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## Critically Appraised Articles

### Is Bexsero<sup>®</sup> effective? The first available data

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**English key words:** child, preschool; heart arrest; intubation, intratracheal; survival analysis.

**Spanish key words:** análisis de supervivencia; infancia; intubación intratraqueal; parada cardíaca.

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# Is Bexsero® effective? The first available data

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**Original article:** Parikh SR, Andrews NJ, Beebeejaun K, Campbell H1, Ribeiro S, Ward C, *et al.* Effectiveness and impact of a reduced infant schedule of 4CMenB vaccine against group B meningococcal disease in England: a national observational cohort study. *Lancet.* 2016;388:2775-82.

## Abstract

**Authors' conclusions:** in UK children, the two-dose Bexsero® priming schedule is highly effective in preventing meningococcal disease B.

**Reviewers' commentary:** if a two-dose vaccination schedule of Bexsero® was implanted in our population, with the current rates of meningococcal disease it would be necessary to vaccinate 388 652 children to prevent a case; however, the severity of the disease, the potential sequelae it can cause and the possible increase in disease rates at any time make the vaccine impact certainly much more favorable.

**Key words:** meningococcal disease; vaccines; 4CMenB; Bexsero; effectiveness.

## ¿Es efectiva Bexsero®? Los primeros datos disponibles

### Resumen

**Conclusiones de los autores del estudio:** en niños de Reino Unido, un esquema de primovacunación con dos dosis de Bexsero® es altamente efectivo en prevenir enfermedad meningocócica B.

**Comentario de los revisores:** si se implantara en nuestra población un esquema de vacunación de dos dosis de Bexsero®, con las tasas actuales de enfermedad meningocócica sería necesario vacunar a 388 652 niños para prevenir un caso; no obstante, la gravedad de la enfermedad, las secuelas potenciales que puede causar y el posible de aumento de tasas de enfermedad en cualquier momento, hacen que el impacto vacunal sea sin duda mucho más favorable.

**Palabras clave:** enfermedad meningocócica; vacunas; 4CMenB; Bexsero; efectividad.

## STRUCTURED ABSTRACT

**Objective:** to assess the effectiveness and impact in children vaccinated with Bexero® of the administration of the vaccine in the first ten months following its inclusion in the national immunisation programme.

**Design:** analytical observational nationwide study of simultaneous cohorts with a prospective cohort and a retrospective cohort.

**Setting:** Public Health England (PHE) provided epidemiological data on vaccination and cases of meningococcal B (MenB) disease in children in England.

**Study population:** the vaccine was offered to infants born in July 2015 and after at ages 2 and 4 months, and to infants aged 3 and 4 months born in May and June of 2015. Cohorts were defined based on whether the children had received one or two doses of the vaccine. Children that developed disease after the first dose were excluded from the second dose. Doses were discounted if MenB disease was diagnosed within 14 days of vaccination, and children diagnosed after the second dose were considered to have received a single dose in the analysis. The unexposed cohort consisted of children of the same age during the same months in the four years preceding the study.

**Risk factor assessment:** the study observed the number of cases of MenB disease diagnosed in the vaccinated cohort over a ten-month period; the data were collected by the PHE national surveillance system.

**Outcome assessment:** vaccine effectiveness was assessed using the screening method, comparing the proportion of MenB disease cases detected by means of a meningococcal antigen typing system (MATS) with the proportion of vaccinated children in the total vaccine-eligible population (vaccine coverage). The authors also analysed the number of cases of MenB diagnosed during this period in children aged less than 5 years (excluding the vaccinated cohort) (incidence rate ratio in vaccine-eligible children) and compared it with the cases in the equivalent cohorts in the four previous years (incidence rate ratio in vaccine-ineligible children) by means of a Poisson regression model adjusted for changes in disease trends. A time series model was fitted to estimate the incidence of MenB disease in the period under study and for comparison with the actual number of cases. The authors used the incidence rate ratio (IRR) and assessed the impact of the vaccine by means of the relative incidence rate ratio (RIRR).

**Main results:** the two-dose vaccine effectiveness was high, of 82.9% (95 CI: 24.1 to 95.2) against all MenB strains and 94.4% for vaccine-covered strains. In the ten months of follow-up, the incidence of MenB dropped by half in vaccinated children compared to the incidence predicted based on previous cohorts (IRR: 0.50; 95 CI: 0.36 to 0.71) (37 versus 74 cases), with a relative reduction of 42% attributable to vaccination (RIRR: 0.58; 95 CI: 0.40 to 0.85). In children aged less than 5 years, there was a 14% reduction in MenB cases in this period compared to previous cohorts (IRR: 0.86; 95 CI: 0.73 to 1.01), but it was not statistically significant ( $P = .07$ ). The time series model of disease trends showed a 36% reduction in cases attributable to vaccination relative to the predicted incidence (RIRR: 0.64; 95 CI: 0.45 to 0.92).

**Conclusion:** in children in the United Kingdom, a two-dose 4CMenB (Bexero®) priming schedule was highly effective in preventing meningococcal B disease.

**Conflicts of interest:** two of the authors disclosed doing contract research for pharmaceutical companies (including GSK), but receiving no personal remuneration.

**Funding source:** Public Health England, which is part of the Department of Health in the United Kingdom.

## COMMENTARY

**Justification:** meningococcal disease is a severe infection caused by *N. meningitidis*, with an estimated mortality of 10% to 14% and development of long-term neurological sequelae in

8% to 20% of survivors;<sup>1</sup> at present, serogroup B is the main causative agent in Spain.<sup>2</sup> The 4CMenB vaccine (Bexsero®) has been available in Europe since 2013. Previous studies have reported a high immunogenicity and safety,<sup>3,4</sup> but this is the first published study that assesses its effectiveness and efficacy after the introduction of routine vaccination in the United Kingdom.

**Scientific validity/rigour:** the exposed and unexposed cohorts were clearly defined. The exposure was clear (vaccination), as was the response (cases of meningococcal B disease). The exposed cohort consisted of the entire vaccine-eligible population, and the unexposed cohort of children of the same age and in the same months in previous years, but to minimise potential biases (because there could have been a reduction in the incidence of disease in the year under study due to causes other than the vaccine), the researchers fitted a time series model to predict the number of expected cases, and also compared all children aged less than 5 years with meningococcal B disease (excluding those vaccinated) in the study period and in the four previous years. The authors established a reliable system for detecting cases and took into account aspects such as the time needed to develop immunity after vaccination, so the study was well designed to assess the preventive intervention of vaccination.

**Clinical relevance:** the effectiveness of the two-dose vaccination regimen was high, of 82.9% against all strains (95 CI: 24.1 to 95.2) and 94% for MATS-positive strains, exceeding the predicted coverage of 88%. The incidence in the period under study was half that in previous cohorts (IRR: 0.5), so the impact was high (it halved the number of cases of MenB). In Spain, the incidence of MenB in 2014 was of 0.31 cases per 100 000 inhabitants,<sup>2</sup> so we would need to vaccinate (number needed to vaccinate [NNV]) 388 652 individuals (95 CI: 338 846 to 1 338 509) with Bexsero® to prevent one case of MenB. Based on these results, vaccination may not seem very efficient. However, while the incidence of MenB has remained stable with a decreasing trend in the past ten years, we know that there are clinical variants of MenB<sup>1</sup> and that incidence rates similar to the 1.02 per 100 000 inhabitants of the 2007-2008 period could happen any time, with a NNV of 118 120 (95 CI: 102 983 to 406 802), which, combined with the high mortality of the disease and its potential sequelae, makes the impact of the vaccine more significant.

**Applicability to clinical practice:** this is the first published study on the effectiveness and efficacy of the Bexsero® vaccine. The population was similar to our population, so it may be possible to extrapolate the results. If the findings were confirmed by long-term evidence, the impact would be considerable: we may be taking a new turn in the prevention of the disease with a tool that was not available until now.

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