
Influenza
Measles/mumps/rubella vaccine
Safety
Tetravalent conjugated meningococcal vaccine

ABSTRACT

Guillain–Barré syndrome (GBS) is an acute, immune-mediated polyradiculoneuropathy. Infections and vaccines have been hypothesized to play a role in triggering GBS development. These beliefs can play a role in reducing vaccination coverage. In this report, data concerning this hypothesis are discussed. It is shown that an association between vaccine administration and GBS has never been proven for most of debated vaccines, although it cannot be definitively excluded. The only exception is the influenza vaccine, at least for the preparation used in 1976. For some vaccines, such as measles/mumps/rubella, human papillomavirus, tetravalent conjugated meningococcal vaccine, and influenza, the debate between supporters and opponents of vaccination remains robust and perception of vaccines' low safety remains a barrier to achieving adequate vaccination coverage. Less than 1 case of GBS per million immunized persons might occur for these vaccines. However, in some casesimmunization actually reduces the risk of GBS development. In addition, the benefits of vaccination are clearly demonstrated by the eradication or enormous decline in the incidence of many vaccine-preventable diseases. These data highlight that the hypothesized risks of adverse events, such as GBS, cannot be considered a valid reason to avoid the administration of currently recommended vaccines.

Contents

1. Introduction

Guillain–Barré syndrome (GBS) is an acute, immune-mediated polyradiculoneuropathy [1]. As poliomyelitis has been nearly eradicated, GBS has become the most common cause of acute flaccid paralysis worldwide. Annually, it occurs in 0.4–4.0 cases per 100,000 population, mainly in males, with the lowest incidence in children and the highest incidence in subjects older than 75 years of age [1–3]. Clinically, several variants of GBS have been identified according to the types of nerve fibres involved (i.e., motor, sensory, sensory and motor, cranial or autonomic), the predominant mode of fibre injury (i.e., demyelinating versus axonal), and the association with mild alterations [1–3]. The classic GBS type is characterized by a progressive bilateral and relatively

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https://doi.org/10.1016/j.vaccine.2018.05.119
0264-410X/

symmetric weakness of the limbs associated with generalized hyporeflexia or areflexia. In the most severe cases, ascending paralysis with involvement of the upper limbs and face occurs. Symptoms typically progress over a period of 12 h to 28 days, before a plateau is reached [1–3]. During the first week of illness, a characteristic albumin-cytologic dissociation in the cerebrospinal fluid is observed in approximately 50% of cases. This percentage increases to 75% in the final stage of the disease [4]. Most patients completely recover in a few weeks, although limb weakness can persist for up to a year in some cases, and approximately 5% of patients can die, generally from respiratory problems or superimposed infections [5]. Moreover, 2–5% of GBS patients relapse after an asymptomatic period of several months to years [6,7].

Based on nerve conduction studies, two main types of GBS have been described, acute inflammatory demyelinating polyradiculoneuropathy (AIDP) and acute motor axonal neuropathy (AMAN) [1–3]. The first type accounts for up to 90% of cases in the Western world; in contrast, AMAN is more common in Asia, where it is diagnosed in 30–65% of patients with GBS. AIDP is generally more severe because respiratory problems and autonomic dysfunction occur more frequently in patients with this type of GBS [8]. However, several subtypes have been identified [1–3]. Among cases included in the AMAN group, one subtype includes cases in which sensory nerves are involved along with motor nerves, including Miller-Fisher syndrome and Bickerstaff's brainstem encephalopathy. The first subtype is clinically more important than the classic AMAN case because of the systemic association of motor and sensory nerve damage. Miller-Fisher syndrome is characterized by acute external ophthalmoplegia and sluggish pupillary reflexes together with variable signs and symptoms of classic GBS. In the second subtype, clinical or magnetic resonance imaging of brainstem involvement can be demonstrated.

Infections and vaccines have been hypothesized to play a role in triggering GBS development. These beliefs can play a role in reducing vaccination coverage. In this report, data concerning this hypothesis are discussed.

2. Infections and Guillain-Barre' syndrome (GBS)

In approximately 60% of patients, GBS is preceded by an infection [9–12]. The most common infectious agents are *Campylobacter jejuni* and cytomegalovirus (CMV), which have been identified in approximately 30% and 10% of cases, respectively. A frequent association with *Mycoplasma pneumoniae* and Epstein–Barr virus has also been reported. Finally, a potential link with some vaccine-preventable infectious diseases, such as varicella, measles, influenza and those due to *Haemophilus influenzae*, has been suggested. However, cases following varicella, measles and *Haemophilus influenzae* infection are very rare and suggest only a temporal association between infection and GBS development [13–15]. In contrast, GBS cases following a previous influenza episode are not uncommon, and a potential causative role of influenza virus infection cannot be excluded. This was already hypothesized at the time of the 1918–1920 Spanish influenza pandemic on the basis of reports from the USA, Canada, Sweden, and Egypt, although data collected during those years are difficult to evaluate [16]. However, in subsequent years, several lines of evidence collected worldwide regarding both seasonal and pandemic influenza periods appeared to confirm the link between influenza or influenza-like illness (ILI) and GBS. Stowe et al. reported that between 1990 and 2005 in the UK, the relative incidence of GBS within 90 days of an ILI episode was 7.35 (95% confidence interval [CI]: 4.36–12.38), with the greatest relative incidence (odds ratio [OR]: 16.64, 95% CI: 9.37–29.54) found within 30 days [17]. Tam et al., studying UK data from 1990 to 2001, showed that ILI was associated with an 18-fold increase in GBS risk (OR: 18.6, 95% CI: 7.5–46.4) [18]. Sivadon-Tardy et al., studying data from France during the period 1996–2004, found a strict relationship between serological evidence of influenza infection in patients with GBS and seasonal peaks of ILI [19]. Ghadery et al. reported that the incidence rate ratio (IRR) of GBS during the 2009 pandemic peak was significantly higher than in other periods (OR: 1.46; 95% CI: 1.08–1.98) in Norway and that the adjusted hazard ratio (aHR) of GBS within 42 days after a diagnosis of pandemic influenza was 4.89 (95% CI: 1.17–20.36) [20]. Finally, indirect evidence of the potential role of influenza viruses has been suggested from data collected by the British Paediatric Surveillance Unit system from September 2009 to August 2010 in the UK. In this country, it was shown that most of the cases of GBS reported during and immediately after the pandemic period were diagnosed in children who had not received the vaccine and, consequently, had no protection against influenza. Even in these cases, the incidence rate of GBS was significantly higher than expected [21].

3. Pathogenesis of Guillain-Barre' syndrome (GBS)

GBS is an autoimmune disease, although each of the main subtypes has a distinct immunopathogenesis. In AIDP, the histology of spinal roots and motor and sensory nerves has shown inflammatory infiltrates of T cells and macrophages associated with areas of segmental demyelination [22]. Although specific antigens have not been precisely identified, it is thought that the disease is caused by a combination of T-cell-mediated autoimmunity to myelin proteins and antibodies to myelin glycolipids. The high T cell concentrations in damaged nerves and antibodies to myelin proteins in the sera of patients with classic GBS support this hypothesis [23]. Autoantibodies are thought to bind to myelin antigens, activate complement, and cause vesicular disruption of myelin through the formation of immune complexes linked to Schwann cells. Macrophages eliminate myelin debris.

In contrast, in acute axonal neuropathies, no demyelination is demonstrable, and lesions typically include only the axons of motor nerves or motor and sensory nerves together.

The damage is primarily dependent on the production of IgG autoantibodies to gangliosides, an important component of myelinated axons. The most common gangliosides are GM1, GD1a and b, GQ1B and GT1a. Molecular mimicry between gangliosides and antecedent infectious agents is the base for the induced autoimmunity. Although several reports suggest that molecular mimicry can induce GBS development following CMV and *Mycoplasma pneumoniae* infection, the best example in this regard is given by *Campylobacter jejuni* infection [24,25]. Lipo-oligosaccharides of the outer membrane of this pathogen mimic the molecular structure of GM1 and GD1a gangliosides. This leads to the production of autoantibodies that bind to nodes and activate complement. Nerve conduction is blocked or slowed, and muscle weakness develops [26]. This mechanism has been reproduced in experimental models of animals immunized with ganglioside mixtures, isolated GM1 or GM1-like lipo-oligosaccharides of the infectious agent [27–29]. Moreover, at least in a portion of patients with axonal neuropathy, an antibody against gangliosides can be detected [30]. Interestingly, the clinical picture of axonal GBS varies according to the characteristics of the microbial lipo-oligosaccharide and the type and site of gangliosides with similar structures. GM1 and GD1a are mainly localized at the nodes of Ranvier and in motor nerve terminals, whereas GQ1b is localized in oculomotor cranial nerves and in the brain. This explains why the CNS is involved in some rare cases. Molecular mimicry involving GM1 and GD1a gangliosides is associated with classic AMAN, as well as its more extensive and less extensive subtypes. Autoantibodies to GQ1b,

Please cite this article in press as: Principi N, Esposito S. Vaccine-preventable diseases, vaccines and Guillain-Barre' syndrome. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.05.119

which cross-react with GT1a, are strongly associated with Miller Fisher syndrome, its incomplete forms and its central nervous system variant, Bickerstaff's brainstem encephalitis [31].

4. Potential link between vaccines and Guillain-Barre' syndrome (GBS) development

As GBS is an autoimmune disease, it has been hypothesised that a vaccine, i.e., a preparation that induces an immune response, may result in GBS development. Moreover, a possible link between GBS development and vaccine administration has been supported by GBS cases described after administration of an old rabies vaccine formulation Both the Semple vaccine, based on an inactivated rabies virus previously inoculated in animal brains, and the suckling mouse brain vaccine have been associated with a paralytic disease resembling GBS. In both cases, inoculation of brain proteins with structural similarities to human nervous system proteins was identified as the cause of autoimmunity and nervous tissue damage in vaccine recipients [32,33]. Moreover, although several anecdotal reports have suggested a potential link between GBS development and all of the currently used vaccines, no evidence of a true association exists for the great majority of presently recommended vaccines [34]. Suggested links between the oral polio vaccine and diphtheria tetanus toxoid pertussis vaccine have been excluded by a number of epidemiological evaluations that clearly demonstrate that the risk of GBS development after these vaccines is no greater than that expected by chance alone [35,36]. Concerns remain, however, for measles/mumps/rubella (MMR), human papillomavirus (HPV), quadrivalent conjugated meningococcal and influenza vaccines.

4.1. Measles and measles/mumps/rubella (MMR) vaccines

Several case reports have shown a temporal association between measles or measles/mumps/rubella (MMR) vaccination and GBS development, suggesting that the attenuated measles virus could cause the disease [37,38]. However, results of the studies specifically planned to evaluate the risk of GBS following MMR vaccination remain controversial, mainly because of the methodological limitations of most of the studies. In some cases, data were derived from passive surveillance systems without any comparison with unvaccinated populations. In other cases, the MMR vaccine was given concomitantly with other vaccines or was administered in subjects who were suffering from an acute infectious disease, making it impossible to establish the actual role of MMR in conditioning for GBS development [38–43]. This explains why the US Institute of Medicine has concluded that the available evidence is not sufficient to accept or reject a causal relationship between MMR vaccination and GBS development [44]. Moreover, lacking definitive statements, the pharmaceutical companies that produce and market measles virus-containing vaccines mention this hypothetical link in the product information leaflets for the measles and MMR vaccine, with the warning that the frequency of this potential adverse event cannot be estimated from available data [45]. However, although it is not possible to definitively state that the MMR vaccine does not cause GBS, there are data that appear to indicate that, if a risk exists, it is so low that it cannot be demonstrated by epidemiological studies that compare GBS incidence between periods with or without MMR vaccine use, even when an extremely large number of subjects are enrolled. This was shown by an active retrospective study performed in Finland, in which the linkage between hospitalization for GBS and MMR vaccination was analysed. A total of 189 GBS cases and approximately 630,000 vaccine recipients that had collectively received 900,000 doses of MMR vaccine were studied. The incidence of GBS in the vaccinated population was no higher than that previously reported in unvaccinated populations. Moreover, no clustering of cases of GBS occurred at any time point after administration of the MMR vaccine [46]. Similar conclusions could be drawn from a study performed in Iran that planned to evaluate whether a measles immunization campaign involving approximately 33 million individuals aged >5 years influenced the frequency of GBS diagnosis. The study results showed that the annual incidence in the 5–14 years age group remained relatively constant over a 3-year evaluation period regardless of vaccine use, ranging from 0.65 to 0.76 per 100,000 [47]. Finally, da Silveira et al. compared the baseline frequency of GBS during a 5-year period (January 1990, to December 1994) with the frequency observed during periods of mass measles vaccination campaigns, each of 1 month duration, in 1992 and 1993 [48]. The study was performed in several countries in South America, and data concerning 2296 GBS cases that had occurred among 73 million immunized children were analysed. The incidence rate of GBS in the campaign periods was 0.67 per 100,000 people per year, a value within the range of the incidence rates of cases diagnosed outside these periods (OR: 0.63, 95% CI: 0.49–0.75). This finding led to the conclusion that no statistically significant association between measles vaccination and GBS could be demonstrated. On the other hand, as highlighted by the US Institute of Medicine, none of the markers of measles-related autoimmunity (i.e., autoantibodies, complement activation, immune complexes, T cells) were identified in subjects that were believed to have MMR-related GBS [44].

Based on these findings and the enormous clinical benefits related to measles vaccine administration, the hypothetical risk of GBS, if any, cannot be considered a legitimate reason to limit MMR administration.

4.2. Human papillomavirus vaccine (HPV)

Regarding the HPV vaccine, doubts concerning its safety were raised when it was noted that epidemiological studies assessing the risk of GBS following HPV vaccination had shown conflicting results. No increased risk of HPV-related GBS was demonstrated in two studies performed in Scandinavian countries [49,50]. In contrast, a study performed in France, initially published online in French on the site of the National Medicine Agency [51] and more recently reported in English [52], had shown a potential risk. In this study, 2,252,716 girls aged 13–16 years between 2008 and 2012 covered by the general health insurance scheme and without a history of HPV vaccination or autoimmune disease were enrolled and followed using French national databases. During a mean follow-up period of 33 months, 37% of these girls were vaccinated, and 43 GBS cases occurred. By comparing vaccinated and unvaccinated subjects, it was shown that the HPV vaccine was significantly associated with GBS development (incidence rates: 1.4 vs 0.4 per 100,000 cases; aHR: 3.78; 95% CI: 1.79–7.98). Based on these discrepancies, the World Health Organization Global Advisory Committee on Vaccine Safety concluded that, despite being low, the presence of a potential risk deserved attention and suggested the need for additional studies in adequately sized populations [53]. Recently, however, more reassuring data were obtained. A large self-controlled case-series analysis was performed in the UK [54]. It enrolled a population of female individuals aged 11–20 years who had received a total of 10.4 million HPV vaccine doses. The risk of hospital admission for GBS (both probable and confirmed) within 3, 6 and 12 months of any HPV vaccine dose administration was evaluated. After adjustment for age, season and time period, it was found that no risk of GBS could be attributed to HPV vaccine administration. Compared to other periods outside the study windows, the relative incidence was 1.04 (95% CI: 0.47–2.28), 0.83 (95% CI: 0.41–1.69) and 1.10 (95% CI: 0.57–2.14) for the

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3-month, 6-month and 12-month risk periods, respectively. When analysis was restricted to confirmed cases, the relative incidence for the 3-months period did not significantly change (1.26; 95% CI: 0.55–2.92). Moreover, no difference was found between the quadrivalent and the bivalent vaccines (relative incidence: 1.61, 95% CI: 0.39–6.54 and relative incidence: 0.84, 95% CI: 0.30–2.34, respectively). A protective effect of HPV vaccines against autoimmune diseases, including GBS, was reported by Grimaldi-Bensouda et al. [55]. These authors conducted a systematic prospective case-referent study specifically planned to assess the risks associated with real-world use of HPV vaccines. The patients included females aged 11–25 years old with incident autoimmune disease diagnosed at specialized centres across France (2008–2014) and individually matched by age and place of residence to controls recruited in general practice. A total of 478 definitive cases were matched with 1869 controls, and all the autoimmune diseases combined were negatively associated with HPV vaccination (adjusted OR: 0.58; 95% CI: 0.41–0.83). Interestingly, GBS was not diagnosed in any of the vaccine recipients. Further indications of the safety for the HPV vaccine were derived from passive surveillance reports [56], from active monitoring in the US Vaccine Safety Datalink [57] and from the US Vaccine Adverse Events Reporting System [58], in all cases based on several millions of distributed doses. Practically, it was concluded from the available data that the existence of a risk for GBS development after HPV vaccine administration could not be demonstrated and, even if such a risk does exist, it could not be higher than 1 case per million doses. Consequently, it could not be considered a legitimate justification to limit the use of this effective prophylactic measure [59].

4.3. Quadrivalent meningococcal vaccine

In 2005, a few months after the inclusion of the meningococcal (groups A, C, Y and W-135) polysaccharide diphtheria toxoid conjugate vaccine (MCV4) in the US immunization schedule for adolescents, an unexpectedly high number of GBS cases were diagnosed in adolescents who had received the vaccine 14–31 days before symptom onset [60]. While waiting for the identification of the true risk of GBS after MCV4 administration, the US Advisory Committee of Immunization Practice (ACIP) stated that this would not be a limitation for the use of the vaccine in adolescents [61]. However, the US Food and Drug Administration recommended that MCV4 should not be administered to subjects with a previous history of GBS and requested the performance of adequately structured studies to evaluate the problem [62].

Velentgas et al. conducted a retrospective study enrolling approximately 9.5 million 11- to 21-year-old subjects in members of five US health plans, among whom 15% had received MCV4 [63]. No confirmed GBS case was diagnosed within 42 days of MCV4 vaccination. Consequently, the incidence rate was 0 (95% CI: 0–2.28 per 100,000 person-years). Outside the 42-day postimmunization window, the incidence rate was 0.45 cases per 100,000 person-years (95% CI: 0.24–0.75), similar to that found in unvaccinated adolescents (0.55; 95% CI: 0.41–0.69). Starting from the upper bound of the one-sided 95% CI for the attributable risk of GBS, the authors concluded that less than 1.5 excess cases per million immunized adolescents could follow GBS administration. Further confirmation of MCV4 safety was provided by a study performed by Yih et al., who combined these data with those collected by the US Vaccine Safety Datalink in order to evaluate the impact of MCV4 on a significantly greater number of adolescents [64]. A total of 2,321,590 doses of MCV4 vaccine were studied. No confirmed GBS case was diagnosed in either study. The precision of the attributable risk estimate was increased, and it was calculated that the risk could not be less than 0.66 excess cases per million adolescents vaccinated. Considering the data from these studies, ACIP removed the limitation for individuals with a previous history of GBS [65]. However, a history of GBS cases after immunization is still reported in the package inserts of both MCV4 and a second quadrivalent vaccine with a different conjugation protein (MenACYW-CRM_{197}), although a temporal association of this formulation with GBS has never been described [66,67].

4.4. Influenza vaccine

The first report of a possible relationship between influenza immunization and GBS dates to 1976 when, following the receipt of a swine influenza vaccine in the USA, an 8-fold increase in the incidence of GBS was reported [68]. A rigorous evaluation of the phenomenon led the Institute of Medicine to conclude that the evidence favoured acceptance of a causal relationship between this vaccine and GBS in adults It was calculated that the influenza vaccine could cause one additional case of GBS for every 100,000 doses administered [69]. The period of highest risk was within the first 6 weeks after vaccine administration, although cases were detected even 9–10 weeks post-vaccination. Since that year, several attempts to verify this potential association have been made, often with conflicting results [17,70–76]. In the majority of cases, no relationship was demonstrated, and the difference in the incidence of GBS between vaccinees and controls was not statistically significant. However, two studies seemed to confirm that the influenza vaccine could trigger GBS. In the first study, performed in Canada, data regarding influenza seasons between 1992 and 2004 were examined. It was found that in the 6 weeks following vaccination, the risk of GBS in people receiving the vaccine was increased (RR: 1.45; 95% CI: 1.05–1.99; p = 0.02) [74]. In the second study, performed in the USA, the period 1992–1994 was evaluated. The RR of GBS in the 6 weeks after immunization was found to be 1.7 (95% CI: 1.0–2.8; P = 0.04). These findings led to different resolutions by US health authorities [76]. The ACIP and the Vaccine Information Statements for influenza vaccines decided to make public the existence of a risk of GBS development after influenza immunization and quantified it as one additional case of disease per million vaccines [77]. In contrast, the Institute of Medicine, considering all the data collected from 1976 to 2008, determined that the evidence was inadequate to accept or reject a causal relationship between influenza vaccination and GBS because of the potential for confounding by season and influenza infection and because of the yearly differences in influenza strains included in the vaccine [78].

Further data were collected during the 2009 influenza pandemic through surveillance programs specifically activated worldwide. In the majority of cases the studies suggested an increased risk of GBS after influenza vaccine administration, regardless of the preparation used. In the USA, where only nonadjuvanted vaccines were used, a meta-analysis combining data from 23 million individuals led to the conclusion that the pandemic 2009 A/H1N1 vaccine was associated with a relative risk of GBS of 2.35 (95% CI: 1.4–4.0) and caused 1–3 additional GBS cases per million persons vaccinated [79]. A similar risk was reported from Canada and Europe, where adjuvanted vaccines were primarily administered [80–85]. Finally, an international study [82] carried out in 15 countries where both adjuvanted and nonadjuvanted pandemic 2009 A/H1N1 vaccine were used evidenced a slight but significant increase in the risk of GBS development in subjects immunized with the monovalent pandemic vaccine (RR: 2.42; 95% CI: 1.58–3.72). All these findings seem to confirm what was suggested by the data collected in 1976, i.e. that influenza vaccine can cause, although rarely, GBS. However, in a few studies different results were reported. For example, in the influenza seasons following the pandemic year, although the trivalent vaccine contained the same A/H1N1 strain that was in the monovalent vaccine, no increase in

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GBS incidence was observed [8]. Moreover, not in all the studies in which a strict relationship between influenza vaccine administration and GBS development was demonstrated, data analyses was correctly performed, leading to debatable results. A good example in this regard is given by the multinational European study by Dieleman et al. [81]. In this study, after adjustment for influenza-like illness (ILI)/upper respiratory tract infection and seasonal influenza vaccination, receipt of pandemic influenza vaccine was not associated with an increased risk of GBS (adjusted OR: 1.0, 95% CI: 0.3–2.7). However, the results of the studies in which a relationship was shown between influenza vaccine administration and GBS may have been influenced by lack of adjustment for confounding. On the other hand, in both the USA [83] and the international study [82] where importance of ILI as confounding factor was differently analysed, it was found that among persons without ILI the adjusted OR was higher than 2.5. Moreover, in addition to influenza causing a greater risk of GBS development than vaccination, the latter was found to be protective from GBS during seasonal or pandemic influenza seasons. Vellozzi et al. used data from the surveillance of GBS cases in a population of approximately 45 million persons during the 2009 influenza pandemic period and found that the vaccinated population had a lower average risk (0.83, 95% CI: 0.63–1.08) and a lower cumulative risk (6.6 vs 9.2 cases per million persons, $p = 0.012$) of GBS [85]. Even greater protection was suggested by the data collected by Kwong et al. [86]. These authors, in a study in which each patient served as his or her own control, analysed data between 1993 and 2011 regarding more than 13 million subjects living in Canada. The incidence rate of GBS within 6 weeks of vaccination was 52% higher than that in the control interval of 9–42 weeks (1.52; 95% CI: 1.17–1.99), with the greatest risk identified during weeks 2–4 after vaccination. However, the risk of GBS within 6 weeks after an influenza episode was greater than that associated with vaccination (15.81; 95% CI: 10.28–24.32). The risk of hospitalization was 1.03 per million vaccinations, compared with 17.2 per million influenza disease cases.

All of these findings indicate that, even if influenza vaccines can cause GBS, the risk is very low. Moreover, although the overall risk/benefit of the vaccine in preventing GBS depends on the risk of contracting influenza if unvaccinated and the effectiveness of the vaccine, it is highly likely that in most of the influenza seasons immunization can be of great benefit reducing the overall risk of GBS development. As influenza vaccines are effective in the prevention of influenza and its complications, influenza vaccination has to be maintained in the list of vaccines that are strongly recommended.

5. Conclusions

An association between vaccine administration and GBS is rarely found. For some vaccines, such as MMR, HPV, MCV4 and influenza, the debate between supporters and opponents of vaccination remains robust and may not represent a marginal barrier to achieving adequate vaccination coverage [87]. However, available data are reassuring because they demonstrate that, if any risk actually exists, it is so low that it cannot be demonstrated even with studies that include several million vaccinees and unvaccinated controls. Attempts to quantify the risk have led to the conclusion that, in general, less than 1 case of GBS per million immunized persons might occur for each of the previously discussed vaccines. In conclusion, the benefits of vaccination are clearly demonstrated by the eradication or enormous decline in the incidence of many vaccine-preventable diseases. The hypothesized, risks of adverse events, such as GBS, cannot be considered a valid reason to avoid the administration of currently recommended vaccines.

Acknowledgments

This review was supported by a grant from the World Association of Infectious Diseases and Immunological Disorders (WAidid). The funding source had no impact on the literature search or preparation of the manuscript.

Conflicts of interest

None to declare.

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Please cite this article in press as: Principi N, Esposito S. Vaccine-preventable diseases, vaccines and Guillain-Barre' syndrome. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.05.119

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