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Short communication

Hepatitis B serosurvey to validate the achievement of regional hepatitis B control targets in Belarus

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ABSTRACT

Belarus conducted a representative, national hepatitis B serosurvey to evaluate the impact of hepatitis B vaccination programme.

We used a multi-stage cluster design to select 3783 children born between 2009 and 2015. We collected demographic and immunization data, as well as venous blood samples, which were analysed for HBsAg by ELISA.

Out of 2870 participants with valid test results, one tested positive for HBsAg, resulting in a weighted seroprevalence of 0.02% (one-sided 95% upper bound = 0.09%). Of the 3731/3783 (99%) participants with immunization records, 86.8% (95% CI: 84.8; 88.6) had received a timely birth dose of hepatitis B vaccine and 85.6% (95% CI: 83.5; 87.4) had received a birth dose and at least two subsequent doses of the vaccine.

This study findings demonstrated the achievement of the regional hepatitis B control targets and significant progress toward the elimination of hepatitis B as a public health threat in Belarus.

1. Introduction

Hepatitis B virus (HBV) infection continues to be a major cause of morbidity and mortality throughout the world. Safe and effective recombinant vaccines against HBV have been available for over 30 years; if the recommended three-dose series is administered within the first year of life (with the first dose within the first 24 hours after birth), 90–95% of infections can be prevented.

The World Health Organization (WHO) launched a group of global health sector strategies to address the epidemics of HIV, viral hepatitis, and sexually transmitted infections for the period 2022–2030; one strategy sets an aim to end the epidemics of viral hepatitis by 2030 [1]. To achieve this aim, the countries of the WHO European Region have adopted Regional Action Plans to achieve the following interim hepatitis B control targets by 2025: 1) ≥ 95% coverage with the three-dose HBV vaccine for children, 2) ≥ 90% coverage of preventative interventions against perinatal HBV transmission, either by giving a dose of hepatitis B vaccine to all newborns within 24 hours of birth or providing post-exposure prophylaxis for at-risk newborns, and 3) ≤ 0.5% prevalence of hepatitis B surface antigen (HBsAg) in vaccinated cohorts [2].

Universal hepatitis B vaccination for newborns was introduced nationally in Belarus in January 2000. Annual vaccination rates have met or exceeded the 95% goal since 2005, except for a drop in coverage in the third dose in 2007 [3]. In addition, during 1999–2015, the country implemented a catch-up immunization campaign for adolescents aged 13 years. Health care workers, medical colleges and university students, and groups at high risk of HBV infection are also prioritized for vaccination. The country also mandates universal screening of pregnant women for HBV and treatment of those who tested positive.

The Ministry of Health of Belarus, with the support of WHO Regional

Abbreviations: HBV, hepatitis B virus; WHO, World Health Organization; HBsAg, hepatitis B surface antigen; PPES, probability proportional to estimated size; ELISA, enzyme-linked immunosorbent assay; UC, upper confidence bound.

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Office for Europe, conducted a representative, national survey of hepatitis B prevalence among children born between 2002–2015 to determine if the control target of HBsAg prevalence of ≤ 0.5% had been achieved.

2. Methods

2.1. Study population

All children born between 2009 and 2015, i.e., aged 6–12 years in 2022, and registered with a pediatrician in Belarus, were eligible for inclusion[1]. Caregivers provided written informed consent.

2.2. Study design

We conducted a national survey using a stratified multi-stage cluster design. Sampling was done in three stages: 1) districts sampled by probability proportional to estimated size (PPES) within each of the seven regions, stratified by level of urbanization, 2) pediatrician precincts selected by PPES (were used as clusters), 3) random selection of six children meeting study criteria. Health care facilities in each district were classified as urban or rural according to the official categorization, with the exception of health facilities in nine districts of the city of Minsk, which were classified as metropolitan.

Assuming an HBsAg prevalence of 0.30% in the target population, a 0.70% alternative, upper bound prevalence, 80% power, $\alpha = 0.05$ and a design effect of 2, we calculated a sample size of 3206. This number was adjusted to 3234 participants to account for the number of pediatricians needed per district in the second sampling stage.

2.3. Data collection

Data collection took place from September to December 2022. Demographic and vaccination data were extracted from the participants' medical records for all selected children. Venous blood samples were collected from children whose caregivers consented and who were present on the day of blood collection. The blood samples were tested for HBsAg by enzyme-linked immunosorbent assay (ELISA) at the HIV and Concomitant Infections Laboratory of the Scientific Research Institute of Hygiene, Toxicology, Epidemiology, Virology and Microbiology, part of the Republican Centre for Hygiene, Epidemiology and Public Health. This laboratory is accredited according to ISO/IEC 17025 "General requirements for the competence of testing and calibration laboratories" for ELISA, polymerase chain reaction, HIV, hepatitis B and C genotyping. Positive samples were retested with confirmatory assays to verify the results.

2.4. Ethical approval

The study protocol was reviewed and approved by the Ethics Committee of the Institute of Advanced Training and Retraining of Healthcare Personnel at Belarus State Medical University. Additionally, the study received an exemption from ethics review by the WHO Research Ethics Review Committee.

2.5. Statistical analysis

Simple proportions were calculated to describe the study population. Weighted estimates of proportions were calculated based on a child-level weight accounting for the three-stage design. A one-sided 95% upper bound for the national HBsAg seroprevalence and two-sided 95% confidence intervals for vaccination coverage estimates were calculated using the likelihood method accounting for stratification (9 metropolitan districts, 2 regions with rural and urban areas combined and an additional 4 rural regions and 4 urban regions as strata), first stage cluster sampling and sampling weights. The analysis was completed in R v 4.3.2 using the *survey* package [4,5].

3. Results

Of the 3783 selected children, caregivers of 2920 (77.2%) children provided written consent to blood collection; 2872 (75.9%) were present on the day of blood collection and were subsequently tested for HBsAg, resulting in an overall response rate of 75.9%. The response rate varied between regions from 53% in Grodzenskaja Voblast to 96% in Magiliowskaja Voblast; the response rate was slightly higher in rural areas (82%) compared to urban (71%) and metropolitan settings (74%). Further details on response rates by level of urbanization are provided in Table 1. Of those tested for HBsAg,1405 (49%) were female and 2858 (99.5%) were born in Belarus, with a mean age of 10.1 years (in 2022). The HBsAg test results for two participants were indeterminate, and they were excluded from further analysis.

Out of 2870 participants with valid test results, one tested positive for HBsAg, resulting in a weighted seroprevalence of 0.02% (one-sided 95% upper bound = 0.09%) in the study population (Table 2). The participant, who tested positive, was from a rural district and was fully vaccinated against HBV, reportedly receiving a timely birth dose, a second dose 17 weeks later, and a third dose a further 17 weeks later.

Immunization records were retrieved for 3731 (99%) of the selected children. Among those with records, 86.8%[2] (95% CI: 84.8–88.6) received a timely birth dose of hepatitis B vaccine (Table 3). Coverage of the timely birth dose varied by level of urbanization. In metropolitan area, 92.3% participants received a timely birth dose, compared to 84.4% in urban and 88.4% in rural settings.

Overall, 85.6% (95% CI: 83.5-87.4) participants had received a birth dose and at least two subsequent doses of hepatitis B vaccine. By urbanization level, 91.7% of participants in metropolitan area, 82.8% in urban districts, and 87.6% in rural districts had received a birth dose and at least two subsequent doses of hepatitis B vaccine[3].

There was no significant difference in vaccination status between consenting and non-consenting participants. Hepatitis B birth dose coverage was 87.6% (95% CI: 86.4-88.8) and 84.9 (95%CI: 82.2-87.2) respectively. Coverage for the birth dose plus at least two additional doses was 87.4% (95% CI: 86.1-988.6) and 83.6 (80.9-86.1) respectively. Discussion

Based on weighted results, we estimated that national seroprevalence of HBsAg in children born from 2009-2015 in Belarus is 0.02% (one-sided 95% upper bound CI: 0.09).

A meta-analysis of previous studies calculated that a median of 98% of children who received a birth dose and completed the series mounted an adequate antibody response against HBsAg to prevent infection [6].

Table 1
Description of participants selected for hepatitis B serosurvey and tested for HBsAg, by level of urbanization, Belarus.

Urbanization level	Study participants	
	No. selected	*No. (%) of enrolled with valid HBsAg results*
Metropolitan	1260	935 (74.2)
Urban	1256	892 (71.0)
Rural	1267	1043 (82.3)
Total	3783	2870 (75.9)

[1] Each child born in Belarus is assigned a pediatrician, who follows the child throughout the first year of life and regularly thereafter until the child is 17 years old.

[2] Weighted coverage

Table 2
Weighted HBsAg prevalence among participants of hepatitis B serosurvey, Belarus.

No. of enrolled children with valid test results	No. of HBsAg positive	Weighted % of HBsAg positive (one-sided 95% upper bound)
2870	1	0.02 (0.09)

Table 3
Weighted percentage of study participants who received a timely hepatitis B birth dose and completed the full hepatitis B vaccination series by level of urbanization, hepatitis B serosurvey, Belarus.

Urbanization level	No. of children with vaccination records	Weighted % with birth dose	Weighted % with birth dose + ≥2 subsequent doses
Metropolitan	1260	92.3	91.7
Urban	1235	84.4	82.8
Rural	1236	88.4	87.6
Total	3731	86.8 (95% CI: 84.8-88.6)	85.6 (95% CI: 83.5-87.4)

Risk factors for primary HBV vaccine failure in childhood include low birth weight, high maternal HBV viral load, and maternal HBeAg positivity [6–9].

Our findings align with other data on declining hepatitis B disease burden in the country. A study based on national surveillance data found that the incidence of acute HBV infection in children decreased from 4.97/100,000 children in 1996 to 0.06/100,000 children in 2016 [10]. Among adolescents and young adults aged 15–20 years (who were offered vaccination at birth) and adults aged 21–29 years (who were offered vaccination at age 13), the incidence of acute hepatitis B declined from 22.7 and 17.1 per 100,000 in 2002 to 0.18 and 0.12 per 100,000 in 2023, respectively. The incidence of newly detected chronic hepatitis B cases among these age groups declined from 70.6 and 48.5 per 100,000 in 2002 to 0.87 and 4.52 per 100,000 in 2023, respectively.

A systematic analysis for the Global Burden of Disease Study estimated the national prevalence of chronic HBV based on HBsAg positivity to be 0.9% across all ages and 0.8% among children under 5 in 1990. By 2019, the estimated prevalence has decreased to 0.6% for all ages and 0.04% for children under 5 [11]. These estimates are confirmed by the statistics of the Ministry of Health of Belarus — between 2021 and 2023, the prevalence of chronic HBV among pregnant women ranged from 0.2% to 0.3%, with screening coverage of 100%.

The low HBsAg seroprevalence from our serosurvey is consistent with data from other national seroprevalence surveys in the WHO European Region. The Republic of Moldova conducted a representative serosurvey in a similarly aged population in 2020, which found a HBsAg positive proportion of 0.21% [12]. Similarly, other serosurveys have documented low seroprevalence in Ukraine in 2017 (0.2%) [13], Georgia in 2021 (0.03%) [14], and Tajikistan in 2010 (0.4%) [15].

As part of this survey, we collected vaccination record data to evaluate vaccination coverage rates. We found that a high percentage of children received a timely birth dose and then completed the vaccine series. While the survey was not powered to conduct subpopulation analyses by urbanization level, the data suggest that birth dose coverage and coverage with birth dose and at least two subsequent doses of vaccine may be lower in rural districts and urban districts outside of Minsk. An investigation of potential barriers to vaccination in these districts could be considered to inform future actions to improve coverage.

Our survey provided a representative sample of the target population, including children from 543 different pediatrician catchment areas in 38 districts. The availability of vaccination records to calculate coverage was also a strength; less than 2% of vaccination data were missing.

Potential limitations of this survey are the parental refusals or absence of children on the day of data collection, resulting in 24.1% of selected children not being tested. This could introduce selection bias if non-consenting participants systematically differed in vaccination status or risk of infection compared to consenting participants. To evaluate the impact of this potential bias on the results, we conducted a simulation study. We randomly imputed test results for these children and recalculated the upper confidence bound (UC). The 95th percentile of 500 estimated UCs did not exceed the threshold 0.5% until the HBsAg seroprevalence in this subpopulation was > 0.2%, substantially higher than the observed seroprevalence of 0.02%. Therefore, it is unlikely that potential selection bias due to non-consenting participants would change the conclusion that Belarus has met the control target.

Since HBsAg may not be detectable in early infection, it is possible that children who had recently acquired HBV infection tested falsely negative; however, because most childhood HBV infections occur during the neonatal period [16], the likelihood of missed acute infections is low.

In this study, we have shown that Belarus has achieved ≤0.5% prevalence of hepatitis B in vaccinated cohorts. Therefore, in 2023, the European Technical Advisory Group of Experts concurred with recommendations of its Working Group on Hepatitis B and validated Belarus's achievement of the regional hepatitis B control targets [17].

4. Conclusion

In this nationally representative sample, we found that Belarus has achieved the regional hepatitis B control target of ≤0.5% prevalence of hepatitis B in vaccinated cohorts. Continued efforts to ensure coverage of a timely birth dose and completion of the subsequent three-dose series in infants are necessary to ensure that the low prevalence of HBsAg positivity is consistently and universally maintained. Additionally, maintaining high coverage of screening of pregnant women for hepatitis B and providing adequate treatment for those who are infected are essential for reaching HBV elimination goal.

CRediT authorship contribution statement

Veronika Vysotskaya: Methodology, Investigation, Data curation, Writing – original draft, Supervision. **Martyna Gassowski:** Methodology, Formal analysis, Data curation, Writing – review & editing. **Amelia Kasper:** Writing – original draft, Visualization. **Elena Gasich:** Methodology, Investigation, Writing – review & editing, Supervision. **Natalia Kolomiets:** Methodology, Writing – review & editing. **Alla Dashkevich:** Methodology, Investigation, Writing – review & editing, Supervision. **Kathleen Wannemuehler:** Methodology, Data curation, Formal analysis, Writing – review & editing. **Oleg Dubovik:** Writing – review & editing, Supervision, Funding acquisition. **Liudmila Mosina:** Conceptualization, Methodology, Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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All authors attest they meet the ICMJE criteria for authorship.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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