Impact of *Haemophilus influenzae* type b vaccine in Mongolia; prospective population-based surveillance, 2002-2010

Scott S,[1] Altanseseg D,[2] Sodbayer D, [3] Nymadawa P,[3] Bulgan D, [2] Mendsaikhan J, [3] Watt JP,[4] Slack M,[5] Carvalho MG,[6] Hajjeh R,[6] Edmond KM[1]

[1]London School of Hygiene and Tropical Medicine, UK

[2]National Center of Communicable Diseases, Ministry of Health, Ulaanbaatar, Mongolia

[3]World Health Organization, Ulaanbaatar, Mongolia

[4] Johns Hopkins Bloomberg School of Public Health, Baltimore, USA

[5]Health Protection Agency, UK, Respiratory and Systemic Infection Laboratory, Health Protection Agency Centre for Infections, London

[6]Division of Bacterial Diseases, Centers for Disease Control and Prevention, Atlanta, USA

Reprints or correspondence: Dr. Susana Scott, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK (susana.scott@lshtm.ac.uk), Tel: (+44) 02079272921, Fax: 02076368739

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ABSTRACT

Objectives

Bacterial meningitis is associated with high mortality and long term complications. This study assessed the impact of *Haemophilus influenzae* type b (Hib) vaccine on childhood bacterial meningitis in Ulaanbaatar, Mongolia.

Study Design

Prospective, active, population-based surveillance for suspected meningitis in children aged 2-59 months was conducted (February 2002-January 2011) in 6 hospitals. Clinical data, blood, and cerebrospinal fluid were collected. The impact of Hib vaccine was assessed by comparing Hib and all cause meningitis data in the 3 years preceding pentavalent vaccine implementation (2002-2004) with three years post implementation (2008-2010).

Results

511 suspected meningitis cases were identified from 2002-2011. Pentavalent vaccine coverage in December 2005 in Ulaanbaatar city was 97%.. The proportion of suspected cases confirmed as Hib meningitis decreased from 25% (50/201) in the prevaccination era to 2% (4/193) in the post-vaccination era ($p < 0.0001$). The annual incidence of Hib decreased from 28 cases per 100,000 children in 2002-2005 to 2 per 100,000 in 2008-2010 ($p < 0.0001$).

Conclusions

This paper demonstrates the marked impact of Hib vaccine introduction on meningitis in Mongolia. It is important to sustain this surveillance system in order to monitor the long term impact of Hib vaccine, as well as other interventions such as pneumococcal and meningococcal vaccines.

INTRODUCTION

Bacterial meningitis continues to be associated with high rates of death and long term complications in children < five years of age.[1] Many studies in Europe, North and South America and Africa [2-6] have shown that the introduction of *Haemophilus influenzae* type b (Hib) vaccine into childhood immunization programs results in a dramatic decrease in both Hib disease and suspected bacterial meningitis without confirmed etiology.[2, 3]

Data on Hib vaccine impact in Asian countries are limited.[7, 8] Mongolia was one of the few countries in Asia to have baseline Hib burden of disease data. These data were available as a result of a population-based active surveillance system that was established in February 2002 at the National Center of Communicable Diseases, Ministry of Health, Mongolia (NCCD) The incidence of Hib meningitis was reported as 28/100,000 in children < 5 years from 2002-2004.[9] Mongolia was also one of the first countries in Asia to introduce Hib vaccine and introduced the combined Diptheria-Tetanus-Pertussis-Hepatits B-Hib (pentavalent) vaccine in January 2005. The primary objective of this study was to assess the impact of this vaccine on childhood bacterial meningitis using the NCCD surveillance system.

METHODS

Study design and population

Prospective, active, population-based surveillance for suspected meningitis in children aged 2-59 months was conducted from February 2002 to January 2011 (2002-2010) in 6 sites (the NCCD, the National Center of Maternal and Child Health (NCMCH), Khan-Uul District Hospital, Songinkhairhan District Hospital, Sukhbaatar District Hospital and Bayanzurekh

District Hospital). These are the only hospitals that admit children with meningitis in Ulaanbaatar ,the capital of Mongolia. Trained clinical staff ascertained clinical details of all children admitted to these hospitals and completed data collection forms from 2002-2010. Full details about the surveillance system and methods have been previously published.[9]

Case identification and definitions

Only hospitalised children aged 2 to 59 months of age were included in the study. A suspected clinical case of paediatric meningitis was defined as a sudden onset of fever ($\geq 38^{o}$C) plus one or more of the following: neck stiffness, bulging fontanelle, altered or reduced level of consciousness, convulsions, poor sucking and irritability, prostration, lethargy, toxic appearance, petechial or purpural rash, or severe vomiting. Clinicians were encouraged to perform lumbar puncture on all suspected meningitis patients. A diagnosis of purulent bacterial meningitis was made if the case fulfilled the clinical criteria for a suspected case plus the cerebrospinal fluid (CSF) had one of the following abnormalities: (i) turbid or cloudy in appearance; (ii) CSF white blood cell count (WBC) >100 cells/mm^3; or (iii) CSF WBC 10-99 cells/mm^3 plus CSF glucose <40 mg/dl and CSF protein >100 mg/dl. Confirmed bacterial meningitis was defined as a suspected or purulent bacterial meningitis case with a pathogenic organism including Hib, *Streptococcus pneumoniae* or *Neisseria meningitidis*. The organisms could be isolated from CSF or blood by microbiological culture techniques or could be identified from the CSF by latex agglutination or real time polymerase chain reaction (PCR). Methods remained consistent over the 9 year period and are described in our earlier paper.[9] All specimens were analysed using culture, latex agglutination and real time PCR.

Vaccination coverage

Routine immunization services are provided in all large health facilities including family clinics and district health offices in Ulaanbaatar (43 health facilities in total). Outreach services are provided by nurses to both urban and remote districts. The private sector does not play a major role in vaccination programmes. The liquid-lyophilised pentavalent vaccine was introduced in January 2005 with support from UNICEF and GAVI. Three doses of the vaccine were provided to all children aged 2, 3 and 4 months. Pentavalent vaccine replaced DTP and monovalent hepatitis B vaccine and nationwide coverage of pentavalent vaccine achieved by 2008. The first phase of introduction in Ulaanbaatar city and five rural provinces was complete by the end of 2005. Coverage of the third dose of pentavalent vaccine in Ulaanbaatar city was reported to be 97% in December 2005 in children aged 12 months.[10] Supplies of the vaccine have been consistent with no reported problems or interruptions of supply throughout the surveillance period (2002-2010).

In this study all families were asked for their child's immunization card when the child was admitted to hospital. Families were asked to bring the card from home if it was not available at the first request. All data were cross checked with Ministry of Health, World Health Organization (WHO) and UNICEF records to ensure completeness. Families were only asked if their child had received any pentavalent vaccines from birth until the time of presentation to hospital and the answer was recorded as "yes/no". The number of doses of pentavalent vaccine was not recorded.

Data analysis

Only Ulaanbaatar residents were included in the surveillance system. Residency was determined by interviewing family members and reviewing identification cards. The population of children aged 2-59 months in Ulaanbaatar was 60,047 in 2005.[11] Annual incidence rates per 100,000 children aged 2-59 months were calculated by dividing the number of meningitis cases in residents by the population in Ulaanbaatar in this age group.

All analyses were performed in Stata SE 12.0 (StataCorp LP, College Station, TX 77845, USA).

RESULTS

From February 2002 to January 2011 (2002-2010), a total of 510 suspected meningitis cases were identified from the 6 Ulaanbaatar hospitals in children aged between 2-59 months. Of these children 477 (93%) were Ulaanbaatar residents (Table 1), 51% (245) were male with a median age of 10.2 months (sd 6.1). Forty seven (9.8%) of the suspected meningitis cases died.

Of the suspected meningitis cases, 349 (73%) met the case definition of purulent meningitis. Of the purulent meningitis cases, 234 (69%) were confirmed with Hib, pneumococcus or meningococcus; 62 Hib (26%), 63 *S.pneumoniae* (27%), 109 *N.meningiditis* (47%). In addition, 10 were confirmed with group B streptococcus (Table 1). There were no cases of non group B *Haemophilus influenzae* meningitis. Twenty four (9.4%) children with confirmed bacterial meningitis died (Table 1).

Figure 1 and Table 2 display the annual incidence of suspected, purulent and confirmed bacterial meningitis in the study population from 2002-2010. The annual incidence of confirmed meningitis decreased from 52 cases per 100,000 children in 2002-2005 to 43 per 100,000 in 2008-2010 ($p = 0.10$, p for trend =0.17). The annual incidence of Hib decreased from 28 cases per 100,000 children in 2002-2005 to 2 per 100,000 in 2008-2010 ($p < 0.0001$) and there were no cases of Hib meningitis by 2010. In contrast the incidence of *S. pneumoniae* slightly increased from 11 cases per 100,000 children in 2002-2005 to 16 per

100,000 in 2008-2010 (p = 0.09, p for trend 0.08). The incidence of *N.meningitidis* increased from 13 cases per 100,000 children in 2002-2005 to 26 per 100,000 in 2008-2010 (p = 0.07, p for trend 0.05) due to an outbreak of serogroup A meningococcus in 2008.

There was no significant change in the annual incidence of suspected meningitis from 2002-2005 (112 cases per 100,000) to 2008-2010 (88 per 100,000) (p =0.09, p for trend =0.10). In addition the annual incidence of purulent non confirmed meningitis increased from 18 cases per 100,000 children in 2002-2005 to 21 per 100,000 in the post vaccination period from 2008-2010 (p =0.99, p for trend =0.87). However, the 2008-2010 post vaccination data included suspected and purulent meningitis cases from the 2008 meningococcal outbreak which was a temporal anomaly unrelated to the use of Hib vaccine. Thus we repeated the suspected and purulent analyses excluding the 2008 data. We found a statistically significant decrease in the annual incidence of suspected meningitis in 2009-2010 (54 per 100,000 , p value =0.04) compared to the 2002-2005 data . We also found a statistically significant decrease in the annual incidence of purulent meningitis in 2009-2010 (6 per 100,000 , p =0.03)compared to 2002-2005 data.

The proportion of suspected cases identified through the surveillance system which were confirmed as Hib meningitis decreased from 25 % (50/201) in 2002-2005 to 2% (4/193) 2008-2011 (p < 0.0001) .

DISCUSSION

The introduction of Hib vaccine in Ulaanbaatar Mongolia resulted in a marked decrease in the incidence of confirmed Hib meningitis. Before vaccine introduction in 2005, Hib was the leading cause of childhood bacterial meningitis with an estimated annual incidence of 28 per

100,000 children[9]. This decreased to 10 per 100,000 children in the first year of Hib vaccine introduction and further decreased to zero as coverage increased in the study population. These observations are consistent with other studies which have reported dramatic declines in Hib paediatric meningitis following the introduction of Hib vaccine.[2-4, 6] In addition to reducing hospitalisation, Hib vaccine has also substantially reduced the disabling sequelae following bacterial meningitis.[5, 12, 13] Our findings are also similar to other studies from low and middle income countries which have shown decline in Hib meningitis and no change in pneumococcal meningitis; including reports from Africa (the Gambia,[3] Senegal,[4] Uganda[2]) and Latin America.[5,6] There have been few studies from Asia, although our findings are also consistent with studies from Bangladesh[7] which reported significant decrease in Hib disease following use of pentavalent vaccine.

There are several limitations to this study. Cases may have been missed due to children with bacterial meningitis not reaching hospital. However, bacterial meningitis is a severe disease and requires hospitalisation for treatment. Health care is freely provided to all children in Mongolia and the network of district hospitals in Ulaan Baatar is easily accessible. Under these circumstances we do not believe that this was a major source of underestimation of meningitis cases. The selective criteria used by Mongolian physicians to diagnose meningitis may also have resulted in some children with meningitis not being ascertained by the surveillance system. However, this was an active surveillance system with high quality reporting and laboratory procedures and all hospital admissions were checked on a regular basis to minimise missing any suspected cases. Another limitation was the relatively small area under surveillance which made measuring the impact of pentavalent vaccine on the incidence of suspected bacterial meningitis difficult because of local trends in meningitis pathogens other than Hib. The effect of the 2008 serogroup A meningococcal outbreak was

especially marked. However, we were able to repeat analyses excluding these data and significant impacts on both suspected and purulent meningitis were detected.

Almost 50% of children with bacterial meningitis were reported to have received antibiotic treatment prior to collection of CSF. This limited the number of cases confirmed by culture as it is difficult to isolate causative organisms from the CSF of children who have received antibiotics. However, latex tests, PCR and blood cultures were also used for bacterial confirmation which increased the sensitivity of the diagnosis of Hib, *S. pneumoniae* and *N. meningitidis.*

This study also found high incidence of *S. pneumoniae* and *N. meningitidis* meningitis in Mongolia and provides evidence to support the introduction of pneumococcal and meningococcal vaccines.[14]

Paediatric bacterial meningitis surveillance is routine in many high income countries and has several uses: providing clinical data to doctors and nurses; monitoring changes in epidemiology of bacterial infections; providing early warning of pathogen re-emergence; and investigating the long term impact of vaccination programs. In the UK there was an increase in the number of Hib cases despite long term sustained high Hib vaccination coverage of 3 doses before 12 months of age. This led to an introduction of a booster dose in children older than 12 months.[15] Our high-quality bacterial meningitis surveillance system was used to monitor the marked impact of Hib vaccine introduction in Ulaanbaatar. This system will be used to monitor the long term impact of Hib vaccine and other interventions such as pneumococcal and meningococcal vaccines in Mongolia. WHO is introducing regional sentinel surveillance in key centres that can provide high quality surveillance in low and

middle income countries. This surveillance is important for ongoing assessment of Hib, pneumococcal and meningococcal vaccine impact in low and middle income countries.

REFERENCES

1. World Health Organisation. WHO position paper on *Haemophilus influenzae* type b conjugate vaccines. (Replaces WHO position paper on Hib vaccines previously published in the Weekly Epidemiological Record. Wkly Epidemiol Rec 2006;81:445-52.

2. Lewis RF, Kisakye A, Gessner BD, et al. Action for child survival: elimination of *Haemophilus influenzae* type b meningitis in Uganda. Bull World Health Organ 2008;86:292-301.

3. Adegbola RA, Secka O, Lahai G, et al. Elimination of *Haemophilus influenzae* type b (Hib) disease from The Gambia after the introduction of routine immunisation with a Hib conjugate vaccine: a prospective study. Lancet 2005;366:144-50.

4. Cisse MF, Breugelmans JG, Ba M, et al. The Elimination of *Haemophilus influenzae* type b meningitis following conjugate vaccine introduction in Senegal. Pediatr Infect Dis J 2010;29:499-503.

5. Lee EH, Corcino M, Moore A, et al. Impact of *Haemophilus influenzae* type b conjugate vaccine on bacterial meningitis in the Dominican Republic. Rev Panam Salud Publica 2008;24:161-8.

6. Danovaro-Holliday MC, Garcia S, de Quadros C, Tambini G, Andrus JK. Progress in vaccination against *Haemophilus influenzae* type b in the Americas. PLoS Med 2008;5:e87.

7. Baqui AH, El Arifeen S, Saha SK, et al. Effectiveness of *Haemophilus influenzae* type B conjugate vaccine on prevention of pneumonia and meningitis in Bangladeshi children: a case-control study. Pediatr Infect Dis J 2007;26:565-71.

8. Shetty S, Cohen AL, Edmond K, et al. A systematic review and critical evaluation of invasive *Haemophilus influenzae* type B disease burden studies in Asia from the last decade: lessons learned for invasive bacterial disease surveillance. Pediatr Infect Dis J;29:653-61.

9. Mendsaikhan J, Watt JP, Mansoor O, et al. Childhood bacterial meningitis in Ulaanbaatar, Mongolia, 2002-2004. Clin Infect Dis 2009;48 Suppl 2:S141-6.

10. UNICEF. State of the World's Children 2006. http://www.unicef.org/sowc06/ (accessed Jan 3, 2012).

11. UNFPA. Population and housing census 2010, Mongolia. http://mongolia.unfpa.org/reports=666/ (accessed 3 Jan 2012).

12. Edmond K, Dieye Y, Griffiths UK, et al. Prospective cohort study of disabling sequelae and quality of life in children with bacterial meningitis in urban Senegal. Pediatr Infect Dis J 2010;29:1023-9.

13. Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. Lancet Infect Dis;10:317-28.

14. World Health Organisation. Pneumococcal conjugate vaccine for childhood immunization--WHO position paper. Wkly Epidemiol Rec 2007;82:93-104.

15. Ladhani S, Slack MP, Heys M, White J, Ramsay ME. Fall in *Haemophilus influenzae* serotype b (Hib) disease following implementation of a booster campaign. Arch Dis Child 2008;93:665-9.