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Meningococcal Quadrivalent (Serogroups A, C, W135 and Y) Tetanus Toxoid Conjugate Vaccine (Nimenrix™)

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Data Selection

Sources: Medical literature (including published and unpublished data) on 'Nimenrix' was identified by searching databases (including MEDLINE and EMBASE) for articles published since 1996, bibliographies from published literature, clinical trial registries/databases and websites (including those of regional regulatory agencies and the manufacturer). Additional information (including contributory unpublished data) was also requested from the company developing the drug.

Search strategy: MEDLINE and EMBASE search terms were 'Nimenrix' and ('meningococcal-vaccine-groups-A-C-Y-W-135-conjugate' or 'quadrivalent-meningococcal-conjugate-vaccine' or 'tetravalent-meningococcal-conjugate-vaccine'). Searches were last updated 9 November 2012.

Selection: Studies in healthy individuals who received Nimenrix™ for active immunization against invasive disease caused by *Neisseria meningitidis*. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred.

Index terms: Nimenrix, MenACWY-TT, meningococcal conjugate vaccine, immunogenicity, tolerability.

Contents

Abstract

Nimenrix™ (MenACWY-TT) is a quadrivalent meningococcal conjugate vaccine, comprising the polysaccharide serogroups A, C, W135 and Y, and tetanus toxoid (TT) as carrier protein. It is the first quadrivalent vaccine (administered as a single dose) to be approved in Europe for active immunization of individuals aged ≥12 months against invasive meningococcal disease caused by *Neisseria meningitidis* serogroups A, C, W135 and Y.

Administration of a single dose of Nimenrix™ elicited a strong immune response against all four vaccine serogroups in healthy toddlers aged 12–23 months, children and adolescents aged 2–17 years and adults aged 18–55 years in randomized, multicentre, phase III trials. In toddlers, Nimenrix™ was noninferior to Meningitec® in terms of seroresponse rates against meningococcal serogroup C 42 days post-vaccination. In children, adolescents and adults, Nimenrix™ was noninferior to Mencevax™ in terms of vaccination response rates against all four serogroups 1 month post-vaccination. Furthermore, several phase II studies and a phase III trial showed that the immune response elicited by Nimenrix™ in all age groups persisted for 7–42 months after the primary vaccination (when evaluated by rabbit serum bactericidal activity), with the vaccine also inducing immune memory in toddlers. In addition, several randomized, multicentre, phase III, noninferiority trials showed that when coadministered with other childhood vaccines or a seasonal flu vaccine, the immunogenicity of Nimenrix™ or that of the coadministered vaccine was generally not altered.

Nimenrix® was generally well tolerated in all age groups whether administered as a single vaccine or coadministered with other routine vaccines. The incidence of grade 3 local or systemic solicited adverse events during the first 4 days following vaccination and of serious adverse events over an extended follow-up period of up to 6 months was low (<4.5%).

Although protective effectiveness and longer-term persistence studies are required, current evidence suggests that Nimenrix™, administered as a single dose, provides a valuable vaccination option for the prevention of meningococcal disease across a broad age group, including children as young as 12 months.

1. Introduction

The primary prevention strategy for meningococcal disease is vaccination.[1,2] As a result of continuous vaccination programmes against *Haemophilus influenzae* type b (Hib), invasive Hib disease has been nearly eliminated in countries with routine immunization programmes; consequently, most (60–65%) cases of bacterial meningitis in the industrialized world are caused by the Gram-negative bacterium *Neisseria meningitidis*.[3,4] Invasive meningococcal infections of *N. meningitidis* are generally caused by strains expressing one of six diverse capsular polysaccharides (A, B, C, W135, Y, and more recently, X).[5-8] Serogroups B and C are mostly prevalent in the Americas and Europe, while serogroup Y is mostly prevalent in the US and Canada and more

recently in Europe.[7,9,10] In Asia and the meningitis belt of Africa, serogroup A is the most prevalent strain,[6,11] although outbreaks of serogroup X have also been reported in Africa.[12] Serogroup W135 has been responsible for outbreaks of meningococcal disease worldwide[9] and more recently in the Middle East.[13]

Purified polysaccharide vaccines against meningococcal serogroups A, C, W135 and Y have been available for many years.[1,14] However, these vaccines are suboptimally immunogenic, do not provide long-lasting immunity or induction of immunological memory, may induce hyporesponsiveness on repeated exposure and have a negligible impact on nasopharyngeal carriage of the bacterium.[1,7,14] In addition, with the exception of serogroup A, polysaccharide vaccines are poorly immunogenic in children aged <2 years.[15,16]

To overcome these shortcomings, conjugate vaccines consisting of capsular polysaccharide antigens covalently linked to a carrier protein have been developed.[17,18] Conjugate vaccines have proven to be effective in protecting against other infectious pathogens, such as Hib and *Streptococcus pneumoniae*, where they have provided immunological memory and decreased nasopharyngeal carriage, which may confer herd immunity.[17] The common carrier proteins used in conjugate meningococcal vaccines include tetanus toxoid (TT), diphtheria toxoid (DT) and a mutant of DT, known as cross-reactive material 197 (CRM_{197}).[18]

Until about mid-2000, the only quadrivalent (otherwise known as tetravalent) meningococcal vaccines available were MPSV4 (Menomune®) and Men-PS (Mencevax™), which contain the non-conjugated polysaccharide serogroups A, C, W135 and Y.[19] Vaccination options against meningococcal disease were expanded with the availability of two quadrivalent (serogroups A, C, W135 and Y) conjugate vaccines that use DT (Menactra®; approved for use in countries including the US) or CRM_{197} (Menveo®; approved for use in countries including the EU and US) as carrier proteins.[20] In the US, Menactra® is approved for use as a two-dose vaccine in individuals aged 9–23 months and as a single-dose vaccine in individuals aged 2–55 years[21] (the vaccine is not approved for use in the EU). Menveo® is approved for use as a single-dose vaccine in individuals aged 2–55 years in the US, while a second dose of the vaccine may be administered in children aged 2–5 years who are at continued high risk of meningococcal disease.[22] In the EU, Menveo® is approved for use as a single-dose vaccine in individuals aged ≥11 years[23] and has received a positive opinion from regulatory authorities for use in children aged ≥2 years.[24] Neither Menveo® nor Menactra® is approved for use as a single-dose vaccine in children aged <2 years.

Nimenrix™ (MenACWY-TT) is a quadrivalent meningococcal conjugate vaccine, comprising polysaccharide serogroups A, C, W135 and Y, and TT as carrier protein.[25] It is the first quadrivalent vaccine (administered as a single dose) to be approved in Europe for immunization of individuals aged ≥12 months against invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W135 and Y.[26] This article reviews the use of Nimenrix™ in healthy toddlers, children, adolescents and adults.

2. Immunogenicity

The immunogenicity of different formulations of Nimenrix™ was initially established in phase II trials in healthy toddlers (aged 12–14 months), children (aged 3–5 years)[27] and adolescents and young adults (aged 15–25 years).[28] In other phase II trials, similar immunogenicity outcomes were demonstrated between Nimenrix™ and Menactra® (in 10–25 year olds)[29] and between Nimenrix™ and Mencevax™ (in 2–10[30] and 11–17 year olds[31]) 1 month post-vaccination. In the study comparing Nimenrix™ with Menactra® (not approved for use in Europe), 81.9–96.1% of Nimenrix™ recipients and 70.7–98.8% of Menactra® recipients had serum bactericidal activity against the four meningococcal serogroups (A, C, W135 and Y) at antibody titres of ≥1 : 8 (tests using human complement [hSBA]).[29] This section focuses on results from phase III studies comparing the immunogenicity of Nimenrix™ with that of meningococcal vaccines approved for use in Europe, including Meningitec® and Mencevax™.

Several large, open-label,[32-38] active comparator-controlled, multicentre, phase III trials assessing

the immunogenicity of Nimenrix™ versus that of Meningitec® (a meningococcal serogroup C [MenC] conjugate vaccine) in toddlers, and Mencevax™ (a quadrivalent non-conjugated polysaccharide vaccine) in children, adolescents and adults are reviewed (section 2.1). Also discussed are studies (including phase II[30,39-44] and extension studies[45-47]) that assessed the use of Nimenrix™ for revaccination following a dose of polysaccharide vaccine (section 2.1.4),[39] and the induction of immune memory and the persistence of immune response elicited by Nimenrix™ (section 2.2.).[30,40-47] In addition, phase III studies assessing the immunogenicity of Nimenrix™ when coadministered with other vaccines (section 2.3) are discussed.[33-35,37,48] Of note, two studies[33,35] compared the immunogenicity of Nimenrix™ with that of a comparator vaccine (Meningitec®), as well as assessing its immunogenicity when coadministered with Priorix-tetra™[33] or Infanrix™ hexa.[35]

Details of the vaccines used in the trials are presented in table I, and trial design and vaccination regimens are summarized in table II.

The phase III studies included healthy meningococcal conjugate vaccine-naive toddlers (aged 12–23 months[33,35,48]), children (aged 2–10 years[32]) or adolescents (aged 11–17 years[34,38]) who had completed childhood routine vaccination[32-35,38,48] at 12 months[33] or ≥180 days[35] before administration of study vaccine(s), or adults (aged 18–55 years[36,37]). Key exclusion criteria (in individuals aged 2–55 years unless otherwise specified) included the following:

- a history of meningococcal disease (in all age groups)[32-36,38,48] or pneumococcal invasive disease (in individuals aged 12–23 months);[48]
- vaccination with a conjugate meningococcal vaccine at any time,[32,34,36,38,48] a meningococcal polysaccharide vaccine within the previous 5 years[32,34,36,38] or any meningococcal vaccine (in individuals aged 12–23 months);[33,35]
- previous vaccination with a TT-containing vaccine[32,34,36,37,48] or with any vaccine[38,48] within 1 month;
- prior exposure to or administration of vaccine against measles, mumps, rubella and varicella (MMRV) virus within 1 month of the study assessing coadministration of Priorix-tetra™ (in individuals aged 12–23 months);[33]
- prior administration of booster vaccination against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis or Hib in the study assessing

Table I. Summary of vaccines used in clinical trials

Vaccine[a] (route)	Definition	Tradename
Meningococcal vaccines		
MenACWY-TT (IM)	Meningococcal polysaccharide serogroups A, C, W135 and Y conjugated to tetanus toxoid protein	Nimenrix™
MenC-CRM_{197} (IM)	Meningococcal polysaccharide serogroup C conjugated to CRM_{197}	Meningitec®
Men-PS (SC)	Meningococcal polysaccharide serogroups A, C, W135 and Y	Mencevax™
MenACWY-D (IM)	Meningococcal polysaccharide serogroups A, C, W135 and Y conjugated to diphtheria toxoid protein	Menactra®
Other routine vaccines		
DTPa-HBV-IPV/Hib (IM)	Diphtheria and tetanus toxoids, acellular pertussis antigens, hepatitis B virus surface antigen, inactivated polioviruses and *Haemophilus influenzae* type b	Infanrix™ hexa
HepA/B (IM)	Inactivated hepatitis A and recombinant DNA-derived hepatitis B protein	Twinrix®
MMRV (SC)	Live attenuated measles, mumps, rubella and varicella vaccine	Priorix-Tetra™
Seasonal influenza vaccine (IM)	Influenza strains A/California/7/2009 NYMC X-181 (H1N1), A/Victoria/210/2009 NYMC X-187 (H3N2), B/Brisbane/60/2008	Fluarix™
PHiD-CV (IM)	10-valent pneumococcal NTHi protein D conjugate vaccine	Synflorix™

a Where reported, Nimenrix™ was administered intramuscularly into the deltoid muscle[32,34,38] or left thigh,[33,35] Meningitec® intramuscularly into the left thigh,[33,35] and Mencevax™ subcutaneously into the upper arm.[32,38]

CRM_{197} = cross-reactive material 197; **IM** = intramuscular; **NTHi** = non-typeable *Haemophilus influenzae*; **SC** = subcutaneous.

Table II. Key design details and vaccine regimens of phase III trials investigating the immunogenicity of Nimenrix™

Trial (subject age)	Vaccine dosage regimens (no. of individuals in immunogenicity population)	Primary endpoints
Memish et al.[32] (2–10 y)	Gp 1: Nimenrix™ at d 0 (793) Gp 2: Mencevax™ at d 0 (269)	NI of Nimenrix™ to Mencevax™ in terms of rSBA VR rates against Men A, C, W135 and Y Incidence of all (solicited and unsolicited) grade 3 systemic AEs
Bermal et al.[38] (11–17 y)	Gp 1: Nimenrix™ at d 0 (760) Gp 2: Mencevax™ at d 0 (252)	NI of Nimenrix™ to Mencevax™ in terms of rSBA VR rates against Men A, C, W135 and Y NI of Nimenrix™ to Mencevax™ in terms of the incidence of all grade 3 systemic AEs in pooled data from two studies[36,38]
Dbaibo et al.[36] (18–55 y)	Gp 1: Nimenrix™ [lot A, B or C] at d 0 (885) Gp 2: Mencevax™ at d 0 (294)	NI of Nimenrix™ to Mencevax™ in terms of rSBA VR rates against Men A, C, W135 and Y Lot-to-lot consistency of Nimenrix™ in terms of rSBA antibody GMTs against Men A, C, W135 and Y
Trials assessing coadministration with other vaccines		
Vesikari et al.[33] (12–23 mo)	Gp 1: Nimenrix™ + Priorix-tetra™ at d 0 and Priorix-tetra™ at d 84 (361) Gp 2: Nimenrix™ at d 0 and Priorix-tetra™ at d 42 and d 84 (366) Gp 3: Priorix-tetra™ at d 0 and d 84 and Meningitec® at d 42 (121) Gp 4: Meningitec® at d 0 and Priorix-tetra™ at d 42 and d 84 (124)	NI of Nimenrix™ to Meningitec® in terms of the SR rate for Men C Post-vaccination SR rates of Nimenrix™ against Men A, C, W135 and Y NI of Nimenrix™ plus Priorix-tetra™ to Nimenrix™ or Priorix-tetra™ alone, in terms of SR rates against Men A, C, W135 and Y, and SC rates against MMRV antigens
Knuf et al.[35] (12–23 mo)	Gp 1: Nimenrix™ + Infanrix™ hexa at d 0 (194) Gp 2: Nimenrix™ at d 0 and Infanrix™ hexa at d 30 (188) Gp 3: Infanrix™ hexa at d 0 and Nimenrix™ at d 30 (188) Gp 4: Meningitec® at d 0 (115)	NI of Nimenrix™ plus Infanrix™ hexa to separate administration of the two vaccines, in terms of SR rates against Men A, C, W135 and Y, SP rates against hepatitis B and Hib components and GMCs of antibodies against pertussis
Ostergaard et al.[34] (11–17 y)	Gp 1: Nimenrix™ + Twinrix® at d 0 and Twinrix® at 1 and 6 mo (360) Gp 2: Nimenrix™ at d 0 (115) Gp 3: Twinrix® at d 0 and 1 and 6 mo (119)	NI of Nimenrix™ plus Twinrix® to either vaccine alone, in terms of GMTs against Men A, C, W135 and Y, SC rates against hepatitis A and SP rates against hepatitis B
Reyes et al.[37] (18–55 y)	Gp 1: Nimenrix™ at d 0 (308) Gp 2: Nimenrix™ + Fluarix™ at d 0 (105) Gp 3: Mencevax™ at d 0 (104)	NI of Nimenrix™ plus Fluarix™ to Nimenrix™ alone, in terms of rSBA antibody GMTs against Men A, C, W135 and Y Acceptable immunogenicity of Fluarix™ plus Nimenrix™ in terms of HI antibody titres, according to standard European Committee for Human Medicinal Products criteria[49]
Ruiz-Palacios et al.[48] (12–23 mo)	Gp 1: Nimenrix™ + Synflorix™ at d 0 (175) Gp 2: Nimenrix™ at d 0 and Synflorix™ at d 30 (81) Gp 3: Synflorix™ at d 0 and Nimenrix™ at d 30 (81)	NI of Nimenrix™ plus Synflorix™ to Nimenrix™ alone, in terms of SC rates against Men A, C, W135 and Y NI of Nimenrix™ plus Synflorix™ to Synflorix™ alone, in terms of anti-pneumococcal antibody GMC ratios

AEs = adverse events; **GMCs** = geometric mean concentrations; **GMTs** = geometric mean titres; **gp** = group; **HI** = haemagglutination inhibition; **Hib** = *Haemophilus influenzae* type b; **Men** = meningococcal serogroup(s); **MMRV** = measles, mumps, rubella and varicella virus; **NI** = noninferiority; **rSBA** = rabbit serum bactericidal activity; **SC** = seroconversion; **SP** = seroprotection; **SR** = seroresponse; **VR** = vaccine response.

coadministration with Infanrix™ hexa (in individuals aged 12–23 months);[35]
- a history of hepatitis A or B or prior administration of hepatitis A or B vaccine in the study assessing coadministration with Twinrix® (in individuals aged 11–17 years);[34]
- previous administration of a fourth dose of a pneumococcal vaccine in the study assessing coadministration with Synflorix™ (in individuals aged 12–23 months).[48]

Inclusion and exclusion criteria in the phase II[30,39-44] and/or extension studies[45-47] were generally similar to those in the phase III studies.

Demonstration of noninferiority between Nimenrix™ and other licensed meningococcal vaccines in terms of immune response was used as a measure to infer vaccine efficacy.[25] Rabbit serum bactericidal activity (rSBA)[32-38,48] or hSBA[33] (biomarkers for protective efficacy against meningococcal serogroups A, C, W135 and Y[25]) were used to assess immunogenicity. Seropositivity rates (polysaccharide-specific antibody concentrations of ≥0.3 μg/mL) against the meningococcal serogroups, as assessed by ELISA, were reported in one study.[34] Antibodies against TT,[32,34-36] pertussis toxin (PT),[35] DT,[35] filamentous haemagglutinin (FHA),[35] pertactin (PRN),[35] polyribosyl-ribitol-phosphate,[35] and hepatitis A or B[34] antigens, and MMRV viruses[33] were measured by ELISA. Antibodies against poliovirus antigens were measured by micro-neutralization assay,[35] and antibody titres against influenza virus vaccine strains A/H1N1, A/H3N2 and B were assessed by haemagglutination-inhibition (HI) assay.[37] Anti-pneumococcal antibody concentrations were determined using a 22F-ELISA and the functional antibody response by measuring opsonophagocytic activity (OPA).[48]

The lot-to-lot consistency (co-primary endpoint) of three lots of Nimenrix™ was demonstrated in a trial in healthy adults aged 18–55 years 1 month post-vaccination.[36] All pairwise comparisons of the geometric mean titre (GMT) ratios between lots for each meningococcal serogroup were between the prespecified 95% CI of 0.5 and 2.0 for noninferiority; consequently, data from Nimenrix™ recipients in this study were pooled for the evaluation of all other endpoints.[36]

2.1 Response to Vaccine Components

2.1.1 In Toddlers Aged 12–23 Months

A single dose of Nimenrix™ elicited a strong immune response against meningococcal serogroups A, C, W135 and Y, as assessed by seroresponse rates in two randomized phase III trials in toddlers aged 12–23 months.[33,35] In one trial,[33] the lower limit of the two-sided 95% CI for seroresponse rates (rSBA antibody titres of ≥1 : 8) was ≥98% for each serogroup 42 days post-vaccination, which exceeded the predefined lower limit of 90% (co-primary endpoint; figure 1). These antibody titres are considered indicative of seroprotection against MenC and were also applied to other serogroups. Furthermore, Nimenrix™ was noninferior to a single dose of Meningitec® in terms of seroresponse rate against MenC 42 days post-vaccination (co-primary endpoint) [figure 1].[33] In this study, prior to vaccination, seroresponse rates

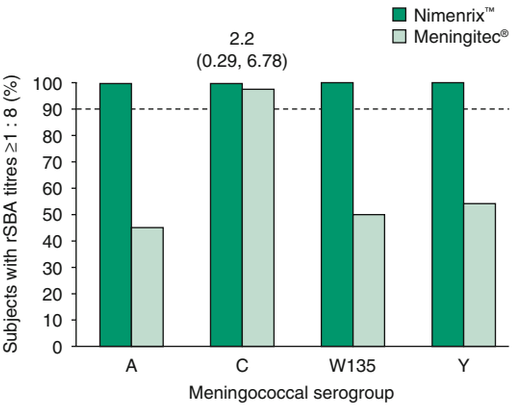

Fig. 1. Immunogenicity of Nimenrix™ in healthy toddlers aged 12–23 months. Seroresponse rates against meningococcal serogroups A, C, W135 and Y 42 days after vaccination with Nimenrix™ (per-protocol immunogenicity cohort [PP] n = 366) or Meningitec® (a meningococcal serogroup C conjugate vaccine; PP n = 124) in a randomized, open-label, multicentre, phase III, noninferiority trial conducted in the EU.[33] The lower limits of the two-sided 95% CIs of the seroresponse rates against meningococcal serogroups A, W135 and Y of Nimenrix™ were 98.4%, 99.0% and 99.0%, and above the predefined limit of 90% (dotted line; co-primary endpoint). Nimenrix™ was noninferior to Meningitec® as the lower limit of the 95% CIs of the between-group difference in seroresponse rate against meningococcal serogroup C was more than the predefined limit of −10% (values above the bar; co-primary endpoint). Seroresponse was defined as the proportion of individuals with rabbit serum bactericidal activity (rSBA) antibody titres of ≥1 : 8.

(rSBA antibody titres of ≥1 : 8) against serogroups A, C, W135 and Y were 34–45%, 22–27%, 43–49% and 55–68%, respectively.[33]

As the use of rabbit complement is known to result in higher SBA antibody titres than the use of human complement,[50] a secondary analysis of immunogenicity using sera tested by hSBA was performed to confirm the immunogenicity of Nimenrix™ (hSBA antibody titres of ≥1 : 4 have been correlated with protection[33,51]). According to this analysis, ≥77.2% of Nimenrix™ recipients had hSBA antibody titres of ≥1 : 8 (a conservative threshold of seroprotection) against each vaccine serogroup, with the response against MenC being significantly higher in Nimenrix™ than in Meningitec® recipients (exploratory analysis; no p-value was reported).[33]

In the other trial,[35] 1 month post-vaccination, ≥97.3% of Nimenrix™ recipients (per-protocol immunogenicity cohort [PP] n = 570) had achieved a seroresponse (rSBA antibody titres of ≥1 : 8) against each of the four meningococcal serogroups, and 98.2% of Meningitec® recipients (PP n = 115) had achieved a seroresponse against serogroup C.

2.1.2 In Children and Adolescents Aged 2–17 Years

Nimenrix™ also elicited a strong immune response against all four vaccine serogroups in healthy children (aged 2–10 years) and adolescents (aged 11–17 years),[32,38] as assessed by vaccine response rates and antibody GMTs in two randomized phase III trials. Vaccine response rates (see table III for definition) of 85–97% and antibody GMTs of 4983–13 865 were observed in Nimenrix™ recipients 1 month post-vaccination (table III).[32,38]

In both trials, Nimenrix™ was shown to be noninferior to Mencevax™ in terms of vaccine response rates against serogroups A, C, W135 and Y 1 month post-vaccination (co-primary endpoint; table III).[32,38] Exploratory analyses showed that vaccine response rates against serogroups A, W135 and Y in individuals aged 11–17 years[38] and against all serogroups in individuals aged 2–10 years[32] were significantly higher in Nimenrix™ than Mencevax™ recipients (no p-values were reported).

Across both trials, the proportion of individuals with rSBA titres ≥1 : 8 against serogroups A, C, W135 and Y 1 month post-vaccination ranged between 99.5% and 100% in Nimenrix™ recipients and between 97.4% and 100% in Mencevax™ recipients.[32,38] In addition, ≥99.2% of individuals in the Nimenrix™ group and ≥94.7% of those in the Mencevax™ group achieved rSBA titres ≥1 : 128 (a more conservative threshold for defining seroprotection) against each meningococcal serogroup 1 month post-vaccination.[32,38] Exploratory analyses showed that the proportion of individuals with rSBA titres ≥1 : 8 and ≥1 : 128 against serogroups C, W135 and Y were significantly higher in Nimenrix™ compared with Mencevax™ recipients in the trial in 2–10 year olds (no p-values were reported).[32]

One study reported that 59–91% of individuals had pre-existing immunity (rSBA antibody titres of ≥1 : 8) against one or more serogroups, with GMTs varying substantially between geographical regions, probably because of local epidemiology and exposure to individual serogroups, as well as exposure to cross-reacting bacteria.[38]

One month post-vaccination, GMTs increased by 27.7- to 323.6-fold in Nimenrix™ recipients and by 9.9- to 185.9-fold in Mencevax™ recipients across both trials.[32,38] Exploratory analyses showed that the antibody GMTs against all serogroups were significantly higher in the Nimenrix™ group than in the Mencevax™ group in both trials (no p-values were reported).[32,38]

Nimenrix™ also induced a strong anti-TT response in trials in children and adolescents aged 11–17 years, reflecting exposure to the TT carrier protein.[34,38] One trial showed that the proportion of individuals with anti-TT antibody concentrations ≥0.1 IU/mL (ten times higher than the level of 0.01 IU/mL, which is indicative of seroprotection) increased from 67.4% pre-vaccination to 97.8% 1 month post-vaccination and geometric mean concentrations (GMCs) increased from 0.421 to 11.017 IU/mL.[38] Similar observations were made in the other trial where anti-TT antibody GMCs increased from 1.0 to 17.3 IU/mL for recipients of Nimenrix™ 1 month post-vaccination (this trial is discussed in section 2.3).[34] However, it is unknown whether this increase in antibody titres represents an increase in functional anti-TT antibody; consequently, Nimenrix™ vaccination

Table III. Immunogenicity of Nimenrix™ vaccine in healthy children, adolescents and adults. Summary of randomized, open-label,[32,36,38] multicentre, phase III, noninferiority trials in individuals who received a single dose of intramuscular Nimenrix™ or subcutaneous Mencevax™. Results at 1 month after vaccination in the per-protocol immunogenicity cohort are reported. Trials were conducted at centres in Asia[32,36,38] or the Middle East/North Africa[32,36]

Vaccine	No. of individuals[a]	Vaccine response rate (%)[b,c]				No. of individuals[a]	GMT			
		A	C	W135	Y		A	C	W135	Y
In children aged 2–10 years[32]										
Nimenrix™	638–771	88.6	95.9	97.4	92.5	788–791	6309.7	4 983.6	11 569.8	10 886.6
Mencevax™	206–258	65.5	89.6	82.5	68.6	265–268	2309.4	1 386.8	2 150.6	2 544.7
Btwn-grp diff		23.02	6.26	14.89	23.87					
95% CI		(**16.33**, 30.15)	(**2.67**, 10.83)	(**10.50**, 20.16)	(**18.16**, 30.04)					
In adolescents aged 11–17 years[38]										
Nimenrix™	525–698	85.4	97.1	96.5	93.1	752–759	6106.8	12 645.5	8 390.1	13 865.2
Mencevax™	171–229	79.5	96.6	88.0	78.0	252	3203.0	8 271.6	2 679.3	5 245.3
Btwn-grp diff		5.83	0.45	8.50	15.03					
95% CI		(**0.11**, 12.28)	(–**1.80**, 3.75)	(**4.66**, 13.35)	(**9.90**, 20.87)					
In adults aged 18–55 years[36]										
Nimenrix™	743–862	80.1	91.5	90.2	87.0		3624.7[d]	8 865.9[d]	5 136.2[d]	7 710.7[d]
Mencevax™	252–288	69.8	92.0	85.5	78.8		2127.2[d]	7 371.2[d]	2 461.3[d]	4 314.3[d]
Btwn-grp diff		10.24	–0.49	4.72	8.19					
95% CI		(**4.11**, 16.78)	(–**3.85**, 3.57)	(**0.49**, 9.65)	(**3.24**, 13.69)					

a Evaluable individuals in the per-protocol population.

b Vaccine response was defined as a post-vaccination antibody titre of ≥1 : 32 (if the pre-vaccination titre was <1 : 8) and a ≥4-fold increase in antibody titre from pre- to post-vaccination in seropositive individuals (pre-vaccination titre ≥1 : 8).

c Primary endpoint: noninferiority between Nimenrix™ and comparator vaccine was achieved if the lower limit of the two-sided 95% CI for the btwn-grp diff in vaccine response rate was at least –10%[32] or more than –10%[36,38] (values in bold).

d Data available from the GlaxoSmithKline clinical trials registry.[52]

btwn-grp diff = between-group difference; **GMT** = geometric mean titre.

should not be considered as a replacement for routine vaccination against tetanus toxoid.[38]

2.1.3 In Adults Aged 18–55 Years

Nimenrix™ was noninferior to Mencevax™ in adults aged 18–55 years in terms of the immune response induced against all four vaccine serogroups, as assessed by the vaccine response rates (co-primary endpoint).[36] One month post-vaccination, vaccine response rates ranged from 80–92% in Nimenrix™ recipients and 70–92% in Mencevax™ recipients (table III).[36] Exploratory analyses showed that the vaccine response rates against serogroups A, W135 and Y were significantly higher in the Nimenrix™ group than in the Mencevax™ group (no p-value was reported). Moreover, the noninferiority of Nimenrix™ versus Mencevax™ in terms of the vaccine response rates against all serogroups was maintained when individuals were stratified according to age (18–25 years and 26–55 years) [exploratory analysis].[36]

Pre-vaccination rSBA antibody titres against all four meningococcal serogroups were relatively high (48.8–79.0% of individuals had titres ≥1 : 128 against any serogroup), which may be because of circulating meningococcal or cross-reacting strains causing asymptomatic nasopharyngeal carriage and/or cross-reactivity of antibodies with other bacteria.[36] However, 1 month post-vaccination, rSBA antibody GMTs against serogroups A, W135 and Y increased by at least 20-fold in Nimenrix™ recipients (vs 10-fold in Mencevax™ recipients) and rSBA antibody GMTs against serogroup C increased 109-fold (vs 81-fold).[36] Exploratory analyses showed significantly higher rSBA antibody GMTs against serogroups A, W135 and Y in Nimenrix™ than Mencevax™ recipients (no p-values were reported).[36]

The proportion of adult individuals with anti-TT concentrations ≥0.1 IU/mL increased from 51.5% pre-vaccination to 79.4% 1 month post-vaccination in the Nimenrix™ group, reflecting exposure to the TT carrier protein, while the proportion of individuals with these concentrations remained relatively unchanged in the Mencevax™ (a non-conjugated vaccine) group (52.2% to 53.2%).[36] Similarly, anti-TT antibody GMCs increased from baseline by 14-fold in the Nimenrix™ group and did not increase in the Mencevax™ group.[36] As noted earlier in section 2.1.2, it is unclear if the response to the carrier protein represents an increase in functional anti-TT antibodies; therefore, Nimenrix™ should not be used as a replacement for routine vaccination against tetanus.

2.1.4 For Revaccination in Individuals Previously Vaccinated with a Polysaccharide Vaccine

A phase II, open-label study compared the immunogenicity of Nimenrix™ administered in individuals (aged 4.5–34 years) who had received a polysaccharide vaccine 30–42 months previously (according-to-protocol population n = 169) with that of Nimenrix™ administered to age-matched individuals who had not been vaccinated with any meningococcal vaccine in the previous 10 years (n = 75).[39] One month post-vaccination, all individuals achieved rSBA antibody titres of ≥1 : 8 against the four vaccine serogroups, regardless of meningococcal vaccine history.[39] However, exploratory analyses showed that individuals who had not been vaccinated with a meningococcal vaccine in the 10 years prior to vaccination with Nimenrix™ had significantly higher antibody GMTs (5494.6–13 895.5 vs 1945.8–7799.9) and vaccine response rates (76.9–97.3% vs 41.1–83.0%) against the four meningococcal serogroups than the group that had received a dose of polysaccharide vaccine 30–42 months prior to Nimenrix™ (no p-values were reported);[39] the clinical relevance of this is currently unknown.[25] These data suggest that a single dose of Nimenrix™ may be used for revaccination if sustained protection against invasive meningococcal disease is needed in individuals who had previously been vaccinated with a polysaccharide vaccine, although the immune response against meningococcal serogroups was observed to be lower in these individuals than in vaccine-naive individuals.[25,39]

2.2 Persistence of Immune Response and Immune Memory

2.2.1 Persistence of Immune Response

The persistence of immune response elicited by Nimenrix™ was evaluated 12–42 months after vaccination in individuals aged 12 months to 55 years (data for persistence at 7 months after vaccination are discussed in section 2.3.4). Results showed that in Nimenrix™ recipients of all age groups, at the persistence timepoint, rSBA antibody GMTs against the four meningococcal vaccine serogroups were higher than the GMTs observed prior to vaccination, and were generally similar to or higher than those elicited by comparator vaccines, indicating that Nimenrix™ induced persisting immune responses against the vaccine serogroups.[25] Some data discussed in this section were obtained from the GlaxoSmithKline clinical trials registry.[53-55]

In Toddlers

In toddlers who received a dose of Nimenrix™, persistence of the immune response against vaccine serogroups was observed up to 3 years post-vaccination when sera were tested using rSBA;[40,45,46] however, a rapid waning of the response against meningococcal serogroup A (MenA) was observed when sera were tested with hSBA.[46]

Persistence of immune response was observed in an extension study[45] that assessed rSBA titres 15 months after primary vaccination in toddlers who had been vaccinated with Nimenrix™ (PP n = 40) or Meningitec® (a MenC vaccine) [PP n = 44] at the age of 12–14 months while participating in a dose-ranging, phase II study.[27] Results showed that 15 months after vaccination with Nimenrix™, ≥92.3% and ≥69.2% of toddlers had rSBA-MenC antibody titres of ≥1 : 8 and ≥1 : 128, respectively, and significantly more Nimenrix™ than Meningitec® recipients had rSBA-MenC antibody titres of ≥1 : 8 (92.3% vs 60.0%) or ≥1 : 128 (69.2% vs 27.5%) [no p-values were reported; exploratory analyses].[45] The rSBA antibody GMTs against serogroups A, W135 and Y decreased 4.3-, 8.2- and 4.4-fold, respectively between month 1

and month 15 post-vaccination; rSBA-MenC antibody GMTs also decreased, but the decrease was 3-fold less in Nimenrix™ than in Meningitec® recipients (5.4-fold vs 15-fold decrease).[45] Despite the decreased levels, antibody GMTs against serogroups A, C, W135 and Y in Nimenrix™ recipients remained higher than pre-vaccination levels (85.6-, 29.2- [vs 5.1-fold in Meningitec® recipients], 39.8- and 14.3-fold, respectively).[54]

In another extension study[46,53] of a phase III study[33] in toddlers (see section 2.1.1) who had received Nimenrix™ or Meningitec® at the age of 12–23 months, at 2 years after the primary vaccination, ≥97.8% of toddlers in the Nimenrix™ group had rSBA antibody titres of ≥1 : 8 against meningococcal serogroups A, W135 and Y, and 88.2% of Nimenrix™ recipients compared with 69.0% of Meningitec® recipients had antibody titres of ≥1 : 8 against serogroup C (no p-value was reported) [2-year cohort n = 188 and 30, respectively].[46] In Nimenrix™ recipients, antibody GMTs against serogroups A, W135 and Y remained 10.1- to 31.4-fold higher and those against MenC remained 10.2-fold (vs 7.4-fold in Meningitec® recipients) higher than pre-vaccination levels.[53] Persistence of immune response against serogroups C, W135 and Y was also observed when the sera were tested using human complement, with ≥87% of Nimenrix™ recipients having hSBA antibody titres of ≥1 : 4 against these serogroups.[46] hSBA antibody GMTs against serogroups C, W135 and Y remained 25.1- (vs 5-fold in Meningitec® recipients), 38.9- and 29.1-fold higher than pre-vaccination levels.[53] However, a rapid waning of hSBA-MenA antibodies was observed in Nimenrix™ recipients, with only 25.1% of toddlers having titres of ≥1 : 4;[46] the antibody GMT at 2 years was 1.9-fold higher than the pre-vaccination level.[53]

Similar results were also observed in a phase IIb open-label study that assessed the persistence of immune response up to 3 years after Nimenrix™ (3-year cohort n = 185) or Meningitec® (n = 38) vaccination in toddlers aged 1 to <2 years.[40] At 3 years post-vaccination, ≥90.8% of Nimenrix™ recipients (vs ≥72.7% of Meningitec® recipients) had rSBA antibody titres of ≥1 : 8 against meningococcal serogroups A, C, W135 and Y. Persistence of immune response against serogroups C, W135 and Y was also observed when the sera were tested using human complement, with ≥73.6% of Nimenrix™ recipients having hSBA antibody titres of ≥1 : 4 against these serogroups.[40] However, a rapid waning of hSBA-MenA antibodies was observed in Nimenrix™ recipients, with only 21.8% of toddlers having titres of ≥1 : 4.[40] rSBA antibody GMTs against serogroups A, C, W135 and Y at 36 months were ≥9-fold higher than pre-vaccination levels in Nimenrix™ recipients; hSBA antibody GMTs against serogroups C, W135 and Y were ≥16.9-fold higher than pre-vaccination levels, while those against serogroup A were 1.65-fold higher than pre-vaccination levels. No significant differences were observed between Nimenrix™ and Meningitec® recipients in terms of the proportion of toddlers with rSBA-MenC titres of ≥1 : 8 and hSBA-MenC titres of ≥1 : 4, according to exploratory analyses.[40]

These data were supported by those from a phase II study in which one group of toddlers was vaccinated with Nimenrix™ at the age of 12 months and the immunogenicity of the vaccine was assessed 1 year later using hSBA. Results showed that ≥80% of Nimenrix™ recipients had hSBA antibody titres of ≥1 : 8 against meningococcal serogroups C, W135 and Y and 20.6% of them had these titres against MenA.[41]

In Children

Persistence of the immune response (as assessed by rSBA) up to 3 years after primary vaccination was also observed in children who had previously received Nimenrix™ vaccination at the age of 3–5 years[45] or 2–10 years.[30] In an extension[45] of a dose-ranging study,[27] 15 months after the primary vaccination, all Nimenrix™ recipients and 59.4–93.8% of Mencevax™ recipients had rSBA antibody titres of ≥1 : 8 against meningococcal serogroups A, C, W135 and Y.[45] From month 1 to month 15 post-vaccination, rSBA antibody GMTs against these serogroups reduced by 4.7- to 7.8-fold in Nimenrix™ recipients and by 7.0- to 15.9-fold in Mencevax™ recipients. Exploratory analyses showed that significantly more Nimenrix™ than Mencevax™ re-

cipients had rSBA antibody titres of ≥1 : 8 against the vaccine serogroups and the antibody GMTs against these serogroups were significantly higher in the Nimenrix™ than Mencevax™ group (no p-values were reported).[45]

Similarly, in a phase IIb study,[30] 3 years after primary vaccination, 98.4–100% of Nimenrix™ recipients (PP cohort n = 197) compared with 81.1–91.2% of Mencevax™ recipients (PP cohort n = 37) had rSBA antibody titres of ≥1 : 8, with the between-group difference being statistically significant according to an exploratory analysis (no p-value was reported). Antibody GMTs against the four vaccine serogroups remained 7.3- to 40.3-fold (vs 2.3- to 6.8-fold in Mencevax™ recipients) higher than pre-vaccination levels in Nimenrix™ recipients.[30]

In Adolescents and Adults

Results in adolescents and adults were generally similar to those observed in toddlers and children, with the immune response elicited by Nimenrix™ against all four vaccine serogroups persisting up to 42 months when evaluated by rSBA,[43,44,47] but a rapid waning of antibodies against MenA was observed when the sera were evaluated at 12 months using hSBA.[44] In one study in adolescents aged 11–17 years, 2 years after primary vaccination with Nimenrix™ (2-year cohort n = 521) or Mencevax™ (n = 168) [in a phase III study;[38] see section 2.1.2], ≥99.3% and ≥95.1% of individuals in the respective groups had rSBA titres of ≥1 : 8 against serogroups A, C, W135 and Y. Antibody GMTs in the two groups were 1122–3716 and 443–1499, respectively,[47] which were 6.5- to 24.1-fold and 3.3- to 30.7-fold higher than pre-vaccination GMTs.[55] An exploratory analysis showed that significantly more Nimenrix™ than Mencevax™ recipients had rSBA titres of ≥1 : 8 against serogroups W135 and Y, and rSBA antibody GMTs against serogroups A, W135 and Y (no p-values were reported).[47]

Similarly, at 36 months post-vaccination, in a phase II study in adolescents and adults aged 11–55 years who had previously received Nimenrix™ or Mencevax™, >99% of individuals in the Nimenrix™ group (36-month cohort n = 344) and >86% of individuals in the Mencevax™ group (n = 116) had rSBA antibody titres of ≥1 : 8 against serogroups A, C, W135 and Y.[42] rSBA antibody GMTs against these serogroups remained higher than pre-vaccination levels in both vaccine groups (quantitative data not available), with the GMTs for antibodies against serogroups A, W135 and Y being significantly higher in the Nimenrix™ than in the Mencevax™ group, according to an exploratory analysis (no p-values were reported).[42]

These results were supported by a small phase II, open-label study[43] in adolescents and adults aged 15–19 years who had received Nimenrix™ or Mencevax™ in an earlier study.[28] At 42 months post-vaccination, all Nimenrix™ recipients (n = 24) and ≥88.2% of Mencevax™ recipients (n = 26) had rSBA antibody titres of ≥1 : 8 against meningococcal serogroups A, C, W135 and Y. At this timepoint, rSBA antibody GMTs against these serogroups were 329.7–1098.0 in Nimenrix™ recipients and 265.5–896.2 in Mencevax™ recipients and were 4.2- to 15.6-fold and 7.6- to 12.2-fold higher than pre-vaccination levels in the respective groups.[43]

A fourth study (phase II) in adolescents and adults aged 11–25 years (n = 368 Nimenrix™ recipients) evaluated persistence of the immune response elicited by Nimenrix™ using hSBA. Results showed that 12 months after primary vaccination, ≥94.9% of recipients had hSBA titres of ≥1 : 8 against meningococcal serogroups C, W135 and Y, while only 29.1% of individuals had these titres against MenA, indicating a rapid waning of the antibodies against this serogroup.[44] At 12 months, hSBA antibody titres against serogroups C, W135 and Y remained 14.3- to 37.9-fold higher than pre-vaccination levels, while titres against MenA were 2.2-fold higher than pre-vaccination levels in Nimenrix™ recipients.[44]

2.2.2 Immune Memory

An extension study in toddlers vaccinated with Nimenrix™ at 12–14 months of age showed that the vaccine induced immune memory against meningococcal serogroups A, C, W135 and Y.[45] Participants were originally randomized to receive either a single dose of Nimenrix™ or Meningitec® and 15 months later received a polysaccharide challenge to assess immune memory.[45] One

month after the polysaccharide challenge, all toddlers receiving Nimenrix™ as primary vaccination achieved rSBA titres of ≥1 : 8 and ≥1 : 128 against all meningococcal serogroups.[45] A high proportion (≥90.0%) of toddlers who originally received Meningitec® as the primary vaccination also achieved rSBA titres of ≥1 : 8 and ≥1 : 128 against all serogroups 1 month after the polysaccharide challenge. The rSBA antibody GMTs increased after the polysaccharide challenge in both vaccine groups, with the GMTs of antibodies against serogroups A, W135 and Y being significantly higher in Nimenrix™ than Meningitec® recipients (exploratory analyses; no p-values were reported). These results suggest that both vaccines induced immunological memory against meningococcal serogroups.[45]

2.3 Coadministration with Other Vaccines

This section discusses data from several randomized, open-label[33-35,48] or partially double-blind,[37] noninferiority, phase III clinical trials that evaluated the immunogenicity of Nimenrix™ when coadministered with routine vaccines. In general, coadministration of Nimenrix™ with Priorix-tetra™,[33] Infanrix™ hexa[35] or Synflorix™[48] in toddlers, with Twinrix® in children and adolescents[34] and with Fluarix™ in adults[37] did not affect the immunogenicity of Nimenrix™ or the coadministered vaccine.

2.3.1 With Priorix-tetra™

When coadministered with Priorix-tetra™ in healthy toddlers aged 12–23 months, Nimenrix™ elicited a strong immune response against all four meningococcal serogroups, as assessed by seroresponse rates and GMTs.[33] Seroresponse rates (rSBA titre ≥1 : 8) of 100% and antibody GMTs of 519.0–2282.4 against serogroups A, C, W135 and Y were observed 42 days post-vaccination in Nimenrix™ plus Priorix-tetra™ recipients.[33] Furthermore, the immune response induced by Nimenrix™ coadministered with Priorix-tetra™ was noninferior to that induced by Nimenrix™ alone, as the lower limits of the 95% CIs for the between-group differences in seroresponse rates against the four serogroups were above the predefined limit of −10% (co-primary endpoint).[33]

Forty-two days post-vaccination, rSBA antibody GMTs against the four serogroups increased by ≥47.8-fold in the Nimenrix™ plus Priorix-tetra™ group and the Nimenrix™ group.[33] Exploratory analyses showed that there was no significant difference between Nimenrix™ plus Priorix-tetra™ recipients and the Nimenrix™ recipients in rSBA antibody GMTs against the four vaccine serogroups. Although titres against serogroups W135 and Y tended to be lower in the coadministration group, this is not thought to be clinically significant, as high proportions of individuals achieved accepted correlates of seroprotection (rSBA titres ≥1 : 8).[33]

Nimenrix™ coadministered with Priorix-tetra™ was also noninferior to Priorix-tetra™ administered alone in terms of seroconversion rates against MMRV viruses.[33] The lower limits of the 95% CIs for between-group differences in seroconversion rates against MMRV 42 days post-vaccination were all above the predefined limit of −10%.[33] All individuals in both vaccination groups had seroconverted against measles and rubella, ≥83% in each group had seroconverted against mumps and ≥94% had seroconverted against varicella virus 42 days post-vaccination.[33] However, exploratory analyses showed that the anti-rubella GMC was significantly lower in the coadministration group compared with the Priorix-tetra™ group (43.1 vs 53.2 IU/mL [95% CIs for the GMC ratio were 0.697, 0.945]), although this is unlikely to be clinically relevant, as the GMC in the coadministration group was well above the 10 IU/L threshold used to define seroresponse.[33]

2.3.2 With Infanrix™ hexa

In healthy toddlers aged 12–23 months, Nimenrix™ coadministered with Infanrix™ hexa elicited a strong immune response against all four meningococcal serogroups, as assessed by seroresponse rates and GMTs.[35] One month post-vaccination, seroresponse rates (rSBA titre ≥1 : 8) of 100% and antibody GMTs of 879.7–4147.0 against serogroups A, C, W135 and Y were observed in Nimenrix™ plus Infanrix™ hexa re-

cipients.[35] Furthermore, the immune response induced by Nimenrix™ coadministered with Infanrix™ hexa was noninferior to that induced by Nimenrix™ alone, as the lower limits of the 95% CIs for the between-group differences in seroresponse rates against the four serogroups were above the predefined limit of −10% (co-primary endpoint).[35]

One month post-vaccination, rSBA antibody GMTs against the four meningococcal serogroups were within the same range in the toddlers who received Nimenrix™ plus Infanrix™ hexa and those who received Nimenrix™ followed by Infanrix™ hexa (1 month later), having increased 51- to 218.3-fold from pre-vaccination levels.[35] However, 1 month after meningococcal vaccination, exploratory analyses showed significantly lower rSBA antibody GMTs against serogroups A, C and W135 in recipients vaccinated with Infanrix™ hexa followed by Nimenrix™ (1 month later) compared with those vaccinated with Nimenrix™ followed by Infanrix™ hexa (1 month later) [no p-values were reported], although this did not result in fewer toddlers achieving serological correlates of 1 : 8 and 1 : 128 in the coadministration group.[35]

Nimenrix™ coadministered with Infanrix™ hexa was also noninferior to Infanrix™ hexa followed by Nimenrix™, in terms of antibody responses against pertussis, hepatitis B and Hib components 1 month post-vaccination (co-primary endpoint).[35] The lower limits of the two-sided 95% CIs for the adjusted GMC ratios of anti-PT, anti-FHA and anti-PRN antibodies were all above the predefined limit of 0.67.[35] In addition, the lower limits of the two-sided 95% CIs for the between-group differences in seroconversion rates against hepatitis B surface antigen (antibody concentrations ≥10 mIU/mL, which were considered seroprotective) and polyribosylribitol-phosphate (antibody concentrations ≥1 μg/mL; primary endpoint) were both above the predefined limit of −10%.[35]

Nimenrix™ coadministered with Infanrix™ hexa was also noninferior to Infanrix™ hexa followed by Nimenrix™, in terms of the immune response induced against DT, TT and poliovirus (secondary endpoint), as the lower limits of the 95% CIs for between-group differences in seroprotective rates were above the predefined limit of −10%.[35]

Whether administered with Nimenrix™ concomitantly or sequentially, at least 99.4% of Infanrix™ hexa recipients achieved DT and TT antibody concentrations of ≥0.1 IU/mL and all recipients were seropositive (cut-off of 5 EL U/mL) for PT, FHA and PRN 1 month after vaccination.[35] Furthermore, all toddlers who received Infanrix™ hexa had seroprotective antibodies against Hib (cut-off ≥0.15 μg/mL) and ≥98.2% had seroprotective antibodies against hepatitis B (cut-off 10 mIU/mL) and each of the three poliovirus types (cut-off 1 : 8 dilution).[35]

2.3.3 With Synflorix™

A booster vaccination study compared the immunogenicity of a single dose of Nimenrix™ coadministered with a booster dose of Synflorix™ vs administration of Synflorix™ alone in healthy toddlers aged 12–23 months who had previously received three doses of Synflorix™.[48] Results showed that Nimenrix™ coadministered with Synflorix™ elicited a strong immune response against all four meningococcal serogroups, as assessed by seroprotection rates and GMTs, with the immune response being noninferior to that induced by Nimenrix™ alone. At 1 month post-vaccination, ≥99.4% of Nimenrix™ plus Synflorix™ recipients compared with ≥97.5% of Nimenrix™ recipients achieved rSBA titres of ≥1 : 8 against all four meningococcal serogroups, with the lower limits of the 95% CIs for the between-group differences being higher than the predefined noninferiority limit of at least −10%. At 1 month post-vaccination, GMTs of the antibodies against the four meningococcal serogroups were 2496.6–11 731.0 in the coadministration group compared with 2044.0–8407.7 in the Nimenrix™ group, an increase of 102.9- to 439.1-fold versus 75.4- to 335.1-fold from pre-vaccination levels.[48]

Nimenrix™ plus Synflorix™ was also noninferior to Synflorix™ in terms of the immune response against all pneumococcal serotypes, apart from serotype 18C, as the lower limits of the 95% CIs of the adjusted antibody GMC ratios were greater than the predefined limit of 0.5 (the lower

limit of the 95% CI for the adjusted GMC ratio for serotype 18C was 0.41).[48] According to the study authors, the lower immune response against serotype 18C in the coadministration group may be because of the choice of TT as carrier protein for serotype 18C (in Synflorix™) and for all meningococcal serogroups (in Nimenrix™). TT is known to influence the response of coadministered conjugate vaccines, with the negative effect of high TT dosages probably related to competition for T-helper cells.[48]

Antibody concentrations of ≥0.2 μg/mL (as assessed by the 22F-ELISA) against the vaccine pneumococcal serotypes were achieved by ≥96.0% of toddlers in the coadministration group and ≥97.5% of toddlers in the Synflorix™ group (including against serotype 18C [100% of toddlers in both groups]).[48] An antibody concentration of 0.2 μg/mL as assessed by the 22F-ELISA is equivalent to an antibody concentration of 0.35 μg/mL as assessed by ELISA without 22F-inhibition, which is the threshold used by the WHO for comparing immune responses elicited by pneumococcal conjugate vaccines at 1 month after the third primary dose.[48]

In addition, at 1 month post-vaccination, ≥92.9% of Nimenrix™ plus Synflorix™ recipients and ≥95.7% of Synflorix™ recipients achieved an OPA antibody titre ≥1 : 8 against all vaccine pneumococcal serotypes (including serotype 18C [98.2% vs 100%]).[48] The GMTs of OPA antibodies against the pneumococcal serotypes at this timepoint were 362.1–5485.4 in the coadministration group compared with 332.7–5616.8, an increase of 3.1- to 192.6-fold versus 2.9- to 425.5-fold from pre-vaccination levels. The study authors state that considering the robust increase in antibody concentration and OPA antibody titres against serotype 18C, the lower GMC ratio between the coadministration group and the Synflorix™ group may be of limited clinical relevance.[48]

2.3.4 With Twinrix®

In healthy adolescents aged 11–17 years, Nimenrix™ coadministered with Twinrix® elicited a strong immune response against all four meningococcal serogroups, as assessed by seroresponse rates and GMTs, with the immune response being noninferior to that induced by Nimenrix™ administered alone.[34] One month post-vaccination, seroresponse rates (rSBA titre ≥1 : 8) of ≥99.7% and adjusted rSBA antibody GMTs of 4404.1–8753.2 for serogroups A, C, W135 and Y were observed in the Nimenrix™ plus Twinrix® group compared with seroresponse rates of ≥99.1% and adjusted rSBA antibody GMTs of 4849.8–8684.3 in the Nimenrix™ alone group. The immune response induced by Nimenrix™ plus Twinrix® was noninferior to that induced by Nimenrix™ alone, as at 1 month post-vaccination, the lower limits of the 95% CIs of the adjusted ratios of rSBA antibody GMTs against all four serogroups were above the predefined limit of 0.5 (co-primary endpoint). The proportion of individuals with pre-vaccination rSBA antibody titres of ≥1 : 8 against each of the four meningococcal serogroups varied between 38.8% and 84.2%, at least partly because of previous vaccination or exposure to the organism.[34]

Vaccine response rates (same definition as that in table III) for the four meningococcal serogroups ranged from 93.8% to 99.1% in the coadministration group compared with 90.2% to 98.2% in the Nimenrix™ group at 1 month post-vaccination. Furthermore, exploratory analyses did not reveal any significant differences between the two groups in vaccine response rates or post-vaccination rSBA GMT ratios.[34]

Post-vaccination seropositivity rates (rSBA antibody titre ≥1 : 8) against the four meningococcal serogroups remained high at month 7 (i.e. 1 month after the last dose of Twinrix®; see table II) for both Nimenrix™ plus Twinrix® recipients and Nimenrix™ recipients (99.4–100% vs 98.2–100%). rSBA antibody GMTs were 2.1- to 4.7-fold lower at month 7 compared with month 1, but remained higher than pre-vaccination levels (GMTs at month 7 were 952.4–4432.7 and 1053.9–4455.6 in the respective groups).[34] Additional data regarding the persistence of the immune response elicited by Nimenrix™ are discussed in section 2.2.

Twinrix® coadministered with Nimenrix™ was no less effective than Twinrix® administered alone in terms of immune responses against hepatitis A and B.[34] One month after the third dose of Twinrix® (i.e. at month 7), the lower limits of

the 95% CIs for the seroconversion rate against hepatitis A and the seroprotection rate against hepatitis B were greater than the pre-specified noninferiority limit of –10%.[34] In both vaccination groups, all individuals seroconverted for hepatitis A antibody and at least 99.1% of individuals were seroprotected against hepatitis B at month 7, with no significant differences between the two vaccination groups in either response according to exploratory analyses.[34]

2.3.5 With Fluarix™

In healthy adults aged 18–55 years, Nimenrix™ coadministered with Fluarix™ was noninferior to Nimenrix™ administered alone in terms of rSBA antibody GMTs against three out of the four meningococcal serogroups.[37] One month post-vaccination, the adjusted rSBA antibody GMTs against serogroups A, W135 and Y were 2860.8–5617.2 in the coadministered group compared with 3895.9–7331.2 in the Nimenrix™ group, with the upper limit of the 95% CIs of the adjusted GMT ratios being ≤2.0 (pre-defined limit) for each serogroup (co-primary endpoint).[37] For MenC, the adjusted rSBA GMT for the coadministered group was 6908.0 compared with 10 299.7 for the Nimenrix™ group, with a between-group adjusted GMT ratio of 1.49 (95% CI 1.10, 2.03), which was just outside the predefined margin for noninferiority.[37] However, despite noninferiority criteria not being met for MenC, a high proportion (97.1%) of all vaccine recipients achieved post-vaccination titres of ≥1 : 128 (a conservative threshold of protection) against all four meningococcal serogroups.

There was also a strong immune response in recipients of Nimenrix™ plus Fluarix™, as assessed by vaccine response rates (same definition as that in table III) against all four meningococcal serogroups.[37] One month post-vaccination, vaccine response rates against serogroups A, C, W135 and Y were 76.5–88.7% in adults who received Nimenrix™ plus Fluarix™ compared with 80.6–92.0% in those who received Nimenrix™ alone.[37]

Recipients of Nimenrix™ coadministered with Fluarix™ met all criteria defined by the European Committee for Human Medicinal Products in terms of seroprotection, seroconversion and seroconversion factors for HI antibodies against all three influenza strains in the Fluarix™ vaccine (co-primary endpoint).[37] Post-vaccination seroconversion rates of 71.4%, 61.9% and 75.7%, antibody GMTs of 537.2, 177.8 and 192.7 and seroconversion factor rates (mean $\log_{10}$ post-vaccination GMT/pre-vaccination GMT) of 9.9%, 5.6% and 9.1% were observed against strains A/H1N1, A/H3N2 and B, respectively.[37] Furthermore, ≥96% of recipients of the coadministered vaccines had anti-HI antibody titres of ≥1 : 40 against the three influenza strains 1 month post-vaccination.[37]

3. Tolerability

This section focuses on data regarding the tolerability of Nimenrix™ in toddlers, children, adolescents and adults derived from the phase III clinical trials discussed in section 2.[32-38,48] In one trial in children aged 2–10 years,[32] the incidence of all (solicited and unsolicited) grade 3 systemic adverse events was defined as a co-primary endpoint. The trial in children and adolescents aged 11–17 years[38] also included an analysis of tolerability data pooled with those from a separate trial in adults[36] and was designed to evaluate the noninferiority of Nimenrix™ with Mencevax™ in terms of the incidence of all grade 3 systemic adverse events (primary endpoint). Evaluation of tolerability data was performed on the total vaccinated cohort[32-38] or the safety cohort.[48] A tabulated list of adverse reactions based on a pooled analysis of >8000 recipients of Nimenrix™ is also available in the European Medicine Agency's summary of product characteristics.[25]

Diary cards were used to record the incidence of solicited local (pain, redness and swelling) and systemic (drowsiness, fever, irritability and loss of appetite in individuals aged ≤5 years and fatigue, fever, gastrointestinal [GI] adverse events and headache in individuals aged ≥6 years) adverse events for 4 days following vaccination, and all other (unsolicited) adverse events for 31[32-38,48] (or 43[33]) days after vaccination. Where defined, grade 3 symptoms included redness and swelling >30 mm (in individuals aged 12 months to 5 years)[32,33] or >50 mm (in individuals aged

>6 years)[32,34,36,38] in diameter, axillary fever >39.5°C[32,34,36,38] or rectal fever >40°C[33] or other symptoms that prevented normal activity.[32,33,36,38] Serious adverse events were monitored throughout the study[34] or for ≤6 months following primary vaccination.[32,33,35-38,48]

3.1 Local Adverse Events

All phase III trials showed that Nimenrix™ was generally well tolerated in terms of the incidence of local solicited adverse events of any intensity in toddlers, children, adolescents and adults.[32,33,36,38] In the pooled analysis of all age groups, the most frequently reported local adverse events following vaccination with Nimenrix™ were pain (24.1–39.9%), redness (14.3–33.0%) and swelling (11.2–17.9%).[25]

In individual clinical trials, redness was the most frequently reported local adverse event in toddlers, whereas pain tended to be more frequently reported in older individuals in the first 4 days following vaccination (table IV). The incidence of local solicited adverse events was generally similar between Nimenrix™ recipients and Meningitec® or Mencevax™ recipients, with the exception of redness, which was reported significantly more frequently in Nimenrix™ than Mencevax™ recipients in individuals aged 11–17 years,[38] and pain, which was reported more frequently in Mencevax™ than Nimenrix™ recipients in individuals aged 6–10 years (table IV).[32]

In the first 4 days following vaccination, the incidence of grade 3 local solicited adverse events was generally low (≤4.4%) in Nimenrix™ recipients in these trials.[32,33,36,38] Less than 1.3% of children, adolescent and adult recipients of Nimenrix™ experienced any local solicited adverse event of grade 3 intensity compared with ≤0.3% of recipients of Mencevax™.[32,36,38] In toddlers aged 12–23 months, grade 3 redness occurred in 4.4% of Nimenrix™ and 0.8% of Meningitec® recipients and grade 3 swelling occurred in 4.1% and 0.8% of individuals in the respective groups.[33] Where reported,[32,38] there was no significant difference between the Nimenrix™ group and the Mencevax™ group in terms of the incidences of individual grade 3 local adverse events.

Table IV. Comparative tolerability of Nimenrix™ in healthy toddlers, children, adolescents and adults. Incidences of all local solicited adverse events of any intensity occurring within 4 d of vaccination in the phase III trials discussed in section 2. Incidences in three studies[32,33,38] were estimated from graphs

Vaccine (no. of subjects)	Adverse event (%)		
	Pain	Redness	Swelling
In toddlers aged 12–23 mo[33]			
Nimenrix™ (354)	29	37	19
Meningitec® (118)	25	31	8
In children aged 2–5 y[32]			
Nimenrix™ (578)	18	14	5
Mencevax™ (190)	20	16	8
In children aged 6–10 y[32]			
Nimenrix™ (547)	19	20	10
Mencevax™ (186)	26*	19	8
In children and adolescents aged 11–17 y[38]			
Nimenrix™ (768)	26.2	12.3*	9.3
Mencevax™ (257)	26.8	6.3	6.3
In adults aged 18–55 y[36]			
Nimenrix™ (927)	19.4	8.8	7.9[a]
Mencevax™ (310)	13.5	4.5	1.9

a The 95% CIs for the two groups did not overlap.

*$p < 0.05$ vs comparator.

Nimenrix™ was also generally well tolerated in toddlers, children and adolescents in terms of local solicited adverse events when coadministered with other routine childhood vaccines including Priorix-tetra™,[33] Twinrix®,[34] Infanrix™ hexa[35] and Synflorix™.[48] In all coadministration trials, the profile of local solicited adverse events at the Nimenrix™ injection site was generally comparable to that seen in the single vaccination trials.[33-35,48] In toddlers receiving Nimenrix™, Synflorix™ or Nimenrix™ plus Synflorix™,[48] pain of grade 3 intensity was reported in 6.8–8.8% of toddlers at the Synflorix™ injection site compared with 2.4–7.8% of toddlers at the Nimenrix™ injection site. Nimenrix™ had an acceptable tolerability profile in adults when coadministered with Fluarix™, with no more than 1.9% of individuals experiencing grade 3 solicited local adverse events.[37]

3.2 Systemic Adverse Events

Nimenrix™ was generally well tolerated in terms of the incidence of systemic solicited ad-

verse events of any intensity in toddlers, children, adolescents and adults.[32,33,36,38] In a pooled analysis of data across all clinical studies, the most frequently reported systemic adverse events in toddlers (aged 12–23 months) and children (aged 2–5 years) who received Nimenrix™ were irritability (36.2% and 7.5%, respectively), drowsiness (27.8% and 8.8%), loss of appetite (20.7% and 6.3%) and fever (17.6% and 6.5%).[25] The pooled analysis also showed that the most frequently reported systemic adverse events in children aged 6–10 years, adolescents aged 11–17 years and adults aged ≥18 years who received Nimenrix™ were headache (13.3%, 16.1% and 17.6%, respectively), fatigue (13.8%, 16.3% and 16.4%), GI symptoms (7.5%, 6.4% and 6.3%) and fever (7.5%, 4.1% and 4.0%).[25]

In individual clinical trials, during the first 4 days following vaccination, irritability was the most frequent adverse event of any intensity reported in toddlers, whereas in older individuals, fatigue and headache were generally the most frequent adverse events (table V).[32,33,36,38]

The incidence of grade 3 systemic solicited adverse events was generally low across all trials.[32,33,36,38] In toddlers, systemic solicited adverse events of grade 3 intensity were reported in ≤1.6% of individuals and no recipients of Nimenrix™ exhibited grade 3 fever.[33] No more than 1% of children or adolescents receiving either Nimenrix™ or Mencevax™ reported systemic symptoms of grade 3 intensity.[32,38] In adult individuals, headache was the most frequently reported grade 3 systemic adverse event, which occurred in 1.5% Nimenrix™ recipients.[36]

However, noninferiority of Nimenrix™ with Mencevax™ in terms of the incidence of solicited and unsolicited systemic adverse events of grade 3 intensity was not met in the analyses of tolerability data from the trial in children aged 2–10 years[32] and the pooled analysis of children and adults aged 10–55 years.[38] In the study in children, which was conducted in the Philippines, India, Lebanon and Saudi Arabia, noninferiority of Nimenrix™ with Mencevax™ in terms of the incidence of grade 3 systemic symptoms (primary objective) was not achieved, as the upper limit of the 95% CI of the between-group ratio (3.34 [95% CI 0.56, 20.25]) was more than the predefined cut-off of ≤3.[32] However, it should be noted that the study was underpowered to meet the primary objective because of differences between the adolescent US population (used as the reference group) and Asian children in terms of the incidence of general symptoms; the incidence of grade 3 systemic symptoms in the Nimenrix™ and Mencevax™ groups was 0.3–0.9% compared with the estimated rate of 3%.[32] When stratified by age, the incidence of grade 3 solicited and unsolicited systemic symptoms was 1% in Nimenrix™ recipients compared with 0% in Mencevax™ recipients among 2–5 year olds, and in the 6–10 year olds the incidence was 0.7% and 0.5%, respectively.[32]

Similarly, in the pooled analysis, the ratio of the incidence of grade 3 solicited or unsolicited systemic adverse events with Nimenrix™ over

Table V. Comparative tolerability of Nimenrix™ in healthy toddlers, children, adolescents and adults. Incidences of all systemic solicited adverse events of any intensity occurring within 4 days of vaccination in the phase III trials discussed in section 2. Incidences in three[32,33,38] studies were estimated from graphs

Vaccine (no. of subjects)	Adverse event (%)			
	Drowsiness	**Fever**	**Irritability**	**LOA**
In toddlers aged 12–23 mo[33]				
Nimenrix™ (354)	28	8[a]	41	23
Meningitec® (118)	32	12[a]	43	27
In children aged 2–5 y[32]				
Nimenrix™ (578)	6	8[b]	5	6
Mencevax™ (190)	2	6[b]	3	3
	Fatigue	**Fever**[a]	**Headache**	**GI**
In children aged 6–10 y[32]				
Nimenrix™ (547)	6	9	9	4
Mencevax™ (186)	10	10	10	8
In adolescents aged 11–17 y[38]				
Nimenrix™ (768)	14	6	13	4
Mencevax™ (257)	14	5	10	3
In adults aged 18–55 y[36]				
Nimenrix™ (927)	12.3	4.0	16.3	4.6
Mencevax™ (310)	9.7	4.5	14.2	3.2

a Rectal temperature ≥38°C.

b Axiliary temperature ≥37.5°C.

GI = gastrointestinal; **LOA** = loss of appetite.

those with Mencevax™ was 1.42 (95% CI 0.67, 3.00).[38] The upper limit of the 95% CI was 3.0024, which marginally exceeded the predefined limit of 3.0.[38] However, exploratory analyses showed no significant differences between the two vaccination groups in the incidences of either solicited or unsolicited systemic symptoms, regardless of intensity.[38] There were also no significant differences between the vaccination groups in the incidence of individual solicited systemic adverse events of any or grade 3 intensity when each study was evaluated separately.[38]

Nimenrix™ coadministered with other vaccines was also generally well tolerated in terms of the incidence of systemic adverse events. The most common systemic solicited adverse event in toddlers receiving Nimenrix™ plus Priorix-tetra™ was irritability (in ≈50% of toddlers; value estimated from a graph).[33] In toddlers receiving Nimenrix™ plus Infanrix™ hexa, drowsiness and fever occurred significantly ($p < 0.05$) more frequently than in toddlers receiving the vaccines separately.[35] The most common solicited systemic adverse events in children and adolescents receiving Nimenrix™ plus Twinrix® were fatigue (in ≈28% of individuals) and headache (≈24%) [values estimated from a graph].[34] No more than 1.9% of individuals receiving Nimenrix™ plus Fluarix™ or Nimenrix™ plus Synflorix™ experienced a grade 3 solicited systemic adverse event.[37,48] In toddlers receiving Nimenrix™, Synflorix™ or Nimenrix™ plus Synflorix™, the most common solicited systemic adverse event in all groups was irritability (incidence 40–49%; values estimated from a graph); one toddler receiving Nimenrix™ had grade 3 fever (rectal temperature ≥40°C), which was considered vaccine related.[48]

3.3 Other Adverse Events

The incidence of serious adverse events was low in Nimenrix™ recipients in all age groups.[32,33,36,38] During the 43-day post-vaccination period in toddlers, serious adverse events were reported in 0.5% of Nimenrix™ recipients and 0.8% of Nimenrix™ plus Priorix-tetra™ recipients.[33] A further 1.6–2.7% of individuals in all study groups (including Meningitec recipients®) reported serious adverse events during an extended follow-up period of 6 months.[33] Similarly, 1.3% of Nimenrix™ and 1.9% of Mencevax™ recipients reported serious adverse events ≤6 months post-vaccination in the trial in children aged 2–10 years;[32] the corresponding values in the trial in 11–17 year olds were 0.4% and 0.8%.[38] None of the serious adverse events were thought to be causally related to vaccination.[32,33,38] In the trial in adults,[36] 0.7% of Nimenrix™ recipients and 0.3% of Mencevax™ recipients reported serious adverse events during 6 months of follow-up. One subject in the Nimenrix™ group reported abdominal pain and gastritis 5 days after vaccination, which were considered to be causally related to the vaccine.[36] All serious adverse events resolved without sequelae.[36]

The incidence of serious adverse events was also low in recipients of Nimenrix™ coadministered with other routine childhood vaccines.[33-35,48] One Nimenrix™ plus Twinrix® recipient reported syncope and concussion, which were considered to be causally related to vaccination,[34] presumably because the recipient passed out, fell and sustained a head injury, although this was not specifically mentioned by the study authors. None of the serious adverse events reported in recipients of Nimenrix™ plus Infanrix™ hexa were thought to be causally related to vaccination.[35] In Nimenrix™ plus Synflorix™ recipients, six (3.3%) toddlers experienced one or more serious adverse events compared with three (3.3%) Nimenrix™ and four (4.4%) Synflorix™ recipients up to 1 month after the last vaccination; however, none of these events were considered to be vaccine related and all events resolved without sequelae.[48]

A low incidence of unsolicited causally related adverse events was reported during 31 days of follow-up in the trial in 11–17 year olds (1.4% of Nimenrix™ and 1.2% of Mencevax™ recipients), none of which were of grade 3 intensity.[38] During the 31-day follow-up period of the trial in adults,[36] 14.4% of Nimenrix™ and 15.1% of Mencevax™ recipients reported unsolicited adverse events of any intensity; the incidence for grade 3 unsolicited adverse events was 1.4% and 1.0%, respectively.

When Nimenrix™ was coadministered with Priorix-tetra™ in toddlers, 31.7% of recipients experienced rash (any) over 43 days of follow-up compared with 29.0% of Priorix-tetra™ recipients, 18.0% of Nimenrix™ recipients and 19.4% of Meningitec® recipients.[33] Measles-/rubella-like rash occurred in 3.7% of Nimenrix™ plus Priorix-tetra™ recipients, 3.2% of Priorix-tetra™ recipients and in none of the recipients of Nimenrix™ or Meningitec®; varicella-like rash was reported by 2.4% of toddlers in the coadministration group, Priorix-tetra™ group and Meningitec® group compared with 1.4% of toddlers in the Nimenrix™ group.[33] Approximately one-third of toddlers experienced an unsolicited adverse event when Nimenrix™ was coadministered with Infanrix™ hexa; grade 3 unsolicited adverse events occurred with a frequency of 0–2.3% over 31 days of follow-up.[35] At least one unsolicited adverse event was experienced by 16.9% of Nimenrix™ plus Twinrix® recipients compared with 10.7% of Nimenrix™ recipients over 31 days of follow-up.[34] In toddlers receiving Nimenrix™, Synflorix™ or Nimenrix™ plus Synflorix™, the proportion of patients experiencing unsolicited adverse events during the 31-day follow-up period ranged between 34.4% and 46.7%. Eleven toddlers in the coadministration group experienced grade 3 unsolicited adverse events compared with eight and five toddlers in the Nimenrix™ and Synflorix™ groups, respectively, none of which were considered vaccine related.[48]

4. Dosage and Administration

Nimenrix™ is approved in Europe for active immunization of individuals aged ≥12 months against invasive meningococcal disease caused by *N. meningitidis* serogroups A, C, W135 and Y.[25] Nimenrix™ may also be used for revaccination in individuals previously vaccinated with a plain polysaccharide meningococcal vaccine. The need for revaccination in individuals receiving Nimenrix™ as primary vaccination has not been determined.[25]

Nimenrix™ is available as a powder and saline solvent that must be reconstituted immediately before administration. It should be administered as a single 0.5 mL intramuscular injection, preferably into the deltoid muscle; in children aged 12–23 months, it may also be administered in the anterolateral part of the thigh. The vaccine should not be administered intravascularly, intradermally or subcutaneously.

Studies have shown a rapid waning of serum bactericidal antibody titres against meningococcal serogroup A when using human complement in the assay 12 months after vaccination with Nimenrix™ (section 2.2).[25] Although the clinical significance of this decline in hSBA-MenA antibody titres is unknown, administration of a second dose of Nimenrix™ may be considered in individuals who are expected to be at particular risk of exposure to MenA and who have received a first dose of the vaccine more than ≈1 year previously.[25]

The safety and efficacy of Nimenrix™ in children aged <12 months has not been determined and it is not approved for use in this age group.[25] Vaccination should be postponed in individuals suffering from acute severe febrile illness and caution is advised in individuals with thrombocytopenia or any coagulation disorder. Nimenrix™ may be administered concomitantly with hepatitis A or B vaccines, MMRV vaccine, 10-valent pneumococcal conjugate vaccine or unadjuvanted seasonal influenza vaccine (section 2.3). It may also be administered concomitantly with diphtheria-tetanus-acellular pertussis (DTaP) vaccines in the second year of life, including combination DTaP vaccines with hepatitis B, inactivated polio or *H. influenzae* type b, such as DTaP-HBV-IPV/Hib vaccine. The vaccines should always be administered at different injection sites.[25]

Local prescribing information should be consulted for detailed contraindications, warnings, precautions and recommendations.

5. Place of Nimenrix™ in the Management of Meningococcal Disease

Invasive meningococcal disease is confirmed by the isolation of *N. meningitidis* from a normally sterile site (e.g. blood or cerebrospinal fluid) from a person with clinically compatible illness.[56] The disease usually presents as meningitis and/or

septicaemia, with other clinical manifestations being pneumonia, arthritis, otitis media, epiglottitis and pericarditis.[57,58] Despite optimal healthcare, meningococcal disease is fatal in 9–12% of cases overall, with a death rate approaching 40% in patients with sepsis.[57] Survivors of meningococcal disease may suffer from permanent brain damage, blindness, hearing loss, kidney failure, amputation and chronic neurological disorders.[57] Infants are most at risk from meningococcal disease, although the incidence peaks again during adolescence and early adulthood, and adolescents generally have the highest rates of related deaths.[58]

The WHO estimated in 2001 that there were approximately 1.2 million cases of invasive meningococcal disease worldwide, leading to 135 000 related deaths annually.[59] However, the epidemiology of meningococcal disease varies by geographic region and time.[6] The highest incidence is found in the 'meningitis belt' of sub-Saharan Africa where the disease (largely caused by meningococcal serogroup A) is characterized by annual outbreaks and cyclical epidemics every 5–12 years;[60] the incidence rate in epidemic years may reach 1000 per 100 000 population.[15] On the other hand, in the US and Europe, there are typically 1–2 cases of meningococcal disease per 100 000 population, with outbreaks occurring in clusters during occasional epidemics.[4,57,61,62] Even with these comparatively low rates, meningococcal disease continues to cause considerable morbidity and mortality in the industrialized world, with the majority of the disease burden borne by younger children. Furthermore, the public health costs associated with invasive meningococcal disease-related sequelae are considerable.[63,64]

According to the recommendations of the UK Health Protection Agency (HPA) Centre for Infections,[2] a dose of MenC conjugate vaccine should be included in the immunization schedule after the age of 1 year. Data from the UK showed that high levels of direct protection against meningococcal disease were maintained for up to 4 years in children and adolescents immunized with a MenC conjugate vaccine between the ages of 5 months and 18 years.[65] In contrast, in individuals aged <5 months, vaccine effectiveness declined to low levels within 1 year of vaccination, necessitating a booster vaccination.[65] Consequently, vaccination with a MenC conjugate vaccine in the second year of life is likely to provide longer-term protection and a simpler dosing schedule for younger children.[2]

In this regard, the introduction of monovalent meningococcal serogroup C conjugate vaccines (e.g. Meningitec® and Menjugate®) in Europe and elsewhere has resulted in a marked and sustained reduction in disease caused by serogroup C.[66] This is most likely due to decreased nasopharyngeal carriage and robust herd protection associated with these vaccines.[67] Meningitec® may be administered from a very early age (usually as a two-dose primary vaccination schedule in infants aged ≤12 months, followed by a booster dose[68]). Encouraging results have also been achieved with a monovalent serogroup A polysaccharide-TT conjugate vaccine (MenAfriVac™) in children and adults,[14] which has been introduced in several African countries.[69]

However, from a global perspective, the emergence of other serogroups (such as W135 and X, for example) underlying meningococcal disease has highlighted the need for vaccines with broader serogroup coverage.[6] Indeed, the UK HPA Centre for Infections[2] and the US Centers for Disease Control and Prevention[70] recommend routine vaccination of adolescents and other persons at risk of meningococcal disease with a quadrivalent meningococcal conjugate vaccine. The non-conjugated quadrivalent vaccines (e.g. Menomune®, Mencevax™) are less immunogenic (except for the response to MenA polysaccharide) in infants aged <2 years.[1,7,14] The availability of the quadrivalent conjugate vaccines Menactra® and Menveo® has expanded vaccination options in younger age groups. However, Menveo® is not approved for use in children aged <2 years and Menactra® must be used as a two-dose schedule in this age group. There is one other quadrivalent polysaccharide-TT conjugate vaccine (TetraMen-T) that is currently in development for administration as a single dose at 1 year of age.[71]

Nimenrix™ is also a quadrivalent meningococcal conjugate vaccine, comprising poly-

saccharide serogroups A, C, W135 and Y, and TT as carrier protein,[25] which is approved in Europe for immunization (as a single-dose) of individuals aged ≥12 months against invasive meningococcal disease caused by *N. meningitidis*. Data from several randomized, multicentre, open-label phase III trials showed that administration of a single dose of Nimenrix™ elicited a robust immune response against the vaccine serogroups (section 2). There is also evidence suggesting that Nimenrix™ could be used for revaccination of individuals who had previously been vaccinated with polysaccharide vaccine (section 2.1.4). Furthermore, several phase III noninferiority trials showed that Nimenrix™ may be safely coadministered with other routine vaccines (including Priorix-tetra™, Infanrix™ hexa, Twinrix®, Fluarix™ and Synflorix™) without compromising the immune responses of either vaccine (section 2.3).

There is also evidence suggesting that Nimenrix™ induces immunological memory in toddlers (section 2.2.2). However, studies have indicated that circulating antibody may be needed for conferring protection against meningococcal disease, as a booster response may not be fast enough to prevent the rapid onset of disease.[72] Results from several studies in all age groups showed persistence of antibodies against the four vaccine serogroups up to 42 months after primary vaccination with Nimenrix™ when evaluated using rSBA (section 2.2).

However, a rapid waning of hSBA-MenA antibodies was observed in Nimenrix™ recipients in several trials (section 2.2), consistent with results observed with other quadrivalent conjugate meningococcal vaccines, Menveo® and Menactra®.[73] Although the clinical significance of this decline in hSBA-MenA antibody titres is unknown,[25] waning of antibody titres could result in increased susceptibility to meningococcal serogroup A disease, which may have implications for regions with high prevalence of this serogroup, such as in parts of Africa. Thus, according to the European summary of product characteristics, administration of a second dose of Nimenrix™ may be considered in individuals who are expected to be at particular risk of exposure to MenA (section 4).[25] As antibody persistence data are limited to up to 42 months after Nimenrix™ vaccination, further studies are required to assess the persistence of immune response in the long term.

Nimenrix™ was generally well tolerated in individuals, whether administered as a single vaccine or coadministered with other routine vaccinations (section 3). In addition, Nimenrix™ generally showed a similar tolerability profile to that of other comparator meningococcal vaccines, in terms of both local and systemic solicited adverse events. The incidence of grade 3 local or systemic solicited adverse events during the first 4 days following vaccination and of serious adverse events over an extended follow-up period of up to 6 months was low (<4.5%; section 3).

In conclusion, several well designed clinical trials showed that a single dose of Nimenrix™ elicited a robust immune response against meningococcal serogroups A, C, W135 and Y, and was generally well tolerated in toddlers, children, adolescents and adults. Studies also showed that Nimenrix™ can be safely administered with other routine vaccines, without compromising immune responses elicited by either vaccine. More limited data have demonstrated the persistence of immunogenicity of Nimenrix™, and longer-term follow-up studies are warranted. Nevertheless, current evidence suggests that Nimenrix™, administered as a single dose, provides a valuable vaccination option for the prevention of meningococcal disease across a broad age group, including children as young as 12 months.

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