Effect of *Haemophilus influenzae* type b vaccination without a booster dose on invasive *H influenzae* type b disease, nasopharyngeal carriage, and population immunity in Kilifi, Kenya: a 15-year regional surveillance study

Laura L Hammitt, Rosie J Crane, Angela Karani, Alex Mutuku, Susan C Morpeth, Polly Burbidge, David Goldblatt, Tatu Kamau, Shahnaaz Sharif, Neema Mturi, J Anthony G Scott

Summary

Background ***Haemophilus influenzae*** **type b (Hib) conjugate vaccine, delivered as a three-dose series without a booster, was introduced into the childhood vaccination programme in Kenya in 2001. The duration of protection and need for a booster dose are unknown. We aimed to assess vaccine effectiveness, the impact of the vaccine on nasopharyngeal carriage, and population immunity after introduction of conjugate Hib vaccine in infancy without a booster dose in Kenya.**

Methods **This study took place in the Kilifi Health and Demographic Surveillance System (KHDSS), an area of Kenya that has been monitored for vital events and migration every 4 months since 2000. We analysed sterile site cultures for *H influenzae* type b from children (aged ≤12 years) admitted to the Kilifi County Hospital (KCH) from Jan 1, 2000, through to Dec 31, 2014. We determined the prevalence of nasopharyngeal carriage by undertaking cross-sectional surveys in random samples of KHDSS residents (of all ages) once every year from 2009 to 2012, and measured Hib antibody concentrations in five cross-sectional samples of children (aged ≤12 years) within the KHDSS (in 1998, 2000, 2004–05, 2007, and 2009). We calculated incidence rate ratios between the prevaccine era (2000–01) and the routine-use era (2004–14) and defined vaccine effectiveness as 1 minus the incidence rate ratio, expressed as a percentage.**

Findings **40 482 children younger than 13 years resident in KHDSS were admitted to KCH between 2000 and 2014, 38 206 (94%) of whom had their blood cultured. The incidence of invasive *H influenzae* type b disease in children younger than 5 years declined from 62·6 (95% CI 46·0–83·3) per 100 000 in 2000–01 to 4·5 (2·5–7·5) per 100 000 in 2004–14, giving a vaccine effectiveness of 93% (95% CI 87–96). In the final 5 years of observation (2010–14), only one case of invasive *H influenzae* type b disease was detected in a child younger than 5 years. Nasopharyngeal *H influenzae* type b carriage was detected in one (0·2%) of 623 children younger than 5 years between 2009 and 2012. In the 2009 serosurvey, 92 (79%; 95% CI 70–86) of 117 children aged 4–35 months had long-term protective antibody concentrations.**

Interpretation **In this region of Kenya, use of a three-dose primary series of Hib vaccine without a booster dose has resulted in a significant and sustained reduction in invasive *H influenzae* type b disease. The prevalence of nasopharyngeal carriage is low and the profile of Hib antibodies suggests that protection wanes only after the age at greatest risk of disease. Although continued surveillance is important to determine whether effective control persists, these findings suggest that a booster dose is not currently required in Kenya.**

Funding **Gavi, the Vaccine Alliance, Wellcome Trust, European Society for Paediatric Infectious Diseases, and National Institute for Health Research.**

Lancet Glob Health 2016; 4: e185–94

Published Online February 4, 2016 http://dx.doi.org/10.1016/S2214-109X(15)00316-2

See **Editorial** page e137

See **Comment** page e142

Department of Epidemiology and Demography, KEMRI-Wellcome Trust Research Programme, Centre for Geographic Medicine Research–Coast, Kilifi, Kenya (L L Hammitt MD, R J Crane MBBS, A Karani BSc, A Mutuku MSc, S C Morpeth FRACP, N Mturi MRCPCH, Prof J A G Scott FRCP); **Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA** (L L Hammitt); **Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK** (R J Crane, S C Morpeth, Prof J A G Scott); **Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, UK** (S C Morpeth, Prof J A G Scott); **Institute of Child Health, University College London, London, UK** (P Burbidge BSc, Prof D Goldblatt MB ChB); **and Kenya Ministry of Public Health and Sanitation, Kilifi, Kenya** (T Kamau MPH, S Sharif MD)

Correspondence to: Dr Laura L Hammitt, Department of International Health, Johns Hopkins Bloomberg School of Public Health, 415 N Washington St, Baltimore, MD 21231, USA **lhammitt@jhu.edu**

Introduction

Inclusion of *Haemophilus influenzae* type b (Hib) conjugate vaccine in the routine infant immunisation programme has led to tremendous reductions in childhood *H influenzae* type b morbidity and mortality in both developed and developing countries.[1,2] Hib vaccine was introduced into the Kenyan childhood Expanded Program on Immunization (EPI) in November, 2001, as a three-dose series administered at 6, 10, and 14 weeks of age. Within 3 years of introduction, invasive *H influenzae* type b disease had decreased to 12% of its baseline level.[3] A booster dose of Hib vaccine is not included in the Kenyan EPI schedule, nor in the schedules of 72 (92%) of 78 low-income and lower-middle-income countries.[4]

In the UK, 10 years after the introduction of the Hib primary vaccination, waning levels of antibody to polyribosylribitol phosphate (PRP)—an *H influenzae* type b polysaccharide capsule component—as well as persistence of *H influenzae* type b nasopharyngeal

Research in context

Evidence before this study

We searched PubMed with the terms "Hib", "*Haemophilus influenzae* type b", "vaccine", "effectiveness", "seroepidemiology", "anti-PRP", "booster", "cross reactive", "carriage", and "colonization" for articles published in any language before May 31, 2015. To identify additional publications we searched the reference lists of retrieved articles. More than a decade after conjugate *Haemophilus influenzae* type b (Hib) vaccines became available, only 2% of the global *H influenzae* type b disease burden was being prevented by vaccination. In 2001, Gavi, the Vaccine Alliance, offered financial support for the introduction of Hib vaccine in developing countries, and Kenya became one of the first African countries to include Hib vaccine in the national immunisation schedule. Like the vast majority of low-income and lower-middle-income countries, Kenya used a three-dose primary series of Hib vaccine, without a booster dose.
A three-dose schedule without a booster is highly effective in reducing the burden of *H influenzae* type b disease in the short term; however, whether a booster dose is required to achieve sustained disease control is unclear. Although data from some countries have prompted the addition of a booster dose, other data show good control of *H influenzae* type b disease in the absence of a booster. The need for a booster dose of Hib vaccine is probably affected by local epidemiology and factors such as the potential for natural boosting.

Added value of this study

This study provides new data documenting the near elimination of invasive *H influenzae* type b disease in Kilifi, Kenya, in the 12 years after introduction of vaccine into the routine infant vaccination schedule without a booster dose. The detailed seroepidemiology work before and after vaccine introduction shows that the vaccine has led to improvements in population immunity in the youngest, highest-risk age groups without compromising immunity in older children.

Implications of all the available evidence

This study delivers compelling evidence of the long-term operational impact of a three-dose primary series of Hib vaccine in a low-income country and provides a clear answer to a pertinent policy question in Kenya: a booster dose of vaccine is not currently needed to control *H influenzae* type b disease.

colonisation and rising rates of invasive disease, prompted introduction of a booster dose of Hib vaccine for children aged 12–15 months in 2006.[5,6] The Government of Mexico also introduced a booster dose of Hib vaccine 9 years after launching the primary vaccination programme, in part because of waning anti-PRP antibodies in children aged 12–59 months.[7] However, persistently low incidence of *H influenzae* type b meningitis in the western region of The Gambia more than a decade after Hib vaccine introduction shows that the disease can be adequately controlled in the absence of a booster dose.[8]

The long-term effectiveness of a primary series of Hib vaccine in infancy can be inferred from incidence of invasive *H influenzae* type b disease, nasopharyngeal carriage prevalence, and seroepidemiological data from the general population. Hib vaccination induces serum antibody production and reduces the nasopharyngeal carriage prevalence of *H influenzae* type b, thereby diminishing the risk of invasive disease. Reductions in carriage also reduce transmission of Hib between individuals. This contributes to herd protection, but also limits the opportunity for intermittent natural boosting of serological immunity. The pattern of *H influenzae* type b serological immunity in different age groups across time and the persistence of *H influenzae* type b serological immunity throughout the years of highest risk for *H influenzae* type b disease are likely to be important determinants of vaccine effectiveness beyond the primary vaccination period.

There is equipoise in the scientific community regarding the need for a booster dose of Hib vaccine to control disease in the long term.[9] Herein we report vaccine effectiveness, the impact of the vaccine on nasopharyngeal carriage of *H influenzae* type b, and population immunity to *H influenzae* type b in the 13 years after introduction of conjugate Hib vaccine in infancy without a booster dose in Kenya.

Methods

Population

This surveillance study took place in the Kilifi Health and Demographic Surveillance System (KHDSS), a rural community on the Kenyan coast covering an area of 891 km².[10] A census of the KHDSS in 2000 defined the resident population and, since 2000, fieldworkers have been monitoring migration events by visiting every participating household roughly every 4 months. The annual population was 199 732 in 2000, 239 396 in 2007, and 279 877 in 2014. The population is served by several government-funded health centres and by one government hospital, Kilifi County Hospital (KCH). Among women attending antenatal care at KCH, the prevalence of HIV infection ranged between 2·4% and 4·6% during 2005–13, with a general downwards trend. The prevalence of HIV in children in Kenya was estimated in 2012 to be 0·9% nationally.[11]

On Nov 1, 2001, the Government of Kenya introduced tetanus-toxoid-conjugated Hib vaccine as part of a pentavalent formulation in which lyophilised Hib vaccine (Hiberix; GlaxoSmithKline, Rixensart, Belgium) was resuspended in the diphtheria, tetanus, whole-cell pertussis, hepatitis B vaccine (Tritanrix, GlaxoSmithKline). The first children eligible to receive a 6-week dose of this