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Seroprevalence of hepatitis B virus infection markers among children in Ukraine, 2017

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Abstract

Background: Before hepatitis B vaccine (HepB) introduction, level of endemicity of hepatitis B virus (HBV) in Ukraine was estimated as intermediate but the prevalence of HBV infection markers has not been measured in population-based serosurveys. Coverage with 3 doses of HepB, introduced in 2002, was 92%-98% during 2004-2007 but declined to 21%-48% during 2010–2016. To obtain data on HBV prevalence among children born after HepB introduction, we tested specimens from a serosurvey conducted in Ukraine in 2017, following circulating vaccine-derived poliovirus outbreak in 2015, among birth cohorts eligible for polio immunization response.

Methods: The serosurvey was conducted in Zakarpattia, Sumy, and Odessa provinces, and Kyiv City, targeting 2006-2015 birth cohorts. One-stage cluster sampling in the provinces and stratified simple random sampling in Kyiv were used for participant selection. All participants were tested for antibodies against HBV core antigen (anti-HBc). Anti-HBc-positive children were tested for HBV surface antigen (HBsAg). We also obtained information on HepB vaccination status for all children.

Results: Of 4,596 children tested, 81 (1.8%) were anti-HBc-positive and eight (0.2%) were HBsAg-positive. HBsAg prevalence was 0.7% (95% confidence interval, 0.3%-1.4%) in Zakarpattia, 0.1% (0.0%-0.4%) in Sumy, 0% (0.0%-0.3%) in Odessa, and 0.1% (0.0%-0.8%) in Kyiv. Across survey sites, the proportion of recipients of 3 HepB doses was 53%-80% in the 2006-2009 cohort and 28%-59% in the 2010-2015 cohort.

Conclusion: HBV prevalence among children in surveyed regions of Ukraine in 2017 was low, including in Zakarpattia—the only site above the 0.5% European Regional target for HBsAg seroprevalence. However, HepB vaccination was suboptimal, particularly among children born

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after 2009, resulting in large numbers of unvaccinated or incompletely vaccinated children at risk of future HBV infection. HepB coverage should be increased to further reduce HBV transmission among children in Ukraine and achieve regional and global hepatitis B control/elimination targets.

Keywords

Hepatitis B virus prevalence; chronic hepatitis B infection prevalence; HBsAg prevalence; Hepatitis B vaccination coverage; hepatitis B; Ukraine; WHO European Region

1. Introduction

Hepatitis B is a substantial public health problem in Ukraine [1–3]. Recent estimates suggest that approximately 514,000 persons among approximately 42 million population are chronically infected with hepatitis B virus (HBV) [3]. Ukraine has the second highest hepatitis B burden among countries of Central and Eastern Europe and Central Asia in terms of disability-adjusted life years (DALY) [2]. However, the prevalence of markers of HBV infection has not been measured in population-based serosurveys. Existing estimates are derived from statistical models or data sources of variable quality (e.g., routine surveillance or convenience sample surveys) and indicate an intermediate level of HBV endemicity¹ in a pre-vaccine era: the estimated prevalence of hepatitis B virus surface antigen (HBsAg) carriers in 1990 ranged across age groups between 2.43% to 5.46% among females and between 2.99% to 5.65% among males [4]. The HBsAg prevalence among women of childbearing age in Ukraine in 2000 was estimated as 3.84% [5]. More recent estimates suggest a lower prevalence in the general population—1.3% in 2008 [3] and 1.45% in 2010 [6]. Situation analysis for hepatitis B in Ukraine, based on the triangulation of various data sources and conducted by the Ministry of Health (MOH) in 2018, also suggests a low level of current overall HBV endemicity in Ukraine [1].

Ukraine has endorsed the Global Health Sector Strategy on Viral Hepatitis adopted by the World Health Assembly in 2016, which calls for the elimination of viral hepatitis as a public health threat by 2030 [7, 8]. Along with all other Member States of the World Health Organization (WHO) European Region, Ukraine also adopted regional goals related to hepatitis B, which includes achieving 0.5% prevalence of chronic HBV infection in vaccinated cohorts by 2020 [9, 10]. However, the prevalence of HBV infection among children born since vaccine introduction in Ukraine has not been assessed.

Hepatitis B vaccine (HepB) was introduced into the national immunization schedule of Ukraine in 2000. The HepB birth dose (HepB-BD) was included in 2001. Initially, the national immunization schedule included three doses of HepB monovalent vaccine given at birth (within 24 hours), one month, and six months of age. Since July 2018, the schedule was changed² to administration at birth, two months, and six months of age. Vaccination coverage with three doses of HepB (HepB3) increased during the first years after the vaccine introduction, reaching 98% by 2004 (Figure 1) [11–13]. However, since 2009, coverage

¹HBV endemicity levels based on the prevalence of HBsAg: low (<2%), lower-intermediate (2–4.99%), higher-intermediate (5–7.99%), and high (>8%) [4]

²By the Ministry of Health (MOH) order #947 dd 18 May 2018 (endorsed by the Ministry of Justice 4 June 2018)

for all vaccines, including HepB, has declined to very low levels (Figure 1). The reasons for this decline included increasing safety fears and mistrust in vaccinations among the general population and health care providers, particularly in the aftermath of the failed measles-rubella nationwide immunization campaign in 2008, when the death of a vaccine recipient due to unrelated causes was attributed to the vaccine [14, 15]; a strong anti-vaccine media environment; and vaccine shortages caused by limited funding and inadequate procurement practices. In addition, political instability, economic crisis, and ongoing armed conflict in the eastern part of Ukraine since 2014 have led to the deterioration of the socio-economic situation and internal displacement of more than one million people, creating additional challenges to an already weakened national immunization program [15–19]. HepB3 coverage began to improve during the period 2017–2018, following improvement in vaccine procurement practices and increased availability of vaccines since 2016, but remained suboptimal. The trends for coverage with HepB-BD were similar (Figure 1) [11–13].

A large-scale serosurvey for vaccine-preventable diseases (VPD) conducted in Ukraine in 2017 provided an opportunity to obtain population-based data on the prevalence of chronic HBV infection among children born after the introduction of HepB into the national immunization schedule. We tested available samples from children enrolled in this serosurvey for markers of HBV infection. The serosurvey also provided an opportunity to assess the HepB vaccination status of children in surveyed birth cohorts.

2. Methods

The primary purpose of this serosurvey was to assess population immunity against polioviruses in the aftermath of the circulating vaccine-derived poliovirus (VDPV) type 1 outbreak in Ukraine in 2015 and the subsequent three nationwide rounds of outbreak response immunization [16]. As implementing nationwide survey was not feasible for logistical reasons, the serosurvey was conducted in four regions of Ukraine, which represented areas with problems related to VDPVs³ and/or challenges with routine immunizations. The areas selected for the survey were located in different geographic regions of Ukraine: Zakarpattia province – in the west, Sumy province, – in the east, Odessa province – in the south, and the capital, Kyiv City – in the central part of the country (Figure 2). The four surveyed areas accounted for approximately 18% of Ukraine’s total population [20].

The serosurvey targeted two age groups based on the eligibility for the nationwide polio outbreak response immunization rounds: children born during 2010–2015 after the decline in immunization coverage in Ukraine who were eligible for all three rounds, and children born during 2006–2009 who were eligible for the third round only. All birth cohorts included in the serosurvey were eligible for routine childhood HepB vaccination.

³Zakarpattia had an outbreak of circulating VDPV type 1 outbreak in 2015. Single VDPVs without the evidence of their further circulation were detected in Ukraine in Sumy and Odessa (classified as ambiguous VDPVs and considered “VDPV events”), indicating the potential for future emergence of circulating VDPVs [16].

We used the lists of children registered with healthcare facilities (HCF) as the sampling frames for the serosurvey because all persons in Ukraine are assigned at birth to an HCF based on where they reside. We selected survey participants, using one-stage cluster sampling in the three provinces and stratified simple random sampling (SRS) in Kyiv City.

We estimated the sample size based on the polio component of the serosurvey and assumed a $\pm 5\%$ margin of error with 95% confidence and 70% expected prevalence of polio antibodies. We inflated the sample size to allow for 20% non-response. In Kyiv, this resulted in 400 children per age stratum targeted for the survey (800 children in total). In Zakarpattya, Sumy, and Odessa, we multiplied the targeted sample size by an assumed design effect of 2.0 to account for cluster sampling, and 800 children per age stratum (1,600 children in total) per province were targeted (40 clusters with 20 children in each). A total of 5,600 children were targeted in the four survey sites.

In Zakarpattya, Sumy, and Odessa, a cluster was defined as an HCF precinct. In each province, we selected 40 clusters with probability proportionate to population size from the lists of all precincts; 20 children per cluster were selected by SRS from the lists of catchment population of eligible age in the given precinct. In Kyiv City, where electronic line-lists were available at HCFs, the sampling unit was a child, and we selected children by stratified SRS from the lists of all children in targeted birth cohorts. The sample was allocated across districts of Kyiv City proportionate to their population. Participant selection was performed separately for the two age strata.

After obtaining verbal informed consent from the caregivers, we collected 3–5 ml of whole blood from participants by venipuncture. We obtained information about the participants' basic demographics (sex, age, and residence) and immunization status (number of doses of hepatitis B vaccine received) from HCF records. To avoid participation bias, we collected immunization information for all children selected for the serosurvey, irrespective of their participation status.

Serum separation was performed on the same day in respective provincial laboratories, and the samples were shipped to the National Virology Laboratory of the Center for Public Health in Kyiv for aliquoting into four portions. Aliquots for hepatitis B testing were stored at -20°C until shipment to the Serology Laboratory at Lugar Center, National Center for Disease Control and Public Health, Georgia, where they were tested for markers of HBV infection.

In accordance with WHO guidelines [21], all specimens were tested for total antibodies against HBV core antigen (anti-HBc)—a marker of HBV infection and positive specimens were tested for HBsAg—a marker of chronic HBV infection. Testing was conducted using Architect *i*2000 Immunoassay Analyzer (Abbott Diagnostics, Abbott Park, IL, USA). Chemiluminescent microparticle immunoassay (CMIA) Architect anti-HBc II was used to detect anti-HBc and Architect HBsAg Qual II CMIA was used to detect HBsAg. For confirmation of the presence of HBsAg by means of specific antibody neutralization, HBsAg-positive specimens were tested by Architect HBsAg Qual II confirmatory CMIA. All testing was conducted in accordance with the manufacturer's instructions. Based on the

testing results, we assigned the survey participants to the final classification categories: uninfected (anti-HBc negative), infected with infection cleared (anti-HBc-positive and HBsAg-negative), and chronic/current infection (anti-HBc-positive and HBsAg-positive). Because the likelihood of encountering acute infections in a cross-sectional survey conducted in a low prevalence setting is very low [21], we assumed that anti-HBc-positive and HBsAg-positive cases found in the survey represented chronic HBV infections.

We used the statistical software Epi Info™ Version 7.2.2.6 for data entry and analyzed the data from each survey site separately, using SAS and R. The main outcome measures were percentages of seropositives for anti-HBc and HBsAg. We calculated 95% confidence intervals (CI) for proportions, using survey procedures in SAS. The estimates were calculated separately for each survey site and were adjusted to account for non-response (due to refusal or not enough sample for testing), survey design, and sampling weights. In cases of zero prevalence, we used unadjusted 95% CI. We made comparisons across the age groups and by sex and immunization status, using chi-square test. The proportion of recipients of 3 doses of HepB by the time of the serosurvey was the main outcome measure in the analysis of immunization status.

The serosurvey was determined by the Human Research Protection Coordinator, Center for Global Health, CDC, to represent public health program evaluation and did not qualify as human subject research. The protocol was approved by the MOH of Ukraine.

3. Results

Among the 5,600 children initially selected for the serosurvey, 93 were found to have moved out of the area; therefore, they were excluded, resulting in 5,507 eligible children. Of these, 5,078 (92.2%) children were enrolled; the parents of 429 (7.8%) children refused participation. Hepatitis B testing was performed for 4,596 participants (83.5% of eligible children) for whom the amount of available serum was sufficient for testing. Across the survey sites, 84.3% to 88.2% of eligible participants in the 2006–2009 birth cohort and 76.1% to 85.2% in the 2010–2015 birth cohort were tested for HBV infection markers (Figure 3). The proportion of children from the older age group (2006–2009 birth cohort) was higher among those tested for hepatitis B, than among those who were not tested (i.e. refused participation or the serum amount was insufficient). This was observed in all sites, except Sumy (p values: Kyiv City, 0.029, Zakarpattia and Odessa <0.001, Sumy, 0.100) (Table 1). The proportion of children who received the recommended 3 doses of HepB was higher among those who were tested for HBV infection markers than among children who were not tested in all sites, except Kyiv City (p values: Zakarpattia, 0.024; Sumy and Odessa, <0.001, Kyiv City, 0.399) (Table 1). However, there were no significant differences among those tested and not tested by sex at any site (p values, >0.05) (Table 1).

Overall, of the 4,596 children tested for HBV infection markers in the four survey sites, 81 (1.8%) were seropositive for anti-HBc and eight (0.2%) were also seropositive for HBsAg. Most of the identified seropositive children were from Zakarpattia, which accounted for 56 (69.1%) anti-HBc-positive and six (75.0%) HBsAg-positive children (Table 2). The prevalence of HBV infection was low in Sumy, Odessa, and Kyiv City, where the proportion

of anti-HBc-positive children ranged between 0.8% and 1.1%. HBsAg prevalence in these sites was 0% to 0.1%, with upper limits of 95% CI ranging between 0.3% and 0.8% (Table 2). In Zakarpattya, 5.2% (95% CI, 3.1%–8.7%) of the children had anti-HBc and 0.7% (95% CI, 0.3%–1.4%) were seropositive for HBsAg.

The analysis by birth cohorts showed a higher prevalence of HBV infection markers in the younger age group compared to the older one in Zakarpattya (Table 3), where HBsAg seroprevalence was 1.0% in 2010–2015 birth cohorts versus 0.1% in 2006–2009 cohorts ($p=0.045$). Similar finding was observed for anti-HBc seroprevalence, but the difference between age groups did not reach statistical significance (6.4% versus 3.3%; $p=0.092$). In other survey sites, anti-HBc seroprevalence in Odessa was significantly lower among the younger birth cohort compared to the older one (0.5% versus 1.6%, $p=0.033$). We noted no statistically significant differences in seroprevalence by age group in Sumy and Kyiv City (Table 3). Because of the overall small number of positive results for HBV infection markers across survey sites, the analysis of seroprevalence by HepB immunization status of the participants was limited to anti-HBc in Zakarpattya, which accounted for most anti-HBc-positive children. In Zakarpattya, children who had received the recommended 3 doses of hepatitis B vaccine had a lower seroprevalence of anti-HBc than children who received <3 doses (3.5% [95% CI, 1.7%–6.9%] versus 6.2% [95% CI, 3.4%–11.1%]); however, the difference did not reach statistical significance ($p=0.176$).

The analysis of HepB vaccination status which included all children selected for the serosurvey enrolment, irrespective of their participation status, demonstrated suboptimal coverage across survey sites and in both age groups, particularly among younger birth cohorts (Table 4). In the 2006–2009 birth cohorts, 53% (in Kyiv City) and 80% (in Sumy) of the children had received at least three doses of HepB. In the 2010–2015 birth cohorts, the proportion of recipients of 3 doses was <50% (range, between 28% and 47%) in all survey sites, except Sumy (59%). Differences in HepB vaccination status between these two age cohorts were statistically significant for all survey sites (p value, <0.001) except Kyiv City (p -value=0.097), which had consistently low coverage in both age groups (Table 4).

4. Discussion

The serosurvey demonstrated that as of 2017, HBV infection prevalence among cohorts eligible for vaccination in the surveyed sites of Ukraine was generally low. In three of the four surveyed areas, the point prevalence of HBV infection markers was 0.1% for HBsAg, with upper limits of 95% CI ranging across sites between 0.3% and 0.8%, and 1.1% for anti-HBc with upper limits of 95% CI ranging across sites between 1.5% and 2.2% (Table 2). The serosurvey findings are consistent with the recent low estimates of overall prevalence of HBV infection markers in Ukraine [3, 6] and with the data from HBV testing routinely conducted for surveillance/monitoring purposes among selected population groups by the MOH⁴ [1]. During 2013–2016, pooled data from this routine testing showed

⁴In Ukraine, routine testing of selected population groups for HBV infection markers includes viral hepatitis patients tested for diagnostic purposes and diverse groups eligible for routine testing for “prophylactic” purposes. The latter include: persons with history of viral hepatitis, HBsAg carriers, contacts, blood donors, pregnant women, institutionalized children (orphanages, boarding schools), health care workers, patients undergoing prolonged hospital treatment, patients of STD and narcological institutions, children aged

HBsAg seroprevalence <1% among pregnant women (0.84%), healthcare workers (0.78%), and blood donors (0.62%) [1]. Overall HBsAg endemicity in all groups tested was low in 20 of the 25 provinces (range, 0.74%–1.82%) and low-intermediate in the remaining five provinces (range, 2.51%–3.03%) [1].

The only survey site with HBsAg point prevalence above 0.5%, the regional target established by the WHO Regional Office for Europe [10], was Zakarpattya (0.7%, upper 95% confidence limit = 1.4%). A higher prevalence of HBV infection markers among young children in Zakarpattya found in the present serosurvey is of concern, particularly in the context of low immunization coverage with both HepB3 and HepB-BD. Additionally, Zakarpattya has been the setting of the circulating VDPV type 1 outbreak in 2015 [16] and is among the regions most affected by the ongoing large-scale measles outbreak since 2017 [22], highlighting systemic problems related to immunization services in the province. However, low immunization coverage alone cannot account for higher HBsAg prevalence in Zakarpattya because hepatitis B vaccine coverage is low throughout the country, including survey sites with lower HBsAg seroprevalence (Figure 4). Based on the pooled data for groups routinely tested during the period of 2013–2016, Zakarpattya was the province with the highest overall HBsAg positivity in Ukraine (3.03%) [1]. In addition, 2.88% of the pregnant women tested in Zakarpattya were seropositive for HBV infection markers⁵ (nationwide, 0.92%) as were 3.17% of the healthcare workers (nationwide, 1.05%) [1]. Although the routine testing data in Ukraine are difficult to interpret because various groups are included and it is unclear how the persons are selected for testing, the data suggest the tendency toward a higher HBV prevalence in certain groups in Zakarpattya versus other regions. The low birth dose coverage, in combination with nearly 3% HBsAg prevalence among pregnant women in Zakarpattya could have contributed to a higher prevalence of HBV among young children in the province. A review of the state of the implementation of WHO-recommended strategies to prevent mother-to-child HBV transmission, such as screening of pregnant women for HBV infection markers, post-exposure prophylaxis with hepatitis B immunoglobulin and timely (within 24) administration of birth dose of hepatitis B vaccine to infants born to HBsAg-positive mothers [7, 10, 21] would help identify potential gaps in these practices and developing approaches to address them.

HBV infection prevalence among children up to 11 years of age in this survey was much lower than estimated overall prevalence across all ages [1–6] indicating that most of the HBV transmission in Ukraine likely occurs later in life. Available limited data on HBV transmission modes in Ukraine suggest the importance of transmission associated with unhygienic practices in HCFs, intravenous drug use and sexual transmission [1, 23]. Screening of pregnant women for hepatitis B is conducted and nationwide, overall positivity is low (<1% during 2013–2016) [1]. In addition, almost all births in Ukraine (>99.9%) are assisted by a skilled birth attendant [24] and the policy of administering HepB_BD is in place. Therefore, mother-to-child transmission of HBV in Ukraine is likely

<1 year with history of transfusion of blood or blood products, children born to HBsAg-positive mothers, healthy persons, persons vaccinated against hepatitis B undergoing assessment of status of immunity [1]. The data from this testing should be interpreted with caution as the criteria for eligibility for testing within subgroups are unclear and various HBV markers tested are not always reported separately.

⁵Most of the results (>90%) are from HBsAg testing, but other markers of HBV infection are also included in aggregate counts [1].

limited. However, because HepB_{BD} coverage is low and it is uncertain what proportion of pregnant women are screened [1], some level of vertical transmission cannot be ruled out. Horizontal transmission during childhood in Ukraine has been demonstrated among institutionalized children residing in boarding schools, particularly among those in contact with HBV-infected children [25]. Timely HepB vaccination is the best way to protect children from acquiring HBV infection later in life. However, the proportion of children vaccinated with the recommended 3 doses of HepB in Ukraine is low, particularly in cohorts born after 2009, which is consistent with officially reported low levels of coverage in all surveyed regions (Figure 4). Hence, large numbers of children who have not yet been exposed to the virus are unvaccinated or under-vaccinated; therefore, they are susceptible to HBV. Unless these children are vaccinated against hepatitis B, they will remain at risk of future HBV infection.

The low coverage with hepatitis B vaccine in Ukraine is related to the overall decline in immunizations for all vaccines since 2009. The lower coverage with hepatitis B vaccine compared to other vaccines in the period before 2009 [11, 12] is likely due to insufficient awareness among the general population and health care providers of the risks and consequences of HBV infection and of the importance of early vaccination in preventing HBV transmission [19, 26, 27]. Widespread use of false contraindications and misguided perceptions about hepatitis B vaccine safety, particularly for newborns among both caregivers and providers, is another contributing factor [27, 28]. Frequent shortages of hepatitis B vaccine in the past, particularly during the period of 2012–2015, also played a part in low coverage [16–18, 29, 30]. Reliance on the monovalent vaccine for hepatitis B in the national immunization schedule, which until mid-2018 required a separate visit at one month exclusively for hepatitis B vaccination, could also have contributed to low vaccine uptake. Recent developments that would help address those challenges include replacement of the one-month dose of monovalent hepatitis B vaccine with a dose of pentavalent vaccine containing diphtheria, tetanus, whole-cell pertussis, *Hemophilus influenzae* type B and hepatitis B components (DTwP-HiB-HepB) at two months of age [29]. This change decreases the number of injections and HCF visits required for completing the immunization series, reduces the burden on cold chain, and increases overall cost-effectiveness of the national immunization program. The use of false contraindications has been a frequent cause of vaccination delays or interruptions. The recent reduction (by the MOH Decree No. 2027 from October 11, 2019) of the list of contraindications to vaccinations which previously included many conditions not recognized as valid contraindications by WHO, should help. Although coverage for most vaccines is still suboptimal, the increase in officially reported coverage observed since 2017, including for HepB, is encouraging (Figures 1 and 4) [11]. Preliminary data for 2019 suggest an increase in coverage to 77% for HepB3 and 96% for HepB-BD, indicating the potential positive impact of the recent changes. Further optimization of the national schedule and securing an uninterrupted supply of quality-assured vaccines and safe injection equipment will help continue strengthening the program and further improve immunization safety while contributing to the prevention of HBV transmission. Given the large numbers of susceptible children, catch-up vaccination for hepatitis B among unvaccinated and under-vaccinated children might help to prevent future HBV infections.

The present serosurvey has certain limitations. The survey was implemented in four regions with concerns related to VDPVs because conducting a nationwide survey was not feasible. Therefore, it provides representative subnational estimates for each surveyed region, but not for the entire country. Information on immunization was limited to the number of vaccine doses received; therefore, timeliness of Hepatitis B vaccinations could not be assessed. Small numbers in some subgroups prevented us from conducting a more detailed analysis of seroprevalence and immunization status. Furthermore, in some sites, there were differences in HepB immunization status by HBV testing status. However, because of the low seroprevalence of HBV infection markers and high participation rates, this difference, as well as certain differences in proportions tested between age groups, was unlikely to have a substantial impact on the overall estimates of seroprevalence in these provinces.

The WHO European Region recently developed a framework for validation of the achievement of regional hepatitis B goals by the Member States [31, 32]. The conditions for validation include meeting all the following criteria: 90% coverage with three or four doses of hepatitis B vaccine for infants, 90% coverage of newborns with timely administered birth-dose of hepatitis B vaccine (for countries implementing universal newborn hepatitis B vaccination policy, including Ukraine), and 0.5% of HBsAg prevalence in vaccinated cohorts [32]. The present survey was not designed to provide nationally representative data on HBsAg seroprevalence for validation purposes; therefore, it was not possible to determine whether the regional target has been met in Ukraine at the national level. Nevertheless, it provided previously unavailable information on current levels of the HBV infection prevalence in diverse parts of Ukraine, demonstrating that as of 2017, HBsAg seroprevalence was very low (0.1%) in most surveyed areas, and was <1% even in the region with the highest observed seroprevalence (0.7%). Ideally, a nationwide survey to obtain national estimate of HBsAg prevalence should be conducted. However, in addition to the demonstration of HBsAg prevalence at 0.5% level, Ukraine would need to increase and sustain HepB3 and HepB_BD coverage at or above 90% to meet all the criteria for validation of the achievement of the regional hepatitis B target.

A full range of interventions aimed at preventing transmission should be implemented to further reduce HBV prevalence throughout Ukraine and achieve the elimination of viral hepatitis as a public health threat [7, 10, 21]. Improving immunization services at the national and local levels should be a high priority [33].

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Highlights

- Prevalence of hepatitis B infection markers among children in Ukraine was unknown
- We found low prevalence of hepatitis B infection among children across survey sites
- Zakarpattia (0.7% HBsAg-positive) was the only site above the 0.5% WHO/EURO target
- Hepatitis B vaccination status across all survey sites was suboptimal
- Large numbers of children at risk of future hepatitis B infection unless vaccinated
- Coverage should be increased to further reduce hepatitis B transmission in Ukraine

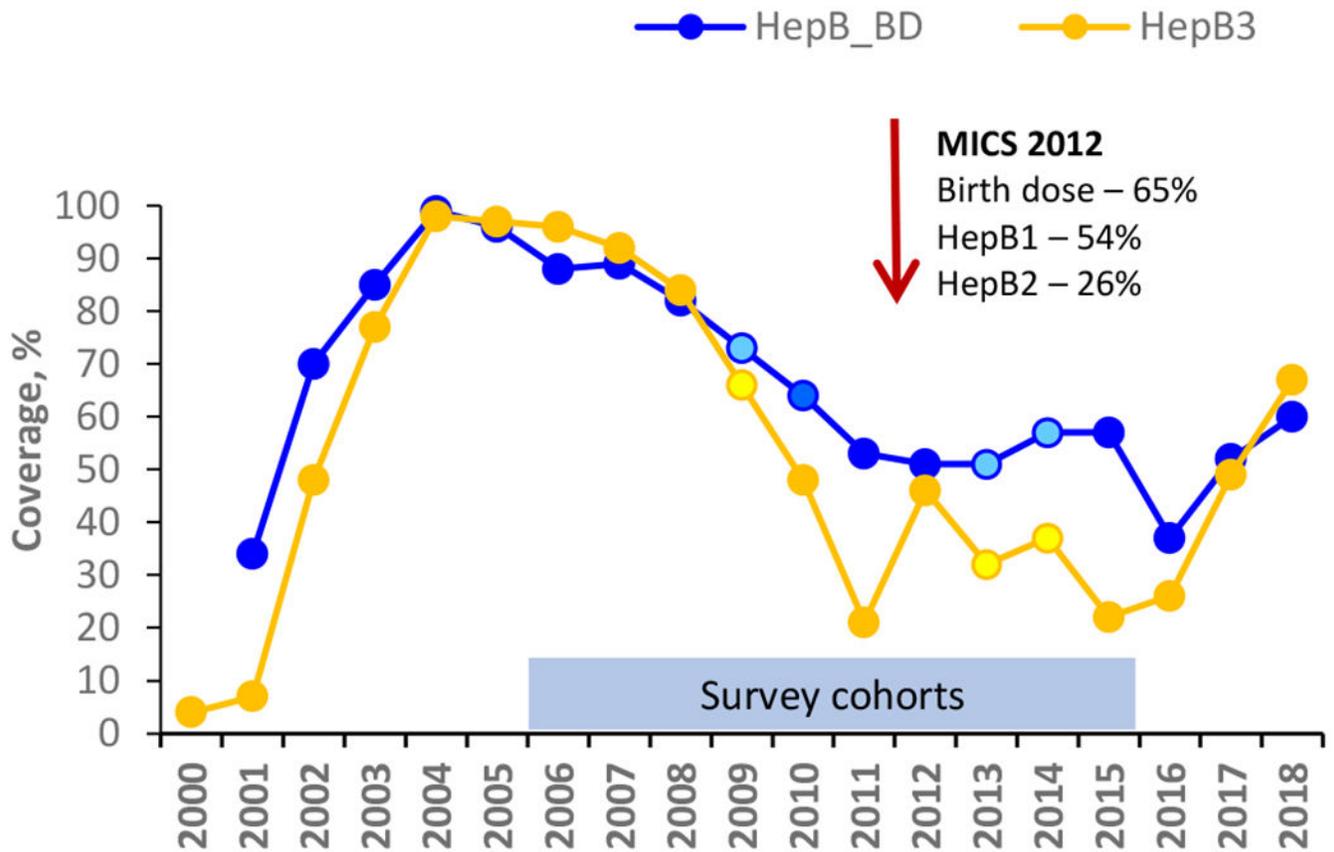


Fig. 1. Nationwide immunization coverage with hepatitis B vaccine birth dose (HepB_BD) and 3rd dose (HepB3) — Ukraine, 2000–2018. Sources: Official coverage data reported to WHO [11], with the exception of 2009, 2013 and 2014, when no reports were submitted. For these years, WHO/UNICEF estimates are used (shown in a lighter shade) [12]. MICS – multiple indicator cluster survey conducted in Ukraine in 2012 [13]. HepB1, 1st dose of hepatitis B vaccine; HepB3, 3rd dose of hepatitis B vaccine; HepB_BD, birth dose of hepatitis B vaccine.

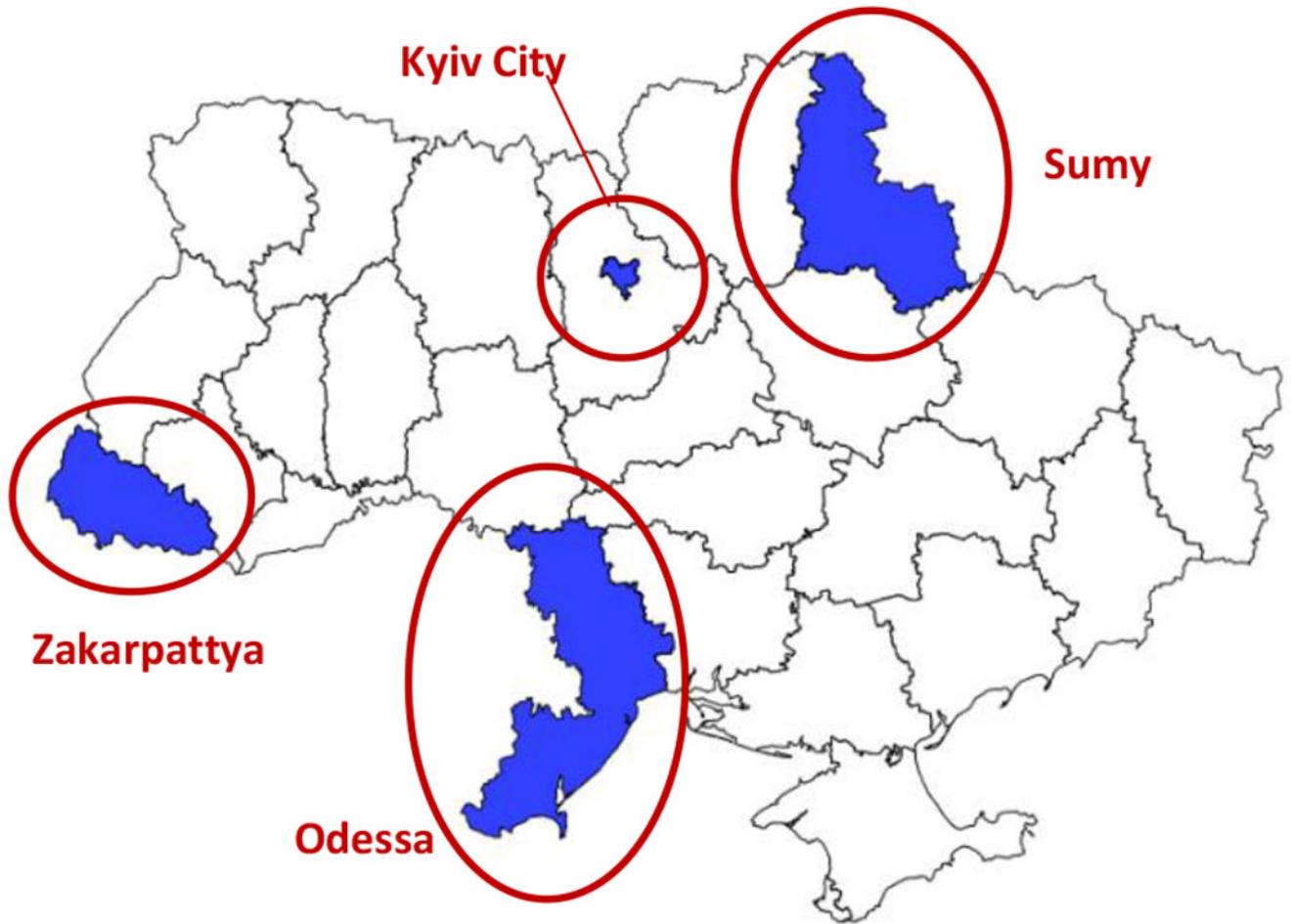


Figure 2.
Sites included in the serosurvey for vaccine-preventable diseases — Ukraine, 2017

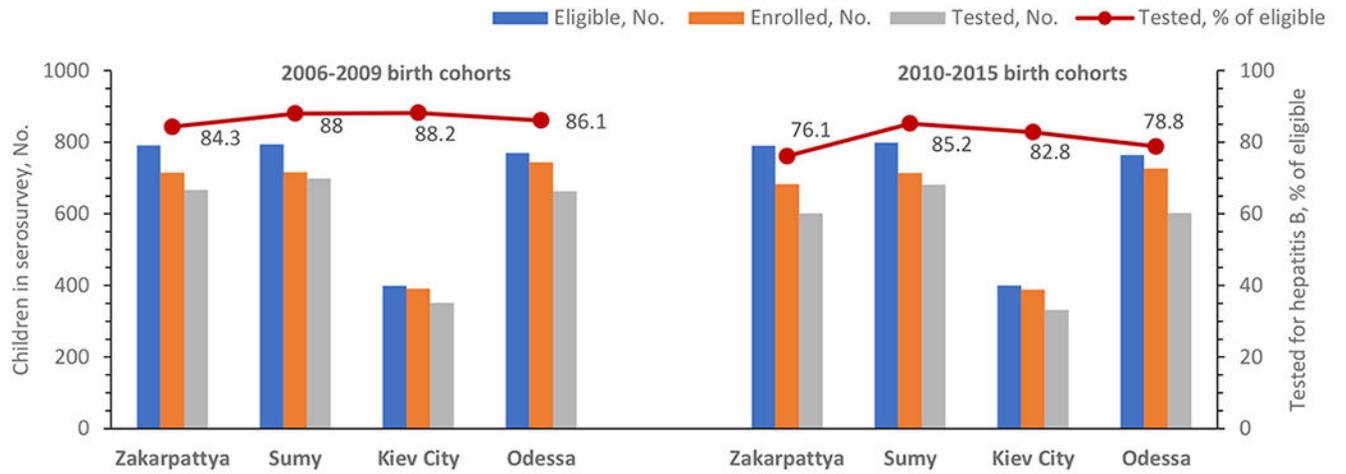


Figure 3. Proportion of serosurvey participants tested for hepatitis B virus infection markers by survey site and age group — Ukraine, 2017

Differences between age groups in the proportion of children tested for hepatitis B virus infection markers were significant for Zakarpattya ($p < 0.001$), Odessa ($p < 0.001$), and Kyiv City ($p = 0.029$), but not for Sumy ($p = 0.100$)

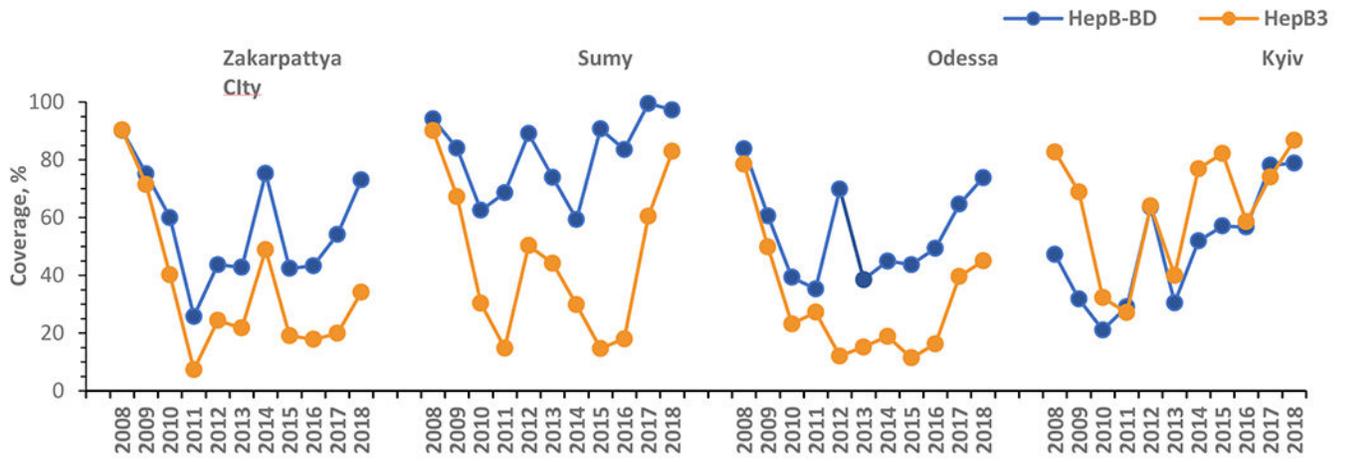


Figure 4. Officially reported immunization coverage with the hepatitis B vaccine birth dose (HepB_BD) and 3rd dose (HepB3) by survey site — Ukraine, 2008–2018

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Table 1.

Comparison of demographic characteristics and vaccination status of children selected for the serosurvey participation by hepatitis B testing status, across survey sites — Ukraine, 2017

Characteristics	Tested for hepatitis B		Not tested for hepatitis B (refused or not enough sample)		P value
	No.	%	No.	%	
Zakarpattya					
Total children	1,268	100.0	313	100.0	n/a
2006-2009 cohorts	667	52.6	124	39.6	<0.001
Female	593	46.8	149	47.6	0.790
Received 3 doses of HepB	538	42.4	109	34.8	0.024
Sumy					
Total children	1,380	100.0	213	100.0	n/a
2006-2009 cohorts	699	50.7	99	44.6	0.100
Female	661	47.9	115	54.0	0.100
Received 3 doses of HepB	1,021	74.0	72	33.8	<0.001
Odessa					
Total children	1,265	100.0	269	100.0	n/a
2006-2009 cohorts	663	52.4	107	39.8	<0.001
Female	611	48.3	141	52.4	0.220
Received 3 doses of HepB	679	53.7	107	39.8	<0.001
Kyiv City					
Total children	683	100.0	116	100.0	n/a
2006-2009 cohorts	352	51.5	47	40.5	0.029
Female	340	49.8	45	38.8	0.290
Received 3 doses of HepB	347	50.8	54	46.6	0.399

Note. Doses of any vaccines containing hepatitis B component are included. Immunization information reflects the status as of July–August 2017, prior to the survey specimen collection in late August–September 2017; n/a – not applicable; HepB, hepatitis B-containing vaccine

Table 2.

Hepatitis B virus infection status among children born in 2006–2015 by survey site — Ukraine, 2017

Survey site	Uninfected (anti-HBc-negative)			Infected, infection cleared (anti-HBc-positive and HBsAg-negative)			Chronic infection (anti-HBc-positive and HBsAg-positive)*		
	No.	Weighted %	95% CI	No.	Weighted %	95% CI	No.	Weighted %	95% CI
Zakarpattia (N=1,268)	1,212	94.8	91.3–96.9	50	4.5	2.6–7.9	6	0.7	0.3–1.4
Sumy (N=1,380)	1,368	99.2	98.4–99.6	11	0.7	0.3–1.5	1	0.1	0.0–0.4
Odessa (N=1,265)	1,251	99.0	97.8–99.6	14	1.0	0.4–2.2	0	0.0	0.0–0.3**
Kyiv City (N=683)	676	98.9	97.7–99.5	6	1.0	0.4–2.1	1	0.1	0.0–0.8

Anti-HBc, antibodies against core antigen of hepatitis B virus; HBsAg, surface antigen of hepatitis B virus; CI, confidence interval; N, total number of children tested

* The likelihood of encountering acute infections in a cross-sectional survey conducted in a low prevalence setting is very low [21], therefore, anti-HBc-positive and HBsAg-positive cases found in the survey are considered chronic HBV infections

** Crude estimate of CI (due to zero value of prevalence)

Table 3.

Prevalence of hepatitis B virus infection markers among children born in 2006–2015 by age group and sex across survey sites — Ukraine, 2017

Variable	Total No. tested	Anti-HBc-positive				HBsAg-positive			
		No. positive	Weighted %	95% CI	P value	No. positive	Weighted %	95% CI	P value
Zakarpattya									
Overall	1,268	56	5.2	3.1–8.7		6	0.7	0.3–1.4	
Age groups									
2006–2009 cohorts	667	21	3.3	2.1–5.2	0.092	1	0.1	0.0–0.8	0.045
2010–2015 cohorts	601	35	6.4	3.4–11.5		5	1.0	0.4–2.2	
Sex									
Male	675	26	4.5	2.6–7.8	0.280	2	0.5	0.1–1.7	0.450
Female	593	30	5.9	3.3–10.4		4	0.9	0.3–2.2	
Sumy									
Overall	1,380	12	0.8	0.4–1.6		1	0.1	0.0–0.4	
Age groups									
2006–2009 cohorts	699	8	1.1	0.4–2.7	0.423	1	0.1	0.0–0.8	n/a
2010–2015 cohorts	681	4	0.6	0.2–1.8		0	0.0	0.0–0.6*	
Sex									
Male	719	5	0.6	0.2–1.6	0.332	0	0.0	0.0–0.5*	n/a
Female	661	7	0.9	0.4–2.0		1	0.1	0.0–0.8	
Odessa									
Overall	1,265	14	1.0	0.4–2.2		0	0.0	0.0–0.3*	
Age groups									
2006–2009 cohorts	663	11	1.6	0.8–3.1	0.033	0	0.0		n/a
2010–2015 cohorts	602	3	0.5	0.1–2.2		0	0.0		
Sex									
Male	654	6	0.9	0.3–2.6	0.669	0	0.0		n/a
Female	611	8	1.1	0.5–2.3		0	0.0		
Kyiv City									
Overall	683	7	1.1	0.5–2.3		2	0.1	0.0–0.8	
Age groups									
2006–2009 cohorts	352	3	0.8	0.3–2.5	0.640	1	0.3	0.1–1.6	n/a
2010–2015 cohorts	331	4	1.2	0.5–3.1		0	0.0	0.0–1.2*	
Sex									
Male	343	3	1.0	0.3–2.9	0.800	0	0.0	0.0–1.1*	n/a
Female	340	4	1.2	0.4–3.1		1	0.2	0.0–1.5	

Note: CI, confidence interval; n/a, not applicable (could not be calculated because of zero prevalence); anti-HBc, antibodies against core antigen of hepatitis B virus; HBsAg, surface antigen of hepatitis B virus.

* Crude estimate of CI (due to zero value of prevalence)

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Table 4.

Hepatitis B immunization status of children targeted by the serosurvey by survey site and age group — Ukraine, 2017

Survey site	Birth cohorts	Total number of children	Received 3 doses of hepatitis B vaccine, weighted %	95% Confidence intervals	P value
Zakarpattia	2006–2009	791	56	46–65	<0.001
	2010–2015	790	28	21–36	
Sumy	2006–2009	794	80	75–85	<0.001
	2010–2015	799	59	54–64	
Odessa	2006–2009	770	66	60–71	<0.001
	2010–2015	764	35	29–42	
Kyiv City	2006–2009	399	53	48–58	0.097
	2010–2015	400	47	42–52	

All children targeted for the serosurvey are included, irrespective of their participation status. Immunization information reflects status as of July–August 2017, prior to survey specimen collection in late August–September 2017. Doses of any vaccines containing hepatitis B component are included.