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# Low Level of Hepatitis B Virus Infection in Children 20 Years after Initiation of Infant Vaccination Program in Wallis and Futuna

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*Abstract.* The prevalence of hepatitis B virus (HBV) in Wallis and Futuna (WAF) was one of the highest in the Pacific and was the driving factor for introducing hepatitis B (HepB) vaccination in 1992 and HepB birth dose (HepB-BD) in 2006. Using lymphatic filariasis (LF) transmission assessment survey (TAS) as a survey platform for eliminating LF, we assessed HBV surface antigen (HBsAg) seroprevalence, HepB vaccination coverage, and its timeliness among schoolchildren in WAF. From one finger prick of all registered fourth and fifth grade students, we tested HBsAg and filariasis antigen simultaneously, and estimated HepB vaccination coverage and timeliness by reviewing students' immunization cards. Since the children targeted were born when the three-dose HepB schedule was 2, 3, and 8 months, we defined timely vaccination if each dose was given by 3, 4, and 12 months. Of 476 targeted, 427 were enrolled. HBsAg prevalence was 0.9%. Estimated HepB vaccination coverage was 97%, 97%, and 96% for the first, second, and third doses, respectively, yielding coverage for all three doses of 96%. Proportion of timely vaccination was lower: 80%, 56%, and 65%, respectively, and less than 50% for all three doses combined. The seroprevalence of HBsAg among schoolchildren in WAF is less than 1%, close to the control goal. HepB vaccination coverage was high, but many children were vaccinated late. We recommend increasing the efforts for timely HepB vaccination. By combining an HBV seroprevalence survey and coverage assessment, we demonstrated the benefit of using TAS as a public health platform to access schoolchildren.

## BACKGROUND

Chronic hepatitis B virus (HBV) infection is one of the leading causes of liver disease and represents a serious public health problem worldwide.[1,2] The prevalence of chronic HBV infection varies in different parts of the world,[3] ranging from high (above 8%), in most resource-limited settings, to low (below 2%), in most developed settings.[4,5] Since the 1980s, a highly effective vaccine has been available to prevent HBV infection, and in 1992 the World Health Organization (WHO) made a recommendation that countries introduce three doses of hepatitis B (HepB) vaccine, to be administered with diphtheria, pertussis, and tetanus vaccine, to their national immunization schedules.[1] In 2009, WHO's recommendation was further specified to administer the first dose as soon as possible after birth, preferably within 24 hours, emphasizing the importance of preventing mother-to-child HBV transmission in controlling HBV infection.[1]

Prior to introducing HepB vaccination, nearly all countries in the WHO's Western Pacific Region had HBV infection prevalence higher than 6%.[6] These HBV infection rates have caused the highest rates of liver diseases in the world.[7] Every country and area in the region responded to controlling HBV infection by including HepB vaccination as a part of their national immunization policy by 2005 and a timely birth dose vaccination by 2007,[7,8] except Japan and New Zealand, where screening of pregnant women and selective immunization was practiced. The regional goal for the control of HBV infection was further set to reduce the prevalence of HBV infection to below 2% among children by 2012, and below 1% by 2017.[6]

Wallis and Futuna (WAF) is one of the French territories in the Pacific, and its high HBV endemicity has been known since the 1970s.[9,10] Following WHO recommendations, WAF introduced HepB vaccination in 1992 and adopted hepatitis B birth dose (HepB-BD) vaccination in 2006.

The impact of HepB vaccination programs can be assessed by conducting a HBsAg seroprevalence survey among children born after the introduction of the vaccine.[11] Most other countries in the region had made extensive efforts to assess the prevalence of chronic HBV infection after the introduction of the vaccine,[11–14] but no assessments of the impact of HepB vaccination had been conducted in WAF. When there was an opportunity to access school-aged children via a lymphatic filariasis (LF) transmission assessment survey (TAS) in 2012, the Public Health Agency of Wallis Futuna decided to assess the impact of the HepB immunization after 20 years from its introduction. As this was the first time to conduct a combined TAS and HBsAg seroprevalence survey, the objective of the present study was not only to assess HBsAg prevalence and HepB vaccination status among school-aged children but also to explore the feasibility of implementing two surveys at the same time.

## MATERIALS AND METHODS

**Study area.** The French overseas territory of WAF is located at about two-thirds of the way from Hawaii to New Zealand (west of Samoa and northeast of Fiji) in the South Pacific (Figure 1). It is made up of three volcanic islands along with 20 islets, which are further divided into two island groups that lie about 260 km apart, namely Wallis Islands and Futuna. The territory occupies a land area of 145 $km^2$ and is one of the smallest countries in the world, with a total population of 12,000. Most of them are inhabitants of the two major islands of WAF proper.[15]

**Study design and sampling strategy.** We designed a cross-sectional survey to measure HBsAg seroprevalence

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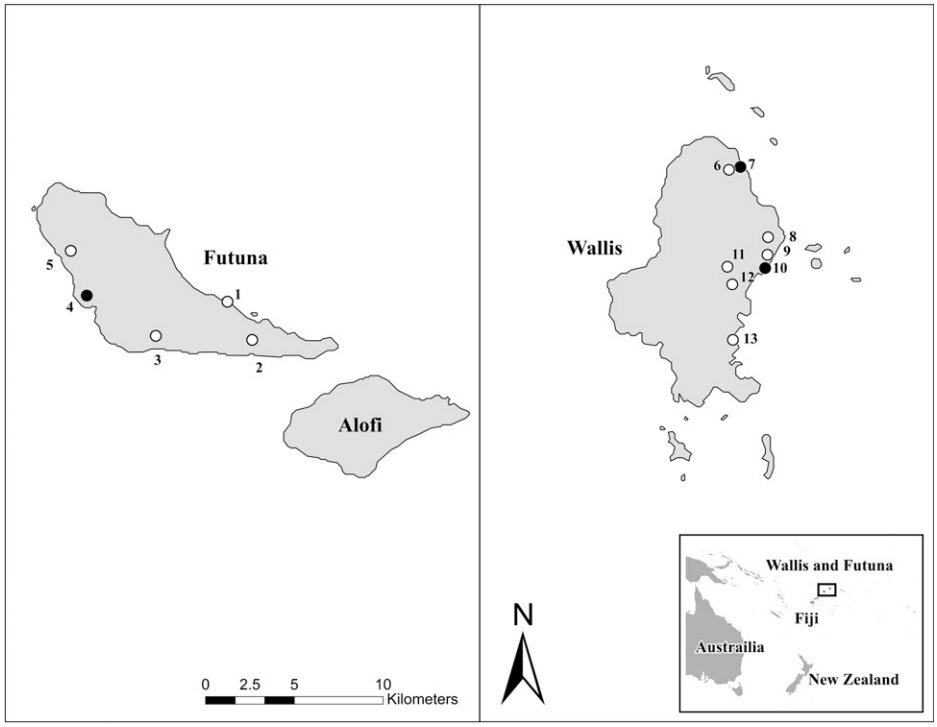


FIGURE 1. Map of Wallis and Futuna showing locations of surveyed schools and schools with positive hepatitis B surface antigen case(s).

and HepB immunization status among school-age children, to assess the impact of HepB vaccine introduction including birth dose for infants. Following the French school system, elementary schools in WAF comprise five grades, from first grade starting at 6 years of age, until fifth grade with children aged up to 11 years. As the WHO guidelines (Survey Sample Builder, Task Force for Global Health) recommended, the LF TAS targeted every students in all five grades of the 13 elementary schools in WAF, resulting in approximately 1,000 students.

For the concurrent HBsAg seroprevalence and HepB vaccination coverage assessment, it would have been sufficient to select a random sample of 165 children of one birth cohort to estimate HBsAg prevalence, where the size of the birth cohort in WAF was estimated to be 178 (2009 census), $\alpha = 0.05$, $P = 0.02$, design effect = 1, and to use a correction factor for finite populations and one-sided 95% confidence interval (CI). However, for logistic reasons, we chose all children enrolled in fourth and fifth grade, which is approximately two of five of the samples for the LF TAS, based on the assumption that HBV seroprevalence would be higher in the elder population.[4]

**Data collection procedure and blood testing.** Before the survey, we contacted school principals of the 13 elementary schools through the Department of Education to explain the purpose of the survey. We also requested lists of students from each school that included the student's name, gender, age, and grade. Field staff from the Public Health Agency were trained on blood sampling procedures and on how to use and interpret the HBsAg and LF antigen rapid diagnostic tests, as described in the WHO monitoring and impact assessment manual[16] and following manufacturer's instruction. Blood was collected from each participant by finger prick and tested on site without any special equipment, apart from buffer solutions for the HBsAg and a capillary tube for LF antigen. A total of 50 μL of sample for the presence of HBsAg by Determine HBsAg (Alere Inc., Waltham, MA) was needed, and the test was to be read at least 15 minutes after the specimen was placed on the test strip, together with 100 μL for the presence of circulating filariasis antigen by BinoxNow (Alere Inc.) The team was composed of a member skilled on specimen collection and conduction of the rapid tests and a second member who was in charge of collecting consent forms and recording data.

**Data management.** The questionnaire included basic demographic information, test results, and HepB vaccination dates copied from the child vaccination cards, if the child brought the card on the survey date. If vaccination cards were not available, investigators obtained information from the Health Agency immunization records that were kept by the national immunization program. The investigators reviewed the questionnaires before leaving the school to ensure completeness of data. Then data were entered in a database programmed with EPIDATA version 3.1 (EpiData Association, Odense, Denmark) and analyzed using STATA version 10 (StataCorp LP, College Station, TX).

We estimated both completeness and timeliness of HepB vaccination coverage. For the comparison of coverage, we applied $\chi^2$ statistics. Completeness was calculated as whether a child received HepB vaccine regardless of the timing; the denominator was all children surveyed for HBsAg testing. Timeliness was calculated based on whether a child was vaccinated within the specified time window. As the children tested for HBsAg in the survey were born during a time when the recommended schedule to administer the HepB vaccine was at months 2, 3, and 8 rather than 0, 1, and 6 months, we defined timeliness as HepB vaccination by 3, 4, and 12 months for each dose. For the purposes of comparison, we applied a 2006 measure of timeliness to this cohort (even though they were born before 2006) and defined it as HepB vaccination

within 24 hours after birth, 2, and 7 months. To describe timeliness, we calculated the cumulative probability of being vaccinated at age $t$, by inverse Kaplan–Meier survival function, or $1 - S_{KM}(t)$ in the vaccinated cohort.[17] Even though the HepB-BD was not included in the recommended immunization schedule when the fourth and fifth graders were born, we also checked how many children received it timely following that schedule to have an idea of the actual practice that could have prevented perinatal HBV infection.

**Ethical considerations.** This study was reviewed and approved by the Public Health Agency of WAF and the WHO Western Pacific Regional Office Ethics Review Committee. As participation was voluntary, we organized a letter to parents explaining the purpose of the survey, requesting their written consent and asking them to have their children bring their vaccination cards to school on the survey date. Children who did not present the consent form were not included in the survey, and students were allowed to opt out from the study any time during the survey.

## RESULTS

**HBsAg prevalence.** Of 476 children registered for fourth and fifth grades in 13 elementary schools of WAF, 447 (94%) were present at the school. A total of 19 refused to be tested yielding an overall participation rate of 90%. The 427 children had their demographic data available thus included in the analysis. They were born between December 1999 and June 2004, their mean age was 10.5 years, and 235 (55%) were males.

Overall HBsAg prevalence was 0.9% (Table 1). Prevalence was higher in Wallis but without any statistical significance, and this tendency was similarly observed in the circulating filariasis antigen (another manuscript on the LF TAS in WAF and other Pacific countries is in preparation). There was no difference for HBsAg prevalence between grades 4 and 5 students. As for four positive children, their ages ranged from 9 to 11 years and three were male. The location of schools with any HBsAg-positive case is shown in Figure 1.

**HepB vaccination status.** Among 427 children included in the statistical analysis, coverage for three doses of HepB vaccine was 97% for the first two doses and 96% for the third dose (Table 2). According to the schedule in place when the children were born, proportion of timely vaccination was 80%, 56%, and 65% for doses 1, 2, and 3, respectively. A total of 49% of children received timely vaccination for all three doses, before 1 year of age. When the current schedule was applied to measure the proportion of children who had timely vaccination, the proportion was 6%, 5%, and 72% for doses 1, 2, and 3, respectively. Figure 2 shows the inverse Kaplan–Meier curves of vaccination coverage by month of age. As for four children who were HBsAg positive, they received all three doses of HepB vaccine. One child received the first dose within 24 hours of birth while the other three received their first does on the dates ranged from 65 to 322 days. As for the second and third doses, the vaccination dates ranged from 31 to 392 days and 60 to 441 days, respectively.

TABLE 1

HBsAg seroprevalence among grades 4 and 5 schoolchildren in Wallis and Futuna, November 2012

| | No. of children tested | No. of children positive | HBsAg prevalence (%) |
|---|---|---|---|
| Administrative division | | | |
| Wallis | 266 | 3 | 1.1 |
| Futuna | 161 | 1 | 0.6 |
| Gender | | | |
| Male | 235 | 3 | 1.3 |
| Female | 192 | 1 | 0.5 |
| Grade | | | |
| 4 | 217 | 2 | 0.9 |
| 5 | 210 | 2 | 1.0 |
| Total | 427 | 4 | 0.9 |

HBsAg = hepatitis B surface antigen.

TABLE 2

Hepatitis B vaccination coverage and its timeliness among grades 4 and 5 schoolchildren in Wallis and Futuna

| Dose | Vaccination regardless of timeliness (%) | No. of students who were vaccinated ($N$ = 427): By 1992–2005 schedule* $N$ (%) | By 2006–2012 schedule† $N$ (%) |
|---|---|---|---|
| HepB1 or HepB-BD | 97 | 344 (80) | 24 (6) |
| HepB2 | 97 | 239 (56) | 21 (5) |
| HepB3 | 96 | 280 (65) | 307 (72) |
| All three doses | 96 | 211 (49) | 0 (0) |

HepB = hepatitis B; HepB-BD = HepB birth dose.
*HepB1, HepB2, and HepB3 schedule was 2, 3, and 8 months, and timeliness was defined as vaccination by 3, 4, and 12 months, respectively.
†HepB-BD, HepB2, and HepB3 schedule is at birth, 1, and 6 months, and timeliness was defined as vaccination within 24 hours of birth, 2, and 7 months, respectively.

## DISCUSSION

In the Pacific, HBV prevalence has been historically high,[9,13,18] and pre-vaccine HBV prevalence in WAF was estimated up to 8% by WHO.[10] A survey conducted in WAF targeting the general population in 1988–1989 found 39% prevalence for HBsAg.[19] Our results of HBsAg prevalence < 1% among grades 4 and 5 children show that WAF has likely greatly reduced early childhood HBV transmission, being close to the WHO's Western Pacific Regional HepB control goal of reducing

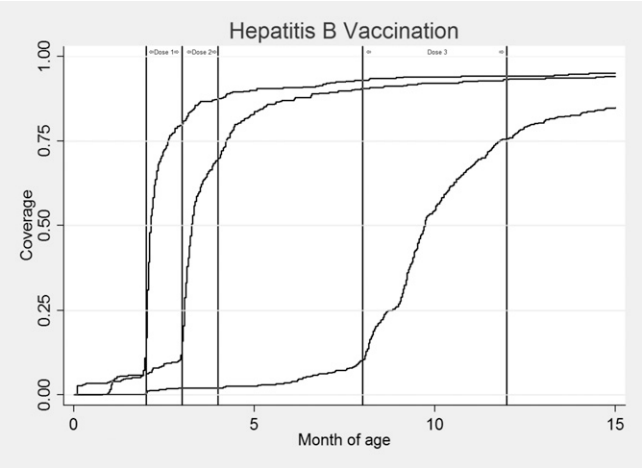


FIGURE 2. Coverage of hepatitis B (HepB) immunization per each dose by inverse Kaplan–Meier survival function up to 15 months. Note that left three vertical lines mark the recommended time interval for the first and second doses of HepB immunization according to the 1992–2005 schedule (dose 1: by 3 months and dose 2: by months), while right two vertical lines mark the recommended timing for the third dose, namely by 12 months.

chronic HepB prevalence to < 1% among children.[6] As these surveyed children were born even before WAF adopted the HepB-BD vaccination policy, it is likely that prevalence in younger cohorts is even lower.

We believe that this low level of HBV infection is the result of a successful HepB vaccination introduced in 1992, not only given that pre-vaccine prevalence was high but also reported three-dose HepB vaccination coverage has been at least 90% according to the national immunization coverage data collected by WHO/United Nations Children's Fund and other partners.[20] This is further verified by our finding that coverage with three doses of HepB vaccine is about 96% among the survey participants.

The impact of the HepB immunization program could have been greater, given that our study showed that less than half of children received all three doses within the recommended time frame using Kaplan–Meier method. It is well known that even in settings with high coverage, delay in receipt of vaccines results poses an unnecessary risk of vaccine preventable infectious diseases.[21] Timeliness of HepB vaccination, too, is critical not only for preventing mother-to-child transmission but also for protecting infants and young children against horizontal HBV transmission,[22] since children under 5 years of age have a higher risk of acquiring chronic infection once exposed to the virus.[12] Among the four children who were found positive for HBsAg in our study, all had received three doses of HepB vaccine; however, only one child received HepB-BD. None of the children who did not receive the birth dose had timely administration of all three doses, so they were therefore at risk for both perinatal and horizontal infections.[23] We encourage that the public health authorities pay continued attention not only to HepB vaccination coverage but also to timeliness for each dose of vaccine.

In this study, we have also explored the feasibility of implementing two surveys at the same time and factors for the success are as follows: 1) The target population and required sampling frames for LF and HBsAg surveys were similar, but the TAS design was more stringent than recommended HBsAg survey requirements, meaning that adhering to the TAS guidance would by default meet requirements of HBsAg survey. By relying on lot quality assurance sampling designs to test whether prevalence is below 1% or 2%, current guideline for LF TAS generally require a larger sample size among elementary school students than other prevalence surveys with point estimates.[16] However, simply mirroring our survey with the TAS would have required much larger resources, we selected a subset of the target population for the HBsAg prevalence and coverage assessments and improved logistic feasibility. 2) Similarity of sample collection and testing methods was highly advantageous in combining two surveys. In our study, HBsAg and LF antigen detection tests both use a finger prick for collecting whole blood, of which necessary amounts were aliquoted on the separate test strips. The team composition and skill set required for both surveys were identical, and there was no need to have extra human resources for field work. This is in contrast to several soil-transmitted helminthes (STH) prevalence surveys undertaken using TAS as an access platform, which included on-site stool smear examination and accompanied microscopist[24,25] or additional teams for STH survey. 3) There was a detailed planning, including several training workshops for the field staff on the use of the test kits and data collection, in collaboration with the Public Health Agency and the technical partner. For instance, the timing for reading results was different, after 15 minutes for HBsAg and at 10 minutes for LF antigen, but this was well managed by explaining the benefit of allowing the teams to read the LF test first and then read the HBsAg strip 5 minutes later during the training workshop. Also it was emphasized that while the time window to read LF results was critical, the HBsAg test required to wait 15 minutes but after it could be read or verified anytime that day. Also the staff was able to adapt a unique approach to have a robust measure of vaccination coverage among survey participants, by obtaining immunization data from the health authority's registry when there was a missing immunization card of the child. This kind of completeness is not feasible in many other settings but was in WAF, because of completeness of records and staff's willingness. Through these comprehensive process and external technical support, a team of two staff was able to complete the surveys in 2 weeks of time in a setting with limited human resource of health.[26] A review of the literature reveals that this is the first time that an LF TAS was implemented together with the HBsAg prevalence survey or vaccine coverage assessments, and we believe that this approach could be easily adapted for other similar surveys in a subset of or together with the TAS target population.

This survey is subject to a number of limitations. First, there is a possibility that actual burden of chronic HepB infection is slightly higher than our estimates given that 1) the rapid test used in our study has sensitivity is of approximately 93.6%,[27] though has specificity of almost 100%; and 2) HBsAg negativity is not sufficient to completely exclude HBV DNA presence, as there are reports of occult HepB virus infection among children in hypoendemic areas who were born to HBsAg positive mothers.[28] It would be useful to organize another survey to cover wider population including younger age group children, using preferably more sensitive test such as enzyme-linked immunosorbent assay. As for the HepB vaccination coverage, we may have underestimated it, as ad hoc queries revealed that several children whose vaccination records were missed in fact emigrated from France and may not have updated their immunization records in WAF. Furthermore, though we have observed a high proportion of untimely immunization, we did not have opportunities to explore the factors associated with it. In retrospect, adding place of birth and reasons for late vaccinations to the questionnaire would have provided more insight on the reasons for missing vaccination or not being vaccinated on time. Finally, the results from this survey may not be entirely representative of the targeted population. It may be possible that the 10% of children who did not participate in the survey have different characteristics from the other 90% in terms of infection and immunization status. For instance, school absence could be linked to a lower likelihood of vaccination.

## CONCLUSION

This HBsAg seroprevalence and HepB vaccination coverage assessment among school children in WAF showed that HBsAg prevalence was meeting the regional HepB control target of below 1%. Furthermore, it showed that vaccination coverage was high, although not always timely.

Combining the HepB seroprevalence survey with the TAS was feasible and efficient in a remote and resource-limited setting. We recommend 1) increasing the efforts for timely HepB vaccination in WAF and 2) utilizing TAS as access platform to school-aged children for other public health programs where these are conducted, to maximize the efficient use of resources.

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