Screen and treat as an intervention programme for hepatitis B virus infection in sub-Saharan Africa: the PROLIFICA experience in The Gambia.

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**Abstract**

**Background:** Despite the introduction of hepatitis B virus (HBV) immunization since 1990s, HBV-related morbidity and mortality remain high in sub-Saharan Africa. Identification and treatment of asymptomatic people with chronic HBV infection should reduce the disease burden. We therefore assessed the feasibility of an HBV “screen and treat” programme in The Gambia, West Africa, and determined the proportion of HBV-infected people with significant liver disease in need of treatment.

**Methods:** Between December 2011 and January 2014, individuals living in randomly selected communities in Western Gambia and blood donors attending the central hospital were offered hepatitis B surface antigen (HBsAg) screening using a point-of-care test. Positive individuals were invited for a comprehensive liver assessment and were offered treatment according to international guidelines.

**Findings:** The coverage of HBsAg screening amongst 8,170 adults from 27 rural and 27 urban communities and 6,832 blood donors was 68.9% (95% CI: 65.0-72.4%) and 81.4% (95% CI: 80.4-82.3%), respectively. HBsAg prevalence was 8.8% (95% CI: 7.9-9.7%) in communities and 13.0% (95% CI: 12.1-13.9%) among blood donors. Prevalence was higher in men and middle-aged participants. Linkage to care, defined as first attendance to the liver clinic was high, with 402 of 495 (81.3%) HBsAg-positive people from the community attending clinic; however, 300 out of 721 (41.6%) of HBsAg positive blood donors linked into care. Treatment indication was met by 18 of 402 (4.4%, 95% CI: 2.5-7.7%) patients from the communities and 29 (9.7%, 95% CI: 6.8-13.6%) from the blood donors. Male gender was strongly associated with treatment eligibility (OR: 4.35, 95% CI: 1.50-12.58, P=0.007).

**Interpretation:** HBV-infection remains highly prevalent in The Gambia. The high coverage rates of community-based screening and linkage into care and the low proportion of HBsAg carriers who require treatment suggest that large scale screening and treatment programmes are feasible in sub-Saharan Africa.

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**Research in context**

**Evidence before this study**

We searched Medline & Embase for articles published before September 2015, with terms incorporating ‘Hepatitis B’, ‘mass screening’ and ‘Africa’. We were unable to find any previous study describing HBV “screen and treat” interventions targeting the general population in Africa.

**Added value of this study**

PROLIFICA is the first “screen and treat” intervention programme in Africa. In addition to the feasibility of such an intervention, this study provides unique data on 1) screening coverage to HBV testing, 2) prevalence of HBsAg, 3) rate of linkage to health care and 4) proportion of chronic carriers with significant liver disease in need of treatment in a community-based and facility (blood bank)-based approach in The Gambia, West Africa.

**Implications of all the available evidence**

By confirming the high endemicity of HBV infection, and the good coverage of HBV screening and care, our study demonstrates the feasibility of a HBV “screen & treat” programme at a large scale in The Gambia. This deserves to be assessed in other resource-limited endemic countries. National health policies in sub-Saharan Africa and the World Health Organization should consider integrating such a programme as a public health strategy to fight against the epidemic of HBV infection in Africa.
INTRODUCTION

Hepatitis B virus (HBV) infection is highly endemic in sub-Saharan Africa (SSA), where 80 million people are chronically infected. Hepatocellular carcinoma (HCC) remains one of the most frequent cancers in the region and is mainly attributable to HBV. Hepatitis B vaccine coverage in SSA is imperfect and a large number of people born before the introduction of the vaccine continue to carry the virus with a risk of cirrhosis and HCC.

The World Health Organization (WHO) recently published its first guidelines on chronic HBV infection with limited recommendations for SSA due to lack of data. In SSA screening and treatment for hepatitis B are rarely accessible and blood banks are the only places where people are offered free HBV testing. However, this is to ensure safety of the blood products, and deferred donors are rarely linked to care. Although in SSA the prevalence of infection is high in the general population, people has very limited opportunity to be tested for HBV unless they are infected with HIV or develop advanced liver disease. Screening and treating interventions targeting the general population have never been evaluated in SSA.

Prevention of Liver Fibrosis and Cancer in Africa (PROLIFICA), the first “screen and treat” programme for HBV mono-infected people in SSA, was started in June 2011 in The Gambia, West Africa. As part of this programme, we evaluated whether a mass screening for HBV infection is justified by referring to the Wilson & Junger WHO criteria. We previously demonstrated that hepatitis B surface antigen (HBsAg) point-of-care (POC) tests perform well in field conditions in the African community setting. For the assessment of liver disease, we validated inexpensive and simple diagnostic tools. We also identified risk factors for liver disease progression through the follow-up of a population-based cohort in rural Gambia.

Here, we assessed the acceptability and feasibility of a “screen & treat” HBV intervention programme in West Africa by analysing 1) the screening coverage, 2) the prevalence of HBsAg, 3) the rate of linkage to care and 4) the proportion of chronic carriers with severe liver disease in need of treatment in a community-based and facility (blood bank)-based approach in The Gambia.

METHODS

Community screening
Screening was conducted in Western Gambia (Figure 1) where 750,000 people live in 1,450 census enumeration areas (EAs), defined by the Gambia Bureau of Statistics. We used EA as a sampling unit, and one EA consists of an entire village, a part of a large village/town, or a cluster of small hamlets. Because HBV prevalence may differ between urban and rural populations, we first stratified 1,450 EAs into urban (n=1,197) and rural (n=253) communities. Then, from each stratum 27 EAs were selected by simple random sampling using a random number generator. In the selected EAs, all inhabitants aged ≥30 years were eligible for screening. We excluded those aged <30 years because the national hepatitis B vaccination programme started in 1990. We organised a meeting in each EA, with the help of the village head. Following community approval, a team of fieldworkers conducted a census by visiting all households to register the name, age and sex of all eligible people and invited them for screening. After pre-test counseling and written consent, finger-prick whole blood was tested for HBsAg using a POC test (Determine®, Alere, USA) whose performance was validated in the field (sensitivity 88.5%, specificity 100%). Results were provided on site to the participants with post-test counseling, and those who tested positive were referred to the liver clinic at the Medical Research Council (MRC) unit in Fajara (Figure 1). People who were invited, but did not attend screening were reminded by the fieldworkers up to three times. Reasons for non-attendance were captured in a standardised form. Additional questions about knowledge of HBV infection and past experience of HBV testing were administered to all individuals screened between August and November 2013.

Facility-based screening

Since 2011, in addition to HIV testing, the Edward Francis Small Teaching Hospital (EFSTH), the sole tertiary care hospital in Banjul, the capital city, started HBV screening at its blood bank using a POC test (Combo Rapid Test, Onsite, CTK Biotech, USA). Its sensitivity and specificity have been reported as 96% and 100% according to the manufacturer, respectively. Donors must be healthy and aged ≥16 years. Those tested positive were referred to a study nurse posted at EFSTH, who provided post-test counseling and advised them to visit the MRC clinic. Subjects co-infected with HIV were referred to the national HIV programme.

Linkage to care
In subjects tested positive for HBsAg, linkage to care was defined as attendance to the first outpatient liver clinic following the HBV screening. Those who did not come to the clinic were reminded up to three times by the fieldworkers using telephone calls. Semi-structured interviews were conducted in a subgroup of HBsAg-positive participants to identify reasons for non-attendance to clinic.

Assessment of liver disease

A standardised comprehensive liver assessment was performed: physical examination, abdominal ultrasound (Portable MyLab25Gold, Esaote, Cambridge, UK), fasting liver stiffness measurement (LSM) using hepatic transient elastography (Fibroscan®, FS402, Echosens®, France), and routine serum hematology and biochemistry tests. Optimal LSM cut-off values were previously determined using liver histology as a reference: 7.9 kPa for significant fibrosis (Metavir ≥F2) and 9.5 kPa for cirrhosis (F4). Unreliable LSM was defined as interquartile range (IQR)/LSM of >0.30 when LSM is ≥7.1 kPa. Blood samples were tested for hepatitis B e antigen (HBeAg) (ELISA-ETI-EBK Plus, Diasorin, Italy), antibodies to hepatitis C (AxSYM, anti-HCV, Abbott, USA) and hepatitis D viruses (ETI-AB-DELTAK-2, Diasorin, Italy). Antibodies to HIV-1 and HIV-2 were detected using enzyme immunoassay (EIA, Genscreen ULTRA HIV Ag-Ab, Bio-Rad, USA). HBV DNA levels were measured using an in-house quantitative real-time polymerase chain reaction (q-PCR) (detection limit of 50 IU/ml) which was validated against a commercial HBV qPCR (Abbott, USA, excellent correlation with the commercial assay \( r^2 \approx 0.90 \)). All samples were tested at the MRC Unit in Fajara. Quality control and HBV genotyping were performed by a reference laboratory in France (INSERM, Lyon).

Antiviral therapy

Eligibility for treatment was determined according to the 2012 European Association for the Study of the Liver (EASL) guidelines (Suppl. Table 3). In the absence of contra-indications, tenofovir (tenofovir disoproxil fumarate, TDF) was provided free of charge. Adherence to treatment was assessed using the Morisky adherence scale.

Ethical consideration

Ethical approval was granted by the Gambia Government/MRC Gambia Joint Ethics Committee.
Statistical analysis

Screening coverage was estimated by dividing individuals screened by those enumerated by the census. The effect of individual-level (sex and age) and community-level variables (urban/rural, screening season, screening during weekend and assistance of village health workers) on the community screening coverage was estimated using logistic regression and adjusted for age and sex. Linkage to care was estimated by dividing individuals who visited the liver clinic by HBsAg carriers identified at screening. The proportion eligible for treatment was estimated by dividing those who fulfilled the treatment criteria by HBsAg-positive participants assessed at the clinic. Logistic regression was used to estimate odds ratios (OR) for the factors associated with linkage to care and treatment eligibility. For the community screening, all the estimates above accounted for survey design (correlation within EAs and stratification by urban/rural area) using “svy” command in STATA 11.0 (Stata Corporation, College Station, Texas, USA). Finite population correction was not applied as the sample size was small relative to the population size.

The HBsAg prevalence, the proportion linked to care and that eligible for treatment among community screening participants were weighted for non-attendance to screening; a reciprocal of the probability of screening coverage derived from a logistic regression with predictors (sex/age/communities).

Role of the funding source

The European Commission had no role in the study design, data collection, analysis or interpretation and did not contribute to the writing of the manuscript. The corresponding author had full access to the data and takes responsibility of these findings.

RESULTS

Screening coverage and HBsAg prevalence

Community screening

Between December 2011 and January 2014, all selected EAs agreed to participate to the study and 5,980 out of 8,170 eligible people (68.9%, 95% CI: 65.0-72.4%) participated in the community screening (Figure 2). Median length of screening per
EA was three days (range: 2-8). Participants’ median age was 43 years (range: 30-105) and 2,328 (38.9%) were males. The screening coverage varied amongst EAs, from 48.9% to 95.1%, and was higher in women (P<0.001) and older people (P<0.001) (Table 1). Among community-level factors, after adjusting for age and sex, rural area (P=0.006), screening in the weekend (P=0.02) and assistance from village health workers (P=0.05) were associated with higher coverage (Table 1). The two commonest causes of non-attendance were absence due to work or travel (36.8% in men and 27.6% in women) and lack of perceived benefit (23.8% in men and 28.5% in women) (Figure 2).

Of 5,980 people screened, 495 (8.8%, 95% CI: 7.9-9.7%) were identified as HBsAg carriers. The prevalence varied between EAs from 1.9% to 18.2%. It was higher in men (10.5%, 239/2328, 95% CI: 8.9-12.1%) than in women (7.6%, 256/3652, 95% CI: 6.5-8.7%, P=0.004) and in both sexes, the prevalence decreased with age (P<0.001) (Figure 3) and it was higher in urban (8.9%) than in rural areas (8.2%), though after adjusting for age and sex the difference was not statistically significant.

Knowledge of HBV infection was extremely low, only two men out of 489 participants (0.4%, 95% CI: 0.0-6.1%) interviewed in 2013 had heard about HBV infection and had been tested for HBV in the past. None of the 54 HBsAg carriers among the 489 participants had been previously tested and knew their status.

**Blood bank screening**

Between January and December 2013, among the 6,832 individuals who came for blood donation at the EFSTH (Figure 2), 5,559 were screened (99.3% men). There were 159, 2,480, 1,932, 766, 175 and 11 male potential donors at the age group of 10-19, 20-29, 30-39, 40-49, 50-59 and ≥60 years old. 1,273 were not tested due to shortage of HBsAg test kits.

HBsAg prevalence was 13.0% (721/5,559, 95% CI: 12.1-13.9%). Among men, the prevalence was the lowest in 16-19 years age group and the highest in the 30-39 years age group (Figure 3). Compared to men from community-based screening, there was no difference in age-specific HBsAg prevalence in men from blood bank screening. In women, there was no clear association between HBsAg prevalence and age, probably because the sample size (n=36) was small. In a subset of potential donors (n=694)
with available information, the vast majority (82.1%) were first-time donors and there was no significant difference in HBsAg-positivity between first-time and repeat donors after adjusting for age.

**Linkage to care and clinical assessment**

Among HBsAg positive individuals identified at community level (n=495), 402 (81.3%, 95% CI: 76.6-85.2%) attended the clinic (Figure 2), and came more frequently from rural than urban areas, with no association with age and sex (Suppl. Table 1). Absence of symptoms and poor understanding of the disease were the main reasons for non-attendance among a subgroup of 25 HBV-infected carriers who did not attend the liver clinic.

Among people screened at the blood bank, linkage to healthcare was lower (41.6%, 95% CI: 38.0-45.3%, P<0.0001), possibly due to the unavailability of the coordinating nurse, particularly during Ramadan and the last months of the year.

The majority (87.9%, 617/702, 95% CI: 85.3-90.1%) of the HBsAg-positive individuals who attended the clinic after screening was classified as inactive chronic carriers (Table 2); 3.3% (13/395) and 7.9% (23/291) were HBeAg-positive from the community and blood bank, respectively.

From the community screening, 48 (12.2%) individuals had elevated ALT ≥40 IU/mL and 41 (10.7%) had HBV DNA ≥ 2,000 IU/ml. After excluding eleven participants without valid LSM, 10 (2.6%) had extensive fibrosis (F3) and 11 (2.9%) had cirrhosis (F4). Co-infection with HIV, HCV or HDV was observed in 3.3%, 1.0% and 2.0% of the participants, respectively.

Among the HBV-infected blood donors, 55 (18.8%) had ALT ≥40 IU/mL, 38 (14.4%) had HBV DNA≥ 2,000 IU/ml and 50 (17.5%) had extensive fibrosis/cirrhosis (≥F3).

**Proportion of patients eligible for treatment**

According to the EASL criteria (Suppl. Table 3), 18, 47 out of the 702 HBV participants (6.7%, 95% CI: 5.1-8.8%) were eligible for treatment. The proportion was higher in blood donors (9.7%, 95% CI: 6.8-13.6%) than in those from the community (4.4%, 95% CI: 2.5-7.7%, P=0.007). Applying the American criteria (Suppl. Table 3) did not change substantially the number eligible for treatment.
The difference in treatment eligibility between community and blood bank disappeared after restring to male participants (Suppl. Table 2). Multivariable analysis showed that male sex and younger age group (<30 years old) were associated with treatment eligibility, although the latter did not reach statistical significance (P=0.07) (Table 3). None of the eligible patients refused antiviral therapy. Twelve months after starting tenofovir therapy, 38 patients (80.9%) had a high adherence score, 7 (14.9%) a medium adherence and 2 (4.3%) a low adherence. At 12 month of treatment, 43/47 (91.5%) achieved a virological response defined by undetectable HBV viral load; 38 (79.7%) had normal transaminases (<40 IU/mL), and 9 (19%) had ALT≥40 IU/mL (median 46 (43-62) IU/mL) with a baseline median (IQR) ALT at 49 (34-104) IU/mL. No clinical or biological adverse events were observed after 12 months of treatment.

DISCUSSION

Though able to prevent chronic carriage, vaccination against HBV has been introduced only recently in SSA; its coverage is less than ideal in many African countries and even vaccination of newborns from HBsAg positive mothers has been barely implemented. Therefore, there is still a large legacy of chronically infected adults who will remain undiagnosed until the development of severe complications. HBsAg prevalence remains high among Gambian adults born after 1990, the year The Gambia integrated HBV vaccine into the national programme; in our study 3.1% blood donors aged 16-19 years were HBsAg positive, a higher figure than previously reported in community-based data on the same age group (1.8%). Despite the implementation of HBV vaccination, the burden of HBV-related liver disease over the next decades will probably remain high. It is therefore critical to identify infected individuals through HBV screening and manage them adequately to prevent liver complications. In The Gambia, HBV community screening using a rapid POC test was well accepted, with coverage of almost 70%, a figure similar to that of HIV (63% in rural Ugandan communities and 86% in semi-rural areas in Mozambique) or malaria (64% in Zanzibar) community screening in SSA. Large-scale HBV screening may be challenging in Africa as the disease is invariably asymptomatic and awareness of HBV infection in the general population and health workers is poor. Indeed, almost no participant enrolled in our study was previously tested for HBV infection and aware of his/her status. In fact there is not even a term to define cirrhosis in Mandinka, the main local language in The Gambia.
In our study, a large proportion of HBsAg-positive individuals identified through community screening attended the liver clinic as advised and adherence to treatment was high; 81% of patients had good adherence one year after the initiation of antiviral therapy, comparable to that (77%) reported for antiretroviral therapy in Africa. In addition 91.5% achieved a virological response at one year. This is in line with data from European HBV cohort.

In contrast to hospital-based studies, which are likely to overestimate the proportion of HBV carriers with advanced liver disease, 90.5% of chronic carriers from community screening were inactive and only 4.4% required antiviral therapy, supporting the feasibility of a community-based “screen and treat” intervention programme for HBV mono-infection in SSA. Blood donors represent a different population from the community, being both younger and predominantly male, with higher proportion of detectable HBV viral loads. However, although the proportion of blood donors eligible for treatment was higher, there was no statistical difference as compared to the community group. This is in line with a previous Ghanaian study conducted in blood donors which reported a similar low proportion of subjects requiring antiviral therapy based on ALT levels alone. By applying our findings to SSA, we estimate that only 4 million chronic HBV carriers (roughly 5% of the 80 million infected subjects) will require treatment; this is half of the HIV-infected patients in need of antiretroviral therapy in SSA.

Screening coverage in the community was lower in young males compared to females or older individuals. This is consistent with community screenings for HIV in SSA. Low coverage in young men is problematic since they are more likely to be infected with HBV and in need of treatment. One third (36.8%) of men who did not attend our community screening were absent because of work/travel during the screening session, suggesting that screening during weekend may increase their coverage. In contrast, many young men came to donate their blood and accepted to be screened for HBV. However, less than half of those identified to carry HBsAg attended the liver clinic. In SSA, care and treatment of deferred donors infected with HBV should be improved as blood banks offer the opportunity of reaching this high-risk and difficult-to-manage group. Nevertheless, the proportion of young men who donate blood is low meaning that the population covered would remain limited.
Importantly, we found that 18.6% of blood donors were not tested for HBV due to shortage in diagnostic kits. This is in line with the 2012 WHO report on blood safety which underlined that 24% of blood banks do not systematically screen for transfusion-transmissible infections in resource-limited countries; irregular supply of test kits being the main barrier. 28

Our study has some limitations. First, although the study implementation was adapted to the real-life local conditions, it had the support of well-trained fieldworkers from a well-known research institution (MRC). As a result, the percentage of screening coverage and linkage to care could have been overestimated. Second, we might have underestimated the prevalence of HBsAg by using a rapid immunochromatography test, whose sensitivity is 88-96% using ELISA as a reference. False-negative results are known to be associated with low quantified HBsAg levels and inactive carrier state 12,29 implying that the clinical impact of their moderate sensitivity is negligible. Interestingly, we found a statistically significant trend in decline in HBsAg prevalence with increasing age, and this may be explained by false-negative results in elder chronic carriers who tend to have low HBsAg titres. Nevertheless, this phenomenon has been consistently observed in population-based sero-surveys in SSA 21,30,31 and is often attributed to spontaneous seroclearance of HBsAg and higher mortality in chronic HBV carriers than non-HBV infected people. Third, we used an in-house qPCR to quantify HBV DNA with a limit of detection slightly higher than the commercial assays (50 versus <20 IU/L), which may have overestimated the proportion of subjects with undetectable HBV DNA. Forth, following the recommendations of the scientific committee, we targeted individuals aged ≥30 years in the community as younger age group would have benefited of the high HBV vaccine coverage, estimated at >90% in The Gambia. Nevertheless, the screening of young blood donors indicates that HBV prevalence remains still important in Gambians younger than 30 years old, with a high proportion of cases requiring antiviral therapy. Fifth, we might have underestimated HBsAg prevalence at the blood bank as we were unable to exclude repeat donors from the analysis. However, its influence should be minimal as HBsAg screening has just recently (2011) started at blood bank with frequent shortage in testing kits and HBsAg prevalence was similar between first-time and repeat donors in a subset of participants with available information on previous history of blood donation. Finally, we assessed the treatment
eligibility at a single time point but the longitudinal follow-up of our cohort is likely to reveal additional eligible patients. We will address this question in the future.

Interestingly, in wealthy countries, community screening for viral hepatitis has been done rarely without assessing the proportion of infected individuals in need of treatment. Thus, our study provides original and important data for clinicians as well as policy makers.

When applying the Wilson and Jungner WHO screening criteria, we confirmed that HBV mass screening is justified in The Gambia (Suppl. Table 4) and our screening strategy in the community is cost-effective (Nayagam et al. this issue). Whether such an intervention should be incorporated within other national screening programmes (HIV or non-communicable diseases) should be evaluated.

In conclusion, HBV screening and treatment programme targeting the general population is a feasible and realistic public health intervention in The Gambia, West Africa. Such an intervention deserves to be assessed on a larger scale in SSA and in other resource-limited countries and eventually integrated within guidelines to fight the burden of HBV infection in endemic areas.

Contributors

MRT is the chief investigator of the PROLIFICA programme and designed the study with ML, YS, RN, HW, SDTR, and MM. ML and RN were responsible for the clinical assessment with the support of GN, ST, LS, AK, and SN; YS, AJ, and WS for fieldwork; LM for qualitative data collection; IC, SG, HFN, AJ, AS, CTK, PS, JH, and MM for laboratory assays; and ML, YS, and MRT for data analyses. MT, ON, TC, HW, and UDA supported the conduct of the study. ML, YS, and MRT drafted the manuscript, and all the authors reviewed and approved it.

Declaration of interest

M Thursz has accepted fees for advisory boards and lectures from Abbvie, BMS, Gilead, Janssen and Merck.

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