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Background Paper for the update of meningococcal vaccination recommendations in Germany: use of the serogroup B vaccine in persons at increased risk for meningococcal disease

In August 2015 the German Standing on Vaccination (STIKO) endorsed a recommendation for the use of the new meningococcal B (menB) vaccine in persons at increased risk of invasive meningococcal disease (IMD). This background paper presents in detail the results of the literature reviews and the grading of the quality of the available evidence underlying the new STIKO recommendations. The document opens with a brief synthesis for rapid orientation. A German version of this background paper is available in the Epidemiologische Bulletin 37/2015 [1].

1 Summary

A surface protein-based vaccine against serogroup B became available in December 2013 (Bexsero®; called 4CMenB in licensure studies) to complement the polysaccharide capsule-based conjugate vaccines against serogroups A, C, W and Y (MenACWY) previously available.

Following evaluation of the available evidence, the German Standing Committee on Vaccination [Ständige Impfkommission, STIKO] recommends MenB vaccination for the following persons at increased risk of IMD after individual risk assessment. Persons at increased risk of IMD due to congenital or acquired immune deficiency or suppression with residual T and/or B cell function, particularly in cases of complement/properdin deficiency, eculizumab therapy (monoclonal antibody against the terminal complement component C5), hypogammaglobulinemia and anatomical or functional asplenia should be vaccinated with a MenB vaccine in addition to a meningococcal ACWY conjugate vaccine (see current STIKO recommendations, *Epid. Bull.* 34/2015). Likewise, household or household-like contacts of a patient with invasive meningococcal disease (IMD) should receive post-exposure vaccination, not only when IMD in the index patient is caused by serogroups A, C, W or Y, but now also when caused by serogroup B. Finally, at-risk laboratory staff (performing work procedures with a risk of *N. meningitidis* aerosol formation) should receive MenB vaccination in addition to vaccination with a MenACWY conjugate vaccine.

The incidence of IMD in Germany has decreased markedly since introduction of mandatory reporting in 2001, to an overall annual incidence of 0.44 IMD cases/100,000 inhabitants (Inh.) in 2010–2013. This corresponds to 250 cases of MenB, 78 MenC and 35 cases due to other serogroups annually. The proportion of IMD cases in persons at increased risk due to underlying medical conditions or through close contact with IMD patients is largely unknown. Clusters of IMD cases due to the same meningococcal strain are rare (< 2 % of all cases), usually affecting only a few persons often living together in one household.

No data are available on the efficacy of Bexsero® against clinical outcomes. A preliminary review of available licensure studies was performed to assess data on immunogenicity. Results based on bactericidal antibodies (hSBA) against the

Table 1 Summary of the estimates for the risk of invasive meningococcal disease due to serogroup B in selected risk groups and the estimated number of respective individuals needed to be vaccinated with Bexsero® to prevent one case (number needed to vaccinate, NNV). See text for details of the calculations with underlying assumptions

Risk group (estimated number of affected persons in Germany)	Risk of IMD due to MenB (cases/100,000 affected individuals/year)	Number of cases/year	In the year after vaccination		Within 3 years after vaccination	
			NNV[a] in the year after vaccination	Cases prevented with vaccination coverage = 100 %	NNV within 3 years after vaccination	Cases prevented with vaccination coverage = 100 %
Asplenia (90,000)	8	7.2	19,000	4.7	6350	14.2
Complement deficiencies (8–10,000)	1550–3100	155–310	49–98	102–204	16–32	306–612[d]
HIV infections[c] (80,000)	1.5–3.0	1.2–2.4	51,000–102,000	1.2–2.3	13,900–27,800	2.9–5.9
Immune deficiencies with hypo or agammaglobulinemia (800–800,000)	Unknown, only slightly elevated	not estimated	Similar to HIV-infected individuals	not estimated	Similar to HIV-infected individuals	not estimated

[a]Assumption: Average term of protection of the vaccination is 1 year or [b]3 years.

[c]Estimate performed for an estimated 10.000 affected.

[d]These calculations clarify the uncertainty regarding the estimate of the number of affected persons in Germany: In the group of complement deficiencies, the maximum estimate of 10,000 appears excessive; as, based on the 5000–10,000-fold increased risk of IMD, the majority of persons with IMD in Germany would have to have a complement deficiency.

four antigens present in the vaccine measured after vaccination are consistent with very good efficacy against infections with strains susceptible to the induced antibodies shortly after vaccination in infants (4 vaccine doses) and toddlers (2–3 vaccine doses), with a marked decline in hSBA after 1 year. Likewise, very good immunogenicity was observed after 2 vaccine doses in adolescents with more stable persistence of protective hSBA 18–24 months after vaccination (**Annex 1**), although the hSBA GMT (geometric mean titer) declined by an order of magnitude in this time period. No data were available on immunogenicity in persons with chronic diseases or immune deficiencies/immunosuppression. Based on data on immune responses to other vaccines, the effectiveness and duration of protection in individuals with immune deficiencies/immunosuppression are likely to be lower than in healthy persons. The 4CMenB vaccine (Bexsero®) cannot prevent all infections with MenB strains, as only 82 % of the meningococcal strains circulating in Germany expressed at least one of the vaccine antigens in 2007–2008.

Reactogenicity and safety of the 4CMenB vaccine were evaluated in detail in accordance with the STIKO Standing operating procedure (SOP) (see Annex 2). Briefly, the randomized studies identified for this evaluation had critical methodological flaws that led to downgrading of the evidence level in accordance with GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) methodology to "low" or "very low". Very rare, potentially severe adverse effects could not be evaluated based on insufficient numbers of cases included. In infants particularly, the available data showed a significantly increased risk for febrile reactions, especially when 4CMenB was administered simultaneously with the routine vaccinations Infanrix hexa® and Prevenar® (> 70 %, compared to 40 % following administration of the routine vaccinations alone). An approximately 4- to 5-fold increased risk of severe tenderness was also seen in infants following 4CMenB (in 13–29 % of those vaccinated). Fever was shown to occur significantly more frequently in adolescents, but not in adults, following 4CMenB vaccination (3.7 %) compared to placebo (1.6 %). Severe local pain and headache also occurred significantly more frequently in adolescents and adults following 4CMenB vaccination. The spectrum of adverse events based on available data from post-marketing surveillance was similar to that based on licensure studies.

The results of narrative literature reviews showed a markedly increased risk of IMD for persons with complement deficiencies (esp. terminal deficiencies and properdin deficiency), but only a slight increase in absolute risk of disease for persons with asplenia and only a marginally increased risk with other immune deficiencies (see **Tables 1 and 2**). Based on these estimates as well as on the estimated vaccine effectiveness (VE), a relatively low number of persons with complement deficiencies (49–98) compared to those with asplenia (approximately 19,000) was estimated to require MenB vaccination to prevent a single case of IMD in the year after the vaccination. For persons with other immune deficiencies, the NNV was higher still than for asplenia (see **Tables 1 and 2**). However, because of the severity of IMD and the immunological plausibility for an elevated IMD risk in persons with the immune deficiencies/immunosuppression considered here, STIKO recommends both MenACWY and MenB vaccination for affected persons based on an individual risk assessment.

Household contacts of persons with IMD have an approximately 100-fold increased risk of contracting IMD in the ensuing year despite post-exposure chemoprophylaxis [2]. Therefore, STIKO recommended vaccination with a MenACWY conjugate vaccine in 2009 for contacts of index cases due to these serogroups [3]. In view of the severity of IMD, STIKO recommends vaccination of household contacts of serogroup IMD cases based on an individual risk assessment despite the likely lower VE of Bexsero® compared to the conjugate vac-

Abstract · Zusammenfassung

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Background Paper for the update of meningococcal vaccination recommendations in Germany: use of the serogroup B vaccine in persons at increased risk for meningococcal disease

Abstract

In December 2013 Bexsero® became available in Germany for vaccination against serogroup B meningococci (MenB). In August 2015 the German Standing Committee on Vaccination (STIKO) endorsed a recommendation for use of this vaccine in persons at increased risk of invasive meningococcal disease (IMD). This background paper summarizes the evidence underlying the recommendation. Bexsero® is based on surface protein antigens expressed by about 80 % of circulating serogroup B meningococci in Germany. The paper reviews available data on immunogenicity and safety of Bexsero® in healthy children and adolescents; data in persons with underlying illness and on the effectiveness in preventing clinical outcomes are thus far unavailable.

STIKO recommends MenB vaccination for the following persons based on an individual risk assessment: (1) Persons with congenital or acquired immune deficiency or suppression. Among these, persons with terminal complement defects and properdin deficiency, including those under eculizumab therapy, are at highest risk with reported invasive meningococcal disease (IMD) incidences up 10,000-fold higher than in the general population. Persons with asplenia were estimated to have a ~ 20–30-fold increased risk of IMD, while the risk in individuals with other immune defects such as HIV infection or hypogammaglobulinaemia was estimated at no more than 5–10-fold higher than the background risk. (2) Laboratory staff with a risk of exposure to *N. meningitidis* aerosols, for whom an up to 271-fold increased risk for IMD has been reported. (3) Unvaccinated household (-like) contacts of a MenB IMD index case, who have a roughly 100–200-fold increased IMD risk in the year after the contact despite chemoprophylaxis. Because the risk is highest in the first 3 months and full protective immunity requires more than one dose (particularly in infants and toddlers), MenB vaccine should be administered as soon as possible following identification of the serogroup of the index case.

Keywords

Neisseria meningitidis · Meningococcal group B vaccination · Germany · Vaccination recommendation · Prevention

Wissenschaftliche Begründung zur Aktualisierung der Meningokokken-Impfempfehlung – Anwendung des Meningokokken-B-Impfstoffs bei Personen mit erhöhtem Risiko für Meningokokken-Erkrankungen

Zusammenfassung

Seit Dezember 2013 ist der Impfstoff Bexsero® zum Schutz vor Meningokokken der Serogruppe B (MenB) in Deutschland verfügbar. Seit August 2015 empfiehlt die Ständige Impfkommission (STIKO) die Anwendung dieser Impfung bei Personen mit erhöhtem Risiko für Meningokokken-Erkrankungen. Diese Begründung fasst die Evidenz zusammen, die der STIKO-Empfehlung zugrunde lag. Bexsero® basiert auf Oberflächenproteinantigenen, die von ca. 80 % der in Deutschland zirkulierenden MenB-Stämme exprimiert werden. Es wird ein Überblick über die Immunogenität und Sicherheit des Impfstoffs bei gesunden Kindern und Jugendlichen präsentiert; entsprechende Daten von Personen mit Grunderkrankungen sowie zur Wirksamkeit in Bezug auf Schutz vor klinischen Endpunkten stehen derzeit noch aus.

Die STIKO empfiehlt eine Impfung mit Bexsero® nach individueller Risikoabschätzung für folgende Personen: 1) Gesundheitlich gefährdete Personen mit angeborener oder erworbener Immundefizienz bzw. -suppression. Von diesen haben Personen mit terminalen Komplementdefekten, einschließlich bei Therapie mit Eculizumab, sowie mit Properdindefizienz, das höchste Risiko für eine invasive Meningokokken-Erkrankung (IME); es liegt bis zu 10.000-fach höher als in der Allgemeinbevölkerung. Das Erkrankungsrisiko für Personen mit Asplenie ist ca. 20- bis 30-fach erhöht und liegt für Personen mit anderen Immundefekten, z. B. mit HIV-Infektion oder Hypogammaglobulinämie wahrscheinlich nicht mehr als 5- bis 10-fach erhöht gegenüber der Hintergrundinzidenz. 2) Laborpersonal, das ein Risiko für Kontakt mit *N.-meningitidis*-Aerosolen hat. Für diese Gruppe wurde ein bis zu 271-fach erhöhtes Risiko für IME berichtet. 3) Ungeimpfte Haushaltskontakte oder enge Kontakte mit haushaltsähnlichem Charakter einer Person mit einer IME durch MenB. Diese haben trotz Erhalt einer Chemoprophylaxe ein ca. 100–200-fach erhöhtes Risiko für IME in den 14 bis 365 Tagen nach dem Kontakt, wobei das Risiko in den ersten 3 Monaten am höchsten ist. Daher, und weil der vollständige Impfschutz insbesondere bei Säuglingen und Kleinkindern mehrere Impfdosen benötigt, sollte die MenB-Impfung der Kontaktperson so bald wie möglich nach gesicherter Serogruppenbestimmung erfolgen.

Schlüsselwörter

Neisseria meningitidis · Meningokokken-B-Impfung · Deutschland · Impfempfehlung · Prävention

cines (see below). Besides the possibility that the household might be situated in a social setting with ongoing circulation of pathogenic meningococci, family members might also have a genetic predisposition for an increased IMD risk that could be reduced by vaccination. Rapid serogroup identification and prompt vaccination is critical for early protection, as approximately 70 % of the late secondary cases occur in the first 3 months following contact with the index case.

Laboratory personnel at risk of exposure to *N. meningitidis* aerosols is also recommended to receive a MenB vaccine in addition to a MenACWY vaccine since they are at increased risk of IMD compared to the general population [4, 5]. While such cases can be avoided through appropriate safety precautions (class II safety workbench; respiratory protection in the case of aerosol formation), human error or laboratory accidents can never be completely avoided.

Table 2 Summary of the estimates for the risk of invasive meningococcal disease due to serogroups C, W or Y in selected risk groups and the estimated number of respective individuals needed to be vaccinated against MenACWY to prevent one case (number needed to vaccinate, NNV). See text for details of the calculations with underlying assumptions

Risk group (estimated number of affected persons in Germany)	Risk of IMD due to MenC (cases/100,000 affected individuals/year)	Number of cases/year	In the year after vaccination		Within 3 years after vaccination	
			NNV[a] in the year after vaccination	Cases prevented with a vaccination coverage = 100%	NNV[b] within 3 years after vaccination	Cases prevented with vaccination coverage = 100%
Asplenia (90,000)	4	3.6	31,250	2.9	10,400	8.7
Complement deficiencies (10,000)	650–1300	65–130	96–192	52–104	32–63	159–312[d]
HIV infections[c] (80,000)	0.7–1.4	0.6–1.1	89,300–178,600	0.4–0.9	29,800–59,500	1.3–2.7
Immune deficiencies with hypo or agammaglobulinemia (800–800,000)	Unknown, only slightly elevated	Not estimated	Similar to HIV-infected individuals	Not estimated	Similar to HIV-infected individuals	Not estimated

[a]Assumption: Average term of protection of the vaccination is 1 year or [b]3 years.
[c]Estimate performed for an estimated 10.000 affected.
[d]These calculations clarify the uncertainty regarding the estimate of the number of affected persons in Germany: In the group of complement deficiencies, the maximal estimate of 10,000 appears excessive; as, based on the 5000–10,000-fold increased risk of IMD, the majority of persons with IMD in Germany would have to have a complement deficiency.

The possible implementation of MenB vaccination in the control of clusters or outbreaks of menB disease was not specifically addressed, as existing STIKO recommendations outline the course of action for all serogroups, see p. 334 of the current STIKO recommendations (*Epid Bull* 34/2015).

To ensure adequate MenB surveillance and evaluation of the current vaccine recommendations, it is crucial that meningococcal strains isolated from patients be sent to the National Reference Center for Meningococci and *Haemophilus influenzae* [Nationales Referenzzentrum für Meningokokken und *Haemophilus influenzae* (NRZMHi)] for further characterization. In particular, only further characterization at NRZMHi can determine whether a MenB strain should or should not have been covered by the 4CMenB vaccine. This is essential for identifying vaccine breakthroughs and estimating VE. Notifications according to the Infection Against Protection Act [Infektionsschutzgesetz (IfSG)] do not include information on a patient's potentially increased IMD risk due to underlying illness/immune deficiency as specified by STIKO or whether the person was infected in a laboratory setting. Thus, the impact of the MenB vaccination recommendation for risk groups cannot be evaluated systematically on the basis of routine notification data.

Finally, according to the Summary of Product Characteristics [6], Bexsero® is subject to additional monitoring. As stipulated by the European Medicines Agency (EMA) in its Assessment Report [7], this includes further studies on safety and clinical efficacy as well as immunogenicity in persons with complement deficiencies. Health professionals in Germany are required in the Summary of Product Characteristics to report every suspected case of an adverse reaction due to Bexsero® to the Paul Ehrlich Institute (PEI). According to § 6 para. 1, no. 3 IfSG, all suspected cases of health impairment exceeding the usual severity of a vaccination reaction should be reported to PEI.

2 Introduction and objectives

An increased risk of invasive infection with *Neisseria meningitidis* (Nm) was reported for individuals with certain types of immune deficiency or suppression, particularly for those with congenital complement deficiencies or those undergoing complement-neutralizing antibody therapy with eculizumab, but also those with asplenia, or hypoglobulinemia [8–11]. In addition, an increased risk for household contacts was observed within a one-year period after contact with an IMD index case, even after they had received chemoprophylaxis [2]. Finally, laboratory staff at risk for contact with *N. meningitidis* aerosols also has an increased risk of disease compared to the general population [4, 5].

Until August 2015, STIKO recommended vaccination with a tetravalent ACWY conjugate vaccine for individuals at increased risk for IMD due to congenital or acquired immune deficiency or suppression with residual T and/or B cell function, particularly complement/properdin deficiencies, hypogammaglobulinemia, functional or anatomical asplenia, provided the vaccine is licensed for the age group. Additionally, STIKO recommended MenACWY vaccination for household or household-like contacts of patients with IMD due to these serogroups and for laboratory staff at risk of

contact with N. meningitidis aerosols. A vaccine against serogroup B, the 4CMenB vaccine (Bexsero®), additionally became available in Germany in December 2013. STIKO considered whether these vaccination recommendations should also apply to this vaccine.

3 Immunization goal

The goal of this recommendation is to lower the IMD burden due to serogroup B in individuals at increased risk of disease (due to immune deficiency/immunosuppression, household contact or professional exposure) through the 4CMenB (Bexsero®) vaccine, available in Germany since December 2013.

4 Methods

STIKO's standing operating procedure (SOP) calls for performance of systematic reviews for questions on efficacy and safety of a vaccine under evaluation and a grading of the quality of evidence by applying the framework of the *Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group* [1]. Further questions can be considered by means of narrative reviews. Evaluation of the safety of the 4CMenB vaccine was performed in accordance with the STIKO SOP by means of a systematic review (see Annex 2). However, only a narrative review was performed regarding the efficacy of the 4CMenB vaccine due to paucity of data—especially for individuals with immune deficiencies. A systematic evaluation of the efficacy/effectiveness of the 4CMenB vaccine according to GRADE will be undertaken for the final evaluation of possible routine MenB vaccination in infants, as soon as data on the protective effect against clinical outcomes become available.

To roughly quantify and compare possible effects of a MenB vaccination for specific risk groups, the number of persons who would need to be vaccinated to prevent one IMD case (*Number needed to vaccinate*—NNV) was calculated under various assumptions of disease risk (IMD incidence in the risk group), vaccine effectiveness (VE) and strain coverage. NNV was calculated according to the following formula [12]:

$$\mathrm{NNV} = \frac{\left(\frac{100{,}000}{\text{IMD cases per } 100{,}000 \text{ inhabitants}}\right)}{(VE) \times (\text{Strain coverage})}$$

5 Pathogen

Meningococci are gram-negative bacteria of the species *Neisseria meningitidis*. They are divided into 12 serogroups [13], with serogroups B (a good two thirds of all cases) and C (approximately one quarter of all cases) primarily responsible for IMD in Germany. Serogroups Y and W135, by contrast, cause only approximately 5 and 2 % of cases, respectively. Meningococci are transmitted by respiratory droplet infection, e.g. by coughing or sneezing. Carriage studies revealed meningococcal colonization of the mucous membranes in the pharynx in approximately 10 % of healthy persons [14]. In certain groups, e.g. in adolescents, soldiers in barracks, men who have sex with men (MSM), markedly higher carriage rates of 20–40 % were reported [14–20]. Colonization with meningococci only rarely leads to invasive disease. This occurs when the pathogen infiltrates the mucosal barrier in the absence of type-specific immunity and is facilitated through non-specific damage to the mucosal membranes (e.g. through viral infections, dry air or smoking [21–24]).

6 Clinical manifestations

IMD usually manifests clinically as meningococcal meningitis or meningococcal sepsis (with or without meningitis). The spectrum of clinical manifestation ranges from transient asymptomatic bacteraemia to a fulminant septic course that can lead to death within a few hours (purpura fulminans, Waterhouse-Friderichsen syndrome [25]). Case fatality in Germany lies at 8 % for MenB and 11 % for MenC disease. It is markedly higher at approximately 18 % in patients with sepsis, than in those with meningitis alone (approximately 2 %). About 10–20 % of survivors of an invasive meningococcal B disease suffer complications such as hearing loss, neurological damage or amputations [26–29].

7 Epidemiology of invasive meningococcal diseases in Germany

From 2010 to 2013 on average 364 persons were notified with IMD annually (0.44 cases of disease/100,000 Inh.) in Germany. Of these, 250 (69 %) were due to serogroup B (0.30 cases of disease/100,000 Inh./year), 78 (22 %) to serogroup C (0.09 cases of disease/100,000 Inh./year), and 35 (10 %) to serogroups A, W, or Y (0.03 cases of disease/100,000 Inh./year). The number of notified IMD cases decreased markedly since 2005; this is particularly due to a decline in cases of MenB and MenC. From 2001 to 2005, the number of annually notified MenB cases ranged from 400 to 570 and the number of MenC cases from 130 to 223. Since 2006, STIKO recommends vaccination against MenC for all children in the second year of life. Incidence of MenC has declined more sharply than that of MenB incidence in age groups with high vaccination coverage (1–19-year-olds, unpublished data, RKI). Infants and toddlers are at highest risk of disease with an additional, smaller incidence peak in adolescents aged 15–19 years (see **Fig. 1**). The proportion of MenB and MenC cases is highest in infants and toddlers, while the proportion of MenW and MenY cases in adults is markedly higher than in children and adolescents (**Fig. 1**, insert). Less than 2 % of all IMD cases are epidemiologically linked.

Compared to other European countries, IMD incidence in Germany is in the lowest tertile. For instance, in 2011 the incidence of serogroup B disease in infants in Germany was 5.9, in Great Britain 25.3 and in Ireland 38.6 cases/100,000 Inh. [30].

Details on the epidemiology of IMD in the risk groups under consideration follow in Sect. 9.

8 The vaccine

Following the positive opinion of EMA in November 2012, a vaccine against serogroup B meningococci (4CMenB) was licensed as Bexsero® (Novartis Vaccines)

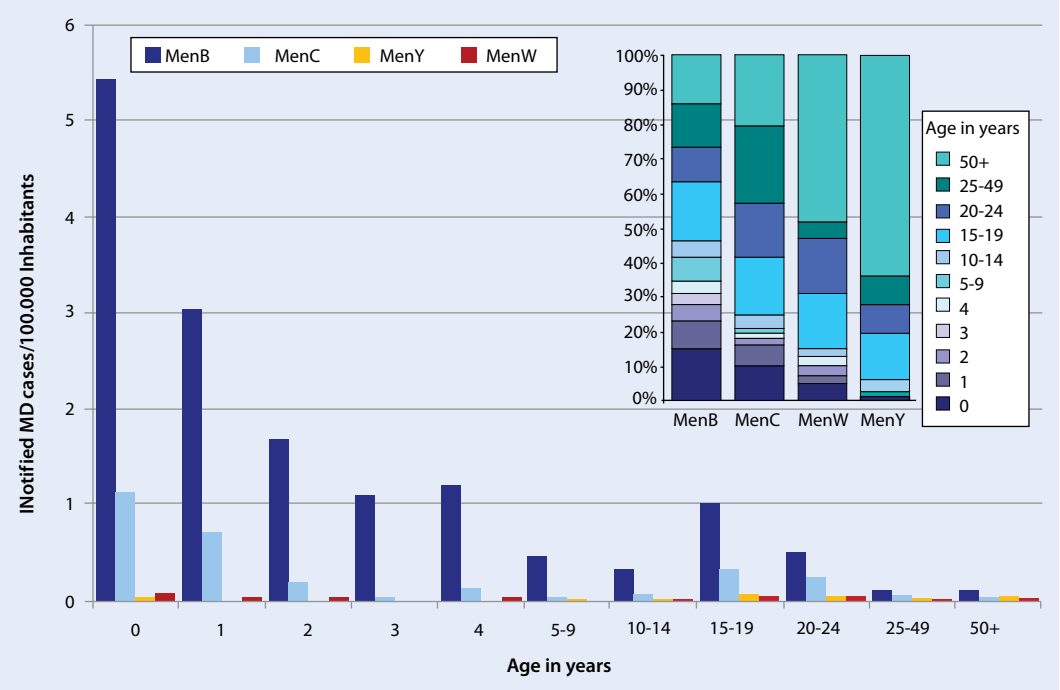

Fig. 1 ◀ Incidence of invasive meningococcal disease by age and serogroup, Germany, 2010–2013. Insert: Age distribution according to serogroup

for the first time in Europe on 22 January 2013 [7, 31]. Bexsero® became available in Germany in December 2013.

Since the MenB capsule is structurally related to a glycolylated embryonic neuronal cellular adhesion protein (NCAM-1) [32] and is therefore poorly immunogenic, it could not be used as a vaccine antigen as was possible for serogroups A, C,W and Y. Particularly immunogenic antigens were identified through reverse vaccinology, i.e. computer-based analysis of the *N. meningitidis* genome for potential surface protein antigens, with subsequent antigen expression and immunization of mice [33]. Thus, the 4CMenB vaccine contains a total of 4 antigen components: The first consists of detoxified outer membrane vesicles (OMV) that contain diverse membrane proteins, Porin A (PorA) being immunodominant. This OMV preparation corresponds to the MeNZB™ vaccine that was used in New Zealand for outbreak control [34]. Two additional antigens, the factor H binding protein (fHbp) and the neisserial heparin binding antigen (NHBA), are each additionally fused to a further surface protein to attain better stability. The fourth antigen is neisserial adhesin (NadA). Each of these proteins is present on meningococci in different variants, between which there is only partial immunogenic cross-reactivity. This is less pronounced in infants than in elderly persons. For each vaccine component, a variant was selected that occurred in a high proportion of European meningococcal B strains.

In children aged 2–5 months, 3 vaccine doses are recommended by the manufacturer for primary vaccination, and 2 vaccine doses in all other age groups. A booster vaccination is additionally required for children vaccinated in the first 2 years of life (see the Summary of Product Characteristics for information on the approved vaccination schedules). Study results on co-administration with Infanrix hexa®, Prevenar 7®, MMRV in infants and toddlers and with Menveo® in adults for the most part showed no impairment of immunogenicity [35–38]. Bexsero® can be administered simultaneously with the following vaccine antigens (as monovalent or in combination vaccines): diphtheria, tetanus, pertussis, *Haemophilus influenzae* type b, poliomyelitis (inactivated vaccine), hepatitis B, heptavalent pneumococci conjugate, measles, mumps, rubella, varicella. To date, there are no data available for co-administration with rotavirus vaccines. Bexsero® is administered as a deep intramuscular injection and is contraindicated only in the event of hypersensitivity to the vaccine components.

8.1 Vaccine effectiveness

Due to the low incidence of MenB disease, the clinical efficacy and effectiveness of 4CMenB can only be studied in postmarketing studies after broad introduction of the vaccine. To date, no studies investigating the effectiveness of 4CMenB by taking into account clinical outcomes have been published.

8.2 Immunogenicity and strain coverage

Currently, the detection of antibodies induced by the vaccine capable of neutralizing meningococcal B strains in serum in the presence of human complement (hSBA) is considered a correlate for protection from the disease [39, 40]. Thus EMA accepts meningococcal hSBA at a titer of ≥ 1:4 as an immunological correlate for protection against disease [7].

While the capsule-based meningococcal conjugate vaccines against serogroups A, C, W and Y protect against all strains expressing the respective serogroup, not all circulating MenB strains express at least one of the antigens contained in Bexsero® as a surface protein. The potential protection achievable with 4CMenB thus depends on what proportion of circulating MenB strains express the vaccine an-

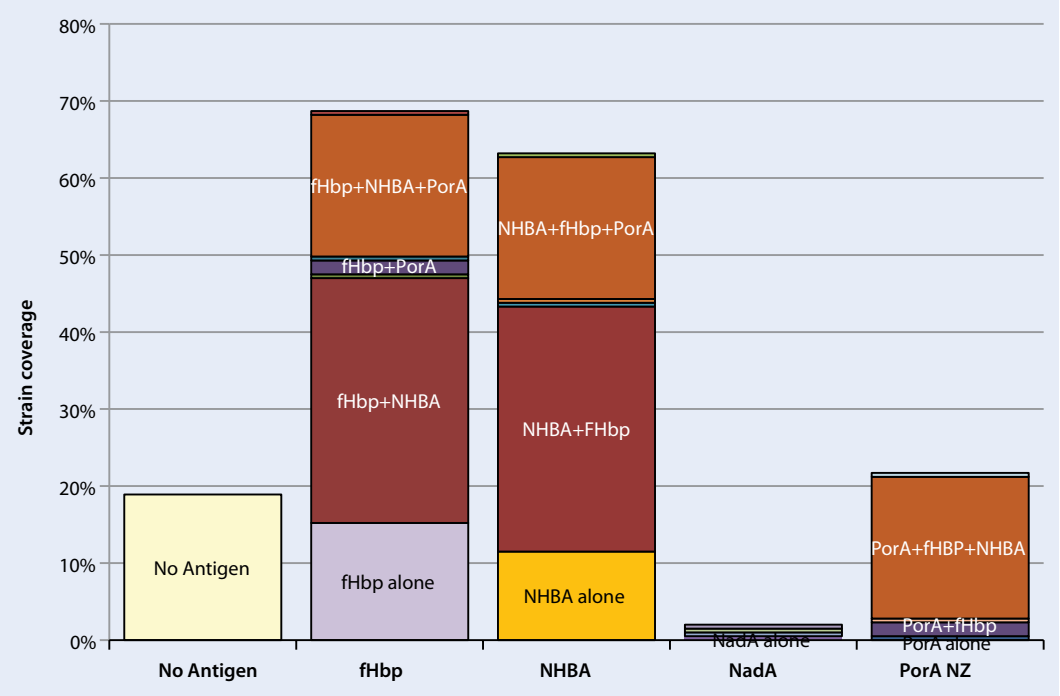

Fig. 2 ◀ Results of MATS (*Meningococcal Antigen Typing System*) analyses on 222 meningococcal strains from IMD patients in Germany from July 2007-June 2008. MATS results permit estimation of the proportion of circulating strains expected to be covered by 4CMenB vaccination (see text). The abbreviations refer to the vaccine antigens factor H binding protein (fHbp), neisserial heparin binding antigen (NHBA), neisserial adhesin (NadA) and Porin A (PorA), identical to the New Zealand vaccine MeNZB® (PorA NZ)

tigens or cross-protective variants thereof. In addition, protection depends on how reliably the antibodies that are induced by the vaccine actually lead to killing of corresponding strains in the hSBA assay. With the exception of the specific PorA allele, detection of the gene for a surface protein does not sufficiently prove that this is also expressed by a meningococcal strain. Therefore, the so-called *Meningococcal Antigen Typing System* (MATS) was developed to determine the proportion of circulating strains expected to be covered by Bexsero® [41]. MATS is based on the detection of the surface proteins by ELISA, shown to correlate with killing of the respective strains in the hSBA assay using pooled sera from infants vaccinated with 4 doses of 4CMenB. Strains with an ELISA value above the protective bactericidal threshold (PBT) for a particular vaccine antigen were killed with high probability by hSBA in the pooled sera. For Germany, 222 strains from all IMD patients diagnosed at the NRZMHi from July 2007-June 2008 were analyzed using MATS. The results revealed an expected overall strain coverage of 82 % [42]. However, the strain coverage was lower in infants and adults ≥ 25 years of age than in 1–24-year-old children and adolescents; a finding confirmed in an extended analysis of all 185 strains received from infants with IMD at NRZMHi from July 2007-June2013 with a strain coverage of 68 % [43].

The frequency with which the individual vaccine antigens—alone or in combination—are expressed by the strains circulating in Germany is also relevant. **Fig. 2** shows that fHbp and NHBA are most commonly expressed. Overall, in 2007–2008 18.9 % of the strains expressed none of the vaccine antigens, 27.5 % expressed only one vaccine antigen (fHbp: 15.2 %; NHBA: 11.5 %; PorA: 0.5 %) and 53.9 % expressed at least 2 antigens [42]. The expression of more than one antigen can theoretically induce a more robust activation of complement and may decrease the risk for mutations leading to variants not susceptible to vaccine-induced antibodies.

The results of MATS analyses must interpreted in the context of the results of clinical licensure studies investigating immunogenicity. In these studies, vaccine antigen-specific hSBA was measured in participants before and after vaccination with 4CMenB by testing whether strains selectively expressing only one of the vaccine antigens were killed. Currently, such immunogenicity data are still lacking for persons ≥ 50 years of age and for those with immune deficiencies or immunosuppression. For this reason, a systematic evaluation of immunogenicity for the risk groups under consideration here was not undertaken. However, a brief summary of some of the key results regarding hSBA responses as observed in the randomized controlled licensure studies for individual antigens is presented here.

In the available immunogenicity studies, study staff responsible for the evaluation of immunogenicity was blinded with regard to the vaccines administered. In infants, protective antibodies against the respective vaccine antigens 1 month after administration of 3 doses of 4CMenB at 2, 4 and 6 months of age [35, 37] were induced in 79–100 % of vaccine recipients (see **Annex 1, Table 3**). When the vaccine was administered at ages of 2, 3 and 4 months, the responses were somewhat lower, especially for antibodies against NHBA [35]. The proportion of children with protective titers markedly declined prior to administration of a 4th dose at 12 months of age, especially in children who had received 3 doses of vaccine at 1 month intervals at ages of 2, 3 and 4 months (see **Annex 1, Table 3**). However, after a 4th dose, hSBA titers ≥ 1:5 were induced in 88–100 % of vaccine recipients. In adolescents, 2 doses of 4CMenB achieved protective antibodies against all antigens (antibodies against NHBA were not measured) [44] (see **Annex 1, Table 4**).

Data on immunogenicity at time points earlier than 4 weeks after vaccination are currently lacking. While data on immunogenicity for infants following a *single* vaccine dose are also lacking, such data are available for a small number of one-year-old children and for adolescents (see **Annex 1, Table 3 and 4**). Particularly in toddlers, the immune response after one dose was markedly lower than after 2 vaccine doses or after 4 vaccine doses in infancy. In all studies, the protective titers in the comparison groups did not increase or only increased slightly compared to the groups vaccinated with 4CMenB.

Smaller studies [45–47] in infants and toddlers, some of which were only published in the *European Public Assessment Report* (EPAR) of the EMA [7], showed a marked reduction in the proportion of vaccine recipients with protective antibody titers 12–28 months after vaccination with 2–4 doses of vaccine. The extent of this reduction varied according to the vaccine antigen (see Annex 1, **Table 3**). In contrast, antibody persistence in adolescents was 82 % 18–24 months after 2 vaccine doses for the antigen most commonly expressed on German strains, fHbp, [48] (see Annex 1, **Table 4**). Data on persistence of NHBA antibodies were, however, not published in this study.

8.3 Effect on meningococcal carriage

Observations after introduction of the meningococcal C conjugate vaccines in countries such as England, in which catch-up campaigns were implemented in all children and adolescents, showed that MenC vaccination led to a 75 % reduction in pharyngeal carriage of serogroup C meningococci [49]. This led to the establishment of herd protection, which plays a key role in the ongoing sustained MenC incidence reduction in the United Kingdom and in The Netherlands [50, 51]. Whether 4CMenB has a similar effect on meningococcal carriage could not be conclusively clarified in the only available study on this issue [52]. However, herd effects would not play a central role for the protection of the relatively small groups of individuals at increased risk for IMD under consideration here.

8.4 Reactogenicity and safety

The reactogenicity and safety of the 4CMenB vaccine were evaluated in accordance with the STIKO SOP. The methods and results are described in detail in Annex 2. No data were identified on safety in persons with immune deficiencies/immunosuppression. Key results are briefly summarized here.

Five randomized studies were identified for the evaluation of the endpoints defined by the responsible STIKO working group as critical or important. These had serious methodological flaws necessitating downgrading of the quality of evidence to "low" or "very low". Very rare, potentially serious side effects could not be evaluated on the basis of insufficient numbers of included participants. These included endpoints classified as "critical", namely seizures, Kawasaki syndrome (KS) and hospitalization for infants and toddlers, as well as juvenile arthritis, Guillain-Barré syndrome, seizures and acute disseminated encephalomyelitis for adolescents and adults. A total of 3 cases of confirmed KS occurred in infants considered possibly or probably associated with 4CMenB vaccination in the licensure studies included in our review [35, 37]. In the adolescent study, 2 cases of juvenile arthritis occurred with possible or probable association with 4CMenB vaccination [44].

In infants, the available data showed a close to 2-fold higher risk for febrile reactions when 4CMenB was administered simultaneously with the routine vaccines Infanrix hexa® and Prevenar® (> 70 %), compared to 40 % after routine vaccines alone. An approximately 4- to 5-fold increased risk of severe local pain was also observed in infants following 4CMenB (in 13–29 % of those vaccinated). Fever was shown to occur significantly more frequently in adolescents, but not in adults, following 4CMenB vaccination (3.7 %) compared to placebo (1.6 %). Severe local pain and headache occurred significantly more frequently in adolescents as well as adults following 4CMenB vaccination (see Annex 2). The interpretation of results regarding the occurrence of fever and pain is complicated by the frequent, sometimes prophylactic, administration of antipyretics particularly in the infant studies.

The reactogenicity spectrum in the week after the vaccination observed in an active surveillance study during a vaccination campaign (> 46,000 vaccine recipients aged from 2 months-20 years) in a region of Québec in 2014 was comparable to that described in licensure studies ([53] see also Appendix 2). However, antipyretics were taken prophylactically by > 70 % of the vaccine recipients (93 % in < 2-year-olds). No cases of KS occurred; however the statistical power was too low to identify the occurrence of possible very rare adverse reactions in specific age groups.

9 Epidemiology of invasive meningococcal diseases in risk groups

Specific antibodies and an intact complement system are crucial for the effective defense against meningococcal infections [8, 9, 11]. An increased risk of IMD was accordingly reported for persons with immune deficiencies, among these, particularly those with complement deficiencies [8, 9], but also others, such as persons with asplenia [8], persons infected with HIV [10, 54, 55] or persons with unreplaced hypogammaglobulinemia [11]. In addition, laboratory staff at risk for contact with *N. meningitis* aerosols are at increased risk of IMD [4, 5] and IMD incidence is increased in household contacts of IMD patients in the ensuing year despite post-exposure chemotherapy [2].

Based largely on available reviews, estimates for the risk of occurrence of IMD in the relevant risk groups are described below. Where possible, the incidence of relevant immune deficiencies in the general population/in IMD patients was also estimated. In addition, available indirect evidence on expected VE was considered, e.g. based on immune responses to other vaccines. Based on these estimates, the number of persons needed to be vaccinated to prevent one case (NNV) was calculated for each risk group.

9.1 Asplenia

9.1.1 Risk of IMD in asplenic individuals

The risk of invasive infections such as sepsis and meningitis is increased after splenectomy, especially through gram-negative pathogens, *Staphylococcus aureus* and pneumococci [8, 55–59]. In persons lacking a spleen, these infections can trigger the syndrome of *Overwhelming postsplenectomy infection* (OPSI), associated with up to 69 % mortality [60]. Based on various prospective studies, the risk of IMD in asplenic individuals ranged from < 1–8 cases/100 person years; depending on definition and study setting. It was highest in the first month after loss of the spleen, and remained markedly elevated in first 1–3 years, decreasing somewhat thereafter [61, 62]. Bisharat et al. [63] reported a mean interval of 23 months between splenectomy and the first severe infection (range: 0.5–180 months). In patients with asplenia due to thalassemia and spherocytosis, severe infections occurred earlier than in patients with other causes. They occurred latest in patients with traumatic splenectomy.

In the few studies investigating the pathogen distribution in infections of asplenic patients, meningococci were rare, reports ranging from 0–3.7 % of infections [56–61]. In the 4 available cohort studies reporting details of the pathogen distribution [56–59], only 4 out of a total of 1117 severe infections were caused by meningococci (0.36 %). If the mean overall risk for severe infections in asplenic patients is estimated at approximately 3 severe infections per 100 person years (see above), their risk for IMD can be estimated as $3 \times 0.0036 \times 1000 \approx 11$ IMD/100,000 asplenic individuals/year. Under the assumption that the serogroup distribution is similar to that of the general population, this would correspond to an annual MenB incidence of $11 \times 0.69 = 7.6 \approx 8$ IMD/100,000 asplenic individuals/year and an ACWY-incidence of $11 \times 0.31 = 3.4 \approx 4$ IMD/100,000 asplenic individuals/year. This rather low absolute incidence may be in keeping with the observation that no differences were observed in the elimination of intraperitoneal Nm infection in splenectomized compared to healthy mice [64]. No figures are available on the proportion of IMD cases in Germany occurring in persons with asplenia. In summary, the absolute risk for IMD in persons with asplenia appears to be only slightly elevated compared to the normal population. However, case fatality may be markedly increased.

9.1.2 Incidence and prevalence of asplenia

According to hospital discharge statistics of the Federal Statistical Office, a total of 8193, 8093, 8113 and 7948 splenectomies were performed respectively in the years 2010–2013 [65]. According to the German Asplenia Network [Deutsches Asplenie-Netzwerk], an estimated 80,000 people currently lack a spleen in Germany. Congenital asplenia within the context of Ivermark syndrome is extremely rare—up until March 2012 one case was registered in the German Network for Primary Immune Deficiencies [Deutsches Netzwerk für Primäre Immundefekte] (PID) [66].

In addition, certain underlying illnesses, particularly sickle cell anemia (1000–1500 patients in Germany [67]) and thalassemias (500–600 patients [67]), malignant hematological diseases such as Hodgkin's lymphoma and chemotherapy can lead to functional asplenia. However, estimates of number of such patients in Germany are generally lacking.

9.1.3 Potential efficacy of MenB vaccination in asplenia

Neither the immune response nor the clinical efficacy of 4CMenB were studied thus far in asplenic individuals. Results from studies on vaccination of asplenic individuals with monovalent MenC conjugate vaccines [68–70] showed that a high proportion (~ 80 %) developed protective antibody titers, albeit a lower proportion than in healthy volunteers. A second dose of vaccine increased the proportion of responders to > 90 %. However, the titers attained were lower than in healthy vaccinees. Persons with splenectomy due to medical conditions had lower vaccine responses than those with splenectomy due to trauma [69]. A review [71] of 3 small studies lacking comparison groups showed that vaccination of asplenic individuals with heptavalent pneumococcal conjugate vaccines likewise led to ≥ 4-fold titer increases against 4–5 of the 7 vaccine antigens in at least half of the recipients. A registry-based study in Canada [72] demonstrated a 54 % lower mortality in asplenic persons who received influenza vaccination compared to those who did not.

Thus it seems asplenic individuals are to some extent able to mount immune responses to a number of vaccines, although perhaps less well than healthy individuals. To what extent this ability can be extrapolated to 4CMenB, however, currently remains unclear.

Based on the only slightly elevated IMD risk for asplenic individuals, the estimated NNV is very high: Under the assumptions of (1) a MenB incidence of 8 cases of disease/100,000 asplenic individuals/year, (2) a VE of 80 % (lower than the 95–100 % assumed in healthy persons) and (3) a strain coverage of 82 %,

$$\text{NNV} = \frac{\left(\frac{100,000}{8 \text{ MenB IMD per } 100,000 \text{ asplenics}}\right)}{(0.80\ (\text{VE}) \times 0.82\ (\text{Strain coverage}))} \approx 19,000 \text{ asplenics}$$

would have to be vaccinated to prevent one MenB case in the year after the vaccination. If the duration of protection is assumed to be longer than 1 year, the NNV decreases proportionally, e.g. for 3 years it would be ~ 6350. The duration of protection is unknown; it is, however, likely to be shorter than in healthy individuals.

Under the assumptions that the incidence of IMD due to **MenACWY** is 4 cases of disease/100,000 asplenic individuals and a VE of 80 % (lower than the ~ 90 % observed in healthy older children/adolescents [73]),

$$\text{NNV} = \frac{\left(\frac{100,000}{4 \text{ MenACWY IMD per } 100,000 \text{ asplenics}}\right)}{(0.80\ (\text{VE}))} \approx 31,250 \text{ asplenics}$$

would have to be vaccinated to prevent one case in the year after the vaccination. If duration of protection were 3 years, the NNV would fall to 10,400.

9.2 Complement deficiencies

9.2.1 Risk of IMD in persons with complement deficiencies

A number of complement deficiencies are associated with increased IMD risk, the most important being deficiencies of the terminal components C5-C9. These are required for formation of the membrane-attack complex. Compared to persons with an intact complement system, the risk for persons with C5-C8 deficiencies is estimated to be 7000–10,000-fold [74] and for persons with C9 deficiencies, 1400-fold higher. Approximately half of affected persons suffer from IMD repeatedly; a prior infection does not appear to protect from further infections [9]. Estimates of the lifetime risk for IMD range from 39 to 56 % [74–76]. Case fatality, however, is markedly lower than in individuals without complement deficiencies, at below 3 % [74, 77], possibly because fewer cell membrane components and toxins are released by the bacteria in the absence of the membrane-attack complex [74]. The first episode of IMD in individuals with terminal complement deficiencies frequently occurs in adolescence, markedly later than in persons with intact complement [8, 9, 78]. While some case series suggest that the rarer serogroups W and Y occur more commonly in IMD patients with late complement deficiencies [79–81], IMD patients with and without complement deficiencies had similar serogroup distributions in a Dutch study [82].

An increased risk for infections with encapsulated bacteria has also been reported for persons with C3 deficiency or defects in the alternative complement pathway (factor D, properdin, factor H) [8, 9, 74], although reports of IMD are rare. In patients with properdin deficiencies, IMD appears to run a more fulminant course than in persons with terminal deficiencies, with up to 65 % mortality; however the risk of recurrent infections is very low [9, 74, 77].

The effect of low concentrations of mannose-binding lectins (MBL) or MBL-polymorphisms on IMD risk appears to be minimal. Thus MBL deficiencies were observed to be more common in IMD patients than in controls only in studies in which the prevalence of a defective MBL gene in the controls was below the expected value for the general population [9]. In the largest case control study published to date, this was not the case, and no association was found between MBL polymorphisms and IMD [83].

Persons with deficiencies of the classical complement pathway are primarily associated with autoimmune diseases. An increased risk for infections (approximately 20 % higher than the background risk) has also been described, especially with encapsulated bacterial pathogens (primarily *Streptococcus pneumoniae*, but in rare cases also *N. meningitidis*) [9, 74, 78, 84, 85].

9.2.2 Incidence of complement deficiencies in Germany

The incidence of congenital complement deficiencies varies in different population groups and is commonly estimated at 0.03 % in available reviews [9, 86] based on a study of > 41,000 German conscripts born in 1944 [87]. The European registry for primary immune deficiencies (PID) ascertained a total of 13,708 patients from 2004–2011 [88]. Of these, 631 had a complement deficiency, the majority (482, 76 %) C1 inhibitor deficiencies (hereditary angioedema) not associated with an increased risk of IMD. Of the remaining 149 cases (24 %), 57 had deficiencies of the classical complement pathway (components 1, 2 and 4) (9 %), 4 had C3 deficiencies (1 %) and 88 (14 %) had deficiencies of the alternative pathway (including the terminal components C5–8, factor H and factor I, which leads to reduced C3 levels, properdin and MBL). Of the included living patients with PID, 1.2 % (149/12,340) thus had complement deficiencies relevant for IMD. Similarly, only very few complement deficiencies were registered from 2004 to March 2012 in the German PID registry: Of a total of 1232 included patients with PID, 13 had complement deficiencies, 8 (62 %) of these with deficiencies that could potentially increase the risk for IMD [66]. Of all patients with PID, 0.65 % (8/1232) thus had complement deficiencies relevant for IMD. On the basis of the patients included in the German PID registry, Gathmann et al. [66] calculated minimum prevalence estimates for all PID in Germany of 1.51 patients/100,000 Inh., which yielded a prevalence of $1.51 \times 0.0065 = 0.01$/100,000 relevant complement defects or one affected person per 10 million Inh. However, substantial under-reporting must be assumed here, as only approximately half of the 43 medical centers identified for the care of patients with immune deficiencies/immunosuppression had reported patients by 2011 and not all patients with complement deficiencies are cared for in such centers. Even with under-reporting by a factor of 10, however, one would however arrive at only one case per 1 million inhabitants, or approximately 80 cases overall. If one were to take the overall prevalence determined by Hässig et al. [87] of 0.03 % for all complement deficiencies to estimate the number of affected persons in Germany, one would arrive at an estimated 5904–15,252 affected persons in Germany (with the assumption that 24–62 % of all complement deficiencies are associated with an increased risk of IMD, see above); therefore around 10,000 affected persons. An estimate from Russia [75] quantified the prevalence of people with terminal complement deficiencies at 12/100,000; which would correspond to ~ 9800 affected persons in Germany.

In addition, acquired complement deficiencies should be considered in any estimate. These are caused either by insufficient synthesis of complement components, e.g. in the case of liver failure, or by increased consumption (autoimmune diseases, immune complex formation, e.g. in the case of systemic lupus erythematosus), or by increased loss (e.g. protein-losing nephropathies) or by pharmacological blockade (e.g. through eculizumab, which blocks terminal complement activation through binding to C5 and is used for the treatment of paroxysmal nocturnal hemoglobinuria (PNH)). Exact figures on most acquired complement deficiencies are not available. The prevalence of PNH in Germany is 13/1,000,000 inhabitants, so that theoretically up to about 1000 persons would be under treatment with eculizumab [89].

The proportion of IMD patients with complement deficiencies was found to range from 0 to 50 % in various studies/

case series, and was found to be negatively correlated with IMD incidence [78].

9.2.3 Potential efficacy of 4CMenB vaccination with complement deficiencies

To date, no studies have been performed in which persons with complement deficiencies were vaccinated with 4CMenB. In five small, uncontrolled studies persons with terminal complement deficiencies showed increases in capsule-specific antibodies following vaccination with bivalent (AC) or tetravalent (ACWY) polysaccharide (PS) meningococcal vaccines [90–94] that were comparable with [92, 93, 95] or lower [91] than those observed in healthy vaccinees. In one study, antibody persistence was shorter than in healthy volunteers [92]. IMD episodes were observed despite vaccination against the causal serogroups in two studies at 2.5–5 years after vaccination [92, 93]. In addition some studies showed an increase in the capacity for serogroup-specific opsonophagocytosis of meningococci following vaccination of persons with complement deficiencies with a meningococcal PS vaccine [90, 93, 94].

Taken together, the available studies suggest a possible benefit of MenACWY vaccination for persons with complement deficiencies, although randomized, controlled studies are lacking. To what extent this might also apply to vaccination with the surface protein-based 4CMenB vaccine remains to be clarified. Andreoni et al. [92] showed that opsonophagocytosis of MenC strains in cases of terminal complement deficiency was indeed supported by antibodies against the capsule antigen, but not against subcapsular antigens. In contrast, Plested et al. [96, 97] showed that serum from a small number of study participants vaccinated with an OMV vaccine with or without an NHBA component and from which C6 was eliminated supported opsonophagocytosis of meningococcal strains with the same PorA as in the OMV components in the presence of polymorphonuclear leukocytes. Finally Ross et al. [98] postulated a more important role for opsonophagocytosis in the defense against MenB compared to MenY infections.

If one were to assume a 4CMenB VE of 80 % with a strain coverage of 82 %, and—particularly applicable for terminal complement deficiencies—a 5000- to 10,000-fold increased incidence of MenB (i.e. 0.31 cases of disease/100,000 Inh. × 5000/10,000 = 1550–3100 cases of disease/100,000 persons with complement deficiencies,

$$\mathrm{NNV} = \frac{\left(\dfrac{100,000}{1550\ (up\ to\ 3100)\ \text{MenB IME per } 100,000\ \text{Persons with complement defects}}\right)}{(0,80\ (\mathrm{VE}) \times 0,82\ (\text{strain coverage}))}$$
$$\approx 49 - 98\ \text{Persons with complement defects}$$

would have to be vaccinated to prevent one MenB case in the year after the vaccination.

Similarly, the risk of IMD through MenACWY would be 0.14 ACWY Inh./year × 5000/10,000 = 700/1400. Therefore, with a VE of 80 %

$$\mathrm{NNV} = \frac{\left(\dfrac{100,000}{700\ (up\ to\ 1400)\ \text{MenACWY IMD per } 100,000\ \text{Persons with complement defects}}\right)}{(0,80\ (\mathrm{VE}))}$$
$$\approx 89 - 149\ \text{Persons with complement defects}$$

would have to be vaccinated to prevent one MenACWY case in the year after the vaccination.

9.3 HIV infection

9.3.1 Risk of IMD in persons with HIV infection

The incidence of IMD in HIV-infected individuals in Western countries with established antiretroviral therapy has only been investigated in a few studies. An increased risk of IMD was observed for HIV-infected individuals in a prospective, active, population and laboratory based surveillance study over 5 years (1988–1993) in Atlanta (RR = 23.8; 95 % CI: 7.4–74.7) [99]. Antiretroviral therapy during this period was not yet widely used. In New York City, a 10-fold elevated risk of IMD was shown for HIV-infected individuals through linkage of meningococcal surveillance data with HIV and mortality registry data from 2000–2011 [54]. HIV-infected individuals with IMD had a higher probability of having lower CD4+ values that HIV-infected controls of the same age. However, information on the proportion of IMD patients and controls on antiretroviral therapy was not available. In this study, HIV-infected individuals with IMD had lower mortality (10 %) than non-HIV-infected individuals with IMD (23 %). The authors attributed this to more rapid access to an infectious diseases specialist through regular care within the context of HIV disease. In contrast, in a laboratory-based surveillance study from South Africa HIV-infected individuals had an in-

creased risk (RR: 11.3, 95 % CI: 8.9–14.3) for IMD that was associated with increased case-fatality (20 % versus 11 % in non-HIV-infected IMD patients, OR = 2.1, 95%CI: 1.1–3.9) [10]. Taken together, the available data suggest that HIV-infected individuals are only at slightly increased risk for IMD, depending on their immune status.

9.3.2 Prevalence and incidence of HIV infection

In Germany at the end of 2013 an estimated 80,000 (95 % CI: 69,000–91,000) persons were infected with HIV; of these ~ 65,000 were men, including ~ 53,000 men who have sex with men (MSM), approximately 15,000 were women and ~ 200 were children. Of these infected individuals ~ 54,000 were receiving antiretroviral therapy (68 %). In 2013, HIV infection was initially diagnosed in approximately 3.500 persons, including 1100 with advanced immunodeficiency.

9.3.3 Potential efficacy of a 4CMenB vaccination in HIV infection

A number of studies show lower immune responses to MenC or MenACWY conjugate vaccines in HIV-infected individuals [100–104]. A recent review concluded that vaccines in HIV patients generally trigger poorer immune responses than in healthy volunteers [105]. Therefore it seems likely that the protective effect of a 4CMenB vaccination would be weaker and of shorter duration for this risk group than for healthy persons.

Assuming a 5- to 10-fold increased incidence of IMD in HIV-infected individuals with a VE of 80 % and strain coverage of 82 %,

$$\text{NNV} = \frac{\left(\frac{100,000}{1.5\ (\text{upto}\ 3.0)\ \text{MenB IMD per}\ 100,000\ \text{HIV - infected}}\right)}{(0,80\ (\text{VE}) \times 0,82\ (\text{strain coverage}))} \approx 51,000\ \text{to}\ 102,000\ \text{persons}$$

HIV-infected individuals would need to be vaccinated to prevent one case.

The corresponding calculation for IMD due to ACWY in HIV-infected individuals, with a VE of 80 % is

$$\text{NNV} = \frac{\left(\frac{100,000}{0.7\ (\text{up to}\ 1.4)\ \text{MenB IMD per}\ 100,000\ \text{HIV - infected}}\right)}{(0.80\ (\text{VE}))} \approx 89,000\ \text{to}\ 179,000\ \text{persons with HIV-infection}$$

Thus, the decision whether to vaccinate HIV-infected patients should take into account their immune status and other possible risk factors for IMD.

9.4 Additional immune deficiencies

9.4.1 Risk of IMD in antibody deficiency states

As specific bactericidal antibodies play a central role in protection against IMD [11], it is not surprising that occasional evidence is present in the literature for an increased risk of IMD in association with antibody deficiencies. However, evidence is based mainly on case reports that do not permit quantification of risk (see review in [106]). Patients with antibody deficiencies are primarily at risk for respiratory infections. Although 2 cases of IMD were described in patients with primary antibody deficiencies under immunoglobulin replacement therapy [106], it seems probable that the risk of IMD in patients receiving immunoglobulin substitution is only minimally elevated compared to the normal population [106].

9.4.2 Incidence of antibody deficiency states in Germany

Both in the European and in the German registry for PID, antibody deficiencies comprise the largest group of immune defects, at 52 % [88] and 62 % [66] respectively. Among these, common variable immunodeficiency (21 and 37 % of all patients respectively) is the most common. The prevalence of all PID in Germany, according to a minimum estimate, corresponds to 1.51 PID patients/100,000 Inh. Assuming the proportion of antibody deficiencies were 62 %, the prevalence would be ~ 1 patient/100,000 Inh., or ≈ 800 patients. In analogy to estimation of the prevalence of complement deficiencies above, however, this is likely to be an underestimate by a factor of 10–1000.

9.4.3 Potential efficacy of a 4CMenB vaccination in antibody deficiency states

In view of a reduced capacity to produce antibodies in this very heterogeneous patient group, VE is likely to be low [107]. However, there appear to be subgroups of patients capable of at least transiently generating adequate antibody responses to the antigens of polysaccharide or protein-based vaccines [107–110]. Due to the high degree of uncertainty surrounding the degree of IMD risk of IMD, the NNV was not estimated for this patient group. It seems likely, however, that the NNV would be similar to that estimated for HIV-infected individuals, since the absolute risk for IMD appears only minimally increased and vaccine effectiveness is likely to be low.

9.5 Recommendation of MenB vaccination for individuals with certain immune deficiencies/ immunosuppression

As summarized in **Table 1**, the risk of IMD is markedly increased only in individuals with complement deficiencies. Accordingly, with the exception of this risk group, the number of persons that need to be vaccinated to prevent one case of MenB IMD is very high. In addition, the number of cases that can potentially be prevented in the risk groups considered is very small, again with the exception of persons with complement deficiencies. However, because of the severity of IMD and the immunological plausibility for an elevated IMD risk in persons with the immune deficiencies/immunosuppression considered here, STIKO recommends both MenACWY and MenB vaccination for affected persons based on an individual risk assessment.

9.6 Household contacts of patients with IMD

9.6.1 Risk of IMD for household contacts of IMD patients

Secondary IMD cases can occur in persons following close contact with cases of IMD. However, the proportion of IMD cases that are epidemiologically linked in Germany is very low at < 2 %. Household contacts are at highest risk for developing IMD. Without chemoprophylaxis, their risk within 30 days after contact with the index case is up to 1000-fold higher compared to the incidence in the general population [111–113]. According to the results of a systematic review, chemoprophylaxis reduces the risk of disease for household contacts by 84 % (95 % CI, 41–97 %) [113]. An estimated 284 persons (95 % CI: 156–1515) need to be treated (*number needed to treat*; NNT) to prevent one case. In addition, results of a systematic review showed that household members are at increased risk of IMD in the 14–365 days following contact with index case even after receiving chemotherapy, estimated at 1.08 IMD/1000 household members [2]. The majority (71 %) of observed secondary cases, however, occurred within 14–90 days after contact with the index case. It was estimated that one IMD case can be prevented through vaccination with a MenACWY conjugate vaccine if 1033 (95 % CI; 638–1678) household contacts receive serogroup-specific vaccination in addition to chemotherapy [2]. These estimates were based on the assumptions that vaccination occurs within 7 days after contact, immunity develops within 7 days following vaccination and VE is 85–95 %. STIKO recommended post-exposure vaccination of unvaccinated household (-like) contacts in addition to chemoprophylaxis if the disease of the index patient was caused by serogroups A, C, W or Y in 2009. Vaccination should take place as soon as possible following contact [3].

In England & Wales, Ladhani et al. investigated whether household contacts of IMD cases might benefit from MenB vaccination with Bexsero® in addition to chemoprophylaxis for the prevention of secondary IMD [114]. The NNV for MenB vaccination was calculated based on the risk of subsequent IMD cases as estimated by Hoek et al. [2] described above. Because the calculated NNV against MenB was higher than for the ACWY vaccination in most scenarios, routine post-exposure vaccination of household contacts of MenB cases was not recommended in England & Wales [115].

9.6.2 Potential efficacy of a 4CMenB vaccination to prevent secondary cases in household contacts of IMD cases

Currently, it is not routinely possible to investigate promptly whether a meningococcal B strain responsible for a case of IMD is covered by the vaccine using MATS. As the decision on vaccine prophylaxis has to be made quickly, for the time being the vaccination series would have to be initiated as soon as the strain is identified as serogroup B, knowing ~ 20 % of strains would not be covered by 4CmenB. Furthermore, data on immunogenicity following a *single dose* of 4CMenB are only available for children aged 1 year or older. These reveal a markedly poorer hSBA response after one dose in one-year-old children [116, 124] than in infants following 4 doses or adolescents following one or two doses (see above and Annex 1, **Table 3**). In addition, data on the dynamics of the antibody increase in the 2 weeks following vaccination were not available.

Because of these uncertainties, the NNV for vaccination of household contacts with Bexsero® was calculated for a range of probable VE. In a favorable scenario that might apply to older children and adults in which the MenB vaccine is administered within 4 days after diagnosis of the index case (assuming that by then the causative serogroup in the index case has been identified), the vaccine is assumed to protect with a VE of 90 % against 82 % of the strains from 14 days after vaccination and the disease risk is 108 IMD cases/100,000 household contacts [2], an estimated.

$$\mathrm{NNV} = \frac{\left(\dfrac{100{,}000}{108\ \text{IMD per}\ 100{,}000\ \text{household contacts}}\right)}{(0.90\ (\mathrm{VE}) \times 0.82\ (\text{Strain coverage}))} = 1{,}254\ \text{household contacts}$$

would have to be vaccinated to prevent one MenB case. When a lower VE of 50 % is assumed, as might apply to infants, the estimated NNV increases to 2258. Taking into account the lower strain coverage in infants of 68 % (see above) would further increase the NNV to 2723. The NNV would also increase if vaccination were undertaken later than 4 days after diagnosis of the index case. Thus, although a precise estimate is not possible based on currently available evidence; the effectiveness of post-exposure vaccination with Bexsero® is likely to be lower than that of MenACWY conjugate vaccines.

In view of the severity of IMD, STIKO recommends vaccination of household contacts of serogroup IMD cases based on an individual risk assessment despite the likely lower VE of Bexsero® compared to the conjugate vaccines. Besides the possibility that the household might be situated in a social setting with ongoing circulation of pathogenic meningococci, family members might also have a genetic predisposition for an increased IMD risk that could be reduced by vaccination.

9.7 Laboratory staff

Cases of IMD in laboratory staff have rarely been described and almost always in association with non-compliance of recommended safety precautions (class II safety workbench; respiratory protection in cases of aerosol formation) [4, 5, 117–120]. Two studies [4, 5] estimated IMD risk in laboratory staff compared to the risk in the general population. In the USA, 6 cases were identified during a global survey from 1996 to 2000, corresponding to an annual incidence of 13 cases of disease/100,000 laboratory employees. In the same period, an IMD incidence of 0.3 was observed in 30–59-year-old persons (relative risk (RR) = 43). An incidence of 271 IMD cases/100,000 person years (95 % CI: 88–634) was estimated based on 5 IMD cases in laboratory staff in England and Wales from 1985 to 1999, compared to a background incidence of 1.47 (RR = 184 (95 % CI 60–431).

Thus, for vaccination of microbiology laboratory staff working with *N. meningitidis*, assuming 95 % VE after 2 doses of Bexsero, it can be calculated that

$$\text{NNV} = \frac{\left(\frac{100,000}{13\ (\text{up to } 271) \times 0.69\ \text{MenB IMD per } 100,000\ \text{laboratory workers}}\right)}{(0.90\ (\text{VE}) \times 0.82\ (\text{Strain coverage}))} / 3\ \text{years (duration of protection)} \approx 229 \text{ to } 4770\ \text{laboratory workers}$$

would have to be vaccinated to prevent one case depending on the assumed incidence (see above). The corresponding calculation for MenACWY would be:

$$\text{NNV} = \frac{\left(\frac{100,000}{13\ (\text{up to } 271) \times 0.31\ \text{MenACWY per } 100,000\ \text{laboratory workers}}\right)}{0.95\ (\text{VE})} / 3\ \text{years (duration of protection)} \approx 441 \text{ to } 9190\ \text{laboratory workers}$$

Considering the severity of the disease and that laboratory accidents can never be completely avoided, STIKO recommends MenB vaccination of laboratory staff at risk of exposure to *N.-meningitis* aerosols.

10 Vaccination strategy

Vaccination with Bexsero® can potentially protect risk groups from IMD due to serogroup B. Persons with terminal complement deficiencies are at highest risk of IMD, while the absolute risk for persons with asplenia, HIV-infected individuals (especially on antiretroviral therapy) or with other immune deficiencies is only slightly higher than that of the general population.

Household contacts of patients with IMD caused by serogroup B can also potentially benefit from MenB vaccination, however to a lesser extent than household contacts of index cases with IMD caused by serogroups ACWY. Since over two thirds of secondary cases that occur in contacts despite their having received chemoprophylaxis occur in the 3 months following contact with the index case, rapid serogroup determination is crucial to enable appropriate postexposure vaccination as promptly as possible.

STIKO likewise recommends vaccination of occupationally exposed persons with a MenB vaccine.

The relevant risk groups and physicians involved in their care should be specifically informed about this vaccine, e.g. via patient networks and through professional societies. In addition, however, the lack of data on clinical efficacy, the incomplete strain coverage and the availability of only rough estimates of IMD risk in persons with various immune deficiencies or immunosuppressive states should also be communicated. Finally, the duration of the potential vaccine protection is also unknown; therefore no advice can be given at present as to whether (or when) a booster vaccination is required.

11 Implementation/feasibility

Household contacts, occupationally exposed individuals and persons with immune deficiencies/Immunosuppression should be vaccinated according to the licensed vaccination schedule, as described in the Summary of Product Characteristics. In addition it appears prudent not to administer 4CMenB simultaneously with other vaccinations if possible, at least in infants and toddlers. Although simultaneous vaccination with Infanrix hexa®, Prevenar7® and MMRV did not compromise the immunogenicity of these vaccine antigens in licensure studies, the risk for local and systemic side effects, especially for fever, was markedly higher in infants and toddlers than with separate administration. Simultaneous administration of antipyretics reduced the risk for fever in infants and toddlers without compromising the immunogenicity of 4CMenB or the mentioned routine vaccines [116]. Evaluation of data from an active surveillance study within the scope of a 4CMenB vaccination campaign in Québec, however, revealed that prophylactic antipyretics had no effect on the risk of fever in children above 4 years of age.

In view of the severity of this disease, acceptance for MenB vaccination by persons at increased risk of disease can be assumed to be very high.

12 Evaluation of the vaccination recommendation

As the ascertainment of IMD in risk groups is not generally established, the

detection of a possible decrease in IMD burden attributable to MenB vaccination will be difficult to identify. MenB cases occurring after introduction of Bexsero®, should, however, be thoroughly investigated. In particular, in the case of meningococcal B disease in a vaccinated person, it is essential to clarify whether the responsible strain should have been covered by the vaccine or not. This can only be tested using MATS to determine the expression of vaccine antigens at the national reference laboratory NRZMHi (www.meningococcus.de), i.e. with a test currently available only from the vaccine manufacturer. Additionally required serological testing to differentiate between primary versus secondary vaccine failure (i.e. absent or insufficient neutralizing antibodies due to an insufficient primary vaccine response versus waning immunity) can also be performed at NRZMHi. Active laboratory surveillance after broader use of the vaccine is also important to identify possible *immune-escape*-variants that might spread in the case of altered population immunity.

The Risk Management Plan (RMP) as outlined by EMA specifies that the risk for anaphylaxis/anaphylactic shock, Kawasaki syndrome, seizures and febrile seizures, Guillain Barré syndrome (GBS) and acute disseminated encephalomyelitis (ADEM) after 4CMenB vaccination should be evaluated more precisely in a post-licensure observational safety surveillance study (V72_36OB) by the end of 2018 at the latest [7]. As 4CMenB vaccination has thus far not been implemented within a routine vaccination program (routine infant vaccination is expected to commence in England and Wales in September 2015), this study has not yet commenced. Furthermore, the RMP calls for performance of a study on safety, tolerability and immunogenicity in persons with complement deficiencies. Such studies would also be desirable in persons with additional immunodeficiencies and/or immunosuppression and should also specifically investigate the duration of immune protection.

The current Summary of Product Characteristics for Bexsero® specifies that the vaccine is subject to additional monitoring to ensure rapid identification of any safety issues. Health professionals in Germany are required to report every suspected case of an adverse reaction due to Bexsero® to the Paul Ehrlich Institute (PEI). According to § 6 para. 1, no. 3 IfSG, all suspected cases of health impairment exceeding the usual severity of a vaccination reaction should be reported to the PEI. This applies regardless of whether or not a vaccination recommendation is endorsed by STIKO (see http://www.pei.de/DE/arzneimittelsicherheit-vigilanz/pharmakovigilanz/meldeformulare-pharmakovigilanz/meldeformulare-pharmakovigilanz-node.html).

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Compliance with ethical guidelines

Conflict of interest. W. Hellenbrand, J. Koch, T. Harder, C. Bogdan, U. Heininger, T. Tenenbaum, M. Terhardt, O. Wichmann, R. von Kries declare no conflict of interest. U. Vogel receives kits from GSK to perform MATS testing on German strains for scientific collaboration as well as for timely testing of circulating strains to determine vaccine strain coverage.

Annex 1

Key results on immunogenicity of 4CMenB (Bexsero®) vaccination as reported in licensure studies

Table 3 Immunogenicity after 4CMenB vaccinations in infancy and toddler age: % of study participants with a hSBA titer≥ 1:5 (1:4)

	% with hSBA titer ≥ 1:5 (1:4)			
	fHbp (%)	NHBA (%)	NadA (%)	PorA-NZ (%)
Infants—priming				
Pre-vaccination ($n = \sim 1320$)	3	33	4	1
1 month after 3 doses (2,4,6 months^R, $n = \sim 1282$) [37][a]	100	84	100	84
1 month after 3 doses (2,4,6 months^R, $n = \sim 525$) [35]	99	ND	99	79
1 month after 3 doses (2,4,6 months, $n = \sim 525$) [35]	99	ND	99	86
1 month after 3 doses (2,3,4 months^R, $n = \sim 270$) [35][a]	99	37	100	82
1 month after 3 doses (2,3,4 months^R, $n = \sim 165$) [116]	100	ND	99	78
Infants pre-booster				
6 months after 3 doses (2,4,6 months^R, $n = \sim 435$) [37][a]	81	61	99	22
8 months after 3 doses (2,3,4 months^R, $n = \sim\sim 246$) [7]	58	25	97	19
8 months after 3 doses (2,3,4 months^R, $n = \sim 70–140$) [116]	53	ND	97	12
Post-booster (1-year-olds)				
1 month after 4 doses (2,4,6,12 months^R, $n = \sim 425$) [37][a]	100	95	100	97
1 month after 4 doses (2,3,4,12 months^R, $n = \sim 70–140$) [116]	100	ND	100	88
1 month after 3 doses (6,8,12 months, $n = 22–24$) [121]	100	ND	100	96
Toddlers				
1 month after 1 dose at 12 months of age ($n = 22$) [124]	73	ND	73	18

Table 3 Immunogenicity after 4CMenB vaccinations in infancy and toddler age: % of study participants with a hSBA titer≥ 1:5 (1:4) (Continued)

	% with hSBA titer ≥ 1:5 (1:4)			
	fHbp (%)	NHBA (%)	NadA (%)	PorA-NZ (%)
1 month after 1 dose at 12 months of age ($n = \sim 70$) [116]	85	ND	93	23
1 month after 1 dose at 40 months of age ($n = 39$) [47][c]	72	62[a]	87	23
1 month after 2 doses at 40 months of age ($n = 39$) [47]	100	72	100	90
Persistence in infants & toddlers				
12 months after 4 doses (2,4,6,12 months[R], $n = 291–299$) [7][a]	62	36	97	17
28 months after 4 doses (2,4,6,12 months[R], $n = 17$) [46][b]	65	67	76	41
28 months after 3 doses (6,8,12 months, $n = \sim 15$) [47][c]	36	79	100	14
20 months after 4 doses (6,8,12,40 months, $n = \sim 9$) [45]	67	45	100	17
20 months after 2 doses (40, 42 months, $n = \sim 23$) [45]	38	83	100	0

ND No data available.
R Concomitantly with routine vaccinations.
[a] $n = 70–100$ for NHBA.
[b] Of 43 newly-recruited controls of the same age, 0–3 % had hSBA titers ≥ 1:5 for PorA and NadA; 63 % for fHbp; 68 % for NHBA.
[c] Of 40 newly-recruited controls, < 3 % had hSBA-titers ≥ 1:4 for fHbp, NadA and PorA and 53 % for NHBA.

Table 4 Immunogenicity after 1 or 2 doses of 4CMenB in adolescence: % of study participants with a hSBA-titer ≥ 1:4

	% with hSBA titer ≥ 1:4			
	fHbp (%)	NHBA[a] (%)	NadA (%)	PorA-NZ (%)
Pre-vaccination ($n = \sim 1471$)	44	88	34	35
1 month after 1 dose ($n = 318$)	92	ND	95	93
1 month after 2 doses 1 month apart, $n = 222$)[c]	100	100	100	100
1 month after 2 doses 2 months apart, $n = 215$)[c]	100	100	100	100
18–24 months after 2 doses[b,d] ($n = 257$)	82	ND	94	77

ND No data available.
[a] $n = 46$.
[b] Intervals of 1, 2 or 6 months between doses.
[c] Santolaya et al. 2012 [44].
[d] Santolaya et al. 2013 [48].

Annex 2

Evaluation of the reactogenicity and safety of the 4CMenB vaccine (Bexsero®)

13 Methods

To perform a systematic review of the reactogenicity and safety of 4CMenB vaccine, we defined "PICO" (*Population, Intervention, Comparator* and *patient relevant outcomes*) according to the recommendations of the *Grading of Recommendations Assessment, Development and Evaluation* (GRADE) working group. Persons of all ages were defined as the population for inclusion, vaccination with 4CMenB was defined as the intervention, vaccination with placebo or with another vaccine or no vaccination were defined as comparators. Outcomes were classified according to their importance for decision making, using a scale of 1–9. Outcomes rated from 7 to 9 and 4 to 6 were classified as "critical" and "important", respectively. In infants and toddlers, fever, seizures, Kawasaki syndrome and hospitalization for clarification/treatment of adverse events (AE) were classified as critical outcomes. Severe local pain and vomiting were classified as important outcomes. In adolescents and adults, seizures, Guillain-Barré syndrome (GBS), juvenile arthritis (JA), seizures and acute disseminated encephalomyelitis (ADEM) were classified as critical, and fever, severe local pain and headache as important. The working group decided to define a temperature threshold for comparing intervention and comparator groups after taking into account the location of temperature measurements and thresholds used in available studies retrieved in the literature search.

Relevant studies published since 2010 addressing outcomes classified as "critical" or "important" were identified according to evidence-based criteria in a systematic literature search via the DIMDI portal using the *searchstring* "f ((MenB vaccin? or 4CMenB or Bexsero) or (meningococc? and (serogroup B) and (vaccin? or immuni?ation))) AND PY > 2009". The literature search was performed using the following databases: Cochrane, MEDLINE, EMBASE, SciSearch, GLOBAL Health, BIOSIS Previews.

Two reviewers independently screened the titles and abstracts of the retrieved references. All full texts of publications considered relevant by at least one of the two reviewers were examined in detail and a

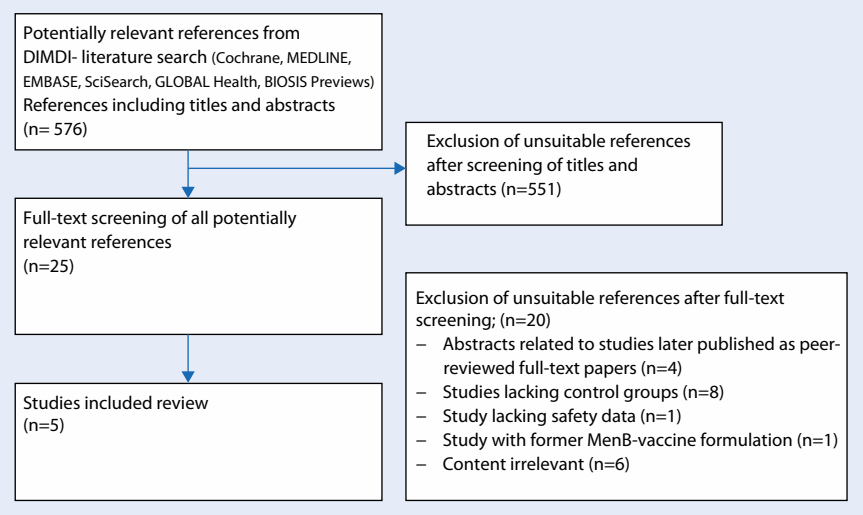

Fig. 3 ▲ Flowchart of the literature search for the review of safety and reactogenicity of the 4CMenB vaccine (Bexsero®)

consensus then reached regarding their inclusion.

Relevant data were systematically extracted using a standardized form, and the internal and external validity of the included studies assessed. Data pertaining to outcomes classified as "critical" or "important" were extracted from the studies and entered into the Review Management Software *Review Manager* (Version 5.2, *The Nordic Cochrane Centre, The Cochrane Collaboration*, 2014). When data were available from several studies without significant heterogeneity these were pooled for meta-analysis. The data were imported into the computer software GRADEprofiler (version 3.6) to create a GRADE evidence profile that was also used for calculation of the risk differences. The quality of evidence of all included studies was assessed for each outcome according to the following criteria: study design, heterogeneity, precision, indirect evidence, strength of effect and publication bias. The lowest quality of evidence for any of the critical outcomes was used to classify to overall level of quality of the evidence.

14 Results

14.1 Systematic literature search

A total of 576 abstracts were retrieved in our literature search after removal of duplicates. Screening of the titles and abstracts led to identification of 25 potentially relevant publications [35, 37, 44–48, 116, 121, 122, 124–137]. Of these, 5 fulfilled the inclusion criteria [35, 37, 44, 116, 128]. **Fig. 3** shows the results of the literature search as a flowchart. None of the included studies reported on the safety of 4CMenB in persons with an increased risk for invasive meningococcal disease (IMD) related to underlying medical conditions.

14.2 Description of included studies

All five studies included in the review of reactogenicity and safety were randomized controlled studies funded by Novartis Vaccines. With the exception of a substudy in [37] and the adolescent study [44], the study participants (or their parents) knew which vaccines were administered. Blinding may also have been incomplete in the adolescent study since the study staff administering the vaccines was aware of the group assignments. Key aspects of the studies included in this review are summarized in **Tables 5 and 6**. As data was not available in all studies on all outcomes classified as "important" or "critical", we considered further, related outcomes for descriptive analysis: Thus, in addition to hospitalization, we looked at the outcome "Medical treatment for vaccination reactions" (see **Table 5 and 6**). In addition, we considered the outcome "Administration of antipyretics and analgesics", as we considered this relevant for the interpretation of the data on febrile reactions and pain. Data on some of the outcomes classified as critical were not or only incompletely addressed in the 5 included studies– sometimes presumably because they did not occur. For instance, studies did not report consistently on how long after vaccination the few reported seizures occurred. In addition differentiation between febrile and non-febrile seizures was not always clear. For these reasons, and because study sizes did not permit assessment of very rare AE, it was not possible to evaluate the outcomes seizures, KS, hospitalizations for AE, JA, GBS and ADEM based on GRADE. Relevant available data were therefore not included in the GRADE profile, but only listed in **Tables 5 and 6**.

Data on the outcomes fever, severe local pain and vomiting in infants and toddlers were included in the GRADE profile [35, 37]. Both studies allowed comparison between reactogenicity after 4CMenB plus routine vaccinations versus after routine vaccinations alone at the ages of 2, 4 and 6 months. Vesikari et al. [37] presented the number of study participants who had experienced the respective safety outcome after at least one of the received vaccine doses, while Gossger et al. [35] presented the number of events per dose administered. Because the incidence of the safety outcomes after each of the three doses in the Gossger study was similar (see **Fig. 4**), only the number of events after the 1st dose were considered in the review to enable use of the same denominator (number of study subjects and not number of all administered doses) for data from both studies. In addition, the study by Gossger et al. [35] permitted the comparison between 4CMenB alone at ages of 2, 4 and 6 months and routine vaccinations alone at ages of 3, 5 and 7 months. In Vesikari et al. [37], a fourth 4CMenB dose was also administered at age 12 months with or without MMRV, but without a comparator group. The objective of the 3rd, much smaller study by Prymula et al. [116], was to evaluate the immunogenicity and reactogenicity of 4CMenB + routine vaccines with and without prophylactic administration of paracetamol; thus an appropriate comparator group was lack-

Table 5 Description of studies included in the review of safety and reactogenicity of the 4CMenB vaccine in infants

Study	Gossger et al. 2012 [35]	Vesikari et al. 2013 [37]	Prymula et al. 2014 [116]
Study design	Phase 2b, open-label RCT	Phase 3 RCT with non-blinded and observer-blinded[a] groups; both comparing three 4CMenB batches	Non-blinded phase 2 RCT
NCT	NCT00937521	NCT00657709; NCT00847145	NCT00937521
Study period	August 2008-July 2010	03.31.2008–08.16.2010	July 2009-November 2010
Study locations	Belgium, UK, Germany, Italy and Spain	Finland, Czech Republic, Germany, Austria, Italy	Czech Republic, Italy, Hungary, Chile, Argentina
Intervention group: 4CMenB vaccination schedule	4CMenB + R (see below) at age 2, 4, 6 months; 4CMenB alone at age 2, 4, 6 months and R at age 3, 5, 7 months; 4CMenB+R at age 2, 3, 4 months	Observer-blinded[a]: 4CMenB + R at age 2, 4, 6 months; Not blinded: 4CMenB + R at age 2, 4, 6 months At age 12 months: 4CMenB-vaccinated children from both study arms randomized for receiving 4CMenB-booster +/− MMRV	At age 2, 3, 4, 12 months: 4CMenB + R or 4CMenB + R + prophylactic paracetamol. At age 13 months: MenC conjugate vaccine (Menjugate®, Novartis Vaccines)
Comparator group: Vaccination and vaccination schedule	R at ages 3, 5, 7 months	Observer-blinded: R + MenC at age 2, 4, 6 months Not blinded: R alone at age 2, 4, 6 months	MenC conjugate vaccine (Menjugate®, Novartis Vaccines) + R at age 2, 3, 4 months. 4CMenB + R at age 12 and 4CMenB at age 13 months
Age at study entry	2 months	2 months	2 months
Study size	Total 1885	Total: 3630	Total: 558
Follow-up	Recording of AE and SAE in a paper diary for 7 days after each vaccination with telephone support from the study team. Documentation of all SAE up to 6 months after the last 4CMenB dose	Recording of pre-defined and all observed AE for 7 days after each vaccination. Any SAE or events requiring medical treatment were documented for the entire study period	Recording of adverse events and SAE for 7 days after each vaccination
Definitions and available data on occurrence of PICO outcomes			
Fever	≥ 38.0 °C (axillary)	≥ 38.5 °C (rectal)	≥ 38.0 °C (rectal)
Severe local pain	Crying when injected limb was moved +/− refusal to move the extremity	Crying when injected limb was moved	Crying when injected limb was moved
Vomiting	No formal definition, but data available	No formal definition, but data available	No formal definition, but data available
Seizures	No formal definition: 1 febrile seizure 2 days after 4CMenB vaccination alone (1/626), 1 seizure after 4CMenB vaccination alone (1/626); 1 seizure after R alone (1/626); 1 seizure after 4CMenB + R (1/941)	No formal definition. After the first 3 doses of vaccine in infants: 2 febrile seizures < 24 h after the 2nd vaccine dose of 4CMenB + R (2 seizures/2478 doses, possibly associated); 2 additional seizures with fever (1x only lower limbs affected, in one case only one arm) < 24 h after 1st 4CMenB + R (2 seizures/2478 doses possibly associated). No seizures after only R or R + MenC. 13 additional seizures with fever 9 days—6 months after 4CMenB + R or 4CMenB + MMRV, which were classified as not associated with the vaccination	No formal definition: No febrile or afebrile seizures were observed
Kawasaki syndrome (KS)	No formal definition. 2 KS cases reported after receiving 4CMenB; one possibly associated (no further details e.g. on time intervals)	Fever > 5 days with at least 4 of the 5 major criteria for the diagnosis of KS (rash, cervical lymphadenopathy, bilateral conjunctival injection, changes in the oral mucosa, changes in the peripheral extremities. Patients, who did not exhibit all criteria but showed abnormalities of the coronary arteries consistent with KS likewise fulfilled the case definition. Cases fulfilling only some of the criteria were classified as incomplete KS. 2 confirmed KS cases were reported 3 and 7 weeks and one incomplete case 14 weeks after 4CMenB + R vaccination. One confirmed case was reported 23 weeks after a MenC vaccination	KS not reported in study
Hospitalization	Number of hospitalizations (6 per 1567 doses of 4CMenB +/− R) due to fever < 2 days after 4CMenB vaccinations, further data not provided	No information	No information

Table 5 Description of studies included in the review of safety and reactogenicity of the 4CMenB vaccine in infants (Continued)

Study	Gossger et al. 2012 [35]	Vesikari et al. 2013 [37]	Prymula et al. 2014 [116]
Medical treatment for vaccine reactions	No information	In the non-blinded sub-study medical treatment for fever was reported for 28/1966 (1.4 %) infants after 4CMenB + R vaccination and in 12/659 (1.8 %) after R vaccination alone. In the observer-blinded sub-study, these proportions were 26/493 (5.3 %) and 13/470 (2.8 %—for R + MenC)	Medical treatment for fever was reported in 9 cases after 855 doses of 4CMenB alone (1.1 %); in 2 cases after 700 doses of 4CMenB + paracetamol (0.3 %), in 4 cases after 545 doses of MenC (0.7 %)
Administration of antipyretics and analgesics	No information	2302/2478 (93 %) after 4CMenB + R; 471/659 (71 %) after R alone	Following 4CMenB vaccination, 36–55 % of 4CMenB recipients who had not received prophylactic paracetamol were given paracetamol therapeutically (no further details provided)

R Routine vaccines: Infanrix hexa® plus Prevenar7®, *MMRV* Measles, Mumps, Rubella-Varicella-vaccination, *(S)AE* (serious) adverse events.
[a]Observer-blinded: In study-arm, parents and study staff, with the exception of staff who administered the vaccine, were blinded regarding the administered vaccine (4CMenB vs. MenC).

Table 6 Description of the studies included in the review of safety and reactogenicity of the 4CMenB vaccine in adolescents and adults

Study	Santolaya et al. 2012/adolescents	Read et al. 2014/adults
Study design	Phase 2b/3, placebo-controlled, randomized, observer-blinded[a] study	Phase 3, placebo-controlled, randomized, observer-blinded study
NCT	NCT00661713	NCT01214850
Study period	June 2008-December 2010	September 2010-December 2011
Study locations	Santiago and Valparaíso, Chile	England
Intervention group: 4CMenB vaccination schedule	4CMenB (0, 1, 2, 6 months, total of 2–3 doses)	4CMenB (0, 1 months)
Comparator group: Vaccine and vaccination schedule	Placebo (aluminum hydroxide) (0, 1, 2, 6 months)	First comparator group: 1st dose MenACWY-CRM (Menveo®) and 2nd dose placebo (aluminum hydroxide) (0, 1 months) Second comparator group: Ixiaro®(0, 1 months)
Age at study entry	11–17 years (mean: 13.8 years)	18–24 years
Study size	Total: 1631	Total: 2968 (subset of $n = 600$ for safety evaluation)
Follow-up	Recording of local and systemic vaccination reactions in a paper diary for 7 days after each vaccination, and SAEs throughout the entire study period	Recording of local and systemic vaccination reactions in a paper diary for 7 days after each vaccination, and SAEs throughout the entire study period
Definitions and available data occurrence of PICO outcomes		
Fever	≥ 38.0 °C (axillary)	≥ 38.0 °C (kind of measurement not described)
Severe local pain	Severity of pain was assessed using a predefined scale from mild (noticeable) to severe (interference with normal activities)	No formal definition
Headache	Severity of pain was assessed using a predefined scale from mild (noticeable) to severe (interference with normal activities)	No formal definition
Seizures	No formal definition; 1 convulsion reported after 1st dose of 4CMenB in participant with paternal history of epilepsy	No formal definition/no data
Juvenile arthritis	No formal definition/two cases of juvenile arthritis, one case evaluated as possibly and one case as probably associated with 4CMenB (170 days and 198 days after the third of the 3 doses of 4CMenB)	No formal definition/no data
GBS	No formal definition/no data	No formal definition/no data
ADEM	No formal definition/no data	No formal definition/no data
Hospitalization	No information	No information
Medical treatment due to vaccination reactions	Medical treatment due to fever (4CMenB: < 1 %, 4/1480), (placebo: < 1 %, 2/1290)	No information
Administration of antipyretics and analgesics	Use of antipyretics: (4CMenB: 4 %, 61/1461), (placebo: 2 %, 22/689), $p < 0.0002$)	Therapeutic use of antipyretics: (4CMenB: 20 %, 75/375), (placebo: 6 %, 11/175); prophylactic use of antipyretics: (4CMenB: 4 %, 16/372), (placebo: 1 %, 2/172);

[a]Observer-blinded: Vaccine recipients, parents, and study staff, with the exception of staff who administered the vaccine, were blinded.

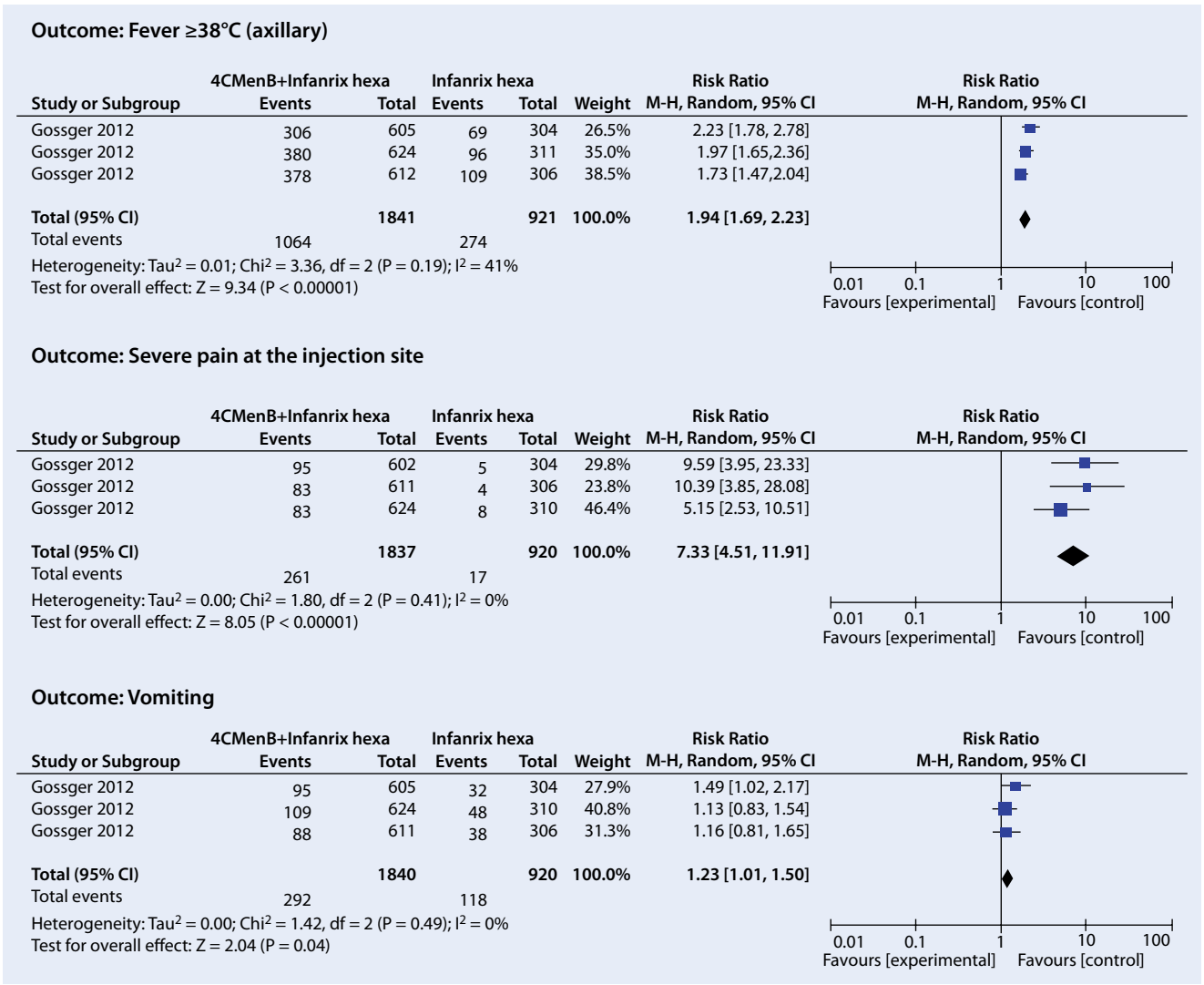

Fig. 4 ▲ Forest plots showing relative risks for reactogenicity and safety outcomes in infants and toddlers receiving 4CMenB plus routine vaccines (Infanrix hexa® plus Prevenar®) versus routine vaccines alone) according to the 1st, 2nd or 3rd vaccine dose based on data from Gossger et al. [35]

ing and the study could not be included in our evaluation. None of the 3 studies allowed a comparison between 4CMenB alone and placebo, which would have been necessary for a completely unbiased description of the reactogenicity of 4CMenB.

A single study each in **adolescents** [44] and **adults** [128] was included for evaluation of the outcomes fever, severe local pain and headache after administration of 2–3 doses of 4CMenB alone versus placebo. In the adult study, one comparator group received 2 doses of the Japanese encephalitis vaccine Ixiaro®. The other comparator group received the quadrivalent meningococcal conjugate vaccine as a first dose and placebo as a 2nd dose. Therefore, safety outcomes observed in recipients of the 2nd 4CMenB dose were compared with those observed in recipients of the placebo dose.

14.3 Evaluation of the reactogenicity and safety of 4CMenB in infants and toddlers

The results of the two studies included for evaluation of reactogenicity and safety outcomes in infants and toddlers showed that vaccination with 4CMenB+ routine vaccinations was associated with increased reactogenicity, particularly due to fever. Compared to vaccination with routine vaccines alone, the risk for fever, severe local pain and vomiting was significantly increased (see *Forest plots* ◘ **Fig. 5** and GRADE profile ◘ **Table 7**). Because of significant heterogeneity of the absolute frequencies and relative and absolute risks for severe pain as well as for vomiting in Vesikari et al. [37] and in Gossger et al. [35] (see below) the data for these outcomes were not pooled. Fever following 4CMenB+ routine vaccinations occurred very frequently after 4CMenB plus routine vaccines (in 74 % of the vaccine doses), but only after 40 % of the vaccine doses with routine vaccinations alone. Thus if 1000 infants were to receive 4CMenB+ routine vaccinations, 335 (95 % CI: 254–419) more febrile reactions would occur than in 1000 children receiving routine

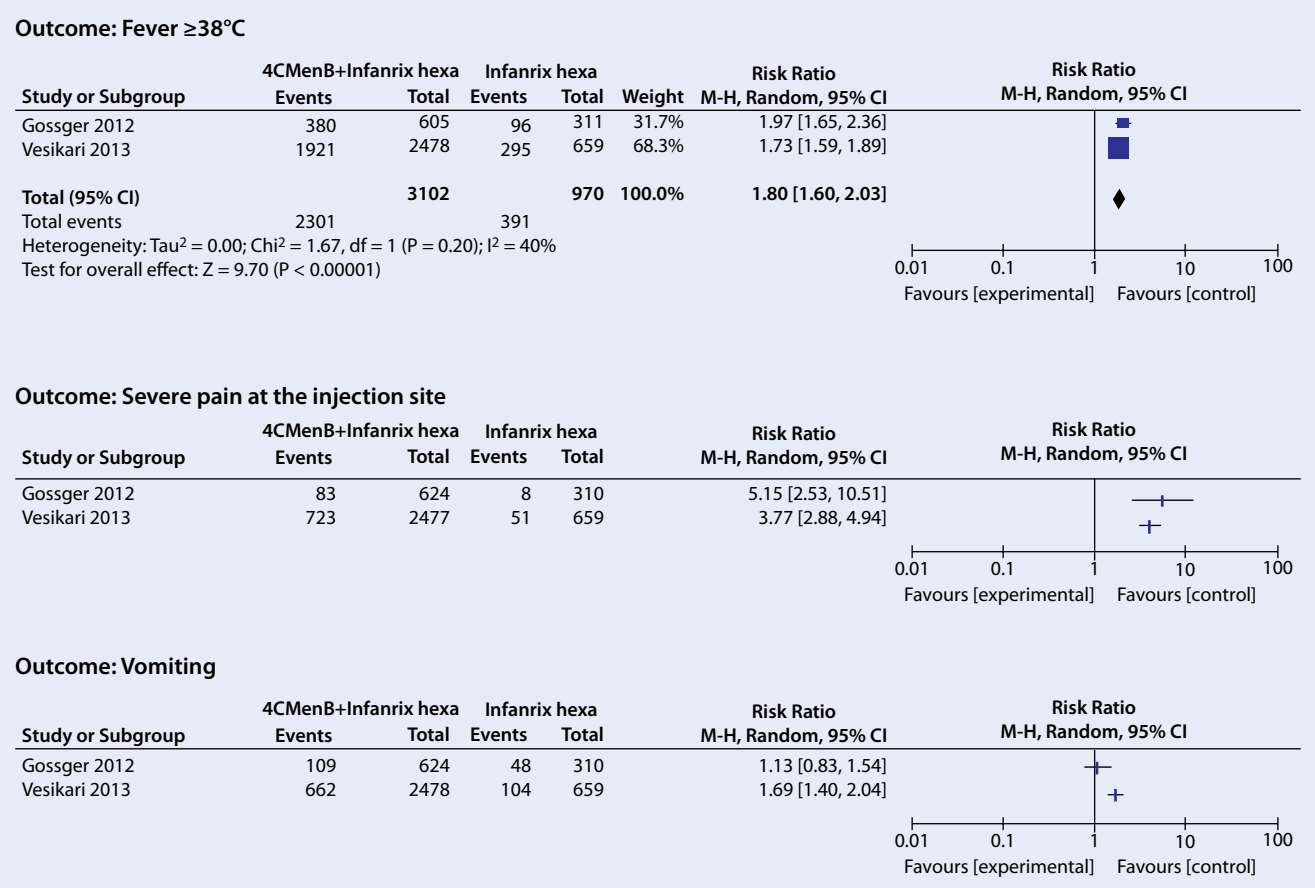

Fig. 5 ▲ Forest plots showing relative risks (RR) for reactogenicity and safety outcomes in infants and toddlers receiving 4CMenB plus routine vaccines (Infanrix hexa® plus Prevenar®) versus routine vaccines alone)

vaccines only. Severe pain also occurred more frequently after 4CMenB + routine vaccinations than after routine vaccinations alone (see **Fig. 5 and Table 7**), but to a greater extent in the study by Vesikari et al. (29.2 vs. 7.7 %) than in the study by Gossger et al. (13.3 vs. 2.6 %). Vomiting occurred more frequently after 4CMenB+ routine vaccinations than after routine vaccinations alone only in the study by Vesikari et al. (26.7 vs. 17.5 %, see **Fig. 5 and Table 7**).

The definition for high fever varied in the included studies. In Gossger et al. [35] 11.5 % (72/624) of infants developed an axillary temperature of ≥ 39.0 °C after the 1st dose of 4CMenB + routine vaccinations in the 7 days following vaccination, while this was the case in only 3.5 % (11/311) of infants who received routine vaccinations alone (RR = 3.26, 95 % CI: 1.76–6.06; risk difference (RD) = 100/1000, 95 % CI: 80–130). In Vesikari et al. [37] 1.2 % of infants developed a rectal temperature ≥ 40.0 °C after at least one of the doses of 4CMenB + routine vaccinations in the 6 h following the vaccination while this was the case for none (0/659) of the children who received routine vaccinations alone (RR = 15.77, 95 % CI: 0.96–257.78); RD = 10/1000, 95 % CI: − 10–30). In addition to varying temperature thresholds and observation periods in the two studies, the frequent receipt of antipyretics in Vesikari et al. (see **Table 5**) might also explain the more seldom occurrence of high fever; however data on receipt of antipyretics are lacking in Gossger et al.

Data from Gossger et al. [35] also permitted a comparison between infants who were vaccinated with 4CMenB only and infants vaccinated with routine vaccinations only. For this comparison, the risk of fever after the 1st dose of 4CMenB was 38.0 % (238/627), still significantly higher than after routine vaccinations (30.9 % (96/311) RR = 1.23, 95%CI: 1.01–1.49). The absolute risk was, however, markedly lower than with concomitant vaccination (74 %, see above). After 4CMenB alone the risk for severe pain in the vaccinated extremity was 10.2 % (64/626), also significantly higher than after routine vaccinations alone (2.6 % (8/310) RR = 4.0, 96 % CI 1.9–8.2). This absolute risk of 10.2 % as well as the risk difference (76/1000, 95 % CI: 47–106), were, however, somewhat lower than for the comparison of concomitant vaccination with routine vaccines alone (13.3 % and 110/1000, respectively, see **Fig. 5 and Table 5**). No significant difference was observed in the occurrence of vomiting after 4CMenB alone and routine vaccinations alone (14.2 vs. 13.6 %). Although the evidence from these two studies was rated low quality due to a number of methodological weaknesses (see below), these results do suggest that 4CMenB vaccination of infants is associated with higher reactogenicity as shown in the more frequent occurrence of local pain and fever than vaccination with rou-

Table 7 GRADE evidence profile: Reactogenicity and safety of the 4CMenB vaccine—infants and toddlers

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reactogenicity Infants & Toddler	Control	Relative (95 % CI)	Absolute		
Fever > 38 °C (follow-up 7 days)												
2	Randomized trials[a,b]	Serious[c]	No serious inconsistency	Serious[d]	No serious imprecision	None	2301/3102 (74.2 %)	391/970 (40.3 %)	RR 1.83 (1.63–2.04)	335 more per 1000 (from 254 more to 419 more)	LOW	Critical
Severe pain (follow-up 7 days; assessed with: parental observation)												
2	Randomized trials[b]	Serious[c]	Serious[e]	Serious[d]	No serious imprecision	None	806/3101 (26 %)	59/969 (6.1 %)	RR 3.77 (2.88–4.94) to 5.15 (2.53–10.51)	214 more per 1000 (from 145 more to 305 more) 107 more per 1000 (from 39 more to 245 more)	VERY LOW	Important
Vomiting (follow-up 7 days)												
2	Randomized trials[b]	Serious[c]	Serious[f]	Serious[d]	No serious imprecision	None	771/3102 (24.9 %)	152/969 (15.7 %)	RR 1.13 (0.83–1.54) to 1.69 (1.40–2.04)	20 more per 1000 (from 26 more to 84 more) 109 more per 1000 (from 63 more to 164 more)	VERY LOW	Important

[a] Gossger: Fever ≥ 38 °C (axillary); Vesikari: Fever > 38.5 °C (rectal).
[b] Risk estimate based on outcomes per patient after the 1st vaccine dose in one study (Gossger) and in the other study (Vesikari) on the outcomes observed after any dose per patient.
[c] Non-blinded, assessment of the outcome by parents with risk for subjectivity.
[d] No placebo comparison available: 4CMenB + Infanrix hexa® vs. Infanrix hexa®.
[e] Major inconsistency of point estimator ($I^2 = 84\,\%$).
[f] Major inconsistency of point estimator ($I^2 = 79\,\%$).

tine vaccines. The reactogenicity of concomitant vaccination with 4CMenB + routine vaccinations was higher still, reflected particularly in a high rate of febrile reactions that occurred in over 70 % of vaccinated infants. In both studies, temperature peaked after 6 h and had normalized 2 days after vaccination in the majority of cases [35, 37].

The evidence quality of all considered outcomes was downgraded by one level in the included infant studies due to indirectness (simultaneous administration of other vaccinations as well as lack of placebo comparison). In addition, the reactogenicity outcomes were measured/observed by the parents. Together with their knowledge of what vaccines their child received (with the exception of a subgroup of parents in Vesikari et al.; in this case, however, the vaccinating staff was not blinded), this increased the risk of bias and therefore led to downgrading of the evidence quality for all outcomes by an additional level. Finally, the studies showed major heterogeneity for the outcomes "severe local pain" and "vomiting" ($I^2 = 84\,\%$ and 79 % respectively). Thus the data could not be pooled and the quality of evidence was further downgraded for these outcomes. The overall evidence underlying the review for infants and toddlers was therefore rated as "low" (see **Table 7**).

The 3 additional outcomes seizures, Kawasaki syndrome and hospitalization, all rated as critical, were not included in a GRADE profile for reasons outlined above (and see **Table 5**). Data on medical consultations (**Table 5**) for fever were available in Vesikari et al. and revealed a lower treatment rate in the non-blinded than in the observer-blinded sub-study. The medical consultation rate for fever after 4CMenB plus routine vaccinations was higher (5.3 %) than after routine vaccinations plus MenC vaccination (2.8 %, $p = 0.07$ (Fischer exact) only in the observer-blinded sub-study. Although febrile convulsions or seizures with fever were reported more frequently after 4CMenB (+/– routine vaccines) than after routine vaccines (see **Table 5**), the small number of observed febrile convulsions after 4CMenB vaccination does not suggest a highly elevated risk of seizures due to the 4CMenB vaccination. How-

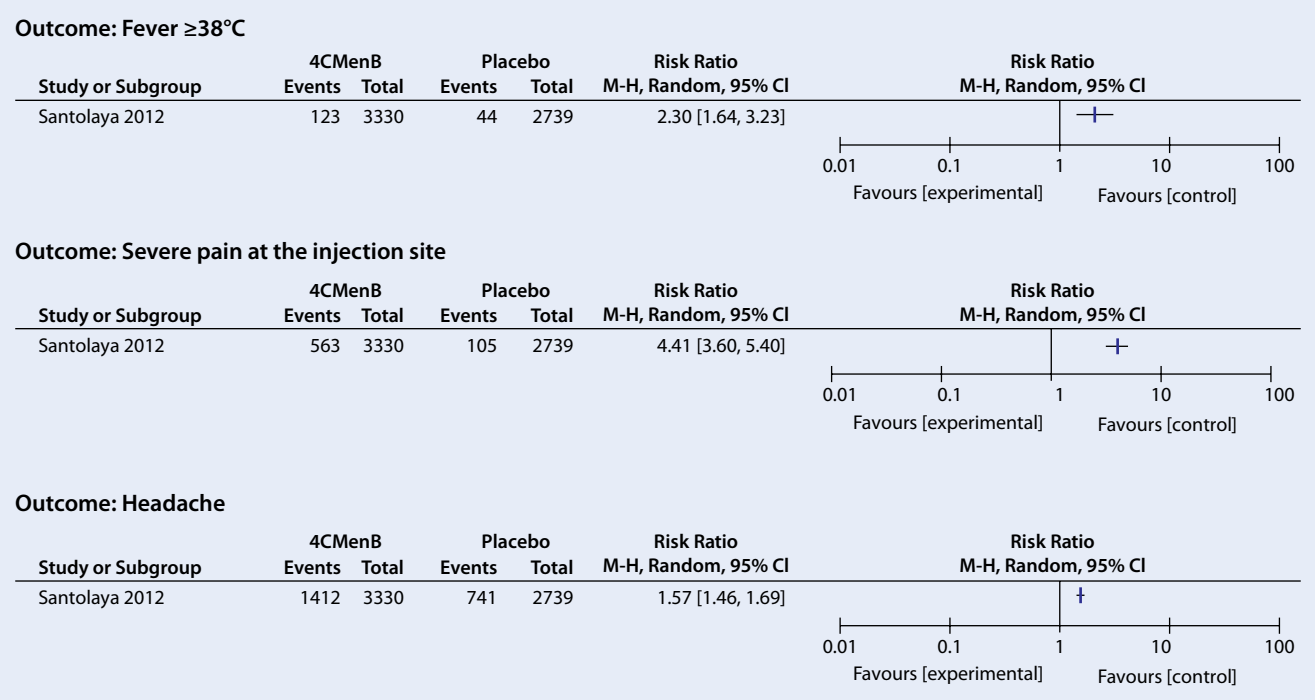

Fig. 6 ▲ *Forest plots* showing relative risks (RR) for reactogenicity and safety outcomes in adolescents receiving 4CMenB versus placebo

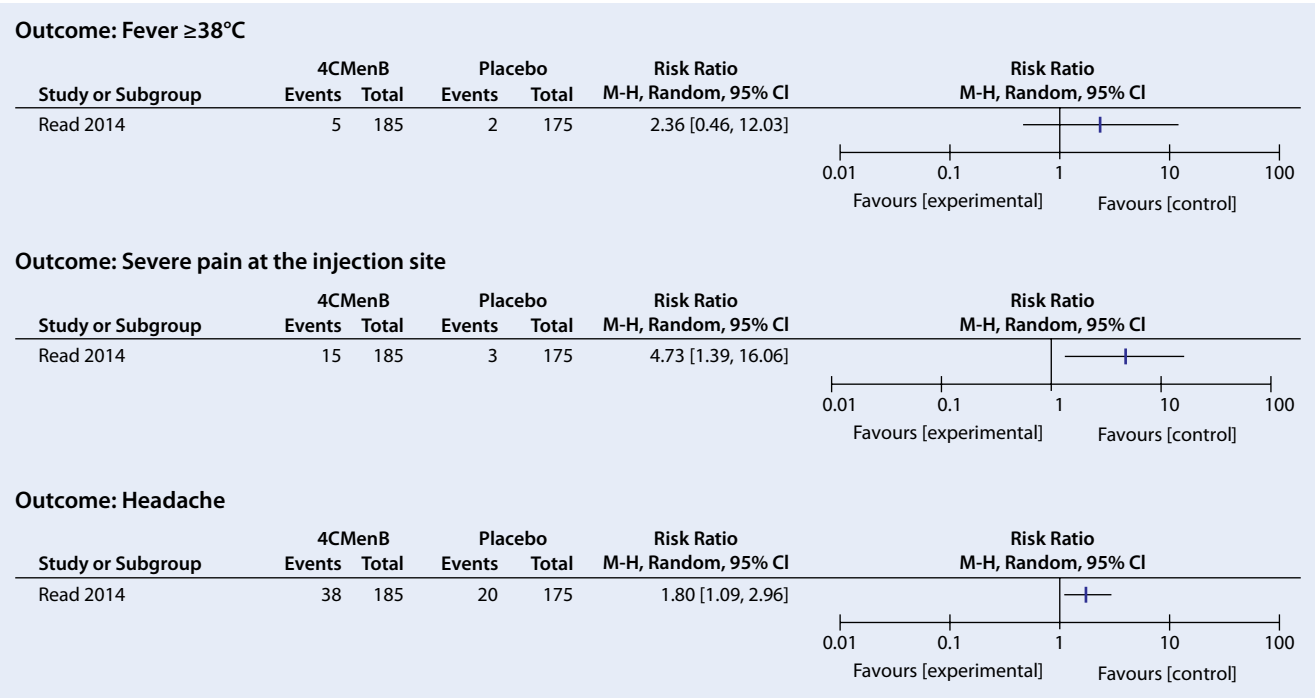

Fig. 7 ▲ *Forest plots* showing relative risks (RR) for reactogenicity and safety outcomes in adults receiving 4CMenB versus placebo

ever, the frequent receipt of paracetamol could have influenced the risk for seizures. Furthermore, to ensure sufficient power for detection of increased risk for very rare AE, a much higher case number would have been necessary. Consequently, as detailed in the *Risk Management Plan* (RMP), EMA requires more precise investigation of the risk for anaphylaxis/anaphylactic shock, Kawasaki syndrome, seizures and febrile seizures in a *post-licensure observational safety surveillance study* (V72_36OB [7].

Table 8 GRADE evidence profile: Reactogenicity and safety of the 4CMenB vaccine—adolescents

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reactogenicity Adolescents	Control	Relative (95 % CI)	Absolute		
Fever > 38 °C (follow-up 7 days)												
1	Randomized trials	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	123/3330 (3.7 %)	44/2739 (1.6 %)	RR 2.3 (1.64–3.23)	21 more per 1000 (from 10 more to 36 more)	⊕⊕OO LOW	Important
Severe pain (follow-up 7 days)												
1	Randomized trials	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	563/3330 (16.9 %)	105/2739 (3.8 %)	RR 4.41 (3.6– 5.4)	131 more per 1000 (from 100 more to 169 more)	⊕⊕OO LOW	Important
Headache (follow-up 7 days)												
1	Randomized trials	Serious[a]	No serious inconsistency	Serious[b]	No serious imprecision	None	1412/3330 (42.4 %)	741/2739 (27.1 %)	RR 1.57 (1.46–1.69)	154 more per 1000 (from 124 more to 187 more)	⊕⊕OO LOW	Important

[a]Only (partially) observer-blinded: In a sub-study, participants were blinded, but not the persons who administered the vaccine. Knowledge of the study arm allocation might have influenced the assessment of the *outcomes*. As there were no differences with regard to the safety outcomes between the non-blinded and blinded sub-studies, data of both sub-studies were analysed together.
[b]Details on the *Outcome* are only available in relation to all doses and not for the individual study subjects.

Table 9 GRADE evidence profile: Reactogenicity and safety of the 4CMenB vaccine—adults.

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Reactogenicity Adults	Control	Relative (95 % CI)	Absolute		
Fever > 38 °C (follow-up 7 days)												
1	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[b]	None	5/185 (2.7 %)	2/175 (1.1 %)	RR 2.36 (0.46–12.03)	16 more per 1000 (from 6 fewer to 126 more)	⊕⊕OO LOW	Important
Severe pain (follow-up 7 days)												
1	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	Serious[c]	None	15/185 (8.1 %)	3/175 (1.7 %)	RR 4.73 (1.39–16.06)	64 more per 1000 (from 7 more to 258 more)	⊕⊕OO LOW	Important
Headache (follow-up 7 days)												
1	Randomized trials	Serious[a]	No serious inconsistency	No serious indirectness	No serious imprecision	None	38/185 (20.5 %)	20/175 (11.4 %)	RR 1.80 (1.09–2.96)	91 more per 1000 (from 10 more to 224 more)	⊕⊕OO MODERATE	Important

[a]Blinding of group allocation unclear, as vaccinating personnel was not blinded.
[b]Wide confidence interval that includes RR = 1.
[c]Wide confidence interval with low number of events.

Table 10 Serious adverse events (SAEs) reported in the studies included in the review of the reactogenicity and safety of 4CMenB

Study (Year) Age group	Study participants Total: (4CMenB group/Control group)	SAEs possibly or probably related to vaccination	SAEs related to 4CMenB (routine vaccinations were also sometimes administered in parallel)	SAEs in the control group
Gossger (2012) [45] Infants and toddlers	Total: $n=1877$ (4CMenB, at least one dose: $n=1567$/ Routine vaccination (Infanrix hexa® + PCV7): $n=310$	$n=20$ (detailed information on 18 cases)	2 seizures (of these 1 febrile seizure); 1 HHE; 1 Kawasaki syndrome; 6 hospitalized children with fever within 2 days after vaccination; 1 aseptic meningitis; 1 retinal dystrophy (probably congenital); 1 synovitis of the right hip; 1 transient hearing loss; 1 transient apnea	2 seizures; 1 HHE
Vesikari [45] **(2013)** Infants and toddlers	Total: $n=3628$ (4CMenB at least 1 dose: $n=2480$/Routine vaccination (Infanrix® + PCV7 or MenC: $n=1148$)	$n=19$ (detailed information on 11 cases)	2 febrile seizures, 2 seizures with simultaneous fever; 2 confirmed Kawasaki syndromes (3 and 7 weeks after 4CMenB vaccination; 1 case of blindness in association with microcephaly; 1 case of pyrexia	1 febrile seizure (9 days after 4CMenB + MMRV, possibly related to MMRV vaccination);
Prymula [117] **(2014)** Infants and toddlers	Total: $n=538$ (4CMenB at least 1 dose: $n=361$/MenC: $n=177$)	none		
Santolaya (2012) [48] Adolescents	Total: $n=1759$ (4CMenB at least 1 dose: $n=1631$/Placebo: $n=128$)	$n=2$	2 x juvenile arthritis	
Read (2014) [44] Adults	Total: $n=1959$ (4CMenB at least 1 dose: $n=974$/Placebo; $n=985$)	$n=3$	1 dyspnea, 1 hand tremor, 1 thyroiditis	

HHE hypotonic hyporesponsive episodes.

14.4 Evaluation of the reactogenicity and safety of the 4CMenB vaccine in adolescents and adults

The 2 studies with results on reactogenicity and safety in adolescents [44] and adults [128] were considered separately because they were conducted on different continents, there was no overlap in the ages of the enrolled study subjects, and the reported frequencies of reactogenicity outcomes differed markedly. In the adolescent study, safety outcomes were presented as the total number of events in relation to the total number of vaccine doses administered and not, as in the other studies, in relation to the number of vaccinated study subjects. Thus vaccine doses administered to the same study participant were regarded as independent events, effectively tripling case numbers and leading to unduly narrow confidence intervals.

Fever, severe local pain and headache occurred significantly more frequently compared to placebo vaccination after 4CMenB vaccination in adolescents, while in adults this applied only to the latter two outcomes (see **Fig. 6 and 7**; **Tables 8 and 9**). As in the infant studies, the use of antipyretics was relevant to the interpretation of febrile reactions in the studies: In the adult study [128], 4 % of vaccine recipients took antipyretics prophylactically for the 1st dose of 4CMenB and 9 % for the 2nd dose and a further 19 and 21 %, respectively, took antipyretics therapeutically. For the placebo dose, 3 % took antipyretics prophylactically and 6 % therapeutically. In the adolescent study [44] antipyretic use was reported by 4 and 2 % of the adolescents vaccinated with 4CMenB or placebo, respectively. This difference possibly explains the higher rate of fever after the 4CMenB vaccination in adolescents (3.7 %) vs. adults (1.9 %). In any case, at < 4 %, the rates of fever in adolescents and adults were very much lower than in infants. Severe local pain also occurred somewhat less often than in infants, following 16.9 % (adolescents) of 4CMenB doses in adolescents and in 8.3 % of adults. Again, the lower incidence of severe pain in the adult study might be due to their more frequent use of antipyretics. The risk differences between the 4CMenB and the placebo groups were markedly increased in both adolescents and adults for severe pain (131 and 64 more events/1000 vaccinations) and headache (with 154 and 91 more events/1000 vaccinations, see **Tables 8 & 9**).

In addition to fever, local pain and headache seizures, GBS and ADEM, and JA were also classified as critical outcomes for older children and adults when PICO were defined. Of the latter four, only seizures and JA were mentioned in the two available studies [44, 128]; thus presumably none of the other 2 safety outcomes was observed. In the 1622 adolescents vaccinated with ≥ 1 dose of 4CMenB, 1 convulsion was observed in a participant after the first 4CMenB dose; this participant reported a family history of epilepsy. In addition, also in the adolescent study, 2 cases of JA occurred 170–198 days following a 3rd dose of 4CMenB; in the 1st case, joint pain and tendinitis had occurred once before in the past. No cases occurred after placebo vaccination. A causal association with the vaccine was therefore assessed by the authors as possible for the 2nd case and probable for the 1st. A much larger study would be necessary to demonstrate a statistically significant association. It should be noted in this context, however, that arthralgia occurred after approximately 24 % of the administered 4CMenB doses, but only after approximately 13 % of the placebo doses (percent values tak-

en from **Fig. 5** taken in [44]). Additional serious adverse events (SAE) observed in the studies are listed in **Table 10**.

The quality of evidence of the adolescent study was downgraded by one level due to the increased risk of bias present due to non-blinding of the personnel administering the vaccines. Because the reactogenicity outcomes were presented in relation to the total number of doses and not to study subjects, the quality of evidence was further downgraded to "low", due to indirectness.

Since in the adult study only 600 study participants were included for observation of reactogenicity and safety, confidence intervals for the RR pertaining to the outcomes fever and headache were very wide (and spanned 1 for fever) due to low event counts. Therefore, the quality of evidence was downgraded due to imprecision. Due to an additional elevated risk of bias attributed to non-blinding of the study personnel administering the vaccines, quality of evidence was further downgraded to "low" for all outcomes.

In the Risk Management Plan, EMA stipulated that—in addition to the aforementioned safety-relevant outcomes of anaphylaxis/anaphylactic shock, Kawasaki syndrome, seizures and febrile seizures for infants and toddlers—the risk of GBS and ADEM after 4CMenB vaccination should be evaluated more precisely by means of a *post-licensure observational safety surveillance study* (V72_36OB) [7].

15 Postmarketing Surveillance

No publications reporting on postmarketing surveillance of Bexsero® following licensure were identified in the literature search. However, through communication with colleagues, a report on active surveillance of possible AE following a vaccination campaign in Saguenay-Lac-St-Jean, Québec (Canada) with longstanding increased incidence of MenB IMD caused by a ST-269 meningococcal B clone was identified. AE were ascertained in the 7 days following MenB vaccination in 0–20-year-old persons. [53]. Of 43,740 persons who had received a dose of 4CMenB in May and June 2014, 28 % completed a questionnaire on the occurrence of AE. The primary objective of the survey was to determine in real time the frequency of absences from work/school/day care and medical consultations attributable to the vaccine in the 7 days after vaccination. In addition, the questionnaire was designed to ascertain the frequency of vaccine-related fever, the effect of prophylactic antipyretics on the risk of fever, febrile convulsions and severe arthralgias. Finally, the influence of AE on the responders' intention to obtain the second dose of Bexsero® was investigated. Active surveillance was supplemented by the already established passive surveillance system for the reporting of adverse drug reactions, through which physicians were legally obliged to report, all unusual clinical manifestations following vaccinations.

The interpretation of the reported AE must take into account that antipyretics (most commonly as paracetamol) were taken prophylactically by 70 % of all study subjects. Use of antipyretics was highest at 93 % in vaccine recipients under 2 years of age, and declined with age to 43 % in > 17-year-olds.

In participants of the active surveillance study, fever within 7 days after 4CMenB vaccination occurred in 10.9 % of vaccine recipients; most often in < 2-year-olds at 14 %, followed by 12 % in 2–4-year-olds and 6.8 % in older children and adolescents. In < 2-year-olds, fever occurred more often when 4CMenB was administered concomitantly with other vaccines (19 vs. 13 %, $p = 0.09$). The incidence of fever following the 4CMenB vaccination in children < 2 years of age was lower in those who had taken antipyretics than in those who had had not: 14 % versus 31 % in 2–11-month-old children and 13 versus 23 % in 2–11-month-olds, $p < 0.001$. Two or more doses of antipyretic led to a greater reduction than only one dose, but only in children under 2 years of age. In children aged 5 and over, antipyretics were no longer associated with a reduction in the occurrence of fever. In children < 2 years of age with co-administration of other vaccines, fever was reported in 7/11 (64 %) children who had not received any antipyretics, in 22/64 (34 %) who had received one dose of antipyretics and in 38/268 (14 %) who had received ≥ 2 doses ($p < 0.001$). The highest mean temperature was 38.9 °C and did not vary significantly with age. Less than 1 % reported fever ≥ 40.5 °C (rectal). The median duration of fever was 2 days. One febrile convulsion was recorded in a 1-year-old child through active surveillance and an additional febrile convulsion in a 6-month-old child through passive surveillance in a total of 3886 with children < 2 years of age vaccinated with 4CMenB. This was fewer cases than expected based on the incidence of febrile convulsions in the licensure studies after 4CMenB. The almost universal prophylaxis with antipyretics may have played a role here.

Arthralgia was reported by 113 vaccine recipients; however, following contact with a nurse, only 5 of these were rated as severe. None of these were associated with warmth, reddening or swelling, signs suggestive of arthritis. However, the observation period was too short to exclude the occurrence of later-onset arthritis with certainty.

Absenteeism of the vaccine recipient or their carers due to fever, malaise or local side effects that occurred within 7 days after vaccination were reported by 6.0 % of responders and 1.2 % reported having consulted a physician because of an AE in this time interval. In addition, 4 hospitalizations > 24 h duration were reported after the 1st 4CMenB dose, but none apparently causally associated with the vaccine. Of all responders, 99 % reported that they intended to receive the 2nd 4CMenB vaccination dose, but this proportion was lower among those who had reported medical consultations or absences due to the 4CMenB vaccination at 92 %.

No cases of GBS, ADEM or Kawasaki-syndrome (KS) were ascertained through the active or the the passive surveillance system. As the authors discuss, however, with only 12,500 vaccinated children ≤ 5 years of age, an expected KS incidence in Saguenay-lac-St. Jean of < 8/100,000 children ≤ 5 years of age and the short observation time in both surveillance systems, the power of the study was insufficient to exclude a slightly increased risk of KS through the vaccine [53].

Further results on the monitoring following additional 4CMenB vaccine doses in Saguenay-Lac-St-Jean were presented in the final report of the active surveillance study [139]. The observations

after a 2nd dose of Bexsero® differed as follows from those after the 1st dose: Fever occurred more frequently (11 vs. 9 %, $p < 0.001$). While after the 1st dose, vaccine recipients taking antipyretics reported fever 49 % less frequently than vaccine recipients who had not taken antipyretics, after the 2nd dose this the case for only 35 % of those taking antipyretics. Absences or medical consultations due to AE occurring in the 7 days after vaccination were reported more frequently after the 2nd dose (9.0 %) than after the 1st dose (6.0 %). After the 2nd dose, there were 4 reported hospitalizations, for conditions possibly related to the vaccine: One case of anaphylaxis following concomitant vaccination with hepatitis A vaccine and Bexsero® and one febrile convulsion following vaccination with Bexsero®.

Since availability of Bexsero® in Germany, a total of 770 AE were reported to PEI on 218 vaccine recipients via the passive reporting system, including 8 seizures (of these 4 febrile convulsions) and one anaphylactic shock reaction. No significant safety signals for Bexsero® were detected in the routine analyses performed at PEI on AE reports after vaccinations (Keller, May 2015, personal communication).

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