Archives of the Balkan Medical Union
vol. 58, no. 4, pp. 388-392
December 2023
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ORIGINAL PAPER

POST-LICENSURE EFFECTIVENESS OF THE HAEMOPHILUS INFLUENZA TYPE B VACCINE ON COMMUNITY-ACQUIRED PNEUMONIA AMONG CHILDREN: A CASE-CONTROL STUDY IN REPUBLIC OF MOLDOVA

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Received 10th Oct 2023, Accepted 19th Nov 2023
https://doi.org/10.31688/ABMU.2023.58.4.11

Abstract

Introduction. *Haemophilus influenzae* type b (Hib) is responsible for many severe diseases, including epiglottitis, pneumonia, sepsis, and meningitis, particularly in young children. The Hib conjugate vaccine is considered protective and safe. The evidence of protection afforded by Hib vaccines in the context of real-world immunization programs is essential for accelerating and sustaining their uptake worldwide.
The objective of the study was to evaluate the effectiveness of Hib conjugate vaccine among children aged 2 to 59 months in the Republic of Moldova.
Material and methods. We designed and carried out a matched case–control study in two main pediatric hospitals in Chisinau, Republic of Moldova: Institute of Mother and Child and the Municipal Children's Clinical Hospital no. 1, between December 2020 – January 2022. The endpoint for this case-control vaccine effectiveness study was non-specific, clinically

Résumé

Efficacité après autorisation du vaccin contre l'Haemophilus grippe de type b sur la pneumonie acquise dans la communauté chez les enfants: une étude cas-témoin en République de Moldova

Introduction. *Haemophilus influenzae* de type b (Hib) est responsable de nombreuses maladies graves, notamment l'épiglottite, la pneumonie, la septicémie et la méningite, en particulier chez les jeunes enfants. Le vaccin conjugué Hib est considéré comme protecteur et sûr. La preuve de la protection conférée par les vaccins contre le Hib dans le contexte de programmes de vaccination réels est essentielle pour accélérer et maintenir leur adoption dans le monde entier.
L'objectif de l'étude a été d'estimer l'impact potentiel sur la santé de l'utilisation à l'échelle nationale de la vaccination contre le Hib en République de Moldova

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confirmed pneumonia, thus the cases were children with established diagnosis of pneumonia, according to World Health Organization criteria. The cases were matched by age and sex with up to three controls who do not have pneumonia and came for treatment at the health center where the research was carried out during the same period as the case group.

Results. To evaluate the effectiveness of Hib vaccine, there were enrolled 89 patients and 267 children in the control group. Vaccine effectiveness (VE) was calculated as (1 – Mantel-Haenszel OR in vaccinated children compared to unvaccinated children) x100%. Thus, the VE of Hib vaccine was revealed to be about 63%, (OR=0.37; CI 95%: 0.15 – 0.89; $p < 0.05$).

Conclusions. Hib vaccination is significantly associated with the prevention of pneumonia in children under five years in the Republic of Moldova. It is mandatory to ensure policies that encourage and support the extension of immunization programs targeting high-risk groups. Future efforts to further reduce the disease burden of Hib infections remain a high priority.

Keywords: vaccine effectiveness, Haemophilus, pneumonia.

List of abbreviations:
CAP – community-acquired pneumonia
WHO – World Health Organization
CI – Confidence Interval
Hib – Haemophilus influenzae type b
OR – Odds Ratio

à travers une étude observationnelle de l'efficacité sur la pneumonie communautaire chez les jeunes enfants.

Matériel et méthodes. Nous avons conçu et réalisé une étude cas-témoins appariée dans deux principaux hôpitaux pédiatriques de Chisinau, en République de Moldova: l'Institut de l'Enfant et de la Mère et l'Hôpital Clinique Municipal pour Enfants no. 1, entre décembre 2020 et janvier 2022. Le critère d'évaluation de cette étude cas-témoins sur l'efficacité du vaccin était une pneumonie non spécifique et cliniquement confirmée. Il s'agissait donc d'enfants avec un diagnostic établi de pneumonie, selon les critères de l'OMS. Les cas ont été appariés par âge et sexe avec jusqu'à trois témoins ne souffrant pas de pneumonie et venus se faire soigner au centre de santé où la recherche a été menée au cours de la même période que le groupe de cas.

Résultats. Afin d'évaluer l'efficacité du vaccin contre l'Hib, 89 cas et 267 enfants ont été inscrits dans le groupe témoin. L'efficacité du vaccin (EV) a été calculée comme suit: (1 – OR de Mantel-Haenszel chez les enfants vaccinés par rapport aux enfants non vaccinés) x 100 %. Ainsi, l'EV du vaccin Hib s'est révélée être d'environ 63%, (OR=0,37; IC 95% : 0,15 – 0,89 ; $p < 0,05$).

Conclusions. La vaccination contre le Hib est associée de manière significative à la prévention de la pneumonie chez les enfants de moins de cinq ans en République de Moldova. Il est obligatoire de garantir des politiques qui encouragent et soutiennent l'extension du programme de vaccination ciblant les groupes à haut risque. Les efforts futurs visant à réduire davantage la charge de morbidité due aux infections à Hib restent une priorité élevée.

Mots-clés: efficacité vaccinale, Haemophilus, pneumonie.

Introduction

Haemophilus influenzae type b (Hib) is a Gram-negative bacteria, most often appearing in the form of small coccobacilli. Isolates are further classified based on the presence of capsular polysaccharides (typeable) versus unencapsulated (nontypeable) strains[1,2]. Typeable strains are subdivided by the expression of one of 6 antigenically distinct capsular polysaccharides[2].

Hib is responsible for causing many severe diseases, including epiglottitis, pneumonia, sepsis, and meningitis, particularly in young children[3,4]. Once Hib vaccination was provided, a substantial decline in Hib disease incidence worldwide was noted among children. Nevertheless, pediatricians should remain vigilant in counseling parents on the dangers of Hib and provide vaccination starting at 2 months of age[5]. The Hib conjugate vaccine is considered protective and safe[3,6].

Evidence of the protection afforded by Hib vaccines in the context of real-world immunization programs is essential for accelerating and sustaining their uptake worldwide[7]. Case-control studies are commonly used to evaluate effectiveness of licensed vaccines after deployment in public health programs[7].

The objective of the study was to evaluate the effectiveness of Hib conjugate vaccine among children aged 2 to 59 months in Republic of Moldova.

Material and methods

The study was designed and carried out as a case-control study in two main pediatric hospitals in Chisinau, Republic of Moldova: Institute of Mother

and Child and the Municipal Children's Clinical Hospital no. 1, between December 2020 – January 2022.

The endpoint of this case-control vaccine effectiveness study was non-specific, clinically confirmed pneumonia, thus the cases were children with established diagnosis of pneumonia, according to World Health Organization (WHO) criteria. The cases were matched by age and sex with up to three controls who do not have pneumonia and came for treatment at the health center where the research was carried out during the same period as the case group. The data were collected by interviewing face-to-face the caregivers with a pre-designed structured questionnaire. Logistic regression analysis was used to test the association between the independent and dependent variables. The strength of the association between the dependent variable and independent variables was expressed using odds ratio (OR) with 95% confidence.

The ethical approval was taken from the Research Ethics Committee. Written informed consent was obtained from one of the parents of each pediatric patient after briefing about the research purpose, methods and involvement at the time of obtaining consent. All the procedures of this study were conducted according to the Helsinki Declaration of ethical approval and consent.

Results

Overall, 407 children were enrolled in the study, 14.7% children aged 2-6 months, 49.5% children aged 6-24 months and 35.8% children aged 24-59 months. The cases group included 140 children who were suspected with the diagnosis of pneumonia, 89 of them were confirmed according to WHO criteria. The control group consisted of 267 children. The mean (± SD) age of the children was 16.68 (±1.27) months. Approximately 54.5 % of patients were males.

According to the data included in Table 1, in the group of study 86.4% (121 children) were vaccinated with one dose of Hib vaccine, 72.8% (102 children) with 2 doses of vaccine, and only 42.8% (60 children) were fully vaccinated. As well, 95.5% (255 children) of controls had one dose of Hib vaccine, 85.4%% (228) had 2 doses and 57.7% (154 children) were completely vaccinated against Hib. Of 407 enrolled children, 252 (61.9%) were permanent urban residents. Vaccination status revealed that 7.6% of children did not receive any dose of Hib.

Further, to estimate the Hib effectiveness, from the total group of cases, only children with the diagnosis of confirmed pneumonia were selected (89 children). Of those 89 children with clinically confirmed pneumonia, 11.25% (10 children) had not received any of the Hib vaccine doses. Vaccine effectiveness (VE) was calculated as (1 – Mantel-Haenszel OR in vaccinated children compared to unvaccinated children) x100%. Thus, the VE of Hib vaccine was revealed to be about 63%, (OR=0.37; CI 95%: 0.15 – 0.89; $p < 0.05$).

Along with vaccination status, there were analyzed several risk factors which could influence the occurrence of pneumonia in children. The statistical results revealed the following risk factors: the exposure to cigarettes smoke for the development of pneumonia (OR=3.0; CI 95%: 1.72-5.21; $\rho < 0.001$); cohabitation in families with 3 or more children (OR=3.05; 95% CI: 1.13-8.21; $\rho < 0.05$); (3) indoor air pollution (OR=1.86; CI 95%: 1.19-2.93; $\rho<0.001$);

Table 1. Vaccination status in both groups

	Cases						*Controls*					
Age group	*1 dose Hib*		*2 dose Hib*		*3 dose Hib*		*1 dose Hib*		*2 dose Hib*		*3 dose Hib*	
<6 months	15	68.2%	2	9%	0	0%	30	75%	10	25%	0	0%
6-12 months	35	89.7%	32	82%	0	0%	47	92.1%	45	88.2%	1	1.96%
12-24 months	36	87.8%	34	83%	27	65.8%	69	88.5%	64	82.1%	50	64.1%
≥24 months	35	92%	34	89.4%	33	86.8%	109	964%	109	96.4%	103	91.2%
Total	121	86.4%	102	72.8%	60	42.8%	255	95.5%	228	85.4%	154	57.7

Table 2. Contingency table showing the association (OR=0.37; CI 95%: 0.15 – 0.89; $p < 0.05$) between being unvaccinated and pneumonia occurrence.

	Case	***Control***
Vaccinated	79 (a)	255 (b)
Unvaccinated	10 (c)	12 (d)

(4) mixed or artificial nutrition in children under 6 months (OR=3.97; 95% CI: 1.31-12.04; $\rho < 0.05$).

Discussion

This observational study is the first to evaluate the impact of Hib vaccine on the burden of childhood pneumonia in the Republic of Moldova. We demonstrated that the introduction of this vaccine was associated with a marked decrease in the numbers of pneumonia cases among children 2 to 59 months old. We found that the introduction of Hib vaccine was associated with a 63% reduction in pneumonia morbidity among Moldovan children.

Over the time, an increasing number of studies have investigated Hib effectiveness worldwide[8-11]. According to the results of a study conducted in Botswana, the protective effect observed in the 5 years after Hib vaccine introduction supports the long-term benefits of these vaccines despite the potential for emergence of non–type b *Haemophilus influenzae* and non-vaccine pneumococcal serotypes[12]. The magnitude of the effect of Hib vaccine introduction on the number of pneumonias was also advocated in an Australian study[13]. In addition, the results from Wahl et al[14] suggest that infants stand to benefit more from vaccination against common pneumonia pathogens. The effectiveness of Hib vaccination was studied on different respiratory outcomes, not only pneumonia; a longitudinal study from Bangladesh found that Hib vaccination was a protective factor not only against pneumonia but also against wheezing, and asthma[15]. Taking into consideration other outcomes, in compliance with a recent meta-analysis, the global burden of Hib meningitis has markedly decreased regarding to implemented vaccination programs[16]. According to a systematic review of Theodoratou et al[17], Hib conjugate vaccines prevent 4–6% of cases of clinical pneumonia and 18% of cases of radiologically confirmed pneumonia among children in low – and middle-income countries.

Carrying out a study on Hib effectiveness regarding invasive pneumonia in children is difficult. In low – and middle-income countries, there are limited surveillance data, and serotyping of clinical isolates is incomplete[18,19]. Evidence of its protective effect against invasive pneumonia in children, since its licensure, were highlighted in several publications[20-22].

Our study had several limitations. First, pneumonia diagnoses were based only on the standardized case definition, not on defined radiological criteria. We also cannot exclude the possibility that pneumonia treatment strategies contributed to the observed declines in pneumonia hospitalizations and deaths. Moreover, the short time interval between introduction of Hib vaccine and PCV-13 in the Republic of Moldova averted analyses of the individual effects of these vaccines on the burden of childhood pneumonia. This study contributes to a growing body of literature supporting the important child health benefits of this vaccine in the Republic of Moldova.

Conclusions

Hib vaccination is significantly associated with prevention of pneumonia in children under five years in the Republic of Moldova. It is mandatory to ensure policies that encourage and support the extension of immunization programmes targeting high risk groups. Future efforts to further reduce the disease burden of Hib infections remain a high priority.

Author Contributions:

N.R., A-M.B. and D.B. were responsible for the methodology, conceptualization. A.H., A.R., A-M.B. and D.B. were responsible for selecting eligible patients for the study; D.B., A-M.B, and A.R. analyzed the data; supervising, N.R.; N.R. and A-M.B. wrote the manuscript. All authors have read and agreed to the published version of the manuscript.

Compliance with Ethics Requirements:

„The authors declare no conflict of interest regarding this article"

„The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law."

Acknowledgments:

The study was carried out in the framework of the National Project 20.80009.8007.08 "The impact of immunization on the morbidity and mortality of children with respiratory diseases in the Republic of Moldova ".

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