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MenHibrix: A New Combination Meningococcal Vaccine for Infants and Toddlers

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Abstract

Objective: To review the immunogenicity and safety of the *Haemophilus influenzae* type b-*Neisseria meningitidis* serogroups C and Y tetanus toxoid conjugate vaccine (Hib-MenCY-TT) for infants and toddlers. **Data Sources:** Studies conducted in humans and limited to publication in English were identified through a MEDLINE (January 2000 to September 2013) search using the terms *Hib-MenCY-TT, MenHibrix*, and *Haemophilus influenzae type b-Neisseria meningitidis serogroups C and Y tetanus toxoid conjugate vaccine*. Clinical trial registries, Web sites, and reference citations from publications identified were reviewed for additional sources. **Study Selection and Data Extraction:** Randomized controlled trials were included to evaluate the safety and immunogenicity of Hib-MenCY-TT. Epidemiological data and recommendations from the Advisory Committee on Immunization Practices (ACIP) were also reviewed. **Data Synthesis:** Hib-MenCY-TT is available for primary vaccination of infants as a 4-dose series at 2, 4, 6, and 12 to 15 months of age. Hib-MenCY-TT has comparable immunogenicity to licensed Hib vaccines and produces high levels of *N meningitidis* antibodies against serogroups C and Y. The most common adverse events were pain and redness at the injection site, drowsiness, and irritability. **Conclusions:** Hib-MenCY-TT has been demonstrated to be a safe and immunogenic vaccination for prevention of disease caused by *N meningitidis* serogroups C and Y and *H influenzae* type b in healthy infants and toddlers. Currently, the ACIP recommends the use of Hib-MenCY-TT specifically in high-risk infants aged 6 weeks to 18 months. Hib-MenCY-TT provides the first therapeutic option for vaccination of infants as young as 6 weeks of age who are at increased risk for meningococcal disease.

Keywords

Haemophilus influenzae type b-*Neisseria meningitidis* serogroups C and Y tetanus toxoid conjugate vaccine, MenHibrix, Hib-MenCY-TT, immunization, vaccine

Introduction

Neisseria meningitidis and *Haemophilus influenzae* type b (Hib) are major causes of bacterial meningitis and other serious infections, including sepsis, bacteremia, and pneumonia. The majority of invasive *N meningitidis* infections are caused by 6 serogroups (A, B, C, W-135, X, and Y). Whereas serogroups A and X cause significant meningococcal disease worldwide, the most common serogroups responsible for disease in the United States are serogroups B, C, and Y.[1] Although the annual incidence of meningococcal disease in the United States has decreased from 0.92 cases per 100 000 population in 1998 to 0.33 cases per 100 000 population in 2007, the highest incidence of disease occurs in infants less than 1 year of age (5.38 cases per 100 000 population between 1998 and 2007).[2] Invasive infections have a notable case-fatality rate of 10% to 14%, with many survivors experiencing the burden of long-term complications such as seizures, hearing loss, and amputation.[3,4]

Hib is a Gram-negative bacteria and one of the 6 encapsulated typeable serotypes. Routine vaccination against Hib has drastically decreased the incidence of disease, particularly in children <5 years of age. Between 3% to 6% of invasive Hib infections are fatal, with 1 in 5 survivors

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Table 1. Hib and Meningococcal Vaccines Licensed in the United States.

Components	Vaccine Trade Name	FDA Approved Ages	Routine Childhood Vaccination Schedule[a]
***Haemophilus influenzae* type b-*Neisseria meningitidis* serogroups C and Y**	MenHibrix	6 Weeks to 18 months	4-Dose series at 2, 4, 6, and 12-15 months[b]
***N meningitidis* serogroups A, C, Y, and W-135**	Menactra	9 Months to 55 years	1 Dose at 11-12 years, with booster dose at 16 years
	Menveo	2 Months to 55 years	1 Dose at 11-12 years with booster dose at 16 years
	Menomune-A/C/Y/W-135	2 To 55 years	1 Dose at 11-12 years with booster dose at 16 years
***H influenzae* type b**	ActHIB	2 To 59 months	4-Dose series at 2, 4, 6, and 12 to 15 months
	Hiberix	15 To 59 months	1 Dose booster at 15 to 59 months
	PedvaxHIB	2 To 59 months	3-Dose series at 2, 4, and 12 to 15 months
***H influenzae* type b, hepatitis B antigens**	Comvax	6 Weeks to 15 months	3-Dose series at 2, 4, and 12 to 15 months
***H influenzae* type b, diphtheria toxin, tetanus toxin, acellular pertussis antigens, poliovirus**	Pentacel	6 Weeks to 4 years	4-Dose series at 2, 4, 6, and 15 to 18 months
***H influenzae* type b, diphtheria toxin, tetanus toxin, acellular pertussis antigens**	TriHIBit	15 To 18 months	1 Dose at 15 to 18 months

Abbreviations: Hib, *Haemophilus influenzae* type b; FDA, Food and Drug Administration.
[a]Recommendations of the Advisory Committee on Immunization Practices (ACIP). Only routine vaccination schedules are listed unless otherwise specified.
[b]Only for high-risk infants, including those with persistent complement component pathway, with functional or anatomical asplenia, and living in communities with meningococcal outbreaks caused by serogroups C and Y.

suffering long-term neurosensory sequelae, including hearing loss.[5]

The Hib-*Neisseria meningitidis* serogroups C and Y tetanus toxoid conjugate vaccine (Hib-MenCY-TT, MenHibrix, GlaxoSmithKline Biologicals) is a newly licensed vaccine that induces active immunization for prevention of invasive disease caused by Hib and meningococcal serogroups C (MenC) and Y (MenY).[6] This novel combination vaccine is the first meningococcal conjugate vaccine to be licensed in the United States for infants as young as 6 weeks through 18 months of age (Table 1). Previously, vaccination was not available for infants <9 months of age in the United States.[7,8] Hib-MenCY-TT joins 2 quadrivalent meningococcal vaccines: MenACWY-DT (Menactra, Sanofi Pasteur) and MenACWY-CRM (Menveo, Novartis). More recently, in August 2013, the Food and Drug Administration (FDA) approved expanding the license of MenACWY-CRM to include a 4-dose series starting at 2 months of age.[9] Of note, neither Hib-MenCY-TT nor the 2 quadrivalent meningococcal conjugate vaccines provide protection against meningococcal serogroup B (MenB), which causes the largest proportion of disease in infants.[2] Development of a vaccine against MenB has been challenging because of poor immunogenicity of vaccines targeting the polysaccharide capsule of MenB.[10,11]

Compared with polysaccharide vaccines, conjugate vaccines produce enhanced immunogenic responses in infants and young children. Conjugate vaccines are made by covalently linking capsular polysaccharide antigens to carrier proteins (eg, tetanus toxoid, diphtheria toxoid, and outer membrane protein). The carrier protein provokes a T-cell-dependent immune response that enhances immunogenicity of the conjugate vaccine and primes the immune system for immunological memory.[12]

This article reviews the immunogenicity and safety data for the use of a new combination conjugate vaccine against *H influenzae* type b and meningococcal serogroups C and Y for infants. Recommendations by the Advisory Committee on Immunization Practices (ACIP) for use of Hib-MenCY-TT in infants at increased risk for meningococcal disease will also be reviewed.

Data Sources

A MEDLINE search (January 2000 to September 2013) was conducted using the key words *Haemophilus*

influenzae type b-*Neisseria meningitidis* serogroups C and Y tetanus toxoid conjugate vaccine, Hib-MenCY-TT, and MenHibrix for clinical trials limited to those conducted in humans and published in English. Additional literature was identified through review of clinical trial registries and Web sites, including those of the manufacturer, the FDA, and the Centers for Disease Control and Prevention. Meningococcal and Hib disease epidemiology literature and ACIP recommendations were also reviewed.

Pharmacology

Hib-MenCY-TT contains 3 distinct polysaccharide-protein conjugates each covalently bound to tetanus toxoid. Each 0.5-mL dose contains 2.5 µg polyribosyl-ribitol-phosphate (PRP) capsular polysaccharide of Hib, 5 µg of *N meningitidis* serogroups C capsular polysaccharide, and 5 µg *N meningitidis* serogroups Y capsular polysaccharide. This conjugation of polysaccharides to a carrier protein improves the immune response and increases the immunogenicity of the vaccine in infants and young children.[12] Of note, the tetanus toxoid carrier protein does not convey immunity against tetanus and is not a substitute for routine tetanus vaccination. Additionally, each dose also contains 96.8 µg of trometamol-HCl, 12.6 mg of sucrose, and ≤0.72 µg of residual formaldehyde. Hib-MenCY-TT is both preservative and latex free.[6]

Clinical Trials

Immunogenicity Against Hib and N meningitidis Serogroups C and Y

Because placebo-controlled trials to demonstrate prevention of disease caused by meningococcal serogroups C and Y and Hib would be unethical, the effectiveness of Hib-MenCY-TT was instead demonstrated by serological assays. Whereas demonstration of noninferior antibody response in comparison to previously licensed vaccines has been utilized for meningococcal vaccine licensure in adults and children older than 2 years, no previous meningococcal vaccines were available for comparison in infants as young as 2 months of age. Based on recommendations from the Vaccines and Related Biological Products Advisory Committee in 2011, the use of bactericidal antibody as measured by human complement-based serum bactericidal activity (hSBA) was deemed as an acceptable method to infer effectiveness of meningococcal antigens in Hib-MenCY-TT in children <2 years of age.[13] A titer of ≥1:4 has previously been associated with protection from meningococcal serogroup C, and the same is accepted for serogroup Y.[13,14] A higher conservative threshold antibody titer of ≥1:8 was selected for both serogroups C and Y to demonstrate the effectiveness of Hib-MenCY-TT.[13]

Effectiveness in the prevention of Hib was also based on immunogenicity data. An anti-PRP level of 0.15 µg/mL has been deemed a minimum protective level based on previous antibody and efficacy studies.[15-17] Because levels of protective antibodies elicited by the capsular polysaccharide of Hib decline over time, a higher anti-PRP level of 1.0 µg/mL, measured shortly after immunization, has been accepted as the threshold for predicting protection against Hib over a longer period of at least 1 year.[18,19]

The immunogenicity and safety of Hib-MenCY-TT has been evaluated in clinical trials of more than 7500 healthy infants and toddlers.[13] Clinical studies were conducted in the United States, Australia, Mexico, Belgium, and Germany.[7] Studies evaluated Hib-MenCY-TT as a 3-dose series in infancy and as a fourth dose in toddlers as well as antibody persistence up to 5-years postvaccination. Details regarding the phase II trials have been previously reviewed.[7,20] The primary focus of this review is the large phase III randomized, international study that evaluated the safety and immunogenicity of Hib-MenCY-TT in healthy infants.[21]

Pivotal Immunogenicity Trial

The immunogenicity and safety of Hib-MenCY-TT was evaluated in the United States, Australia, and Mexico in a phase 3, randomized, single-blind controlled trial in 4180 healthy infants (Hib-MenCY-TT, n = 3136; Hib, n = 1044). At 2, 4, 6, and 12 to 15 months of age, participants received either Hib-MenCY-TT or the licensed Hib tetanus toxoid conjugate vaccine (Hib-TT, ActHib) and Hib conjugated to *N meningitidis* outer membrane protein (Hib-OMP, PedvaxHIB) at 12 to 15 months along with routine pediatric immunizations. Three different study cohorts were established based on participant enrollment location. For the 3-dose primary vaccination series, the United States cohort was evaluated for safety and immunogenicity and included 695 participants (Hib-MenCY-TT, n = 522; Hib, n = 173), whereas a second cohort evaluated 2989 children (Hib-MenCY-TT, n = 2242; Hib, n = 747) from all 3 countries for safety end points. For descriptive purposes, the safety and immunogenicity of Hib-MenCY-TT were also evaluated for a third cohort of 181 infants (Hib-MenCY-TT, n = 135; Hib, n = 46) from a single center in Mexico. The fourth vaccination dose phase of the study evaluated a total of 3692 infants (Hib-MenCY-TT, n = 2769; Hib, n = 923). Of those infants, 690 from the US cohort (Hib-MenCY-TT, n = 513; Hib, n = 177) were evaluated for predose 4 persistence, and 521 from the US cohort (Hib-MenCY-TT, n = 389; Hib, n = 132) were further included in the postdose 4 immunogenicity evaluation.[21]

N meningitidis hSBA bactericidal titers were measured for serogroups C (hSBA-MenC) and Y (hSBA-MenY) and reported for a threshold of ≥1:8. Enzyme-linked

immunosorbent assay (ELISA) was utilized to measure antibodies against *N meningitidis*. Immunogenicity for the US cohort against meningococcal serogroups C and Y was demonstrated if the lower limit of the 95% CI in the percentage of participants with hSBA-MenC or hSBA-MenY titer of ≥1:8 was ≥90% after dose 4 and if the lower limit of the 95% CI of the postdose 4/predose 4 geometric mean antibody titer (GMT) ratio was 2 or greater.[21]

Anti-PRP antibodies were also measured by ELISA and reported for concentrations ≥0.15 μg/mL and ≥1.0 μg/mL. Noninferiority between the anti-PRP antibody responses of Hib-MenCY-TT and the control vaccines was established if the lower limit of the 2-sided 95% CI describing the difference in the percentage of those with anti-PRP concentrations of ≥1.0 μg/mL was −10% or higher when evaluated after the third and fourth doses.[21]

Lot-to-lot vaccine consistency was also evaluated, and the vaccines were considered consistent if the 2-sided 95% CI for the geometric mean concentration or GMT ratio between lots was within the interval (0.5; 2.0) for each comparison.[21]

Secondary end points included the immunogenicity of MenC and MenY 1 month after dose 3. Immunogenicity for this follow-up time point was determined if the lower limit of the 95% CI of the percentage with a bactericidal titer of ≥1:8 was ≥90% for MenC and ≥85% for MenY serogroups. Safety was monitored by soliciting local and general symptoms for 4 days (days 0-3) after vaccination, as recorded by parents or guardians. Other adverse events were recorded for 30 days after each vaccine dose, whereas serious adverse events (SAEs) were monitored until 6 months after dose 4. All study participants who received at least 1 study or control vaccination were included in the safety analysis.[21]

The percentage of infants who achieved hSBA titers ≥1:8 after vaccination at 2, 4, and 6 months was 98.8% for serogroup C and 95.8% for serogroup Y. Prior to dose 4, hSBA titers remained ≥1:8 for at least 96% and 92.8% of participants against MenC and MenY, respectively. Following dose 4, the percentage of participants with hSBA titers ≥1:8 increased to 98.5% and 98.8% against MenC and MenY, respectively. The corresponding GMTs increased 12-fold (95% CI = 10.4-13.8) against MenC and by 11.8-fold (95% CI = 10.2-13.8) against MenY.[21]

At 1 month after dose 3, the anti-PRP antibody levels were ≥1.0 μg/mL for 96.3% of infants who received Hib-MenCY-TT compared with 91.2% of infants who received the control vaccines, demonstrating noninferiority (group difference = 5.10%; 95% CI = 1.20-10.49). At 1 month after dose 4 also, noninferiority was demonstrated, with 99.2% of participants in each group retaining anti-PRP concentrations ≥1.0 μg/mL.[21]

The safety profile of Hib-MenCY-TT was similar, in general, to that of Hib control vaccines. Pain at the injection site, drowsiness, and irritability were the most common symptoms after each dose in both treatment groups. Pain, redness, swelling, and irritability tended to be reported less after vaccination with Hib-MenCY-TT when compared with that in controls.[21]

Antibody Persistence Trials

Persistence of immunogenicity was evaluated in a single-blind, US-based study that evaluated the fourth vaccination dose given at 12 to 15 months of age. A total of 690 participants had previously been randomized to either Hib-MenCY-TT or the Hib-TT conjugate vaccine for primary vaccination at 2, 4, and 6 months of age, of whom 498 received a fourth dose, and 270 participated in the 1-year persistence study,[22] 201 in the 3-year persistence study,[23] and 181 in the 5-year persistence study.[23] All those who received Hib-MenCY-TT for the initial 3 doses were given Hib-MenCY-TT for the fourth dose at 12 to 15 months of age. Children who received Hib vaccine for the initial 3 doses were rerandomized to receive Hib-MenCY-TT or Hib for the fourth dose. All patients concomitantly received the 7-valent pneumococcal conjugate vaccine (PCV7), in accordance with the childhood immunization schedule at the time when the study was conducted.[23]

Persistence of immunogenicity was based on the primary end points of anti-PRP levels ≥0.15 μg/mL and hSBA titers ≥1:8 against MenC and MenY. At 5 years, anti-PRP antibody levels were ≥0.15 μg/mL in 98.8% of participants who received all 4 doses as Hib-MenCY-TT, 97.3% of participants who received only the fourth dose as Hib-MenCY-TT, and 92.3% of participants who received all 4 doses as Hib. Immunogenicity against MenC and MenY was demonstrated in 82.9% and 69.5% of participants who received only Hib-MenCY-TT, and 73.5% and 54.3% of participants who received Hib-MenCY-TT for the fourth dose only, and 21.1% and 18.4% of participants who received the Hib control, respectively. Although the Hib control group did not receive vaccination against *N meningitidis*, the observed immunogenicity rates can be attributed to normal childhood acquisition of natural immunity. Collectively, protective antibody levels were demonstrated at 5 years whether Hib-MenCY-TT was given as a complete series or as a single toddler dose.[23]

Adverse Events

The most commonly reported adverse events among phase II and phase III trials were redness and pain at the injection site, drowsiness, and irritability.[21,22,24] Most studies recorded solicited events up to 8 days (days 0-7) after vaccination,[22,24-26] with other adverse events monitored for 31 days[21,22,24-27] and SAEs evaluated for 6 months postvaccination.[21,22,25,27] Incidence of redness at the injection site was lower in the Hib-MenCY-TT group compared with Hib-TT

($P < .05$) controls.[25] Drowsiness, including drowsiness preventing normal daily activities or prompting medical attention, was lower in the Hib-MenCY-TT group compared with MenC and Hib controls ($P < .05$).[24,26] Irritability[21,25] and pain[21,25,26] were significantly lower in the Hib-MenCY-TT group compared with the Hib-TT group ($P < .05$ in all cases). Swelling (grade 3 swelling defined as preventing normal activity) was lower in the Hib-MenCY-TT versus Hib-TT ($P < .05$),[21,25] Hib-OMP,[21] and MenC ($P < .05$) groups.[24]

SAEs such as spontaneous pain or pain on moving limb, complete loss of appetite, redness or swelling >30 mm, fever >40°C, or drowsiness or irritability that prevented normal activity were similar in a phase III study between the Hib-MenCY-TT group and Hib controls (5.2% vs 6.2%, respectively; $P = .2662$).[21] In a phase II study, 1 patient receiving Hib-MenCY-TT experienced a hypotonic-hyporesponsive episode, considered a SAE possibly related to Hib-MenCY-TT but recovered 1 day after vaccination without sequelae.[27] Incidence of fever varied among studies, with 1 study reporting tendency of lower incidence with Hib-MenCY-TT compared with MenC and Hib control,[27] and 2 studies reporting significantly fewer cases with Hib-MenCY-TT than Hib control ($P < .05$ in both studies).[25,26] Two cases of serious fever (>40°C) were reported in the Hib-MenCY-TT group in a phase III trial, but both resolved in 1 day.[21]

Safety was also evaluated in a pooled analysis of more than 8500 infants who received a 4-dose series of either Hib-MenCY-TT (n = 6414) or Hib vaccines (n = 2157), in addition to routine age-appropriate vaccines.[28] The analysis combined 2 primary vaccination and 2 dose 4 studies.[21,29] Solicited local (injection site pain, redness, and swelling) and general (fever ≥38°C, drowsiness, irritability, and loss of appetite) symptoms occurred at similar rates in both groups, with the exceptions of pain at the injection site and irritability, which were reported at significantly ($P < .05$) lower rates after vaccination with Hib-MenCY-TT than Hib.[28]

Similar rates were observed for SAEs, new onset of chronic disease, rash, and adverse events prompting emergency room visits after vaccination with either Hib-MenCY-TT or Hib vaccines. Only anemia was reported more frequently in the Hib group than the Hib-MenCY-TT group (0.1% vs 0.0%, respectively; $P = .03$). Viral gastroenteritis leading to an emergency room visit was reported more frequently in the Hib-MenCY-TT group than in the Hib group (0.2% vs 0.0%, respectively; $P < .05$).[28]

Drug Interactions

Concomitant Vaccine Administration

To allow for safe incorporation into the childhood vaccination schedule, the coadministration of Hib-MenCY-TT with other primary infant and toddler vaccinations has been investigated to ensure acceptable immune responses. Concomitant age-appropriate vaccinations were permitted in phase II and phase III clinical trials of Hib-MenCY-TT.[21-28] Additionally, 2 pooled analyses have evaluated the potential for immune interference with PCV7 and combined diphtheria-tetanus-acellular pertussis-hepatitis B-inactivated poliovirus vaccine (DTaP-HepB-IPV) in infants and measles-mumps-rubella (MMR) and varicella vaccines in toddlers. Immunological responses to PCV7, DTaP-HepB-IPV, MMR, and varicella were noninferior after coadministration with Hib-MenCY-TT as compared with US-licensed Hib vaccines in both analyses.[30,31]

Marshall et al[30] investigated the immune response to PCV7 (Prevnar) and DTaP-HepB-IPV (Pediarix) when separately coadministered with either Hib-MenCY-TT or Hib-TT at 2, 4, 6 (n = 606), and 12 to 15 months of age (n = 366). Postvaccination immune responses, as measured by antibody concentration, for all pneumococcal serotypes present in PCV7 1 month after the third and fourth doses were noninferior when PCV7 was coadministered with Hib-MenCY-TT versus Hib-TT (ActHIB). One month after the third dose of DTaP-HepB-IPV, no statistical differences in concentration of pertussis, diphtheria, tetanus, hepatitis B, and poliovirus antigens were observed after coadministration with Hib-MenCY-TT versus Hib-TT.

Concomitant vaccination with measles, mumps, rubella (M-M-R) and varicella (Varivax) vaccines were investigated in 1257 toddlers who were given a fourth dose of Hib-MenCY-TT or Hib-OMP (PedvaxHIB) at 12 to 15 months of age.[31] Immune responses at 42 days postvaccination, defined by seropositivity data obtained from pooled immunogenicity data from 2 trials,[21,27] were statistically noninferior when coadministered with a fourth dose of Hib-MenCY-TT as compared with those in the Hib-OMP control group.[31]

Insufficient data are available from clinical trials to determine a lack of immune interference between Hib-MenCY-TT and coadministration with influenza, rotavirus, or hepatitis A vaccines.[13]

Contraindications, Warnings, and Precautions

Vaccinations should be given in a setting equipped to manage acute anaphylactic reactions. Hib-MenCY-TT is contraindicated in individuals with a history of severe allergic reaction to any component of Hib-MenCY-TT or previous vaccination with any meningococcal-, *H influenzae* type b-, or tetanus toxoid-containing vaccine.[6]

Among premature infants, intramuscular vaccine injection has been associated with apnea. Therefore, the decision to administer intramuscular vaccine to a premature infant

should be based on the individual's medical status as well as a risk versus benefit assessment.[6]

Although the safety and efficacy of Hib-MenCY-TT has not been established in immunocompromised children, the ACIP recommends use of Hib-MenCY-TT in patients with persistent complement component pathway deficiency or functional or anatomical asplenia, including sickle cell disease, as discussed later.[6,32]

Dosage and Administration

Hib-MenCY-TT is supplied only as a single-dose vial. Each 0.5-mL dose in the 4-dose series (given at 2, 4, 6, and 12 through 15 months of age) is administered intramuscularly immediately after reconstitution of the lyophilized vaccine with the accompanying saline diluent. The first dose can be given as early as 6 weeks of age and the fourth dose as late as 18 months of age. The anterolateral aspect of the thigh is the preferred injection site for children less than 1 year of age. The deltoid muscle may be used in older children.[6]

Recommendations

After the FDA approval of Hib-MenCY-TT in June 2012, the ACIP published updated recommendations for the prevention of meningococcal disease in infants. Given the current historically low rates of *N meningitidis* in the United States and the lack of a vaccine that includes serogroup B protection, routine vaccination of all infants is not recommended at this time. Rather, a strategy targeting vaccination only for infants at increased risk of meningococcal disease is recommended. Hib-MenCY-TT, as a 4-dose series, should be administered to infants at increased risk for meningococcal disease, which includes infants with persistent complement component pathway deficiency or functional or anatomical asplenia.[32] Of note, the prescribing information for Hib-MenCY-TT cautions that immunosuppressed children may have an inadequate immune response to vaccination, and the vaccine's safety and immunogenicity has only been studied in healthy infants and toddlers.[6]

The ACIP also recommends Hib-MenCY-TT for healthy infants residing in communities with meningococcal outbreaks caused by MenC or MenY. Broader meningococcal protection against serogroups A and W-135 is recommended for infants and children traveling to the Hajj or to the "meningitis belt" of sub-Saharan Africa, where endemic rates of meningococcal disease are high. Because these serogroups are not included in Hib-MenCY-TT, such infants should receive an age-appropriate quadrivalent meningococcal conjugate vaccine prior to travel. Current ACIP recommendations for quadrivalent meningococcal conjugate vaccination options include a 2-dose series of MenACWY-D (Menactra) for infants aged 9 to 23 months or a single dose of either MenACWY-D (Menactra) or MenACWY-CRM (Menveo) for children aged 2 years and older.[32]

Summary

The available data from clinical trials in healthy infants and toddlers demonstrates that Hib-MenCY-TT generates a robust immune response against *H influenzae* type b and *N meningitidis* serogroups C and Y when administered as a 4-dose series concomitantly with recommended primary infant vaccinations.[21] In clinical trials, Hib-MenCY-TT has shown a clinically acceptable safety profile that is comparable with that of other childhood vaccinations.[21] Persistence of protective antibody levels against Hib, MenC, and MenY has also been demonstrated for up to 5 years after the fourth dose of Hib-MenCY-TT.[23]

Current ACIP recommendations support the use of Hib-MenCY-TT as a 4-dose series but only for those infants and toddlers at high risk for meningococcal disease.[32] Hib-MenCY-TT allows for early immunization in the age group most vulnerable to serious *H influenzae* or *N meningitidis* infections. It also provides an additional source of Hib vaccination without adding additional injections to the primary immunization schedule for children. However, there remains an unmet need in the United States for an effective meningococcal vaccine targeting serogroup B.[10,11] Further information is also needed to evaluate Hib-MenCY-TT with other concomitant infant vaccines, including the hepatitis A vaccine, influenza vaccine, and rotavirus vaccine and to confirm the long-term persistence of protective antibodies.

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References

1. Harrison LH. Epidemiological profile of meningococcal disease in the United States. *Clin Infect Dis*. 2010;50(suppl 2):S37-S44. doi:10.1086/648963.
2. Cohn AC, MacNeil JR, Harrison LH, et al. Changes in *Neisseria meningitidis* disease epidemiology in the United States, 1998-2007: implications for prevention of meningococcal disease. *Clin Infect Dis*. 2010;50:184-191. doi:10.1086/649209.
3. Centers for Disease Control and Prevention. Meningococcal disease. http://www.cdc.gov/meningococcal/clinical-info.html. Accessed March 15, 2012.

4. American Academy of Pediatrics. Meningococcal infections. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Disease*. 29th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2012:500-509.
5. Centers for Disease Control and Prevention. *Haemophilus influenzae* disease (including Hib). http://www.cdc.gov/hidisease/clinicians.html. Accessed March 15, 2012.
6. Menhibrix (meningococcal groups C and Y and *Haemophilus* b tetanus toxoid conjugate vaccine) [product information]. Research Triangle Park, NC: GlaxoSmithKline; 2012.
7. Bryant KA, Marshall GS. *Haemophilus influenza* type b-*Neisseria meningitidis* serogroups C and Y tetanus toxoid conjugate vaccine for infants and toddlers. *Expert Rev Vaccines*. 2011;10:941-950. doi:10.1586/erv.11.90.
8. Poland GA. Prevention of meningococcal disease: current use of polysaccharide and conjugate vaccines. *Clin Infect Dis*. 2010;50(suppl 2):S45-S53. doi:10.1086/648964.
9. Food and Drug Administration. August 1, 2013 approval letter: Menveo. http://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm363785.htm. Accessed August 25, 2013.
10. Cohn AC, Harrison LH. Meningococcal vaccines: current issues and future strategies. *Drugs*. 2013;73:1147-1155. doi:10.1007/s40265-013-0079-2.
11. Nadel S. Prospects for eradication of meningococcal disease. *Arch Dis Child*. 2012;97:993-998. doi:10.1136/archdischild-2012-302036.
12. Goldblatt D. Conjugate vaccines. *Clin Exp Immunol*. 2000;119:1-3.
13. Food and Drug Administration. Clinical review of biologics license application for GlaxoSmithKline Biologicals' meningococcal C and Y and *Haemophilus* b conjugate vaccine. http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM315680.pdf. Accessed March 15, 2012.
14. Goldschneider I, Gotschlich EC, Artenstein MS. Human immunity to the meningococcus: I. The role of humoral antibodies. *J Exp Med*. 1969;129:1307-1326.
15. Peltola H, Käyhty H, Sivonen A, Mäkelä PH. *Haemophilus influenzae* type b capsular polysaccharide vaccine in children: a double-blind field study of 100,000 vaccinees 3 months to 5 years of age in Finland. *Pediatrics*. 1977;60:730-737.
16. Robbins JB, Parke JC, Schneerson R, Whisnant JK. Quantitative measurement of "natural" and immunization-induced *Haemophilus influenzae* type b capsular polysaccharide antibodies. *Pediatr Res*. 1973;7:103-110.
17. Ambrosino DM, Landesman SH, Gorham CC, Siber GR. Passive immunization against disease due to *Haemophilus influenzae* type b: concentrations of antibody to capsular polysaccharide in high-risk children. *J Infect Dis*. 1986;153:1-7.
18. Anderson P. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis*. 1984;149:1034-1035.
19. Käyhty H, Peltola H, Karanko V, Mäkelä PH. The protective level of serum antibodies to the capsular polysaccharide of *Haemophilus influenzae* type b. *J Infect Dis*. 1983;147:1100.
20. Perry CM. Meningococcal groups C and Y and Haemophilus b tetanus toxoid conjugate vaccine (HibMenCY-TT; MenHibrix®): a review. *Drugs*. 2013;73:703-713. doi:10.1007/s40265-013-0048-9.
21. Bryant KA, Marshall GS, Marchant CD, et al. Immunogenicity and safety of *H influenzae* type b-*N meningitidis* C/Y conjugate vaccine in infants. *Pediatrics*. 2011;127: e1375-e1385. doi:10.1542/peds.2009-2992.
22. Marshall GS, Marchant CD, Blatter M, et al. Immune response and one-year antibody persistence after a fourth dose of a novel *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine (HibMenCY) at 12 to 15 months of age. *Pediatr Infect Dis J*. 2010;29:469-471. doi:10.1097/INF.0b013e3181cdd379.
23. Marshall GS, Blatter M, Marchant C, Aris E, Mesaros N, Miller JM. Antibody persistence for up to 5 years after a fourth dose of *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine (Hibmency-TT) given at 12-15 months of age. *Pediatr Infect Dis J*. 2013;32:662-668. doi:10.1097/INF.0b013e3182840e35.
24. Habermehl P, Leroux-Roels G, Sanger R, Machler G, Boutriau D. Combined *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C (HibMenC) or serogroups C and Y-tetanus toxoid conjugate (and HibMenCY) vaccines are well-tolerated and immunogenic when administered according to the 2,3,4 months scheduled with a fourth dose at 12-18 months of age. *Hum Vaccin*. 2010;6:640-651.
25. Marchant CD, Miller JM, Marshall GS, et al; HibMenCY-TT 005 Study Group. Randomized trial to assess immunogenicity and safety of *Haemophilus influenza* type b and *Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine in infants. *Pediatr Infect Dis J*. 2010;29:48-52. doi:10.1097/INF.0b013e3181c3ce88.
26. Nolan T, Lambert S, Roberton D, et al. A novel combined *Haemophilus influenzae* type b-*Neisseria meningitidis* serogroups C and Y-tetanus-toxoid conjugate vaccine is immunogenic and induces immune memory when co-administered with DTPa-HBV-IPV and conjugate pneumococcal vaccines in infants. *Vaccine*. 2007;25:8487-8499.
27. Nolan T, Richmond P, Marshall H, et al. Immunogenicity and safety of an investigational combined *Haemophilus influenzae* type B-*Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine. *Pediatr Infect Dis J*. 2011;30:190-196. doi:10.1097/INF.0b013e3181fcb2bf.
28. Rinderknecht S, Bryant K, Nolan T, et al. The safety profile of *Haemophilus influenzae* type b-*Neisseria meningitidis* serogroups C and Y tetanus toxoid conjugate vaccine (HibMenCY). *Hum Vaccin Immunother*. 2012;8:304-311. doi:10.4161/hv.18752.
29. Bryant K, Marshall GS, Marchant CD, et al. *Haemophilus influenzae* type b–*Neisseria meningitidis* serogroups C and Y tetanus toxoid conjugate vaccine (HibMenCY) was immunogenic with an acceptable safety profile in two Phase 3 trials (abstract no. 22739). In: *Programs and Abstracts of the 44th National Immunization Conference*.
30. Marshall GS, Marchant CD, Blatter M, Friedland LR, Aris E, Miller JM. Co-administration of a novel *Haemophilus influenzae*

type b and *Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine does not interfere with the immune response to antigens contained in infant vaccines routinely used in the United States. *Hum Vaccin*. 2011;7:258-264.
31. Bryant KA, McVernon J, Marchant CD, et al. Immunogenicity and safety of measles-mumps-rubella and varicella vaccines coadministered with a fourth dose of *Haemophilus influenzae* type b and *Neisseria meningitidis* serogroups C and Y-tetanus toxoid conjugate vaccine in toddlers. *Hum Vaccin Immunother*. 2012;8:1036-1041. doi:10.4161/hv.20357.
32. Centers for Disease Control and Prevention. Infant meningococcal vaccination: advisory committee on immunization practices (ACIP) recommendations and rationale. *Morb Mort Wkly Rep*. 2013;62:52-54.