Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

J Pediatr. Author manuscript; available in PMC 2018 January 02.

Published in final edited form as:

J Pediatr. 2013 July ; 163(1 Suppl): S1–S3. doi:10.1016/j.jpeds.2013.03.022.

Progress towards Demonstrating the Impact of *Haemophilus influenzae* Type b Conjugate Vaccines Globally

Rana Hajjeh, MD,

Division of Bacterial Diseases, National Center of Immunization and Respiratory Diseases Centers for Disease, Control and Prevention

Kim Mulholland, MBBS, FRACP, MD,

Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine London, United Kingdom

Anne Schuchat, MD, and

National Center of Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

Mathuram Santosham, MD, MPH

Johns Hopkins Bloomberg School of Public Health, Baltimore, Maryland

Prior to the introduction of vaccines, *Haemophilus influenzae* type b (Hib) was the most common cause of bacterial meningitis and an important cause of severe pneumonia in children <5 years of age. Hib conjugate vaccines were introduced in developed countries during the early 1990s, resulting in a virtual elimination of Hib disease.[1] However, the introduction of Hib vaccine in developing countries was delayed significantly due to multiple barriers, with major obstacles being the lack of local data on disease burden and the lack of awareness of the potential impact of the vaccine. In 2002, a group of scientific experts and public health officials gathered in Arizona, US, to discuss the epidemiology and control of Hib disease and recommended a multifaceted approach to overcome barriers for Hib vaccine introduction.[2] In 2005, the GAVI Alliance funded the Hib Initiative, a consortium of public and private institutions (Johns Hopkins School of Public Health, the World Health Organization [WHO], the London School for Hygiene and Tropical Medicine, and the US Centers for Diseases Control and Prevention) to assist countries eligible for GAVI funding in making evidence-based decisions regarding the introduction of Hib vaccines into national immunizations programs. The Hib Initiative adopted a strategy based on improved communications, coordination with key partners at country, regional, and global levels, and supporting selected research studies to address gaps in Hib knowledge, particularly studies that could provide evidence and capacity to sustain vaccine programs beyond the period of GAVI support. Fortunately, significant progress in introduction of Hib

Reprint requests: Rana Hajjeh, MD, Division of Bacterial Diseases, Centers for Disease Control and Prevention, 1600 Clifton Road NE, MS C-25, Atlanta, GA 30333. RHajjeh@CDC.gov.

Author Disclosures

M.S. received research funding from GlaxoSmithKline, Merck, and Pfizer (previously Wyeth Lederle Vaccines), has served on the scientific advisory boards of GlaxoSmithKline, Merck, and Pfizer, and received honoraria for these activities. The other authors declare no conflicts of interest, real or perceived.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

vaccines has occurred over the last few years with all GAVI countries, having either introduced the vaccine already or are expected to introduce in 2013.[3]

There frequently is tension in implementation programs regarding the appropriate role for research. The Hib Initiative focused on critical issues and geographic locations where scientific gaps remained and where strengthened capacity and systems could bridge to long term impacts. A decade after the Arizona meeting, the proceedings of which were reported in *The Journal of Pediatrics*, many scientific gaps have been filled, but a few questions still need to be answered.[2] This Supplement features a number of projects that were supported by the Hib Initiative and that provide valuable lessons for meningitis and pneumonia control and accelerate uptake of new and underutilized vaccines.

A major focus of these studies was to generate additional data on impact of Hib vaccines. In Asia and Eastern Europe, there were many doubts as to whether the burden of Hib disease was sufficient to justify introduction of the vaccine. The studies reported here from Pakistan, Bangladesh, and Ukraine reveal the dramatic impact this vaccine has had on disease incidence and its high effectiveness at preventing bacterial meningitis and pneumonia. In Mongolia, one of the earliest countries in Asia to introduce Hib vaccine, surveillance revealed the impact on the burden of bacterial meningitis overall, including culture-negative purulent meningitis, one of very few studies in the literature demonstrating such an effect.[4] Though many studies had documented the impact of Hib vaccines in Africa, data from The Gambia, the first African country to introduce Hib vaccine, show the lasting impact on disease incidence, even though the Gambian national immunization schedule does not include a booster dose.[5] In Mozambique, a similar impact was demonstrated, in spite of a high HIV prevalence.[6] HIV infection is an important consideration for African countries[7] that continue to face the HIV epidemic and struggle to attenuate its burden on their children.

To provide highly sought after local burden of disease estimates, the Hib Initiative, together with its partner initiative, Pneumococcal Vaccines Accelerated Development and Introduction Plan, supported the WHO Global Burden of Disease project to estimate burden of Hib and pneumococcal disease in children <5 years old.[8] In addition, country-based studies were funded to further highlight additional aspects of disease burden. The report from Vietnam reveals the high rate of Hib carriage among children <5 years old and documents the incidence of radiologically confirmed pneumonia, providing a baseline against which the impact of Hib and later pneumococcal vaccine introduction can be measured.[9] Hib vaccine was introduced in Vietnam in 2009, and surveillance is ongoing to evaluate its impact on severe pneumonia. The studies from Pakistan and Bangladesh[10,11] illustrate the long-term community impact of bacterial meningitis overall, including that caused by Hib and focus on neurologic sequelae. These findings support those of an earlier study in Senegal, also supported by the Hib Initiative.[12] These long-term complications have devastating implications for children and their families in developing country settings, and often are overlooked when bacterial meningitis is being discussed. We hope that children whose long-term suffering is described in these reports are among the last such victims of vaccine preventable diseases.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Finally, this Supplement includes reports from 2 cost-effectiveness analyses. These data are becoming increasingly important to support evidence-based decisions for vaccine introduction, as countries have limited health resources and have to prioritize among multiple health interventions. Griffiths et al identified key determinants that drive cost-effectiveness analysis for Hib vaccine, based on a user friendly model that makes it easier for countries to conduct such analysis.[13] The analysis from India[14] reveals the high cost-effectiveness of the vaccine, using various scenarios. Fortunately, and after a long delay, India has introduced Hib vaccine in late 2011 in 2 states and 6 additional states are planning to introduce the vaccine by the end of 2012. Several other states have requested the central government of India to provide the vaccine for their respective immunization programs. It is expected that by the end of 2013, Hib vaccine will be used in majority of the states in India.

Although the studies reported in this Supplement have answered key questions and provided much needed policy support, there were multiple challenges encountered both as part of the studies' implementation and interpretation of some results. The difficulties conducting quality surveillance for invasive bacterial diseases have been extensively discussed in the past.[15] The report from the surveillance network established in the WHO Eastern Mediterranean region[16] specifically addresses the benefits of conducting such surveillance using standardized protocols, but also the practical and field challenges of coordinating a surveillance network, especially as many regions face political instability and have difficulties transferring specimens and supplies across borders. It remains difficult to explain the high estimates of vaccine effectiveness reported through case-control studies, as seen in this supplement in Ukraine[17] and Pakistan,[18] and as was observed earlier in Bangladesh.[19] Various reasons related to study design and control selection have been proposed and efforts are currently ongoing to systematically avoid such biases in future studies.[20]

A few questions remain to be answered to fully understand the epidemiology of Hib disease and the impact of the vaccine. The very low Hib burden described in some Asian settings such as in Thailand and Hong Kong remains a mystery.[21] Various explanations have been proposed, the most convincing of which is the excessive use of antibiotics very early in the illness for children with nonspecific febrile illnesses. That being the case, it can be expected that in poor and disenfranchised Asian communities Hib will remain a problem, as was described among Vietnamese refugees living in Hong Kong.[22] However, as Hib vaccine is rapidly becoming a global infant immunization, this will render the argument about Hib burden in Asia of academic interest only.

Multiple lessons were learned from the various research and surveillance studies that were summarized earlier.[3] We hope that the studies reported in this Supplement have helped improve the global knowledge about Hib disease and vaccine and will be useful for introducing countries to sustain their vaccine programs long term. As part of its mandate, the Hib Initiative saw these studies as opportunities to build and further support research capacity at the country level, in the expectation that this capacity will be sustained and provide a platform for other relevant studies. Some of these projects are already evaluating the impact of pneumococcal vaccines, a key intervention for prevention of bacterial meningitis and severe pneumonia. We also hope that the methodology and results of these studies showing the dramatic vaccine impact will be useful to the few remaining countries

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

that have not yet introduced Hib vaccine, thus, allowing global vaccine coverage and expansion of its benefits worldwide. Although debates regarding the optimal balance between implementation and research will continue, we propose that incorporating a learning agenda into all program delivery activities is a vital opportunity to improve public health.

Acknowledgments

The authors would like to thank Dr Thomas Cherian (WHO, Geneva, Switzerland) for his support of the Hib Initiative research activities and his thoughtful contributions.

Glossary

Hib	*Haemophilus influenzae* type b
WHO	World Health Organization

References

1. Wenger JD. Epidemiology of *Haemophilus influenzae* type b disease and impact of *Haemophilus influenzae* type b conjugate vaccines in the United States and Canada. Pediatr Infect Dis J. 1998; 17:S132–6. [PubMed: 9781746]
2. Watt, JP., Levine, OS., Santosham, M. Global reduction of Hib disease: what are the next steps?. J Pediatr; Proceedings of the meeting Scottsdale; Arizona. September 22–25, 2002; 2003. p. S163-87.
3. Hajjeh RA, Privor-Dumm L, Edmond K, O' Loughlin R, Shetty S, Griffiths UK, et al. Supporting new-vaccine introduction decisions: lessons learned from the Hib Initiative experience. Vaccine. 2010; 28:7123–9. [PubMed: 20659515]
4. Scott S, Altanseseg D, Sodbayer D, Nymadawa P, Bulgan D, Mendsaikhan J, et al. Impact of *Haemophilus influenzae* type b vaccine in Mongolia; prospective population-based surveillance, 2002–2010. J Pediatrics. 2012
5. Oluwalana C, Howie SRC, Secka O, Ideh R, Ebruke B, Sambou S, et al. Incidence of Haemophilus influenzae type b (Hib) disease in The Gambia 14 years after introduction of routine conjugate Hib vaccine immunization. J Pediatrics. 2012
6. Sigauque B, Vubil D, Sozinho A, Quintó L, Morais L, Sacoor C, et al. *Haemophilus influenzae* type b (Hib) disease among children in rural Mozambique: impact of vaccine introduction. J Pediatrics. 2012
7. Mangtani P, Mulholland K, Madhi SA, Edmond K, O'Loughlin R, Hajjeh R. *Haemophilus influenzae* type b disease in HIV-infected children: A review of the disease epidemiology and effectiveness of Hib conjugate vaccines. Vaccine. 2009; 28:1677–83. [PubMed: 20034606]
8. Watt JP, Wolfson LJ, O'Brien KL, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by *Haemophilus influenzae* type b in children younger than 5 years: global estimates. Lancet. 2009; 374:854–6. [PubMed: 19748384]
9. Yoshida LM, Nguyen HA, Watanabe K, Le M, Nguyen A, Vu H, et al. Incidence of radiologically confirmed pneumonia and *Haemophilus influenzae* type b carriage before Hib vaccine introduction in central Vietnam. J Pediatrics. 2012
10. Khowaja AR, Mohiuddin S, Cohen AL, Khalid A, Mehmood U, Naqvi F, et al. Mortality and neurodevelopmental outcomes of acute bacterial meningitis in children aged <5 years in Pakistan. J Pediatrics. 2012
11. Ahmed ASM, Khan NZ, Hussain M, Amin MR, Hanif M, Mahbub M, et al. Follow up of *Haemophilus influenzae* type b (Hib) meningitis cases to determine its long term sequelae. J Pediatrics. 2012
12. Griffiths UK, Dieye Y, Fleming J, Hajjeh R, Edmond K. Costs of Meningitis Sequelae in Children in Dakar, Senegal. Pediatr Infect Dis J. 2012

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

13. Griffiths UK, Clark A, Hajjeh R. Cost-effectiveness of *Haemophilus influenzae* type b vaccine in low- and middle-income countries: regional analysis and assessment of major determinants. J Pediatrics. 2012

14. Clark AD, Griffiths UK, Abbas S, Rao K, Privor-Dumm L, Hajjeh R, et al. Impact and cost-effectiveness of *Haemophilus influenzae* type b vaccination in India. J Pedatrics. 2012

15. Levine OS, Cherian T, Hajjeh R, Knoll MD. Progress and future challenges in coordinated surveillance and detection of pneumococcal and Hib disease in developing countries. Clin Infect Dis. 2009; 48(Suppl 2):S33–6. [PubMed: 19191617]

16. Teleb N, Pilishvili T, Van Beneden C, Ghoneim A, Amjad K, Mostafa A, et al. Bacterial Meningitis Surveillance in the Eastern Mediterranean Region, 2005–2010: Successes and Challenges of a Regional Network. J Pediatrics. 2013

17. Pilishvili T, Chernyshova L, Bondarenko A, Lapiy F, Sychova I, Cohen A, et al. Evaluation of the effectiveness of *Haemophilus influenzae* type b conjugate vaccine introduction against pneumonia in young children in Ukraine. J Pediatrics. 2012

18. Kowaja AR, Mohiuddin S, Cohen AL, Mrza W, Nadeem N, Zuberi T, et al. Effectiveness of *Haemophilus influenzae* type b vaccine on radiologically confirmed pneumonia in young children in Pakistan. J Pediatrics. 2012

19. Baqui AH, El Arifeen S, Saha SK, Persson L, Zaman K, Gessner BD, 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. [PubMed: 17596795]

20. O'Loughlin RE, Edmond K, Mangtani P, Cohen AL, Shetty S, Hajjeh R, et al. Methodology and measurement of the effectiveness of *Haemophilus influenzae* type b vaccine: systematic review. Vaccine. 2010; 28:6128–36. [PubMed: 20655402]

21. Shetty S, Cohen A, Edmond K, Ojo L, Loo J, O'Loughlin R, 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. J Pediatr Infect Dis. 2010; 29:653–61.

22. Lau YL, Low LC, Yung R, Ng KW, Leung CW, Lee WH, et al. Invasive *Haemophilus influenzae* type b infections in children hospitalized in Hong Kong, 1986–1990. Hong Kong Hib Study Group Acta Paediatr. 1995; 84:173–6.