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Safety review: Two outer membrane vesicle (OMV) vaccines against systemic *Neisseria meningitidis* serogroup B disease

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Abstract

MenBvac is an OMV vaccine against systemic serogroup B *Neisseria meningitidis* disease. MenBvac was developed for control of a B:15:P1.7,16 subtype epidemic in Norway and administered to 180,000 subjects in 28 clinical studies. MeNZB, a daughter vaccine of MenBvac, was developed for a clonal B:4:P1.7b,4 epidemic in New Zealand and administered to 1 million people <20 years. The vaccines were similar regarding reactogenicity profile. Serious adverse events (SAEs) in general and particularly neurologic SAEs were very rare.

Despite frequently reported local reactions and fever in those under 5 years, these OMV-based vaccines containing 25 μg antigen can be considered safe for use in all age groups.

Keywords: Reactogenicity; Neurological adverse events; Epidemiological follow-up

1. Introduction

The vaccines described here, MenBvac and MeNZB, are intended for intramuscular injection to provide immunity against serious systemic disease caused by *Neisseria meningitidis* serogroup B in infants, children and adolescents. Systemic serogroup B meningococcal disease is manifest in the form of septicaemia or meningitis. Usually, the disease develops rapidly and the fatality rate is approximately 4–10%. Those who survive frequently suffer from permanent tissue damage and neurological sequelae [1–6].

In an exceptional national effort MenBvac was evaluated in 28 studies including three large phase III trials, and an epidemiological follow-up study was performed on a cohort of persons born in 1972–1977 and living in Norway in 1988–1990, a total of 345,000 persons of whom 149,000 had been vaccinated [7].

For the two vaccines reviewed here safety data are available for 180,000 subjects (approx. 350,000 doses) who have received MenBvac in clinical studies and 1391 subjects who have received MeNZB in clinical studies, supported by enhanced surveillance data from 1 million children and young people (approx. 3 million doses) in New Zealand who have received MeNZB.

The purpose of this compilation of safety data was to further review whether OMV vaccines, despite the well documented high incidence of local and systemic reactions, from the safety point are an acceptable option for future immunisation campaigns.

2. Materials and methods

2.1. Vaccines

MenBvac was prepared from a B:15:P1.7,16 meningococcal strain (44/76) by fermenter growth and extraction of the bacteria with the detergent deoxycholate [8]. Similarly,

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MeNZB was prepared from a B:4:P1.7b,4 meningococcal strain (NZ98/254) [9]. Intact and fragments of OMVs were purified by ultracentrifugation and adsorbed to $Al(OH)_3$. One vaccine dose (0.5 ml) of either vaccine contained 25 μg antigen, 1.65 mg $Al(OH)_3$ and excipients. The preservative thiomersal was used until 2000 (when it was removed in accordance with EMEA/CPMP/1578/00). Placebo-controlled studies used 1.65 mg $Al(OH)_3$ per dose. The vaccines were administered intramuscularly in the deltoid region of the non-dominant arm according to a 2-, 3- or 4-dose schedule.

2.2. Vaccinees

All studies were conducted according to at the time existing international guidelines on good clinical practice. At least one dose of the MenBvac vaccine has been given to approximately 180,000 subjects. Twenty of the studies on MenBvac were conducted in Norway and the others in Iceland, Chile [10], U.S., New Zealand [11] and U.K. The majority of the subjects were 13 years or older. A total of 62 infants, 64 toddlers (16–24 months old), 61 children aged 2–4 years and 61 children aged 8–12 years received MenBvac. Ninety-eight adults, 547 8–12-year olds, 261 16–24-month-old toddlers, 235 6–8-month-old infants and 250 6–10-week-old infants received at least one dose of MeNZB in clinical studies. In July 2006, a total of 3 million doses of MeNZB had been administered in a national vaccination campaign for all <20 years of age in New Zealand.

2.3. Safety monitoring

In phase I and II studies on MenBvac and MeNZB conducted in adults, adolescents and 8–12 years old school children local (i.e., erythema, swelling, induration and pain at the injection site) and systemic reactions (i.e., nausea, malaise, myalgia, arthralgia and headache) and body temperature were recorded for 2–7 days after each dose. The parents/legal guardians of infants and 16–24 months old toddlers were requested to record local (i.e., erythema, induration, swelling and tenderness at the injection site) and systemic reactions (i.e., vomiting, diarrhoea, change in eating habits, irritability, sleepiness and rash) and body temperature. All other adverse events (AEs) were collected during 7 days after each dose. Serious adverse events (SAEs) and/or AEs necessitating a physician's visit and/or resulting in the subject's withdrawal from the study were collected throughout the trials.

In the phase III studies on MenBvac systemic meningococcal disease was to be reported as an endpoint and not as an SAE. Only at least possibly related SAEs were collected in these studies.

For MenBvac the passive surveillance system used during the phase III trials was complemented with an epidemiological follow-up study performed on a cohort of persons born in 1972–1977 and living in Norway during the efficacy trials, a total of 345,000 persons of whom 149,000 had been vaccinated. National hospital discharge registers were searched for cases of specified neurological diagnoses in the cohort. The patients' hospital records were reviewed by the independent ethical monitoring committee of the phase III trials. Any causes and the possibility of an association with MenBvac were also reviewed by a multidisciplinary working board. The incidence in two immediate post-vaccination periods (30 and 56 days, respectively) was compared to the incidence outside these periods and in non-vaccinated individuals.

3. Results

The incidence of local (injection site) and systemic reactions was high after administration of MenBvac or MeNZB. In the clinical studies local and systemic reactions were more commonly reported in the MenBvac and MeNZB groups than in $Al(OH)_3$-containing placebo/other control groups. However, local and systemic reactions were commonly reported also in the placebo groups [12].

In all age groups local reactions of short duration were very common. Pain at the injection site was most frequently reported among the oldest subjects (Fig. 1).

Most systemic reactions were mild or moderate in severity and of short duration. Among infants and toddlers, irritability, change in eating habits, impaired sleeping, diarrhoea and vomiting were common or very common after vaccination (Fig. 2). However, these occurred at a similar rate in the control vaccine group. In 8–12-year olds, adolescents and adults, commonly or very commonly reported AEs included headache, malaise, myalgia, nausea and arthralgia. The incidence and intensity of local and systemic reactions were similar after the first, second, third, and when applicable, the fourth dose.

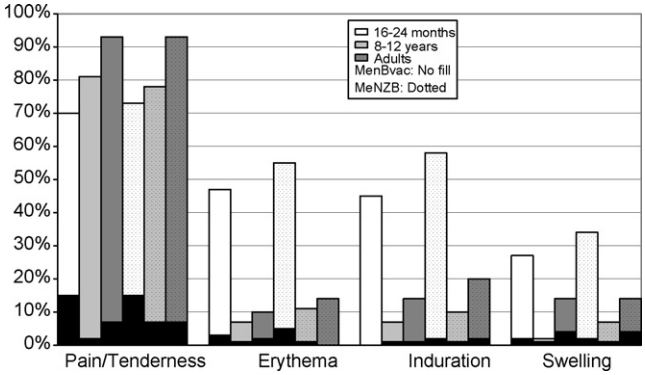

Fig. 1. Incidence of local reactions over all doses of MenBvac or MeNZB given during the studies. The black areas in the bars represent the percentage of doses associated with reactions of the most severe intensity. Erythema, induration and swelling were categorized as none, mild (10–<26 mm in diameter), moderate (26–50 mm in diameter) or severe (>50 mm in diameter). Number of MenBvac doses included: 188 doses in toddlers, 176 doses in children aged 8–12 years and 162 doses in adults. Number of MeNZB doses included: 772 in toddlers, 1606 in school children aged 8–12 years and 283 in adults.