

Burden and impacts of chronic hepatitis B infection in rural Senegal: study protocol of a cross-sectional survey in the area of Niakhar (AmBASS ANRS 12356)

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BMJ Open Burden and impacts of chronic hepatitis B infection in rural Senegal: study protocol of a cross-sectional survey in the area of Niakhar (AmBASS ANRS 12356)

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ABSTRACT

Introduction Though Senegal has one of the highest estimated prevalence rates of chronic hepatitis B virus (HBV) infection worldwide, epidemiological data in the general population are lacking and consequences of the infection remain undocumented. The ANRS-12356 AmBASS study aims at evaluating the health and socioeconomic burden of chronic HBV infection at the individual, household and population level. Its specific objectives are (1) to document the epidemiology of chronic HBV infection, including prevalence and risk factors; (2) to assess the acceptability of home-based testing and first clinic visit; (3) to investigate the repercussions of chronic HBV infection on living conditions; and (4) to estimate the public health impact of chronic HBV infection at the population level and the feasibility of a decentralised model of HBV test and treat.

Methods and analysis This multidisciplinary cross-sectional survey includes a twofold data collection: (1) home-based screening using dried blood spot (DBS) sampling and collection of sociodemographic, economic and behavioural data, and (2) additional clinical and biological data collection in chronic HBV carriers at the first clinic visit. The prevalence of chronic HBV infection will be estimated in the general population and in key subgroups. Risk factors for HBV acquisition in children will be explored using case-control analysis. HBV burden will be assessed through comparisons of health and economic outcomes between households affected by the disease versus non-affected households. Last, an economic evaluation will assess costs and health benefits of scaling-up HBV care.

Ethics and dissemination This study was approved by the Senegalese National Ethical Committee for Research in Health, and received authorisation from the Senegalese Ministry of Health and the French Commission on Information Technology and Liberties (Senegalese Protocol Number: SEN17/15). The study results will be presented in peer-review journals, international conferences and at a workshop with national stakeholders in order to contribute to the design of programmes to address the HBV pandemic.

Trial registration number NCT03215732; Pre-results.

Strengths and limitations of this study

- The AmBASS study is a cross-sectional survey, which combines biological, clinical and socioeconomic data collection to assess both health and socioeconomic burden of the hepatitis B virus (HBV) infection at the individual, household and population level.
- After home-based pretest counselling and HBV testing using dried blood spots, participants are invited to visit their local healthcare facilities to get their results and benefit from post-test counselling.
- Additional clinical and biological data are collected in healthcare facilities among participants diagnosed with chronic HBV infection to provide an estimation of HBV treatment needs and to document the economic feasibility of expanding access to HBV testing and treatment.
- Important work migrations in the study area may introduce bias in the population sample.
- The Niakhar area may not be representative of the whole country of Senegal or of other countries in West Africa.

INTRODUCTION

Epidemiology of hepatitis B in sub-Saharan Africa: a significant burden

In 2015, an estimated 257 million people were chronically infected with hepatitis B virus (HBV) worldwide, and chronic HBV infection was responsible for 887 000 deaths.¹ With 60 million people living with chronic HBV infection and an estimated prevalence of 6.1% in the adult population, Africa is the second most affected region in the world after Asia, a burden that has long been neglected.² HBV prevalence is particularly high in West Africa with estimated rates between 6% and 16% in the adult population, depending on the country.^{3 4} In this

region, most HBV infections occur in early childhood, through mother-to-child transmission (MTCT)—that is, vertical transmission—and contact with other infected young children—that is, horizontal transmission.^{5–8} Primary HBV infection remains most often asymptomatic, but can lead to chronic infection in up to 90% of cases when infection occurs at less than 6 months of age and in 20%–60% of cases in children infected between the ages of 6 months and 5 years (vs only 5% when infection occurs at adulthood).⁹ Left untreated, 15%–40% of chronic HBV carriers will develop severe complications, including cirrhosis, hepatic failure and hepatocellular carcinoma (HCC)—the most common form of liver cancer—which can lead to death.¹⁰ In sub-Saharan Africa, liver cancer is among the cancers with the highest mortality, with approximately 200 000 deaths each year, and a mean survival estimated at only a few months after diagnosis.¹¹

Hepatitis B prevention and treatment: major challenges to address the needs

The cornerstone of preventing HBV is active immunisation.¹² An effective vaccine against HBV has been available since 1981. It has been included in the Expanded Programmes on Immunisation (EPI) of most African countries over the past 15 years, generally in combination with other vaccines administered beginning 6 weeks after birth.¹³ However, a first administration of HBV vaccine at birth (within the first 24 hours of life) is essential to effectively reduce MTCT of the virus as recommended by the WHO in highly endemic areas since 2009.^{14–16} The implementation of this key intervention remains a challenge in sub-Saharan Africa, with a significant number of women still giving birth at home. Furthermore, as of 2015, the birth dose was only included in a few EPI of sub-Saharan African countries resulting in an estimated 10% of birth dose coverage in this region.¹

Effective antiviral treatments can control HBV replication, prevent disease-associated complications and significantly reduce HBV-related mortality.¹⁴ These lifelong treatments include interferon, pegylated interferon, and six nucleos(t)ide analogues (NAs) (lamivudine, telbivudine, emtricitabine, entecavir, adefovir and tenofovir).¹⁴ The WHO recommends the use of NAs with a high barrier to drug resistance (ie, tenofovir and entecavir in adults, and entecavir in children aged 2–11 years) in individuals with cirrhosis (defined as an obvious clinical diagnosis and/or AST to Platelet Ratio Index (APRI) score >2 regardless of ALT/AST (ALT, alanine transaminase/aminotransferase; AST, aspartate transaminase) levels, HBeAg status and HBV DNA levels), and in individuals who are 30 years of age and above with abnormal ALT/AST levels and high viral replication (HBV DNA >20 000 IU/mL regardless of HBeAg status).¹²

However, access to affordable testing and treatment for people living with chronic HBV infection remains suboptimal in sub-Saharan Africa.^{17 18} According to the WHO, few people with chronic HBV infection have been

diagnosed (ie, 9% worldwide but much less in sub-Saharan Africa) and only a small fraction (estimated at 8% in 2015) of those diagnosed can access treatment.¹

Hepatitis B socioeconomic burden

The literature on the socioeconomic burden of hepatitis B and on its impacts on the living conditions of infected people remains scarce in high endemic areas.^{19–22} Quality of life with chronic hepatitis B has been documented in several studies, mostly conducted in Asia,^{23–30} showing impaired quality of life in chronic HBV carriers compared with the general population. However, only one study in sub-Saharan Africa—in Uganda—assessed the relationship between HBV infection and poverty and showed a negative correlation between wealth index and HBV infection.³¹

In contrast, there is a vast literature addressing the economic value of HBV treatments in the setting of high-resource countries,^{32–39} but practically no cost-effectiveness analysis in sub-Saharan Africa, with the exception of a recent study on the cost-effectiveness of community-based HBV screening and treatment in Gambia.⁴⁰ A few studies have also been conducted on the cost-effectiveness of HBV vaccine in low and middle income countries.^{41–43} However, there is a lack of economic evaluations on the public health impacts of hepatitis B as well as on the public health benefits and budget implications of scaling-up HBV testing and treatment in sub-Saharan Africa.

Hepatitis B in Senegal

Hepatitis B is hyper endemic in Senegal. It is estimated that 85% of the population has been infected with HBV,⁴⁴ and according to a 2015 systematic review, the prevalence of chronic HBV infection reaches 11% or more.⁴ However, currently available prevalence data rely on cross-sectional studies conducted within at-risk populations (drug users, HIV coinfecting individuals) or specific subpopulations (eg, military, blood donors)^{45–52} but no study has been carried out in the general population. In addition, as 60% of people may have been infected with HBV before turning 5 years old,⁵³ HBV-related morbidity and mortality is expected to remain high. According to the WHO, liver cancer is the second cancer with the highest incidence and mortality rates in Senegalese men, and the third in Senegalese women.¹³ Despite this critical situation, the burden and impacts on living conditions of chronic HBV infection in the general population of the country remain undocumented.

Key actors in the fight against HBV in Senegal include the national hepatitis programme set up in 1998 by the Senegalese government,³⁹ the Senegalese Society of Gastro-Enterology and Hepatology (SOSEGH) founded in 2007 to gather hepatitis experts in the country, and the HBV patient association ‘Saafara Hépatites Sénégal’ which was established in 2011 to encourage HBV testing and outreach to the general population. Despite the implementation of several HBV vaccine trials in Senegal (including in the Niakhar area) in the late seventies,

the national EPI only introduced systematic vaccination against HBV in 2004 with a three dose schedule (pentavalents 1, 2 and 3 to be administered at 6, 10 and 14 weeks, respectively⁵⁴). The recent objective of the health authorities has been to enhance HBV screening in pregnant women and to implement vaccination in newborns (birth dose) which is part of the country's EPI since February 2016.¹³ According to estimates of the national hepatitis programme, HBV vaccine birth dose coverage had reached 82% in December 2017.¹³

In contrast, both HBV testing in adults and global access to HBV treatment remain a very important challenge. A working group was launched in 2016 to develop national guidelines to promote access to HBV treatment at the decentralised level of the healthcare system. However, these guidelines are yet to be officially adopted, and access to antiviral treatment is only available in major hospitals located in the country's two main cities (Dakar and St-Louis). Moreover, with the exception of HBV specialists, the majority of caregivers, including physicians, still have incomplete knowledge of hepatitis B screening and care, including treatment initiation and follow-up.⁵⁵

OBJECTIVES

The overall objective of the study is to assess both the health and socioeconomic burden of chronic HBV infection at the individual, household and population level.

Specific objectives

1. To document the epidemiology of HBV infection in the Niakhar area general population including (i) estimation of the prevalence of chronic HBV infection in the whole population and in different subgroups according to age and gender and (ii) identification of behavioural and environmental risk factors of HBV acquisition in children.
2. To assess the acceptability of home-based HBV testing and first clinic visit.
3. To investigate the consequences of chronic HBV infection on living conditions of infected individuals and their households.
4. To estimate the public health impact of chronic HBV infection at the population level and feasibility of a decentralised model of HBV test and treat.

METHODS AND ANALYSIS

Study design

The ANRS 12356 AmBASS study is a multidisciplinary cross-sectional survey which is conducted within a representative sample of the population living in the Niakhar area with a two-level data collection: (1) at home for HBV screening using dried blood spot (DBS) sampling and collection of sociodemographic, economic and behavioural data using face-to-face questionnaires, and (2) in healthcare facilities for test results delivery and post-test counselling to all participants as well as additional

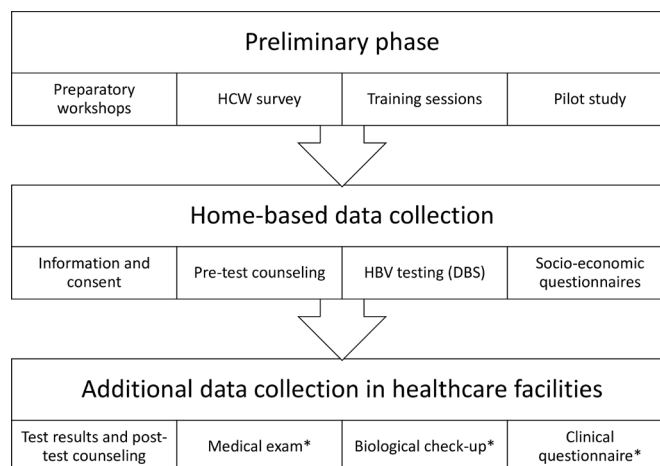


Figure 1 General design of the ANRS 12356 AmBASS survey. DBS, dried blood spot; HBV, hepatitis B virus; HCW, healthcare workers; *Only for chronic HBV carriers.

clinical and biological data collection in chronic HBV patients. The study also includes a preliminary phase to inform national and regional health authorities as well as local community leaders about the research and its public health challenges, to assess the local healthcare workers' (HCW) knowledge in the field of prevention, care and treatment of chronic HBV infection, to train the study team and HCW working in the healthcare facilities of the study area and to conduct a pilot survey (figure 1). This preliminary phase took place between April 2017 and August 2018. The main data collection started in October 2018, and is expected to end mid-2019.

Study setting: the Niakhar Health and Demographic Surveillance System

The survey is conducted in the area of the Niakhar Health and Demographic Surveillance System (HDSS), the oldest HDSS of Senegal, and one of the oldest in Western Africa. Created in 1962, the Niakhar HDSS is located 135 km East of Dakar, covers 203 km² and a population of 44854 individuals (January 2018 census) distributed across 30 villages.⁵⁶ The Niakhar HDSS has local health and demographic surveillance infrastructures (Niakhar station) including offices, information technology and basic laboratory equipment, vehicles and staff on site, mainly interviewers and technicians trained in questionnaire administration and collection of biological data.⁵⁷ The population of the Niakhar area is regularly followed-up, and events such as migrations, marriages, pregnancies or death are recorded in the HDSS database. The area of Niakhar counts four local public clinics, with the support of two healthcare centres in Niakhar and Fatick districts (referral centres at the district level) and a regional hospital in Fatick, located 15 km from Niakhar.

Study population

The study population includes all individuals living in randomly selected households in the Niakhar area for at least 6 months during the year (eg, seasonal workers

or individuals studying outside the Niakhar area are also included),⁵⁶ aged at least 6 months (for feasibility purposes) and who have given informed consent to participate to the study (for children under 15 years old, parental consent is required). There is no specific exclusion criterion at the household level. At the individual level, exclusion criteria are as follows: being an adult unable to sign informed consent, or being a child whose parent or legal guardian is not present in the household at the time of the survey.

Sample size calculation

The calculation of the sample size was based on the following standard formula used for prevalence surveys⁵⁸: $N = (Z_{1-\alpha})^2 (P(1-P)/D^2)$, where $Z_{1-\alpha}$ corresponds to the value of the Z statistic for the chosen level of confidence (eg, 1.96 for 95% CIs), P is the estimated prevalence based on data from the literature and D is the required precision (generally set between 3% and 5%), which corresponds to half the width of the 95% CI for the estimated prevalence. The sample size was determined to provide an estimated prevalence of chronic HBV infection in the general population of the area with 1.2% precision, and an estimated prevalence of chronic HBV infection in women of childbearing age (15–49 years old) and in the main age groups (<15 years old, 15 to 35 years old, and >35 years old) with 3% precision. Based on available data in the literature on HBV prevalence in Senegal,^{4 20 52} we hypothesised a minimum HBV prevalence of 10%, and a maximum prevalence of 17%. On the basis of response rates observed in previous sociodemographic and medical surveys conducted by the HDSS team in the area, we hypothesised a 90% participation rate in the AMBASS survey. In addition, a 3% loss rate is expected for DBS (corresponding to unexploitable DBS samples, for which HBV screening will not be possible). These hypotheses, together with the expected precision in estimated prevalence rates, resulted in a target sample size of 3200 participants.

Selection of participating households

Sampling relies on a two-stage stratified design. The sampling frame is made of 26 villages located in the Niakhar area, which corresponds to all villages in the area with the exception of four villages due to their very low participation rates in previous surveys including blood tests. The households included in the pilot survey were excluded from the study sampling frame. Villages were then classified according to their infrastructures and equipment into rural villages or semiurban villages (stratum variable).⁵⁶ Participating villages were selected at the first stage. The three semiurban villages and a random sample of nine rural villages (39%) drawn with simple random sampling were selected. All households listed in the 12 participating villages constituted the second stage of the sampling. Given that the average size of a household is 11 individuals in the Niakhar area, the number of households to select using simple random sampling

was estimated at 291. Thirty-two additional households were randomly selected (complementary list) in order to take into account potential refusals to participate in the survey. Randomisation was performed by the study statistician before data collection.

Study procedures and data collection tools

Preliminary phase

The preliminary study phase (April 2017–August 2018) includes preparatory workshops with local and national health authorities, meetings with village leaders to present the study and obtain prior agreement to conduct the research in the community, and training of the study team and local HCW. Information and training needs about hepatitis B screening, prevention and care in HCW were first assessed through a preliminary survey. Caregivers in the Niakhar area were then trained in HBV pretest and post-test counselling, with support from the Saafara Hépatites Sénégal patients-centred association that plays a key role in public awareness. In July 2018, an advanced training in HBV care management took place at the Fatick regional hospital, with the participation of the SOSEGH president, Pr Pape Saliou Mbaye. In addition, a pilot survey was conducted in October–November 2017 among 10 households (102 participants) living in two different villages of the Niakhar area in order to validate standard operating procedures and data collection tools.

First level: home-based HBV testing and data collection

The cross-sectional survey includes two levels of data collection corresponding to two successive steps (table 1). First, data are collected at home and HBV testing is offered to all eligible household members in randomised households. After the authorisation to enter the concession is obtained from the head of household, interviewers present the survey objectives and benefits/risks individually to each member of the household aged at least 18 years and to children in the presence of their parents or legal guardian. Then, professional nurses trained in study procedures perform HBV testing using DBS in all individuals and their children willing to participate. This rapid and simple technique requires a few drops of blood from a finger stick, which are placed on the five preprinted circles of a Whatman 903 Protein saver card. This procedure is in line with the latest WHO recommendations that a single assay with reactive HBsAg is compatible with chronic HBV infection in areas where the HBsAg seroprevalence is above 0.4%, and that DBS sampling may be used for HBsAg in settings where venous blood sampling is not feasible and rapid diagnostic tests are not available.⁵⁹

Right after DBS collection, the interviewer administers face-to-face questionnaires to all participants born before 1 September 2003 (considered as ‘adults’). This questionnaire focuses on the economic situation, HBV screening and liver disease history, perceived health and quality of life, as well as medical conditions, healthcare

Table 1 Schedule of the ANRS 12356 AmBASS survey

	Home		Local healthcare facility	
	Preinclusion	Screening	Test results First clinic visit	Chronic HBV follow-up Second clinic visit
Information	X			
Consent		X		
HBV counselling		X	X*	X*
Clinical examination			X*	
Treatment eligibility				X*
Referral to the hospital				X*
Biological samples				
Dried blood spots		X		
Venous blood			X*	
Biological examinations				
HBsAg		X		
Anti-HBs		X†		
Anti-HBc		X		
HBeAg			X*	
Anti-HBe			X*	
HBV DNA (viral load)			X*	
Anti-HIV			X*	
Antihepatitis D Virus			X*	
AST/ALT			X*	
Prothrombin time			X*	
Full blood count			X*	
Platelets			X*	
Face-to-face questionnaires				
Individual questionnaire		X		
Household questionnaire		X		
Clinical questionnaire			X*	

*Only for HBV chronic carriers.

†Only for participants born after 1 September 2003.

Anti-HBc, hepatitis B core antibodies; Anti-HBe, antibody to the hepatitis B e-antigen; Anti-HBs, antibody to the hepatitis B surface antigen; AST/ALT, concentration ratio between the aspartate transaminase (AST), and the alanine transaminase/aminotransferase (ALT) enzymes; HBeAg, hepatitis B e-antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.

consumption and expenditures (table 2). For participants born after 1 September 2003 ('children'), a specific questionnaire is completed by the participant's parent or legal guardian. This questionnaire documents health condition, vaccination records and risk factors (table 3). Finally, a questionnaire describing the main characteristics of the household (composition, agricultural production, assets, food security and housing conditions) is also administered to the head of the household (table 4).

All DBS are transported to the Niakhar station laboratory where they are dried, then frozen at -20°C before being transferred for analysis to the *Institut de Recherche en Santé, de Surveillance Épidémiologique et de Formation* (IRESSEF). HBV biomarkers are measured using chemoluminescence microparticle immunoassay (Abbott

Diagnostics, Sligo, Ireland). Study participants are invited to get their HBV test results and receive post-test counselling in their local healthcare facility.

Second level: healthcare facility-based HBV test results and additional data collection among chronic HBV carriers

HBV testing results are delivered at the local healthcare facilities by the local HCW with the support of the clinical research team composed of a referral physician and two nurses, and of the HBV patients association Saafara Hépatites Sénégal. Participants are provided with individual or family-based postdiagnosis HBV counselling, according to their preference. Individuals receive information on hepatitis B transmission routes and prevention measures including, but not limited to, MTCT,

Table 2 Adult questionnaire (participants born before 1 September 2003)

Main theme	Specific themes
General information	Gender, date of birth, marital status, number of children, residence status, migration for work or studies during the past year (duration of the absence and location)
Economic activity	Participation to the household's agricultural work (main or secondary activity, time worked), paid farm work (income), independent agricultural work (crop, area, income), other economic activities (type, status, time worked, income), other status (retired/retiree, unemployed, disability, student)
Health and quality of life	Impact of health condition on working productivity and on daily activities, health-related quality of life (SF-12) ⁶³ , fatigue (current, history, impact), disability
Maternal health*	Full-term pregnancy (number, history of C-section), current pregnancy, prenatal consultations, last delivery (date, setting, assistance)
HBV screening and liver disease	Liver disease (knowledge, family history), knowledge of hepatitis B (organ affected, known routes of transmission), vaccine (knowledge, perceived efficacy and safety), history of HBV screening (health record, circumstances, date, result, treatment)
Healthcare utilisation and expenditures	Hospitalisation in the past 12 months, episodes of illness in the past 3 months (impact on work and daily activities, symptoms, medical attention, self-medication), health insurance (type, members, contribution, coverage), healthcare utilisation and expenditures in the past 3 months (out-of-pocket and identity of the payer for medication, consultation, medical examinations, hospitalisation), transport costs, Senegalese indigent status or certificate for subsidised care (heard of, ever applied to, date, result, amount)

*Only for women of childbearing age (15–49 years old).
HBV, hepatitis B virus.

horizontal transmission among children and the importance of immunisation. Additional data are collected by the physician among chronic HBV carriers after post-test counselling. Participants identified as chronic HBV patients undergo additional clinical and biological examinations—including venous blood sampling—in order to assess the stage of liver disease and treatment eligibility. As for DBS, blood samples are transported, frozen and stored at the Niakhar station laboratory before being transferred to the IRESSEF laboratory where they are analysed. Clinical data collected using a face-to-face questionnaire include medical and family history, clinical symptoms of liver disease and risk factors of disease evolution (table 5). People are invited to come back to the facility to obtain the results of the additional biological tests. During this second clinical visit, which is also carried out by the team physician, a monitoring scheme and a

reference at the Fatick hospital is offered depending on the stage of the infection.

Study outcomes

Main outcome

The main study outcome is the prevalence of chronic HBV infection in the general population of the Niakhar area, defined by positive HBsAg detected in DBS samples collected during home visits. Drawing from a previous study⁶⁰ and results of the pilot study, adjusted cut-off values of 1 (for negativity) and 1.5 (for positivity) were identified to define HBsAg status. For HBsAg values between 1 and 1.5 IU/mL, a second measure of HBsAg was performed using venous blood sampling collected in the healthcare facility when HBV testing results were delivered.

Table 3 Child questionnaire (participants born after 1 September 2003)

Main theme	Specific themes
General information	Age, gender, birth order, school attending*, field labour, domestic work, paid work
Health	Specific health impairment (disability, chronic disease), hospitalisation in the past year, illness in the past 3 months (symptoms, healthcare utilisation and expenditures)
HBV vaccination and risk factors	HBV vaccination records (HBV-specific birth dose, and pentavalent doses), place of birth, mode of delivery, support during delivery, medical history (surgery, blood transfusion, dental care, wounds, stitches/stitches, infusion therapy, syringe), scarification, tattoos, piercing (ear, nose, other), acupuncture or assimilated, sharing of hygienic equipment (toothbrush, razor, hair needles, manicure and pedicure equipment), consumption of prechewed food, circumcision (age, circumstances)†

*Only for children above 5 years old.

†Male children only.

HBV, hepatitis B virus.

Table 4 Household ('kitchen') questionnaire (head of the household or next of kin)

Main theme	Specific themes
General information	Number of households in the concession, number of people in the household (adults, children), individual questionnaires completed
Agricultural production	Agricultural activity, land status, household participation, non-family labour, millet (area cultivated, last harvest, sales, current granary stock), peanuts (area cultivated, last harvest, sales), niébe (last harvest, sales), bissap (last harvest, sales), other crops (last harvest, sales), draught animals, farm equipment
Livestock	Feeder animals (possession and sales of fowl, small stock and cattle)
Other sources of income	Money from relatives in Senegal or abroad (frequency, amount), government family grant (application, outcome, date of the first payment, amount of the last payment)
Food security	New millet, food assistance, loan and grant received and given
Household characteristics	Consumption goods (inventory and rental income), shop, water supply, power supply (lighting, cooking)
Type of housing	Occupancy status, number of rooms, rooms for rent (amount, rental income), characteristics of the main room (roof, walls, floor)

Secondary outcomes

Secondary outcomes include prevalence of chronic HBV infection in different subgroups, including adults aged 15–49 years, women of childbearing age (15–49) and age groups 0–15, 15–35 and >35 years. Behavioural and environmental risk factors of HBV acquisition in children will be explored through data on circumstances of birth and circumcision (male children), history of invasive medical care, scarification, tattoos, piercing, sharing habits regarding hygienic equipment and consumption of prechewed food. The acceptability and uptake of home-based HBV testing and first clinic visit will be assessed with the proportion of participants (i) who agree to be tested for HBV among those eligible, (ii) who know their HBV status (ie, came to the local healthcare facility to receive their results) among those who have been tested and (iii) HBsAg-positive participants who accept the first step of HBV care—that is, assessment of the disease stage through additional biological and clinical examinations, including venous blood sampling.

Consequences of chronic HBV infection on living conditions of individuals and/or households affected by the disease will be investigated using several health and socioeconomic outcomes including liver disease stage, HBV-related morbidity and mortality (for health outcomes) and health-related quality of life, economic

situation, productivity, income loss and food security (for socioeconomic outcomes). In addition, treatment needs will be estimated in chronic HBV carriers according to the WHO criteria.¹² Finally, public health and economic impacts of chronic HBV infection will be estimated at the population level using the number of quality-adjusted life years and costs assessed from the society perspective (ie, including indirect costs related to productivity and income loss) in the absence of HBV treatment versus in different scenarios of access to HBV testing and treatment.

Statistical analysis plan

Descriptive analysis of the study population

Description of the overall participation will include the participation rate and the comparison of the main socio-demographic characteristics of the participants with that of the whole population living in the Niakhar area to identify potential selection bias. In case of significant differences, weighting and calibration procedures will be used to ensure the representativeness of the study sample. The study population will be described in terms of socio-demographic and economic characteristics of the households and individuals, overall as well as by gender and age groups (<15; 15–35 and >35 years). Missing values higher than 10% will be accounted for with multiple imputation methods or Heckman type model.⁶¹

Table 5 Clinical questionnaire

Main theme	Specific themes
Clinical examination	Weight, height, blood pressure, body temperature, body mass index, assessment of hepatitis or liver disease symptoms
Medical and family history	Diagnosed infections, recent hospitalisation, past or ongoing hepatitis treatment, family medical history (HCC and cirrhosis) and ongoing treatments
Risk factors of liver disease evolution*	Alcohol consumption and tobacco use, sexual behaviour, history of imprisonment

*Only for participants born before 1 September 2003.
HCC, hepatocellular carcinoma.

Epidemiology of chronic HBV infection

Estimation of prevalence of chronic HBV infection in the whole population and in the different subgroups will be computed as the ratio of the number of chronic HBV infections over the corresponding population size and their respective 95% CIs will be reported. HBV antibodies (anti-HBs and anti-HBc) will be described to measure the proportion of participants (i) with vaccination-induced immunity (negative HBsAg, negative anti-HBc and positive anti-HBs; only in children), (ii) with cured HBV infection (negative HBsAg and positive anti-HBc and positive anti-HBs) and (iii) susceptible (negative HBsAg, negative anti-HBc and negative anti-HBs), respectively. Behavioural and environmental factors associated with HBV infection in children will be analysed using case-control (1–3) in multilevel regression models accounting for potential households' effects.

Acceptability of home-based HBV testing and first clinic visit

Acceptability of home-based HBV testing will be estimated through its uptake—that is, the proportion of participants who accepted to be tested at home for HBV among all those eligible for the study. The acceptability assessment will also take into account participation at the local healthcare facilities level including the proportion of participants that come to get their results, the proportion of chronic HBV carriers who participate in the additional clinical and biological data collection, as well as the subproportion of those participants who come back for evaluation of their treatment eligibility. Factors associated with the acceptability of home-based HBV testing and first clinic visit will also be explored at each of the previous steps in multivariate analysis.

Consequences of chronic HBV infection on living conditions at individual and household level

Liver disease stage, HBV-related morbidity and treatment needs will be described in chronic HBV carriers using biological and clinical data collected in healthcare facilities. HBV-related mortality will be estimated in the participating households using the ratio of the number of individuals whose cause of death was identified as chronic liver diseases at year *n* (using mortality data from the Niakhar demographic system) over the average corresponding population at year *n*. Furthermore, economic characteristics (agricultural production, poverty, food insecurity) of the households affected by chronic HBV infection, including current advanced liver disease in at least one household member and recent HBV-related mortality (health shock), will be compared with those of unaffected households. Individual socioeconomic characteristics (economic situation, productivity, income, quality of life) will be compared between those chronically infected and those non-chronically infected. These comparisons will identify direct effects of the health shocks such as decrease in household earnings, as well as intrahousehold coping strategies, including substitution effects in terms of labour market participation.

Public health and economic impacts of chronic HBV infection at the population level

Building on previous studies,^{32–34 40} HBV-related morbidity and mortality and HBV treatment needs will be estimated for the whole population of the Niakhar area, as well as for the whole country. The model parameters will be defined based on the epidemiological data produced by the AmBASS study completed by a literature review for non-available data. At a given time *t*, we will consider the following three main groups of individuals in the population of the area/country depending on HBV infection status: ongoing chronic infection, past infection or vaccination-induced immunity and uninfected susceptible individuals. Once HBV infected, individuals can either spontaneously clear the virus or develop chronic hepatitis B infection that can evolve towards liver fibrosis stages 1–4, cirrhosis and liver cancer potentially leading to death, with different probabilities of transitioning from one state to another depending on whether people receive treatment or not. We will estimate both the public health and economic impacts of several hypotheses on HBV testing and treatment coverage (varying from 0% corresponding to the absence of treatment to 80%). Estimation of treatment needs will take into account the probability to be diagnosed as a chronic HBV carrier, and the probability to follow each of the steps in the HBV treatment and care cascade. Two main scenarios of treatment financing will be considered. In the first scenario, individuals will cover all the costs associated with HBV care (including transport, treatment and examinations). In the second scenario, a third party—which could be the national government or an international donor—will finance a variable share of total costs (subsidies ranging from 0% to 100%). These scenarios will be used to estimate the total cost of HBV care and associated health benefits as well as the financial contributions of the different parties (populations, national government or international assistance), given the number of people that access care.

All analyses will be performed using the SAS V.9.4 for Windows and Stata Stata/SE V.12.1 for Windows.

Patient and public involvement

Patients are not involved in the development of the research questions, the design, recruitment or implementation of this study. Healthcare professionals, public health leaders and representatives of the patients association contributed to the design of the study through a preparatory workshop organised in Dakar in May 2015. They also participated in the implementation of the study as members of the steering committee. Results will be disseminated to patients using posters displayed in all three local healthcare facilities involved in the delivery of test results. Results will be presented to the patients association, healthcare professionals and public health leaders during a workshop in Dakar.

ETHICS AND DISSEMINATION

Ethical considerations

This study respects the ethical principles defined in the current revised version of the Helsinki Declaration (64th World Medical Association's annual Assembly in Fortaleza, Brazil–October 2013). The sponsor and the research teams are committed to conduct this project in compliance with the applicable national and international regulations on ethics and research involving humans currently in force in Senegal and in France.

Information, consent and data confidentiality

All participants enrolled in the study sign two copies of the informed consent form before undertaking any examination associated with the study, and after the trained interviewer explained the objectives, the nature, and the foreseeable constraints and risks of the study. A study-specific anonymous identification number is assigned to each participant, which ensures correspondence between all data sources (consent form, home-based questionnaire, medical information form and biological samples). Face-to-face questionnaires are administered using electronic tablets for immediate data input. All data sent to the research teams are anonymous, and the research teams undertaking analyses will not have access to nominative data. At the end of the study, all study documents (including case report, and information and consent forms) will be stored at the VITROME-IRD facilities in Dakar for 15 years after the end of the study.

Expected benefits and risks for survey participants

The main risk for participants is to learn their HBV status following home-based screening, which may have psychological repercussions given the chronic nature of infection and the necessity of lifelong antiviral treatments. In contrast, the expected benefits of participation in the survey include access to information and counselling on hepatitis B and access to care for chronic HBV carriers. The study participants diagnosed with chronic HBV infection will benefit from a comprehensive medical examination and biological check-up to assess the stage of their liver disease and treatment eligibility. They will then be referred to the Fatick regional hospital for appropriate follow-up and care in accordance with the national and international guidelines.¹² Access to HBV treatment will be possible via the National Viral Hepatitis Programme once decentralisation is effective, with the first year of treatment covered by the study in the meantime. Pregnant women with chronic HBV infection, HBeAg positive and with HBV viral load above 200 000 UI/mL will be prescribed tenofovir from the last trimester of gestation until postpartum week 4,⁶² paid for by the study. Following the National Viral Hepatitis Programme guidelines, individuals diagnosed with advanced liver disease will be referred to hospitals in Dakar.

Expected results and dissemination plan

The survey results will help fill the lack of epidemiological data on chronic HBV infection in the general population in rural Senegal. Results of the AmBASS survey will give a snapshot of the burden and impacts of hepatitis B in a rural area of Senegal, and provide stakeholders with an estimation of HBV treatment needs and the economic feasibility of expanding access to HBV treatment. The reinforcement of local capacities using caregivers training and information/education of the local communities are also among the study's expected results. Those results will be presented during a workshop in Dakar to local community leaders and HCW involved in the research as well as key stakeholders of the fight against HBV in Senegal, including the Saafara patients association, members of the SOSEGH, members of the National Hepatitis Programme, members of the Ministry of Health and Social Action, and members of the Senegalese ethical committee (CNER). They will also be published in international journals and presented in international conferences to help document treatment needs, and fuel the advocacy for decentralised access to HBV care in Senegal.

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Contributors SB and AD are the principal investigators and supervised the study protocol development. MDS, FM and MPC contributed to the design of the research project. MDS conducted the literature review. FM is responsible for the statistical

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