

Potentially Preventable Number of Cases and Deaths Associated with Pneumococcal Diseases and Haemophilus Influenzae in Iran during (2010-2013)

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Abstract

Background: Streptococcus pneumoniae and Haemophilus influenzae type b (Hib) is a leading cause of bacterial pneumonia, meningitis, and sepsis in children under 5-year of age. This study aims to estimate potentially preventable number of cases and deaths caused by Hib and pneumococcal in Iran.

Materials and Methods: We used the burden of diseases model estimates of the World Health Organization (WHO) to calculate the number of cases and deaths caused by Streptococcus pneumoniae and Haemophilus influenzae in children less than 5 years old. Efficacy of Hib and pneumococcal vaccine was obtained from literature. Vaccine coverage was cited of published report from Ministry of Health and Medical Education Iran (National Committee on Immunization). Hib and Streptococcus pneumoniae diseases burden was obtained from the WHO global burden of disease project.

Results: We found that the number of potentially preventable cases and deaths from meningitis caused by Hib among under five years old children in 2013 were 5,414 (95% confidence intervals [CI]: 2838, 11630), and 61 (95% CI: 31, 93), respectively. Estimated number of Streptococcus pneumoniae related pneumonia cases in 2010 and 2013 were 37,732 (95% CI: 22,183, 58,334), and 30,728 (95% CI: 17,023, 50,412), respectively. The corresponding values for pneumonia related deaths from Streptococcus pneumonia were 438 (95% CI: 257, 677), in 2010 and 356 (95% CI: 197, 586), in 2013.

Conclusions: Findings favor the effects of both Hib and Pneumococcal conjugate vaccine (PCV) in reducing the burden of disease and death in Iran. Policy makers are advised to introduce PCV to National immunization program.

Keywords: Children, Iran, Haemophilus influenzae type b, Immunization, Streptococcus pneumoniae.

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1- INTRODUCTION

Streptococcus pneumoniae is the major cause of bacterial pneumonia, meningitis and Septicemia in children around the world (1). Pneumococcal is a major cause of pneumonia and death among children under five years old in developing countries (2-4). *Streptococcus pneumoniae* is the most common etiologic agent of bacterial meningitis in America. *Haemophilus influenzae* type b (Hib) is known as one of the major causes of meningitis and bacterial pneumonia spread among in children, and 90% of the patients with meningitis are under five years old (5).

Meningitis is one of the major causes of death of 180,000 children under five years old per year and 20 percent of survivors experience the resulted long-term complications and disabilities (6, 7). It is estimated that more than 1,200,000 people are diagnosed with bacterial meningitis annually. Bacterial meningitis incidence and mortality is different in terms of region, country, pathogens and age groups. Therefore, having access to accurate information, getting aware of the disease situation and predicting its process play an important role in preventing and reducing the symptoms of the disease (8).

Pneumococcal polysaccharide vaccine is prescribed to prevent from pneumococcal disease in some high-risk groups including people over 65 years old, those with no spleen, those who are alcoholics and smokers in the United States of America (USA) (9). At the end of 2014, Conjugated *Haemophilus Influenzae* vaccine was included in routine vaccination schedule and its part of the Childhood Immunizations Program in 192 countries. Moreover, 130 countries around the world have introduced Pneumococcal Conjugate Vaccine (PCV), in the national immunization program and six countries planned to PCV introduction (10).

Iran has introduced the pentavalent vaccine (a combination of five vaccines in one: diphtheria, tetanus, whooping cough, hepatitis B and Hib) to national immunization program in December 2014 and performed the necessary planning for the inclusion of PCV (11). Potential impacts of Hib including bacterial carriage reduction and providing herd immunity among target population of Hib vaccine were shown in published literature (12, 13). Consider to the role of both *Streptococcus pneumoniae* and Hib carriage and the risk of antimicrobial resistance among non-vaccinated population, it is necessary to implementing preventive measures (14-16).

Accordingly, this study aimed to estimate the number of deaths caused by Hib and *Streptococcus pneumoniae* spread among children less than five years old in Iran.

2- MATERIALS AND METHODS

The study population was children 1-59 months of Iran and study design was a cross-sectional study. We used the methodology of WHO to estimate the potential preventable number of cases and deaths associated with pneumococcal diseases and Hib as summarized in **Table.1** (17).

In 2009, WHO published global, regional and country-specific estimates of the burden of pneumococcal and Hib disease as part of a Global Burden of Disease (GDB) project (18). This project provided the number of cases and deaths per year of pneumococcal and Hib meningitis, pneumococcal and Hib pneumonia, and non-pneumonia, non-meningitis invasive pneumococcal and Hib disease. These numbers were calculated by modelling available country-level data from well-conducted disease burden studies, aggregating these data to derive regional and global estimates, and applying estimates of the proportion of pneumonia

caused by Hib or pneumococcus to the Pneumonia. The estimates give the burden of disease in 2000 before widespread global use of PCV and Haemophilus Influenzae type b Conjugate Vaccine (HibCV). These estimates can be useful in estimating the number of cases and deaths potentially averted by a vaccination programme in a particular country, especially where local data are not available. The impact of PCV and HibCV on pneumonia can be extrapolated by applying the ratio of pneumococcal pneumonia to meningitis cases to the measured impact on purulent or laboratory-confirmed pneumococcal meningitis.

The ratio of pneumococcal pneumonia to meningitis cases can be estimated based on a review of pneumococcal clinical trials, surveillance data from other countries and WHO Global Burden of Disease (WHO GDB) project (19). The number of birth per year (2010- 2013), and monthly (April-March) was extracted from National Organization for Civil Registration (NOCR) official website (20).

Effectiveness of PCV and Hib vaccines was obtained through the analysis of the published literature related to vaccine efficacy. In this study, the efficacy of Hib vaccine adopted from the study of Moradi Lakeh et al. was considered to be 84% (13, 21). Efficacy for pneumococcal vaccine based on the study of Andrews et al. in the UK was 75% (22).

Hib vaccine was included in the Iranian immunization program, also known as Expanded Immunization Program (EPI), along with diphtheria, tetanus, pertussis and hepatitis B under the trade name of pentavalent in December 2014 and it was injected to 2, 4 and 6 months old babies. In this study, the third coverage of DPT and Hepatitis B vaccines was used as proxy for pentavalent. The vaccine coverage for all vaccines in the country in June 2014 was

estimated number of overall cases of more than 95% (23). PCV was injected four times (two, four, six months old and a booster dose at 12 or 15 months). PCV was not included in the EPI and not inoculated at the time of this study. In case of the decision of policymakers regarding PCV introduction to EPI, it is logical to refer to pentavalent vaccine coverage. Accordingly, we estimated PCV coverage as the same as pentavalent vaccine. The burden of disease and death from meningitis and pneumonia caused by Haemophilus influenzae and Streptococcus pneumoniae spread among children under five years old was extracted from the WHO Global Burden of Disease project (GBD Compare) and UNICEF in 2013, 2010, 2005 and 2000 (19).

Burden of disease and death from sepsis caused by Haemophilus influenzae and pneumococcus could not be calculated due to the lack of the required data. The only data available on the number of deaths due to neonatal sepsis is related to all cases from 2007 to 2011.

The number of cases was estimated by multiplying the expected performance of Hib vaccine by diseases burden of meningitis and pneumonia. Corresponding values of the number of deaths caused by pneumococcal were estimated by multiplying the expected performance of pneumococcal vaccine by coverage and death burden of meningitis and pneumonia.

The exclusion criterion in this study was infants under one month. Accordingly, we recruited children less than 5 years of age (1-59 month) in our estimations. Descriptive statistics and Excel spreadsheet program were used for data analysis. All of the main estimations around estimated numbers of cases and death were reported using 95% confidence intervals (CI).

Table1: WHO methodology to estimate potential preventable number of cases and deaths associated with pneumococcal diseases and Haemophilus influenza in Iran (24)

Expected vaccine effectiveness or efficacy	Pneumococcal and Haemophilus influenza vaccines (3rd dose) coverage in the country	National estimate of severe invasive bacterial disease cases caused by vaccine serotypes pneumococcus and Haemophilus influenzae	National estimate of invasive bacterial disease deaths from pneumococcus and Haemophilus influenza	Estimated no. of severe invasive bacterial disease cases averted by pneumococcal and Haemophilus influenza	Estimated no. of invasive bacterial disease deaths averted by Pneumococcal and Haemophilus influenza
(A)	(B)	(C)	(D)	=A * B * C	=A * B * D
90%–95% for serotype specific invasive pneumococcal or Hib disease *	Obtained by the recorder local data or Ministry of Health official statistics **	Obtained by the overall estimates of disease burden or local data Global Burden of Disease project (GBD Compare) ***	Obtained by the overall estimates of disease burden or local data Global Burden of Disease project (GBD Compare) ***		

*Source: Published literature or local vaccine efficacy or effectiveness studies. **Source: WHO / UNICEF joint reporting form or country immunization records. ***WHO Global Disease Burden project. For PCV, will need to account for the estimated amount of pneumococcal disease caused by serotypes included in the PCV used.

3- RESULTS

We found that the number of potentially preventable cases and deaths from meningitis caused by Hib among children under five years old in 2010 were 6416 (95% CI: 3683, 9170) and 73 (95% CI: 41,103), respectively. Details are shown in **Figure.1** and disaggregated by age groups (**Figure.1**). Such potential preventable cases and deaths in 2013 were estimated to be 5,414 (95% CI: 2838, 11630) and 61 (95% CI: 31, 93), as well (**Table.2**).

As shown in **Table.2**, estimated Numbers of pneumonia related cases, which caused by Hib, in 2010 and 2013 were 26,819 (95% CI: 2685, 55993) and 22,186 (95% CI: 2222, 46651), respectively. The corresponding values for pneumonia related deaths were 311(95% CI: 31,645) in 2010 and 256 (95% CI: 25,542) in 2013

(**Figure.2**). In 2010, the number of cases and deaths from Pneumonia associated with Hib 409.27(95% CI: 40.98-848.98) and 4.75(95% CI: 0.47-9.84) per 100,000 in 1–59 months, were estimated. This value for 2013 is 317.49(95% CI: 31.80-667.60) and 3.67(95% CI: 0.36-7.75) (**Table.2**).

In case of Streptococcus pneumoniae, we found that the potentially numbers of preventable cases and deaths from meningitis among children under five years old in 2010 were 2,996 (95% CI: 1663, 4324) and 34 (95% CI: 18.34-49.14), respectively. Such potential preventable cases and deaths in 2013, were estimated to be 2406 (95% CI: 1414, 3646) and 27 (95% CI: 15, 41), as well

(Table.3). As shown in Table.3 estimated numbers of pneumoniae related cases which caused by Streptococcus pneumoniae in 2010 and 2013 were 37,732 (95% CI: 22,183, 58,334), and 30,728 (95% CI: 17,023, 50,412), respectively.

The corresponding values for pneumonia related deaths from Streptococcus pneumoniae were 438 (95% CI: 257, 677) and 356 (95% CI: 197, 586) in 2013, respectively.

Table-2: The number of avoidable death and disease caused by Haemophilus influenzae type B in 2010-2013

Year	Expected vaccine effectiveness or efficacy	Haemophilus influenza vaccines (3rd dose) coverage in the country	National estimate of severe invasive bacterial disease cases caused by vaccine serotype Haemophilus influenzae	National estimate of invasive bacterial diseases deaths from Haemophilus influenza	Estimated number of severe invasive bacterial disease cases averted by Haemophilus influenza	Estimated number of invasive bacterial disease deaths averted by Haemophilus influenza
	(A)	(B)	(C)	(D)	(E)=A * B * C (Per 100,000)	(F)=A * B * D (Per 100,000)
2010	84%	95%	122.70 (70.43-175.37)	1.40 (0.80-2.02)	97.91 (56.20-139.94)	1.11 (0.63-1.61)
The number of avoidable disease and death in children under 5 years (meningitis)					6416 (3683-9170)	73 (41-103)
2010	84%	95%	512.88 (51.36-1063.14)	5.96 (0.60-12.34)	409.27 (40.98-848.98)	4.75 (0.47-9.84)
The number of avoidable disease and death in children under 5 years (Pneumonia)					26819 (2685-55993)	311 (31-645)
2013	84%	95%	97.10 (50.91-145.91)	1.11 (0.57-1.67)	77.48 (40.62-166.43)	0.88 (0.45-1.33)
The number of avoidable disease and death in children under 5 years (meningitis)					5414 (2838-11630)	61 (31-93)
2013	84%	95%	397.86 (39.84-838.60)	4.61 (0.46-9.72)	317.49 (31.80-667.60)	3.67 (0.36-7.75)
The number of avoidable disease and death in children under 5 years (Pneumonia)					22186 (2222-46651)	256 (25-542)

A: Efficacy of Haemophilus influenzae vaccines; B: The vaccine coverage for Haemophilus influenzae vaccines and DPT3; C: Estimates of burden disease caused by Haemophilus influenzae in Iran (GBD project); D: Estimates of burden deaths from Haemophilus influenzae in Iran (GBD project); E: Estimated number of disease cases averted by Haemophilus influenza; F: Estimated number of disease deaths averted by Haemophilus influenza.

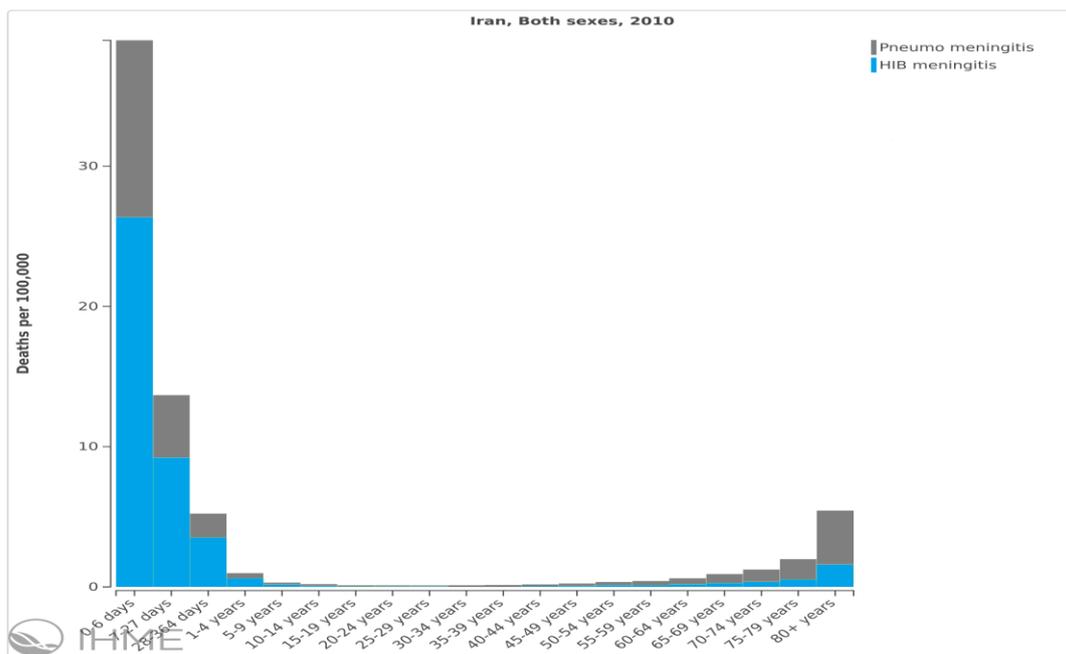


Fig.1: The mortality rate of meningitis caused by Haemophilus influenzae type B and Streptococcus pneumoniae by age group in Iran in 2010 (18).

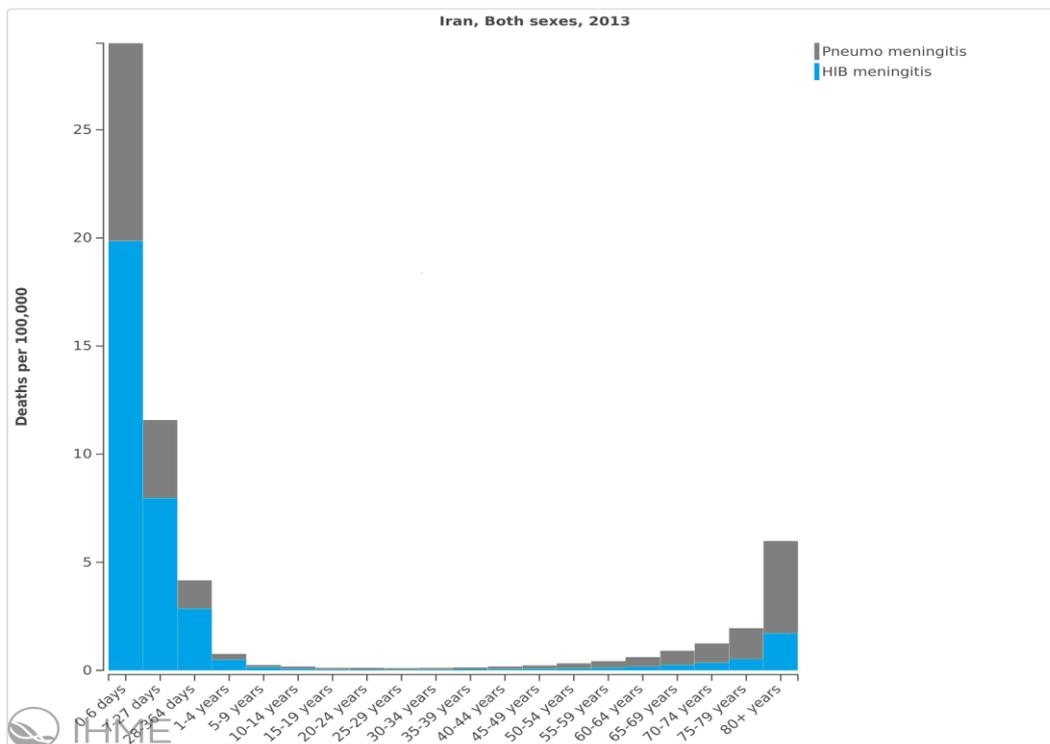


Fig.2: The mortality rate of meningitis caused by Haemophilus influenzae type B and Streptococcus pneumoniae by age group in Iran in 2013 (18).

Table-3: Number of avoidable death and disease caused by pneumococcus in 2010-2013

Year	Expected vaccine effectiveness or efficacy	Pneumococcal vaccines (3rd dose) coverage in the country	National estimate of severe invasive bacterial disease cases caused by vaccine serotypes pneumococcus	National estimate of invasive bacterial disease deaths from pneumococcus	Estimated no. of severe invasive bacterial disease cases averted by pneumococcal	Estimated no. of invasive bacterial disease deaths averted by Pneumococcal
	(A)	(B)	(C)	(D)	E=A * B * C (Per 100,000)	F=A * B * D (Per 100,000)
2010	75%	95%	64.17 (35.62-92.62)	0.73 (0.40-1.06)	45.72 (35.37-65.99)	0.52 (0.28-0.75)
The number of avoidable disease and death in children under 5 years (meningitis)					2996 (1663-4324)	34 (18.34-49.14)
2010	75%	95%	808.16 (474.46-1249.43)	9.39 (5.51-14.51)	575.81 (338.52-890.21)	6.69 (3.92-10.33)
The number of avoidable disease and death in children under 5 years (Pneumonia)					37732 (22183-58334)	438 (257-677)
2013	75%	95%	48.40 (28.40-73.24)	0.54 (0.31-0.83)	34.48 (20.23-52.18)	0.38 (0.22-0.59)
The number of avoidable disease and death in children under 5 years (meningitis)					2406 (1414-3646)	27 (15-41)
2013	75%	95%	617.18 (341.91-1012.54)	7.16 (3.97-11.77)	439.74 (243.61-721.43)	5.10 (2.82-8.38)
The number of avoidable disease and death in children under 5 years (Pneumonia)					30728 (17023-50412)	356 (197-586)

A: Efficacy of Pneumococcal vaccines; B: The vaccine coverage for Pneumococcal vaccines and Hib vaccine; C: Estimates of burden disease caused by pneumococcus in Iran (GBD project); D: Estimates of burden deaths from pneumococcus in Iran (GBD project); E: Estimated number of disease cases averted by pneumococcus; F: Estimated number of disease deaths averted by pneumococcus.

4- Discussion

This study was performed to estimate the number of infections and avoidable deaths of meningitis, pneumonia and septicemia caused by Hib and Streptococcus pneumoniae spread among children under five years old in 2010-2013; the results of this study showed that the bacterial agents Hib, and Streptococcus pneumoniae were the most common causes of meningitis, pneumonia and septicemia in a population study and the burden of disease and death in country is remarkable. So that in 2010, in average, the number death cases of meningitis

caused by Hib and Streptococcus pneumoniae in Iran was 73 and 34, respectively; in 2013, 61 and 27 was obtained. The number of death cases of Pneumonia caused by Hib and Streptococcus pneumoniae in 2010 was 311 and 438, respectively; in 2013, 256 and 356 have been estimated. The average number of meningitis cases caused by Hib and Streptococcus pneumoniae in the Iran was 6,416 and 2,996 in 201 and 5,414 and 2,406 estimated in 2013. The number of pneumonia cases caused by Hib and Streptococcus pneumoniae in 2010 was 26,819 and 37,732, respectively; in 2013, 22,186 and 30,728 have been estimated.

For each 100,000 children from 1-59 months in 2010, the numbers of cases of infections and avoidable deaths due to meningitis caused by Hib were 97.91 and 1.11 and the numbers of cases of pneumonia caused by Hib were 409.27 and 4.75 and the estimation for pneumococcal pneumonia was 45.72, 575.81 and 6.69 cases, every hundred thousand children under five years old. In 2013, the numbers of infections and avoidable death cases of meningitis caused by Hib were 77.48 and 0.88 cases and the pneumonia caused by it was 317.49 and 3.67 cases, and this estimation for pneumococcal pneumonia was 34.48, 0.38, 439.74 and 5.10 cases.

Because of the unavailability of data on mortality, incidence, prevalence and death rates, it was not possible to estimate the number of infections, death cases and lost years due to sepsis caused by Hib. The results showed that Hib and *Streptococcus pneumoniae* are the main causes of meningitis, pneumonia and sepsis in children under five years old and have a relatively high burden of disease and death. According to the World Health Organization recommendation, this estimation method is essential to ensure the continued immunization with pentavalent vaccine (25, 26). According to the estimations of incidence and mortality caused by Hib, adding the vaccine to the country program is essential and it should be continued.

In this study, the numbers of infections and avoidable death cases of meningitis and pneumonia caused by pneumococcal in children under five years old in 2010 were 40,728 and 472; and 33,134 and 383 cases in Iran in 2013 which is consistent with the study of Brien et al. in 2009, and they estimated the number of infections and avoidable deaths caused by *Streptococcus pneumoniae* in children under five years old and it was 14.5 million and 826,000 cases in the world in 2000 (1). Also, in the present study, the numbers of infections

and avoidable deaths of meningitis and pneumonia caused by Hib in children under five years old in 2010 were 33,235 and 384 cases, and 27,600 and 317 cases in 2013, which is consistent with the study of Watt et al. in 2009 and they estimated the numbers of infections and avoidable deaths caused by *Haemophilus influenzae* in children under five years old as 8.13 million and 371,000 cases in the world in 2000 (27).

In Kim et al. study (2004) entitled "the development of Hib and other diseases attacking the children of South Korea", the incidence of invasive disease caused by Hib in children under five years old was 6.8 per one hundred thousand and the highest age-specific incidence was in 23 months old babies (13.6 per one hundred thousand), and its fatality rate was 7 percent. By increasing the use of vaccine during the period under study, the number of children with probable and confirmed symptoms decreased for 25% which was consistent with the results of the present study in terms of mortality and incidence (28). According to the study of Saha et al. (2005), in Bangladesh 1,412 cases reported to have meningitis and 2,434 cases reported to have pneumonia, Hib was the major cause of 425 cases of meningitis and that of 455 cases of pneumonia (29). Another study by Thoon et al. (2007) in Singapore, indicated that the most common symptoms of disease were caused by Hib, meningitis (58%) and pneumonia (26%) (30).

The study conducted by Mahmoud et al. (2002) in the United Arab Emirates before Hib vaccination estimated the incidence of meningitis as to be 2.6 to 5.9 cases per one hundred thousand and of 128 reported meningitis, 59 (46%) cases were due to Hib (31). Al-Mazrou et al. (2004) conducted on children under five years old in Saudi Arabia indicated that of 208 cases of bacterial meningitis, 58 cases were due to Hib (28%) and the incidence of disease

was 17 cases per one hundred thousand Qotaslu et al. (2014) accounted for acute bacterial meningitis (ABM) as one of the most serious infectious diseases with neurological complications and 1,074 cases of the total number of 18,163 registered cases within 23 years, were consistent with the bacterial meningitis standards. The most common factors associated with ABM streptococcus pneumoniae was Haemophilus influenzae. Streptococcus pneumoniae is still the leading cause of bacterial meningitis (35, 36). This study stated that the number of infections and deaths caused by meningitis and pneumonia caused by Hib and pneumococcus is still high in countries such as Iran that have not included Hib vaccine in their immunization programs.

5- CONCLUSIONS

According to the results, the number of potential preventable infections and deaths caused by Hib and pneumococcus among Iranian children is high. This finding favors the effect of both Hib and PCV vaccines in reducing the burden of diseases and deaths in Iran. Accordingly, policy makers are advised to introduce PCV to national immunization program and continue to vaccinate children with the pentavalent vaccine.

6- CONFLICT OF INTEREST: None.

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8- REFERENCES

1. O'Brien KL, Wolfson LJ, Watt JP, Henkle E, Deloria-Knoll M, McCall N, et al. Burden of disease caused by Streptococcus

children under five years old (32-34).

pneumoniae in children younger than 5 years: global estimates. *The Lancet*. 2009;374(9693):893-902.

2. Plotkin S, Orenstein W, Offit P. *Vaccines*. Philadelphia: Saunders. Elsevier; 2008.

3. Greenwood BM, Weber MW, Mulholland K. Childhood pneumonia: preventing the world's biggest killer of children. *Bulletin of the World Health Organization*. 2007;85(7):502-3.

4. Mulholland K. Childhood pneumonia mortality—a permanent global emergency. *The Lancet*. 2007;370(9583):285-9.

5. Esteghamati A, Askari F, Goudarzi N. *Guide line of meningitis surveillance*. 2 ed. Tehran 2006.

6. 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. *The Lancet infectious diseases*. 2010;10(5):317-28.

7. Black RE, Cousens S, Johnson HL, Lawn JE, Rudan I, Bassani DG, et al. Global, regional, and national causes of child mortality in 2008: a systematic analysis. *The Lancet*. 2010;375(9730):1969-87.

8. Ramezankhani R, Kaveh F, Javydrad HR, Zahraei SM, Bianati A. *The Meningitis Atlas*. 1 ed. Tehran 2014.

9. World Health Organization. *Pneumococcal vaccines WHO position paper*. *Weekly epidemiological record*. 1926;88(14):129-44.

10. World Health Organization. *Number of countries having introduced Hib (containing) vaccines to date 2014*. Available from: http://apps.who.int/immunization_monitoring/globalsummary/timeseries/tswucoveragebc.

11. Karami M, Zahraei SM, Gouya MM. *Perspective of Iranian Vaccine-Preventable Diseases Surveillance System in the Era of Newly Introduced Pentavalent Vaccine: Possibility of Implementing a Sentinel*

Hospital-Based Surveillance System. Iranian journal of public health. 2015;44(12):1712.

12. Adegbola RA, Mulholland EK, Secka O, Jaffar S, Greenwood BM. Vaccination with a Haemophilus influenzae type b conjugate vaccine reduces oropharyngeal carriage of H. influenzae type b among Gambian children. Journal of Infectious Diseases. 1998;177(6):1758-61.
13. Shakerian-Rostami S, Moradi-Lakeh M, Esteghamati A. Vaccine Efficacy against Haemophilus Influenzae Type b in Under-5 Children; Systematic Review and Meta-analysis. Journal of Isfahan Medical School. 2010;28(109).
14. World Health Organization. Haemophilus influenzae type b (Hib) in the Eastern Mediterranean Region (EMR). [Online]. 2009. Available at: <http://www.hibaction.org/resources/HibinEMR O.pdf>
15. Wenger JD, DiFabio J-L, Landaverde JM, Levine OS, Gaafar T. Introduction of Hib conjugate vaccines in the non-industrialized world: experience in four 'newly adopting' countries. Vaccine. 1999;18(7):736-42.
16. Peltola H. Worldwide Haemophilus influenzae type b disease at the beginning of the 21st century: global analysis of the disease burden 25 years after the use of the polysaccharide vaccine and a decade after the advent of conjugates. Clinical microbiology reviews. 2000;13(2):302-17.
17. World Health Organization. Measuring impact of Streptococcus pneumoniae and Haemophilus influenzae type b conjugate vaccination. Geneva, Switzerland: WHO Press; 2012.
18. GBDCmpare. WHO 2010-2013. Available at: <https://vizhub.healthdata.org/gbd-compare>.
19. World Health Organization. The global burden of disease: 2004 update [R/OL.(2008)[2012-10-16]. http://www.who.int/healthinfo/global_burden_disease.GBD_report_2004update_full.pdf.
20. National Organization Civil Registration; 2010-2013. Available at: www.sabteahval.ir/Default.aspx?tabid=4762.
21. Moradi-Lakeh M, Shakerian S, Esteghamati A. Immunization against Haemophilus influenzae type B in Iran; cost-utility and cost-benefit analyses. International journal of preventive medicine. 2012;3(5): 332-40.
22. Andrews NJ, Waight PA, Burbidge P, Pearce E, Roalfe L, Zancolli M, et al. Serotype-specific effectiveness and correlates of protection for the 13-valent pneumococcal conjugate vaccine: a postlicensure indirect cohort study. The Lancet Infectious Diseases 2014;14(9):839-46.
23. Ministry of Health and Medical Education. Tehran; 2010. Available at: <http://health.behdasht.gov.ir>.
24. World Health Organization. Measuring impact of Streptococcus pneumoniae and Haemophilus influenzae type b conjugate vaccination. 2012.
25. Karami M, Alikhani MY. Serotype Replacement and Nasopharyngeal Carriage Due to the Introduction of New Pneumococcal Conjugate Vaccine to National Routine Immunization. Jundishapur J Microbiol. 2015;8(10): e24807.
26. Hosseini SM, Poorolajal J, Karami M, Ameri P. Prevalence of Nasopharyngeal Carriage of Streptococcus pneumonia in Iran: A Meta-Analysis. Journal of research in health sciences 2015;15(3):141-6.
27. 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 2009. 903-11 p.
28. Kim J, Jang Y, Kim J, Park T, Park J, Kilgore P, et al. Incidence of Haemophilus influenzae type b and other invasive diseases in South Korean children. Vaccine 2004;22(29):3952-62.
29. Saha SK, Baqui AH, Darmstadt GL, Ruhulamin M, Hanif M, El Arifeen S, et al. Invasive Haemophilus influenzae type b diseases in Bangladesh, with increased

resistance to antibiotics. *The Journal of pediatrics* 2005;146(2):227-33.

30. Thoon KC, Chong CY, Ng WYM, Kilgore PE, Nyambat B. Epidemiology of invasive *Haemophilus influenzae* type b disease in Singapore children, 1994–2003. *Vaccine* 2007;25(35):6482-89.

31. Mahmoud R, Mahmoud M, Badrinath P, Sheek-Hussein M, Alwash R, Nicol A. Pattern of meningitis in Al-Ain medical district, United Arab Emirates—a decadal experience (1990–99). *Journal of infection* 2002;44(1):22-5.

32. Al-Mazrou YY, Al-Jeffri MH, Al-Haggar SH, Musa EK, Mohamed OM, Abdalla MN. *Haemophilus* type B meningitis in Saudi children under 5 years old. *Journal of tropical pediatrics* 2004;50(3):131-6.

33. DeAntonio R, Yarzabal J-P, Cruz JP, Schmidt JE, Kleijnen J. Epidemiology of community-acquired pneumonia and implications for vaccination of children living

in developing and newly industrialized countries: A systematic literature review. *Hum Vaccin Immunother* 2016;12(9):2422-40.

34. Amin M, Ghaderpanah M, Navidifar T. Detection of *Haemophilus influenzae* type b, *Streptococcus agalactiae*, *Streptococcus pneumoniae* and *Neisseria meningitidis* in CSF specimens of children suspicious of Meningitis in Ahvaz, Iran. *The Kaohsiung Journal of Medical Sciences* 2016;32(10):501-6.

35. Ghotaslou R, Sefidan FY, Salahi-Eshlaqi B, Leylabadlo HE. Etiology of Acute Bacterial Meningitis in Iran: a Systematic Review. *Acta Medica Iranica* 2015;53(8): 454-61.

36. Bijlsma MW, Brouwer MC, Kasanmoentalib ES, Kloek AT, Lucas MJ, Tanck MW, et al. Community-acquired bacterial meningitis in adults in the Netherlands, 2006–14: a prospective cohort study. *The Lancet Infectious Diseases* 2016;16(3):339-47.