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# Effectiveness of Hepatitis B rapid tests towards linkage to care: results of a randomized, multicenter study.

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**SHORT TITLE: Effectiveness of HBV rapid tests**

# ABSTRACT

**Objectives:** Worldwide, many infected individuals are unaware of their hepatitis B virus (HBV) status. We evaluated the effectiveness of HBV rapid-testing in promoting linkage-to-care.

**Methods:** In 2012, volunteers were recruited from five Parisian centers. Participants were randomized 1:1 to receive standard serology (S) or rapid-testing (VIKIA®-HBsAg/Quick ProfileTM-anti-HBsAb) with confirmatory serology (R+S). Primary endpoint was percentage of individuals with appropriate linkage-to-care (non-immunized individuals starting vaccination or HBsAg-positive individuals receiving medical evaluation). Secondary outcomes were percentage receiving HBV-test results and performance of HBV rapid-tests.

**Results:** In total, 995 individuals were screened. Among HBV-infection groups included in the primary endpoint (n=409), 20 (4.9%) received appropriate linkage-to-care, with no difference between S and R+S groups (5.7% vs 4.1%, p=0.5). Two of 8 HBsAg-positive participants had a medical visit (1/6 and 1/2 in the S and R+S groups, respectively) and 18/401 (4.5%) non-immunized participants initiated HBV-vaccination (11/205 and 7/196). Factors tending to be associated with linkage-to-care were female-gender, birth country of high HBV-prevalence and extended medical stay. Test results were not obtained in 4.7% of participants, which was significantly higher in the S arm ($p$=0.02). Sensitivity and specificity were both 100% for the VIKIA®-HBsAg rapid-test and 94.4% and 80.8%, respectively, for the anti-HBsAb Quick Profile™ rapid-test.

**Conclusions:** Despite a higher proportion of participants obtaining their results in the R+S arm and better performance of anti-HBsAb rapid-tests than previously described, we found no evidence that HBV-screening based initially on rapid-tests leads to increased HBV-vaccination rates or medical evaluation. This strategy needs evaluation in more hard-to-reach populations.

**Keywords:** HBV; HBsAg testing; missed opportunities; screening; risk factors; Rapid test.

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**TEXT**

**BACKGROUND**

With more than 15 million infected persons and 38,000 attributed deaths each year in the United States (1) and Europe (2), hepatitis B virus (HBV) is one of the most frequent chronic infectious diseases, with a higher prevalence than human immunodeficiency virus (HIV) and hepatitis C virus (HCV) infection.  More than two-thirds of HBV-infected persons in Europe and the United States are unaware of their infection status (3, 4).These persons do not benefit from adequate medical care and constitute a reservoir of HBV transmission, which could be a source of new infections, such as the case for HIV (5).

In France, HBV prevalence was estimated at 0.65% in 2004, representing 281,000 individuals with positive hepatitis B surface antigen (HBsAg).  In addition, 7.3%, or 3.2 million, were anti-Hepatitis B core antibody (anti-HBcAb) positive, indicating previous exposure to HBV (6). Among chronic carriers of HBsAg, 55% (155,000) were unaware of their HBV status. Since 1994, France's HBV immunization policy has focused on two broad aims:  identifying, testing, and vaccinating persons high at-risk of HBV-exposure; and vaccinating all individuals during infancy, childhood or adolescence (7). Despite these recommendations,  vaccine coverage rates remained inadequate among infants until 2007 (7, 8) and were less than 50% in high at-risk groups (9-11).

HBV-testing is essential for several reasons. It confirms whether individuals have been vaccinated or effectively acquired anti-hepatitis B surface antibodies (anti-HBsAb), identifies persons at-need of HBV vaccination, and provides a gateway to necessary care for infected persons, especially at early stages of disease (1). A number of recommendations are currently available, insisting upon increased HBV testing and turnaround time in returning results (1, 4, 12).

HBV tests are usually based on standard enzyme-linked immunoabsorbant assays (ELISA), which require long periods of time to process. With the recent development of HBV rapid tests, results with high sensitivity and specificity can be given within minutes (13). Consequently, tested persons would no longer need to collect their test results at a later time (14, 15) and more appropriate patient counseling could be delivered at first consultation. However, no study to-date has formally evaluated the effectiveness of rapid testing interventions as a means to increase linkage-to-care among persons unaware of their HBV-status.

The main objective of the Optiscreen B II study was to determine the usefulness of incorporating HBV rapid tests during screening in order to more adequately provide care for those tested. To this end, we conducted a randomized, multicenter trial determining if appropriate care was given when either rapid tests with confirmatory ELISA or standard ELISA was used.

**METHODS**

**Study design and participants**

The Optiscreen-B II study was a multi-center, parallel-group, randomized trial comparing the use of standard HBV tests to rapid tests. The study was approved by the Hôtel-Dieu Hospital Ethics Committee (Paris, France) in accordance with the Helsinki Declaration.

Volunteers were recruited from five study centers in the Paris metropolitan region, which actively participate in HBV screening, vaccination, and care – two STD clinics, one primary health care center, one general screening center, and one travel clinic. From 29 February 2012 to 05 July 2012, participants were included if seeking care at any of the participating centers, ≥18 years old, and could be available for further contact and medical follow-up at a single university teaching hospital.

Only persons eligible for HBV-screening were invited to participate. In a pre-randomization phase, participants were asked questions on potential risk factors associated with HBV-transmission during a face-to-face interview with a clinical research associate. This questionnaire (16) was based on screening/vaccination recommendations from the United States Centers of Disease Control and Prevention (CDC) (1) and the French council that determines immunization policies (17). If a participant did not have any one of the criteria recommending HBV-testing, they were not included in the study. Second, since one major factor steering the decision to test in practice is complete certainty of prior HBV-infection or vaccination status, participants with a confirmed HBsAg-positive, anti-HBsAb-positive, or anti-HBcAb-positive test (requiring irrefutable proof of result) were deemed ineligible for HBV-screening.

Participants were not included if they were unwilling to participate, already participated in the Optiscreen-B I validation study (13), or were not covered under the national health care system. Signed written informed consent was obtained for all eligible participants prior to randomization.

**Study interventions**

Eligible participants were randomized 1:1 to receive one of two possible interventions: standard HBV test (S) or rapid HBV test with confirmatory ELISA (R+S). The central data management center (Inserm U707, Paris, France) was responsible for randomization. A computerized random number generator was used to select random permuted block sizes of 3 and 6 within each center. The randomization list was concealed from investigators, who assigned participants to testing groups through a Web site after validating eligibility criteria.

In the S arm, approximately 10 mL of blood was drawn and then tested for HBsAg, anti-HBsAb, and anti-HBcAb. Serostatus was determined using a commercially-available ELISA assay (MONOLISA AgHBs Ultra, anti-HBs plus, anti-hepatitis B core antibody-anti-HBc-plus, BIORAD, Hercules, USA). Results were given 7-14 days after testing and, depending on the study center, were either mailed to participants or left at the study center for collection.

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In the R+S arm, a 10 mL blood draw was collected. Before the blood sample coagulated, a few drops were immediately taken and applied to a rapid test determining HBsAg (VIKIA® Biomérieux, Marcy-L'Etoile, France) and anti-HBsAb status (Quick ProfileTM, Lumiquick, Santa Clara, CA, USA). Rapid tests were performed and interpreted per manufacturer's instructions by a trained clinical research associate, as previously detailed (13). Due to the poor sensitivity and negative predictive value of the rapid anti-HBsAb test (13), the remaining blood sample was further tested using standard ELISA (as described in the S arm above). A presumptive diagnosis was made during the study visit based on results from the two rapid tests (Table 1). All participants were asked to obtain their ELISA results available 7-14 days after rapid testing.

For both arms, we established HBV-infection groups using ELISA results and defined them as follows: HBsAg-positive, resolved infection, isolated anti-HBc Ab+, vaccinated, and non-immunized.

**Study end-points**

The primary outcome was the percentage of participants appropriately seeking care if needed. Since this only applied to infection groups that required a medical intervention, analysis was restricted to HBsAg-positive and non-immunized individuals. Considering that follow-up recommendations for isolated anti-HBcAb-positive patients were unclear (1, 18), we decided not to evaluate the primary end-point in this HBV-infection group. However, the treating physician could recommend further evaluation.

HBsAg-positive persons were given instructions to schedule a comprehensive medical exam at Saint-Antoine Hospital, in accordance with European recommendations (19). Appropriate care was then determined if a full evaluation of HBV-disease was performed 6 months after screening. Non-immunized persons were contacted at most three times 4 to 6 months after screening via telephone by a clinical research associate. These participants were asked if they had been vaccinated and, if so, the date of first HBV vaccination. Appropriate care was then determined if

HBV vaccination was initiated between screening and the time of telephone interview. Participants unable to be contacted were considered as non-vaccinated in analysis

The secondary outcome was percentage of participants receiving their HBV-test result. For those study centers where HBV-test results were mailed, all participants were considered to have obtained their results (n=567). For those centers where HBV-test results were not mailed out, participants were considered as receiving their result if they returned to the clinic to obtain printed results (S and R+S arms) or had a reliable rapid test result that did not necessarily require ELISA (R+S arm, Table 1). In order to evaluate the effect of bias from mailing results, we performed subgroup analysis including only centers where the test result was not mailed.

**Statistical analysis**

Power calculations were performed to detect a >15% difference in immediate linkage-to-care and vaccination (20). Since virtually no data were available before the start of this study, discussions from an expert panel of clinicians concluded that an estimated 30% of participants would have appropriate care with a standard HBV test. Assuming Type 1 error of 0.05 and 80% power, a minimum 152 participants for each group would be needed. As roughly 40% of the population would be either non-immunized or HBsAg-positive from previous epidemiological studies (13), a minimum of 375 participants for each group would be required.

Outcomes were compared using Pearson's χ² or Fisher's Exact test. In order to understand the reasons for not obtaining HBV-test results and for seeking appropriate care, we used random-effects logistic regression to determine the univariable association between each outcome and a variety of demographic and HBV-transmission risk factors, while accounting for within-center correlation. Risk factors with a $p \leq 0.2$ in univariate analysis and study arm were retained and used to create a predictive, multivariable model.

In patients randomized to the R+S arm, we evaluated the performance of HBsAg and anti-HBsAb rapid tests compared to ELISA. Sensitivity (Se), specificity (Sp), positive and negative predictive values (PPV and NPV, respectively), and area under the receiving operator characteristic curves (AUROC) were estimated for each rapid test, without taking into account indeterminate results.

All statistical analysis were performed using STATA (v12.1, College Station, TX) and significance was determined using a *p*-value <0.05. This trial is registered at ClinicalTrials.gov (NCT01767597).

**RESULTS**

**Study participants**

Figure 1 illustrates the flow of study participation. A total of 2061 participants were initially screened for eligibility, of whom 1000 (48.5%) were randomized to receive either S or R+S testing. Among them, five did not fully complete study intervention. Thus, a total of 995 participants were included in analysis.

Half of participants were male with an average age of 40.4 (SD=15.8) years. A slight minority of participants were born in country of intermediate or high HBV-prevalence (HBsAg-positive 2.0-8.0%: *n*=253, 25.4%; and HBsAg-positive>8.0%: *n*=175, 17.6%, respectively). Almost 6% of participants lived in difficult social situations. No significant differences were observed between study groups (Table 2), yet there was a higher proportion of participants who had received tattoos in the R+S than S arm (*p*=0.04).

**HBV-infection status**

Overall, there were 8 participants with HBsAg-positive serology (R+S group: $n$=2, S group: $n$=6), giving an HBsAg-positive prevalence of 0.8% (95%CI: 0.3-1.6). All other participants had resolved infection ($n$=124, 12.5%), isolated anti-HBcAb ($n$=34, 3.4%), were vaccinated ($n$=428, 43.0%) or non-immunized ($n$=401, 40.3%). No difference between randomization groups and HBV-infection status was observed ($p$>0.09).

**Performance of HBsAg and anti-HBsAb rapid tests in the R+S arm**

Table 3 gives the classification probabilities of both rapid tests compared to standard serology for participants randomized to the R+S arm. While considering the very low prevalence of HBsAg-positive serology, the VIKIA® rapid HBsAg test had perfect Se, Sp, PPV, NPV. While including only patients with definitive anti-HBsAb results from standard serology ($N$=443), the QUICK PROFILE[TM] anti-HBsAb test had high Se, with moderately high Sp, PPV, and NPV.

**Obtaining HBV test results**

Of the 995 participants, 95.3% acquired their test results, while this proportion was fairly similar across HBV-infection groups ($p$=0.15, Figure 2). Among the participants included in centers where results were not mailed ($n$=428), 381 (89.0%) received their HBV-test result, while a significant difference was observed between S and R+S groups (85.4% and 92.6%, respectively, $p$=0.02). In multivariable analysis (data not shown), the only significant risk factor associated with failure to obtain results was the S study arm after adjusting for age, parents from a country of high HBV-prevalence, and HBV-infection status.

**Appropriate care for HBV-infection groups in need of medical intervention**

Among those HBV-infection groups in need of medical intervention ($n$=409), 20 (4.9%) received appropriate care, with no difference between study arms ($p$=0.5, Figure 2). Two of 8 (25.0%) HBsAg-positive participants came for medical consultation to ascertain their HBV-disease status

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(1/6 and 1/2 in the S and R+S groups respectively, $p$=0.3) and 18 of 401 (4.5%) non-immunized participants initiated HBV vaccination (11/205 and 7/196 in the S and R+S groups respectively, $p$=0.5). Even when excluding patients who were unable to be reached by telephone, there was no difference in vaccination rates between S ($n$=12, 6.6%) and R+S ($n$=8, 4.9%) interventions ($N$=346, $p$=0.5).

In multivariable analysis (data not shown), males were borderline significantly less likely than women to receive appropriate HBV-care ($p$=0.05). Participants from high HBV-endemic countries and those who had an extended stay at a medical facility tended to receive more adequate care ($p$=0.08 and $p$=0.07, respectively).

**DISCUSSION**

To the best of our knowledge, this is the first randomized study that directly evaluates whether additional HBsAg and anti-HBsAb rapid testing has any benefit compared to confirmatory ELISA. There was a higher proportion of participants obtaining their results in the rapid testing arm, yet there was no evidence that rapid testing led to increased HBV vaccination rates or "linkage-to-care". Even though no clear determinant was observed for more appropriate care, tendencies were indeed noted with female-gender, originating from a high HBV-endemic countries, and prolonged stay at a medical facility.

Among HBsAg-positive participants, no association between randomized groups and linkage-to-care was observed. This finding could be attributed to the low prevalence of HBV infection, in particular, compared to a previous evaluation among individuals without national healthcare (0.8% versus 2.1% respectively) (21). With higher HBsAg-prevalence, the benefit of rapid testing would probably be more readily observed in specific sub-populations at-risk for HBV-infection (i.e. immigrants, intra-venous drug users, men who have sex with men, etc.) (6, 21-23), as has been

suggested for HIV (24, 25)  and/or HCV (26, 27).  The most notable of them are "hard-to-reach" populations (i.e. those with difficult access to care).  )As all participants came to a medical center on their own initiative and were required to have some form of health insurance, individuals with barriers to healthcare were not well represented.

Rapid tests also failed to demonstrate any effect on HBV-vaccination rates, which were largely inadequate (11, 28). This finding might reflect a general problem with vaccination coverage in France (29). However, it needs to be stressed that, as a major limitation, the Quick Profile[TM] anti-HBsAb rapid test could not be used to confirm non-immunized HBV-status (13). Since this rapid test had poor sensitivity, a definitive result at the initial visit could not be given to participants with a negative anti-HBsAb rapid test.  This problem prevented us from providing appropriate counseling on HBV vaccination without resorting to serological testing, thus making it difficult to evaluate the potential impact of anti-HBsAb rapid testing.  Unfortunately, no other alternative rapid test with high classification probabilities was available, specifically one that has been evaluated apart from the manufacture (30).

However, we did observe somewhat satisfactory performance of the anti-HBsAb rapid test, contrary to our earlier report (13).  The test used in our previous evaluation was a dual HBsAg and anti-HBsAb test (Ref 71069-1, Lot No 10081601 and Lot No 11052410), whereas the one used herein was a different, single anti-HBsAb test from the same manufacture (Ref 71006, Lot No 12021401).  As no further laboratory analysis was done, we cannot offer any other technical explanations for the discrepancies between these tests.

Interestingly, our results resonate with the "cascade" of care, which has been well-established in HIV (31) and HCV infection (32).  In such a framework, specific steps of healthcare involvement, starting from identifying those infected via testing to those receiving adequate care, are evaluated at each level.  In our study, we demonstrate encouraging findings on the proportion of participants receiving test results, thus allowing infected individuals to be identified.  However, this effect depended on the reliability of rapid test results (i.e. no need to obtain serological results after

rapid testing), which was less the case among non-immunized individuals. The distribution of HBV status groups needs to be considered when comparing our results to others. In any case, infection awareness has provided a major step towards linkage-to-care in the past (33, 34), yet, there was a substantial drop-off in the proportion of patients adequately seeking care in our study. Further research would be needed to determine if this finding is due to the low-risk of HBV-related disease perceived by participants, laxness of HBV-related care by the physician, or a combination of both.

One limitation of our study relates to the conditions under which serological results were obtained. Blood samples were immediately drawn after the study visit, contrary to routine practice where participants would have to test at a clinical laboratory located at a different facility. This may have increased the proportion of patients obtaining HBV test results. Second, participants could have had a strong preference to receive rapid testing and when allocated to the S arm, would have been disappointed and even less likely to obtain screening results. However, such a bias, likely to favor the R+S arm, appeared to be minimal considering no difference between randomized arms was observed.

Notwithstanding these limitations, our study adds novel insight in the use of rapid tests during routine care. This is the first study to evaluate the clinical impact of adding rapid testing by randomizing participants to a specific intervention. While at the same time, we used a composite end-point reflecting healthcare interventions that affect both the individual (i.e. protection against HBV-infection, assessing the need for HBV-specific care) and the population (i.e. vaccination coverage). Finally, we demonstrate the complexity of evaluating interventions conditional on the status of HBV infection, which should be considered in future testing campaigns.

**CONCLUSION**

In conclusion, rapid testing for HBV with confirmatory ELISA might not increase vaccination for non-immunized and linkage-to-care for infected individuals when compared to standard practice. However, the lack of reliable anti-HBsAb tests may have compromised any advantage with rapid testing, stressing the usefulness of tests with higher sensitivity and specificity in identifying non-immunized individuals. Furthermore, rapid testing should be evaluated in populations with higher HBsAg-seroprevalence. Seeing that these individuals are also at high risk of exposure to HIV and HCV, algorithms incorporating simultaneous rapid testing for these viruses are warranted.

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**FIGURE LEGENDS**
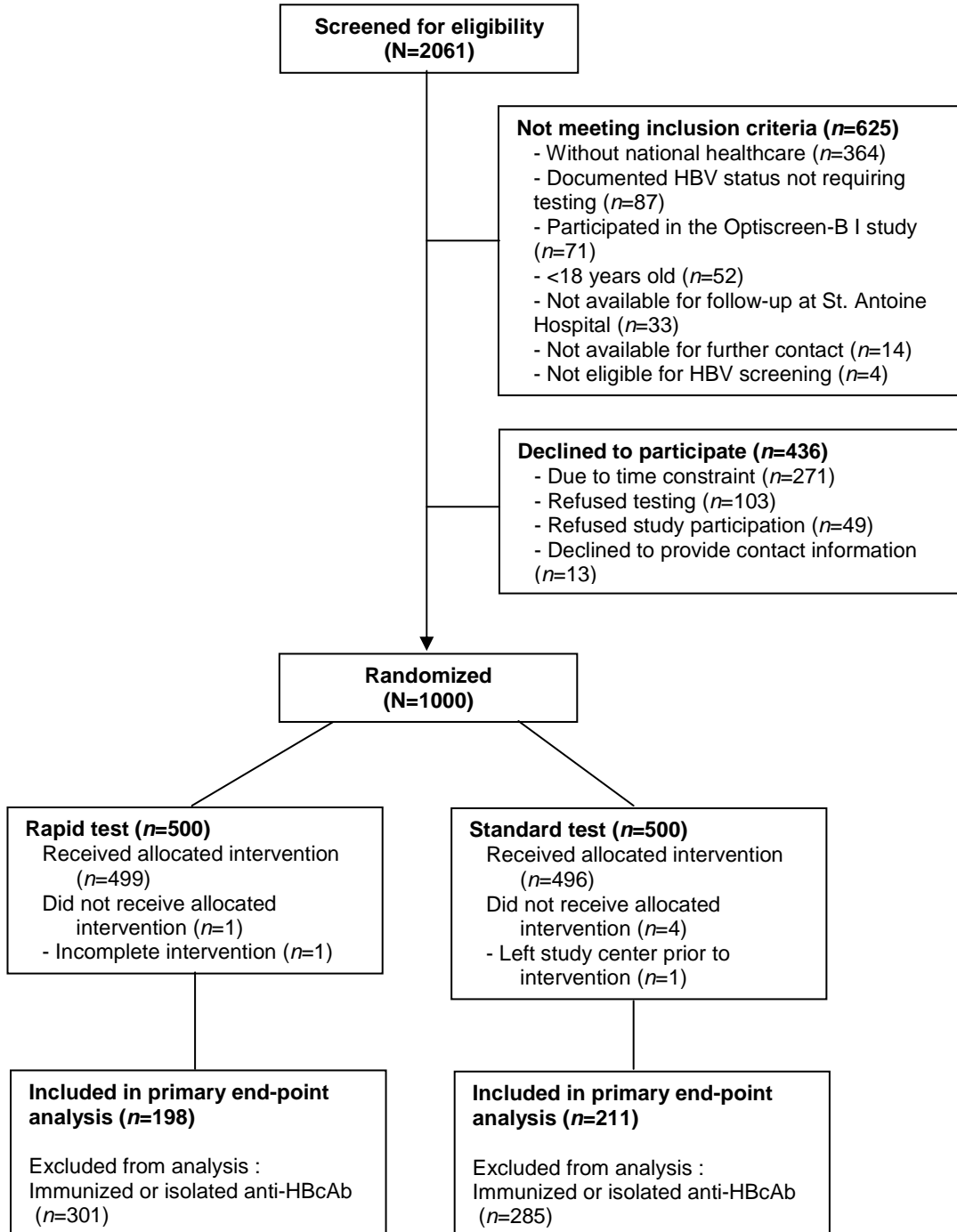
**Figure 1. Study Flow Diagram**

**Figure 2. HBV status and linkage-to-care**
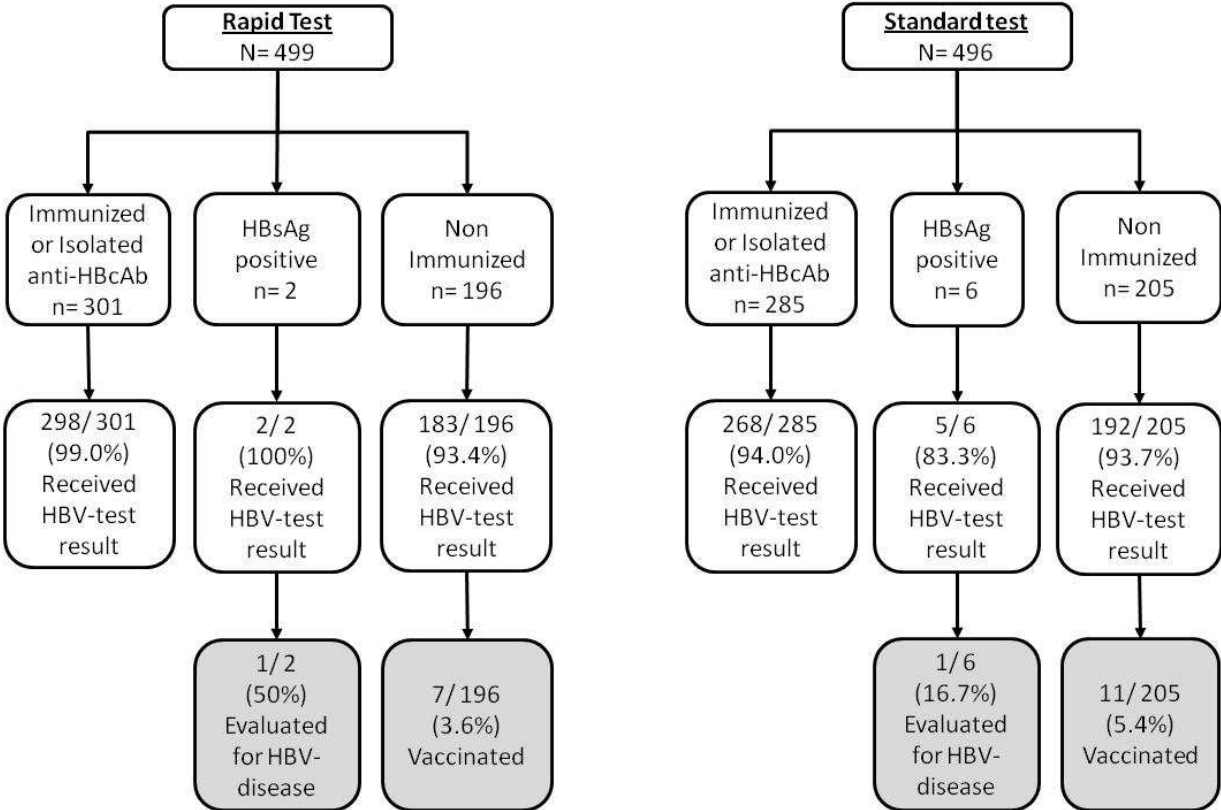


Distribution of HBV-infection groups is given for both rapid test and standard test intervention arms. The proportion of participants who were informed of their HBV-status (i.e. received their test results) are then given for each HBV-infection group, while assuming that mailed results were received and read by the participant. Finally, the primary end-point of appropriate care is illustrated in the shaded box below, with no significant difference between intervention arms for HBsAg-positive ($p$=0.3) or non-immunized ($p$=0.5) individuals (combined groups, $p$=0.5).

**TABLES**

**Table 1. Interpretation of HBV rapid tests and results needed to declare obtention**

| HBV Rapid Test | | Presumptive diagnosis | Tests results needing to be obtained** |
|---|---|---|---|
| **HBsAg** | **anti-HBsAb** | | |
| + | -/ind | Infected with HBV | R |
| - | + | Immunized against HBV | R |
| + | + | Person very likely infected with HBV | R |
| - | -/ind | Person probably a non-carrier of HBV | R+S |
| ind | + | Person probably immunized against HBV | R+S |
| ind | -/ind | Completely uncertain | R+S |

*ind=indeterminate

**Combination of results needed from rapid test (R) and/or serological test (S) in order to be considered as successfully obtaining test results.   All participants listed as R did not necessarily need confirmation with ELISA (diagnosis from rapid test was considered reliable).  All participants listed as R+S required confirmation with ELISA (diagnosis from rapid test was considered unreliable).

**Table 2. Description of the study population per intervention arm**

| | Intervention Arm | | $p^*$ |
|---|---|---|---|
| | Standard test (*n*=496) | Rapid test (*n*=499) | |
| Male | 246 (49.6) | 227 (45.5) | 0.2 |
| Age *years* | 40.7 (16.0) | 40.1 (15.6) | 0.6 |
| Completed high-school education or higher | 341 (68.8) | 315 (63.1) | 0.06 |
| Employment | | | 0.18 |
|    Employed | 262 (52.8) | 271 (54.3) | |
|    Student | 68 (13.7) | 62 (12.4) | |
|    Unemployed | 62 (12.5) | 83 (16.6) | |
|    Retired | 61 (12.3) | 53 (10.6) | |
|    Other | 43 (8.7) | 30 (6.0) | |
| HBV prevalence of birth country | | | 0.3 |
|    Low (<2.0%) | 292 (58.9) | 275 (55.1) | |
|    Intermediate (2.0-8.0%) | 116 (23.4) | 137 (27.5) | |
|    High (>8.0%) | 88 (17.7) | 87 (17.4) | |
| Parents born in high HBV-endemic region | 108 (21.8) | 100 (20.0) | 0.5 |
| Traveled to high HBV-endemic region[1] | 86 (17.3) | 88 (17.6) | 0.9 |
| Surgical intervention in high HBV-endemic region | 40 (8.1) | 46 (9.2) | 0.5 |
| Health insurance plan | | | 0.6 |
|    Social security | 465 (93.8) | 472 (94.6) | |
|    CMU[2] | 31 (6.3) | 27 (5.4) | |
| Received transfusion before 1992 | 30 (6.1) | 30 (6.0) | 0.9 |
| Received acupuncture | 96 (19.4) | 86 (17.2) | 0.4 |
| Received tattoos | 48 (9.7) | 69 (13.8) | 0.04 |
| Received piercing | 257 (51.8) | 259 (51.9) | 0.9 |
| Number of life-time sexual partners | | | 0.6 |
|    0-1 | 56 (11.3) | 61 (12.2) | |
|    2-9 | 213 (42.9) | 226 (45.3) | |
|    ≥10 | 227 (45.8) | 212 (42.5) | |
| Nasal drug-use | 57 (11.5) | 63 (12.6) | 0.6 |
| Intravenous drug-use | 2 (0.4) | 2 (0.4) | 0.9 |
| Long-term stay at a medical center | 17 (3.4) | 25 (5.0) | 0.2 |
| Previously incarcerated | 27 (5.4) | 16 (3.2) | 0.08 |
| Main services provided at recruiting center | | | 0.9 |
|    General care and testing | 284 (57.3) | 283 (56.7) | |
|    Free and anonymous STD testing | 162 (32.7) | 164 (32.9) | |
|    Immigrant and low SES care | 50 (10.1) | 52 (10.4) | |

All numbers above represent *n* (%), except for age where mean (SD) is given.

*Statistical comparison between arms was performed using Pearson's $\chi^2$ test or Fisher's exact test for categorical variables and Student's *t* test for continuous variables.

[1]Period of stay was longer than 3 months.

[2]Couverture médicale universelle, health insurance coverage that is given to persons living in precarious social situations (i.e. unemployed, poverty, etc.).

**Table 3. Classification probabilities comparing rapid HBsAg and anti-HBsAb tests to ELISA**

| | HBsAg serology ELISA | | AUC (95% CI) | Se | Sp | PPV | NPV |
| | Positive | Negative | | | | | |
|---|---|---|---|---|---|---|---|
| VIKIA® | (*n*=2) | (*n*=497) | 1.000 (-) | 100 | 100 | 100 | 100 |
| Positive | 2 | 0 | | | | | |
| Negative | 0 | 497 | | | | | |
| | | | | | | | |
| | HBsAb serology ELISA | | | | | | |
| | Positive | Negative* | | | | | |
| QUICK PROFILE™ | (*n*=285) | (*n*=158) | 0.876 (0.844-0.908) | 94.4 | 80.8 | 88.1 | 90.5 |
| Positive | 251 | 15 | | | | | |
| Negative | 34 | 143 | | | | | |

HBsAg, hepatitis B surface antigen; anti-HBsAb, anti-Hepatitis B surface antibodies; ELISA, enzyme-linked immuno-assay; AUC, area under the curve; Se, sensitivity; Sp, specificity; PPV, positive predictive value; NPV, negative predictive value.

*n=56 patients were excluded because they had intermediate results from the ELISA test.