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Original research

The importance of triple panel testing for hepatitis B and the burden of isolated anti-hepatitis B core antibodies within a community sample

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ABSTRACT

Within the United States (US), 2.4 million individuals are living with chronic hepatitis B, but less than 20% are diagnosed. Isolated anti-hepatitis B core (iAHBc) antibodies indicate serology in an individual that is positive for anti-HBc antibodies, while negative for surface antigen (HBsAg) and surface antibodies (anti-HBs). A result of iAHBc could indicate a chronic occult bloodstream infection, necessitating further testing. This study assesses the prevalence and risk factors associated with anti-HBc and iAHBc within community high-risk screening in Greater Philadelphia. Participants (n = 177) were screened for HBsAg, anti-HBs, and anti-HBc during community screening events in 2022. Chi-square tables and Firth logistic regression were used to describe the data and to assess the odds of iAHBc. The findings indicate that there was an iAHBc prevalence of 7.3% (n = 13) within our study. The odds of anti-HBc were increased for immigrants from the Western Pacific (4.5%) and Africa (11.9%). Individuals born in Africa had 7.93 greater odds for iAHBc than those born in the Americas, and these odds are multiplied by 1.01 for every 1-year increase in age. Our data show a high burden of iAHBc within high-risk and often hard-to-reach communities. Triple panel screening should be incorporated into all HBV screening programs, in accordance with current Centers for Disease Control and Prevention (CDC) universal screening recommendations, to ensure a comprehensive picture of the disease burden and reduce the risk of missing people with occult hepatitis B and those at risk for viral reactivation or liver complications.

Chronic hepatitis B affects approximately 296 million people worldwide, with 65% of individuals unaware of their infection.[1,2] Globally, 15–40% of those with hepatitis B (HBV) may develop cirrhosis, hepatocellular carcinoma (HCC), or liver failure, with 820,000 deaths annually due to cirrhosis, HCC, and risks inherent in liver transplantation.[2,3] Within the United States (US), approximately 2.4 million individuals are living with chronic hepatitis B, but less than 20% are estimated to be diagnosed.[4]

Individuals are typically screened for HBsAg and the antibody to the surface antigen (anti-HBs) and occasionally the antibody to the core antigen (anti-HBc).[5] A positive result for the surface antigen indicates a current infection in an individual while a positive surface antibody at 10 IU/mL or above indicates immunity from the infection.[5,6] An isolated anti-hepatitis B core (iAHBc) is defined as a laboratory HBV serology result that is only positive for total anti-HBc, while negative for HBsAg and anti-HBs.[7]

The US Preventive Services Task Force has recommended screening with HBsAg since 2014 for at-risk adolescents and adults.[8] The Centers for Disease Control and Prevention (CDC) aligned with this recommendation until 2023 when they published updated recommendations for universal screening of HBV for adults >18 years of age with the triple panel (HBsAg, anti-HBs, anti-HBc).[9] The American Association for the Study of Liver Diseases (AASLD) recommends serological testing for total anti-HBc for patients living with HIV; about to undergo therapy for hepatitis C; taking anticancer therapy; taking immunosuppressive therapy; receiving renal dialysis; or donating blood or organs.[5]

Not including anti-HBc in HBV screening may lead to challenges in the interpretation of screening results and could miss identifying people with immune control who are at risk for reactivation.[10,11] Between 2001 and 2018, the estimated prevalence of individuals with iAHBc was

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approximately 0.8% or about 2.1 million US adults, with over two-thirds being US born.[12]

iAHBc can occur for several reasons. Most commonly, iAHBc indicates a previous acute infection with waning immune control, as these individuals will not have HBsAg or detectable HBV DNA.[10,11] iAHBc can also indicate a window period during seroconversion for a resolving acute infection, as antibodies are being formed against HBV.[13] With a possible acute infection of HBV, IgM testing may help confirm infection classification. Additionally, iAHBc could result from an occult blood infection (OBI), a state of low-level chronic viremia.[13] iAHBc-positive individuals sometimes have detectable levels of HBV DNA, indicating viral presence and necessitating management and the possibility of anti-retroviral therapy.[13] A negative HBsAg result may be seen due to methylation of the covalently closed circular DNA (cccDNA), which will reduce transcription and lead to undetectable levels of HBsAg.[14] An OBI can also occur due to a mutation in the HBsAg, causing it not to be detected in standard serological studies.[15] The risk of OBI increases in those with risk factors for HBV, including co-infection with hepatitis C virus (HCV) infections and HIV.[16] HCV can inhibit normal HBV DNA replication, while individuals with HIV are at risk of viral reactivation when antiretroviral regimens effective against HBV are stopped. In addition, those with a history of intravenous (IV) drug use, dialysis, HCC, cryptogenic cirrhosis, or a history of a liver transplant are also at risk of OBI.[16]

Significant public health issues associated with HBV include a low rate of diagnosis; limited awareness by those who are infected; low treatment rates; and, critical for this study, surveillance guidelines that often do not incorporate anti-HBc for HBV screening.[4] Spradling et al. (2022) found that 80% of those with iAHBc were not infected with HCV, and 95% were not infected with HIV, both of which are indications for anti-HBc screening.[12] Fortunately, the CDC recently updated HBV screening recommendations with HBV triple panel screening, including anti-HBc.[9] Not including anti-HBc, unfortunately, can result in many individuals with iAHBc being missed, not being treated, and being at risk for reactivation. Reactivation can occur spontaneously but is commonly triggered by immunosuppressive therapies.[17] Reactivation can also cause significant morbidity and mortality but is preventable if at-risk individuals are identified through screening and provided with antiviral prophylaxis if indicated.[17]

iAHBc is an effective predictive marker for OBI and is strongly associated with HCC.[18] Individuals with OBI, additionally, have an increased risk of liver cancer above those who are anti-HBs-positive and anti-HBc-positive, regardless of country of origin.[18] This study aims to describe the burden of iAHBc and OBI among a community-based sample in Greater Philadelphia and emphasizes the importance of screening for the HBV triple panel to ensure comprehensive patient evaluation of HBV infection.

1. Materials and methods

This cross-sectional analysis aims to assess the prevalence and risk factors associated with having iAHBc. Data were obtained for this case-control study from individuals aged 18 or older who were considered high risk for HBV within the Greater Philadelphia area. This study was performed using data collected as a part of a local community-based screening program. The demographic survey analysis methodology was previously validated in HBV community screening events.[19] The screening events in this study targeted communities that are known to have a high burden of HBV infection. Demographic survey contents included questions on age, gender, country of origin, insurance status, provider status, past HBV screening, vaccination, and any family history of HBV or liver cancer. The Heartland IRB approved this study.

1.1. Data collection

Data were collected in the Greater Philadelphia area through community health screening events at churches (4.5%), community centers (20.7%), and health fairs (74.9%) from August to December of 2022. A total of 177 participants were recruited from high-risk communities within Philadelphia. Individuals were excluded if they were under 18 (n = 1) or were missing screening analysis data (n = 6). Free HBV blood testing was offered at the events alongside a demographic survey to assess risk factors for HBV. After obtaining informed consent, survey data were collected in each participant's preferred language with assistance from a translator when necessary. Participants were tested for HBV with a blood draw performed by a licensed phlebotomist and sent to Quest laboratories for analysis to test for HBsAg, anti-HBs, and anti-HBc. Individuals who were screened were mailed a copy of their test results along with a letter explaining test results, and additional resources in their preferred language 2 weeks after the initial test date. HBsAg-positive individuals or those needing vaccination received phone calls and text messages for follow-up care by a linkage to care coordinator.

1.2. Data cleaning

Data were cleaned and organized before analysis. The data regarding country of origin were collapsed into groups based on the World Health Organization (WHO)-defined regions: Africa, the Americas, Southeast Asia, the Mediterranean, Europe, and Western Pacific. Education level was collapsed into 3 groups: less than high school, high school graduate or GED, and some higher education or technical school to simplify statistical analysis.

1.3. Data analysis

Analysis of the collected data was performed with SPSS version 28.0.0. A descriptive analysis was performed using large category contingency tables against the survey responses and screening results. The following variables were used as the predictors of a binary outcome (having or not having iAHBc) using a Firth logistic regression model: region of origin, age, insurance status, if a provider was seen in the past year, if a participant has a primary care provider, gender, education, vaccination, family history of hepatitis B and family history of liver cancer. Firth logistic regression model was used to provide a better analysis of rare events by reducing the small sample bias in the maximum likelihood estimates of coefficients.[12]

2. Results

The sampled population identified as first-generation individuals who emigrated from Africa (55.9%, n = 99), mainly from the Western African countries of Mali (17.5%, n = 31), Burkina Faso (8.5%, n = 15), and Liberia (6.8%, n = 12). Other participants identified as first-generation from the Western Pacific (26.6%, n = 47), with those from China (12.4%, n = 22) and Korea (11.3%, n = 20) comprising the most considerable portion. The remaining participants were those born in the US (16.4%, n = 29) (Table 1). The average age of the sample was around 50 years old but was not normally distributed according to a Shapiro-Wilk test of normality (0.981, p = 0.016).

Of the population sampled, 58.2% (n = 103) showed immunity with anti-HBs above 10 IU/mL, with 21.4% (n = 38) being immunized with negative anti-HBc and 36.7% (n = 65) having a prior acute infection with positive anti-HBc (exposed and persistent HBV cccDNA in their liver). A total of 50.8% (n = 90) of the sampled population had anti-HBc, with iAHBc (7.3% n = 13) or current infection (6.8% n = 12) defined as HBsAg-positive.

Within the African immigrant population, the prevalence of anti-HBc was 65.6% (n = 64); within the Western-Pacific immigrant population, the prevalence was 46.8% (n = 22). Those who immigrated from Africa had 12.1 (95% CI: 3.9, 37.4) times greater odds of screening positive for anti-HBc, while those who immigrated from the Western Pacific had 5.5

Table 1
Prevalence of demographic factors by serology category.

Descriptive Variable (Chi-Square, df, p-value)	At risk	% At Risk	Immune	% Immune	Resolved infection	% Resolved Infection	IAHBc	% IAHBc	Current infection	% Current Infection	Total	% Total
Totals (n = 177)	49	27.7	38	21.40	65	36.70	13	7.30	12	6.80	177	100.0
Mean Age (95% CI)	48.08	(42.74, 53.42)	43.42	(37.95, 48.90)	55.6	(52.43, 58.77)	58.54	(46.99, 70.09)	50.5	(42.00, 59.00)	50.87	(48.45, 53.29)
Categorical Age (61.86, 24, <0.001)												
18 to 24	9	18.4	4	10.5	0	0.0	0	0.0	1	8.3	14	7.9
25 to 34	4	8.2	11	57.9	3	4.6	1	7.7	0	0.0	19	10.7
35 to 44	9	18.4	7	18.4	12	18.5	3	23.1	1	8.3	32	18.1
45 to 54	7	14.3	7	18.4	11	16.9	0	0.0	6	60.0	31	17.5
55 to 64	9	18.4	3	7.9	22	33.8	5	38.5	3	25.0	42	23.7
65 to 74	6	12.2	5	13.2	12	18.5	0	0.0	1	8.3	24	13.6
75+	5	10.2	1	2.6	5	7.7	4	30.8	0	0.0	15	8.5
Sex (1.90, 4, 0.755)												
Female	32	65.3	23	60.5	38	58.5	6	46.2	8	66.7	107	60.5
Male	17	34.7	15	39.5	27	41.5	7	53.8	4	33.3	70	39.5
Race (15.40, 8, 0.052)												
Asian/Pacific Islander	11	22.4	19	50.0	18	27.7	2	15.4	1	8.3	51	28.8
Hispanic	1	2.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5
Black	37	75.5	19	50.0	47	72.3	11	84.6	11	91.7	125	70.6
Education (34.05, 20, 0.026)												
Less than High School	13	26.5	6	15.8	14	21.5	3	23.1	5	41.7	41	23.2
High School Diploma or GED	13	26.5	8	21.1	26	40.0	6	46.2	5	41.7	58	32.8
Technical/ Vocational Training	1	2.0	0	0.0	3	4.6	1	7.7	0	0.0	5	28.8
Some College	4	8.2	1	2.6	3	4.6	0	0.0	0	0.0	8	4.5
College Degree	15	30.6	13	34.2	13	20.0	2	15.4	2	16.7	45	25.4
Graduate Degree	1	2.0	10	26.3	5	7.7	0	0.0	0	0.0	16	9
Missing	2	4.1	0	0.0	1	1.5	1	7.7	0	0.0	4	2.3
Vaccinated for HBV (5.87, 8, 0.55)												
Yes	5	10.2	8	21.1	8	12.3	2	15.4	2	16.7	25	14.1
No	37	75.5	23	60.5	42	64.6	9	69.2	10	83.3	121	68.4
Unsure	7	14.3	7	18.4	15	23.1	2	15.4	0	0.0	31	17.5
Health Insurance (6.00, 4, 0.199)												
Yes	34	69.4	22	57.9	33	50.8	9	69.2	5	41.7	103	58.2
No	15	30.6	16	42.1	32	49.2	4	30.8	7	58.3	74	41.8
Regular HCP (0.17, 4, 0.996)												
Yes	31	63.3	23	60.5	39	60.0	8	61.5	7	58.3	108	61
No	18	36.7	15	39.5	26	40.0	5	38.5	5	41.7	69	39
Saw HCP in the Past Year (2.56, 4, 0.634)												
Yes	38	77.6	28	73.7	42	64.6	9	69.2	9	75.0	126	71.2
No	11	22.4	10	26.3	23	35.4	4	30.8	3	25.0	51	28.8
Year arrived in the US (42.23, 20, 0.003)												
Missing or Does Not Apply	23	46.9	6	15.8	7	10.8	1	7.7	0	0.0	37	20.9
Before 1990	3	6.1	4	10.5	7	10.8	2	15.4	0	0.0	16	9
1990–1999	0	0.0	4	10.5	9	13.8	0	0.0	1	8.3	14	7.9
2000–2009	6	12.2	6	18.8	15	23.1	5	38.5	5	41.7	37	20.9
2010–2019	11	22.4	11	28.9	17	26.2	4	30.8	4	33.3	47	26.6
After 2020	6	12.2	7	18.4	10	15.4	1	7.7	2	16.7	26	14.7
Tested for HBV in the Past (5.25, 8, 0.73)												
Yes	13	26.5	12	31.6	19	29.2	2	15.4	5	41.7	51	28.8
No	27	55.1	19	50.0	33	50.8	7	53.8	7	58.3	93	52.5
Don't Know	9	18.4	7	18.4	13	20.0	4	30.8	0	0.0	33	18.6
Past Hepatitis B Results[a] (20.16, 12, 0.064)												
Positive	0	0.0	0	0.0	1	1.9	0	0.0	2	16.7	3	2.1
Negative	10	25.0	9	29.0	16	30.8	1	11.1	1	8.3	37	25.7
Don't Know Result	3	7.5	3	9.7	2	3.8	1	11.1	2	16.7	11	7.6
Never Done	27	67.5	19	61.3	33	63.5	7	77.8	7	58.3	93	64.6
Family Members with HBV (7.56, 8, 0.477)												
Yes	1	2.1	5	13.2	4	6.2	1	7.7	0	0.0	11	6.3
No	42	87.5	28	73.7	54	83.1	10	76.9	9	75.0	143	81.3
Not Sure	5	10.4	5	13.2	7	10.8	2	15.4	3	25.0	22	12.5
Which Family Member has HBV (19.15, 16, 0.261)												
Spouse	0	0.0	1	20.0	2	50.0	0	0.0	0	0.0	3	25
Sibling	1	100.0	1	20.0	1	25.0	0	0.0	0	0.0	3	25
Child	0	0.0	0	0.0	0	0.0	0	0.0	1	100.0	1	8.3
Aunt/Uncle	0	0.0	1	20.0	0	0.0	0	0.0	0	0.0	1	8.3
Nephew/Niece	0	0.0	2	40.0	1	25.0	1	100.0	0	0.0	4	33.3
Household HBV (13.54, 8, 0.095)												

(*continued on next page*)

Table 1 (*continued*)

Descriptive Variable (Chi-Square, df, p-value)	At risk	% At Risk	Immune	% Immune	Resolved infection	% Resolved Infection	IAHBc	% IAHBc	Current infection	% Current Infection	Total	% Total
Yes	1	2.0	2	5.4	0	0.0	0	0.0	2	18.2	5	2.9
No	44	89.8	33	89.2	57	91.9	11	84.6	8	72.7	153	89
Don't Know	4	8.2	2	5.4	5	8.1	2	15.4	1	9.1	14	8.1
Family Members with HCC (12.23, 12, 0.428)												
Yes	4	8.2	2	5.3	0	0.0	1	7.7	1	8.3	8	4.5
No	37	75.5	31	81.6	55	84.6	10	76.9	9	75.0	142	80.2
Don't Know	3	6.1	1	2.6	2	3.1	2	15.4	0	0.0	8	4.5
Did Not Answer	5	10.2	4	10.5	8	12.3	0	0.0	2	16.7	19	10.7
Region of Origin (55.50, 12, <0.001)												
Country of Origin (135.85, 96, 0.005)												
Western Pacific (WHO Region)	7	14.3	18	47.4	19	29.2	2	15.4	1	8.3	47	26.6
Korea	4	8.2	7	18.4	7	10.8	2	15.4	0	0.0	20	11.3
China	3	6.1	8	21.1	10	15.4	0	0.0	1	8.3	22	12.4
Philippines	0	0.0	1	2.6	0	0.0	0	0.0	0	0.0	1	0.6
Taiwan	0	0.0	1	2.6	2	3.1	0	0.0	0	0.0	3	1.7
Vietnam	0	0.0	1	2.6	0	0.0	0	0.0	0	0.0	1	0.6
Africa (WHO Region)	19	38.8	16	42.1	42	64.6	11	84.6	11	91.7	99	55.9
Africa (not specified)	0	0.0	0	0.0	1	1.5	0	0.0	0	0.0	1	0.6
Sierra Leone	0	0.0	0	0.0	1	1.5	0	0.0	0	0.0	1	0.6
Nigeria	2	0.0	1	2.6	0	0.0	0	0.0	0	1.0	2	1.1
Benin	0	0.0	1	2.6	1	1.5	0	0.0	0	0.0	2	1.1
Mauritania	2	4.1	0	0.0	1	1.5	0	0.0	0	0.0	3	1.7
Guinea	1	2.0	1	2.6	5	7.7	1	7.7	3	25.0	11	6.2
Senegal	0	0.0	0	0.0	0	0.0	1	7.7	0	0.0	1	0.6
Ivory Coast	0	0.0	1	2.6	1	1.5	1	7.7	1	8.3	4	2.3
Mali	6	12.2	6	15.8	16	24.6	1	7.7	2	16.7	31	17.5
Burkina Faso	2	4.1	2	5.3	7	10.8	2	15.4	2	16.7	15	8.5
Niger	0	0.0	0	0.0	1	1.5	0	0.0	0	0.0	1	0.6
Liberia	0	0.0	1	2.6	6	9.2	3	23.1	2	16.7	12	6.8
Ethiopia	4	8.2	2	5.3	2	3.1	2	15.4	0	0.0	10	5.6
Togo	1	2.0	0	0.0	0	0.0	0	0.0	1	8.3	2	1.1
Kenya	0	0.0	1	2.6	0	0.0	0	0.0	0	0.0	1	0.6
Cameroon	1	2.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.6
Democratic Republic of the Congo	1	2.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.6
Southeast Asia (WHO Region)	1	2.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.6
Pakistan	1	2.0	0	0.0	0	0.0	0	0.0	0	0.0	1	0.6
Americas (WHO Region)	22	44.9	4	10.5	4	6.2	0	0.0	0	0.0	30	16.9
United States	22	44.9	4	10.5	3	4.6	0	0.0	0	0.0	29	16.4
Grenada	0	0.0	0	0.0	1	1.5	0	0.0	0	0.0	1	0.6
Primary Language (68.26, 44, 0.011)												
Cantonese	0	0.0	0	0.0	1	1.5	0	0.0	0	0.0	1	0.6
Mandarin	0	0.0	3	8.3	5	7.7	0	0.0	0	0.0	8	4.6
Chinese (dialect not specified)	3	6.3	4	0.0	6	9.2	0	0.0	0	0.0	13	7.5
Korean	3	6.3	6	16.7	5	7.7	0	0.0	0	0.0	14	8.1
French	8	16.7	5	13.9	22	33.8	5	38.5	5	45.5	45	26
Mandingo	3	6.3	3	8.3	5	7.7	1	7.7	1	9.1	13	7.5
Bambara	0	0.0	0	0.0	0	0.0	0	0.0	1	9.1	1	0.6
Soninke	1	2.1	1	2.8	0	0.0	0	0.0	1	9.1	3	1.7
Fulani	2	4.2	0	0.0	2	3.1	0	0.0	1	9.1	5	2.9
Amharic	4	8.3	2	5.6	2	3.1	2	15.4	0	0.0	10	5.8
Kru	0	0.0	0	0.0	0	0.0	1	7.7	0	0.0	1	0.6
English	24	50.0	12	33.3	17	26.2	4	30.8	2	18.2	59	34.1
Pregnancy Status (Female only)												
Yes	1	3.1	0	0.0	2	5.1	0	0.0	0	0.0	3	2.8
No	30	93.8	20	87.0	37	94.9	6	100.0	8	100.0	101	93.5
Don't Know	1	3.1	0	0.0	0	0.0	0	0.0	0	0.0	1	0.9
Missing	0	0.0	3	13.0	0	0.0	0	0.0	0	0.0	3	2.8

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCP, health care provider; IAHBc, Isolated anti-hepatitis B core; WHO, World Health Organization.

[a] n = 144 omitted those who don't know if they tested before.

(95% CI: 1.7, 18.2) times greater odds of screening positive for anti-HBc compared to those born in the Americas (Table 2). Expectedly, individuals born in the Americas (the US and Grenada) had a considerably lower prevalence of anti-HBc (13.3%, n = 4). Most anti-HBc cases in Philadelphia are seen in individuals who immigrated from Mali, followed by China, Liberia, Burkina Faso, Guinea, and Korea. Individuals from Mali, Liberia, Burkina Faso, and Guinea had more positive than negative cases of anti-HBc.

Within the sampled population, 58% (n = 103) had health insurance, 14.1% (n = 25) reported being vaccinated, 61% (n = 108) had a primary

Table 2
Odds of core antibodies by demographic factors.

Categories	Chi-square (df, p-value)	Positive Screening Result	% Positive	Negative Screening Result	% Negative	Odds Ratio (95% CI)
Age	25.47(6, <0.001)					
18-24		1	1.1	13	14.8	Ref.
25-34		4	4.4	15	17.0	3.47 (0.34, 35.06)
35-44		16	17.6	16	18.2	13.00 (1.52, 111.46)
45-54		18	19.8	14	15.9	16.71 (1.95, 143.57)
55-64		30	33.0	12	13.6	32.50 (3.82, 276.59)
65-74		13	14.3	12	13.6	14.08 (1.59, 124.59
75+		9	9.9	6	6.8	19.50 (1.99, 190.88)
Sex	0.55 (1, 0.460)				0.0	
Male		38	41.8	32	39.1	1.255 (0.69, 2.29)
Female		53	58.2	56	60.9	Ref.
WHO Region	25.39 (2, <0.001)				0.0	
Country of Origin	50.82 (24, 0.001)				0.0	
Western Pacific		22	24.3	26	29.9	5.50 (1.66, 18.19)
Korea		9	9.9	11	12.5	
China		11	12.1	12	13.6	
Vietnam		0	0.0	1	1.1	
Philippines		0	0.0	1	1.1	
Taiwan		2	2.2	1	1.1	
Africa		65	71.4	35	40.2	12.07 (3.90, 37.37)
Africa (not specified)		1	1.1	0	0.0	
Sierra Leone		1	1.1	0	0.0	
Nigeria		0	0.0	2	2.3	
Benin		1	1.1	1	1.1	
Mauritania		1	2.2	2	2.3	
Guinea		9	9.9	2	2.3	
Senegal		1	1.1	0	0.0	
Ivory Coast		3	3.3	1	1.1	
Mali		19	20.9	12	13.6	
Burkina Faso		11	12.1	4	4.5	
Niger		1	1.1	0	0.0	
Liberia		11	12.1	1	1.1	
Cameroon		0	0.0	1	1.1	
Ethiopia		4	4.4	6	6.8	
Togo		1	1.1	1	1.1	
Democratic Republic of the Congo		0	0.0	1	1.1	
Kenya		0	0.0	1	1.1	
Americas		4	4.4	26	29.9	Ref.
Grenada		1	1.1	0	0.0	
United States		3	3.3	26	29.5	
Southeast Asia[a]					0.0	
Pakistan		0	0.0	1	1.1	
Education	8.92, 2, 0.012				0.0	
Less than High School		22	24.7	19	22.1	1.84 (0.85, 3.97)
GED or High School Graduate		38	42.7	21	24.4	2.87 (1.42, 5.82)
Some Higher Education or Technical School		29	32.6	46	53.5	Ref.
Vaccinated	0.048, 1, 0.826				0.0	
Yes		12	16.4	13	17.8	0.91 (0.38, 2.15)
No		61	83.6	60	82.2	Ref.

[a] Region was excluded due to low counts (n = 1).

care physician, 71.2% (n = 126) said that they saw a primary care physician in the past year, and 28.8% (n = 51) stated that they were tested for HBV before. Of those tested, 5.9% (n = 3) self-reported a prior HBV infection (72.5%; n = 37), and 21.6% reported that they do not remember their past results. Interestingly, 60.5% (n = 23) of those with results indicating prior immunization (anti-HBs-positive, anti-HBc-negative, and HBsAg-negative) reported not being immunized, and 10.2% (n = 2) of those screened for having iAHBc reported being vaccinated for HBV. Most participants with iAHBc had health insurance (69.4%, n = 34), had a primary care provider (61.5%, n = 8), and saw a health care provider in the past year (77.6%, n = 9). Additionally, no one screened as iAHBc reported a positive prior test (Table 2).

Firth logistic regression was used to explore the adjusted odds of having iAHBc across the various predictors (Table 3). There was a slight positive relationship with age. With every 1-year increase in age, the odds of screening positive for iAHBc increased by about 3% (95% CI: 0.996, 1.071). Individuals 75 and older had 11.3 (95% CI: 1.04, 1562.4) times greater odds compared to those aged 18–24, though the uncertainty in this estimate is quite large. There was also a slight relation between having iAHBc and reporting being unsure if a family member has HCC compared to those who answered not having a family member with HCC. There was also a slight association between individuals who immigrated from Africa with 7.93 greater odds of screening for iAHBc than individuals reporting the Americas as their region of origin (95% CI: 0.98, 1028.64). However, the odds of screening for iAHBc in individuals who immigrated from the Western Pacific were no different compared to those from the Americas. Individuals from Southeast Asia were excluded from this calculation due to the low sample size (n = 1). The rest of the age categories have the same odds of having iAHBc as the 18–24 years group. The odds of having iAHBc was not significantly different based on an individual's sex, race, level of education, or family history of HBV. There is no difference in the odds of having iAHBc based on whether an individual was vaccinated, has health insurance, has a regular primary care provider, or if they saw a health care provider in the past year (Table 4). With immunized individuals set as a reference, there was still no difference in odds of having iAHBc seen based on

Table 3
Odds of IAHBc against not having IAHBc.

Categories	Odds Ratio (95% CI)
Age	1.03 (1.00, 1.07)
Family History	
Yes	1.82 (0.18, 9.04)
No	Ref.
Don't Know	1.55 (0.28, 5.88)
Insurance	
Yes	1.57 (0.51, 5.57)
No	Ref.
Region of Birth	
Western Pacific	3.35 (0.26, 468.72)
Africa	7.92 (0.98, 1028.65)
America	Ref
Gender	
Female	0.54 (0.17, 1.64)
Male	Ref.
Vaccination	
Yes	1.26 (0.23, 4.83)
No	Ref.
Primary Care Provider	
Yes	0.99 (0.33, 3.23)
No	Ref.
Seen by Provider in Past Year	
Yes	0.85 (0.28, 3.04)
No	Ref.
Family History of HCC	
Yes	2.53 (0.25, 13.36)
No	Ref.
Don't Know	4.86 (0.81, 22.11)
Age Group	
18-24	Ref.
25-34	2.35 (0.12, 353.54)
35-44	3.44 (0.30, 474.38)
45-54	0.46 (0.00, 87.01)
55-64	4.25 (0.44, 571.92)
65-74	0.59 (0.00, 112.06)
75+	11.35 (1.04, 1562.43)
Year Arrived in US	
Before 1990	Ref.
1990–1999	0.20 (0.01, 4.54)
2000–2009	0.98 (0.21, 5.98)
2010–2019	0.60 (0.12, 3.74)
2020+	0.34 (0.03, 2.82)
HBV in the Household	
Yes	1.13 (0.01, 11.02)
No	Ref.
Education Level	
Less than High School	Ref.
High School Graduate or GED	1.36 (0.36, 6.03)
Some Higher Education, College, or Technical School	0.54 (0.11, 2.65)

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IAHBc, Isolated anti-hepatitis B core.
Note: Maximum iterations = 250; maximum beta step size = 5; maximum step halving = 5; Log-Likelihood Convergence Criterion = 0.00001; Beta Change Convergence Criterion = 0.00001.

Table 4
Odds of IAHBc against immunized serology.

Categories	Odds Ratio (95% CI)
Family History of HBV	
Yes	0.74 (0.07, 4.37)
No	Ref.
Don't Know	1.23 (0.20, 6.10)
Family History of HCC	
Yes	1.80 (0.15, 15.18)
No	Ref.
Don't Know	5.00 (0.60, 59.44)
Primary Care Provider	
Yes	1.02 (0.29, 3.73)
No	Ref.
Insurance	
Yes	1.55 (0.44, 6.09)
No	Ref.
Seen by Provider in the Past Year	
Yes	0.78 (0.21, 3.14)
No	Ref.
Vaccination	
Yes	1.37 (0.30, 8.31)
No	Ref.
Tested for HBV in the Past	
Yes	0.52 (0.09, 2.36)
No	Ref.
Year Arrived in the US	
Before 1990	Ref.
1990–1999	0.20 (0.01, 5.45)
2000–2009	1.52 (0.22, 10.38)
2010–2019	0.70 (0.11, 4.67)
2020+	0.36 (0.03, 3.72)
Region of Birth	
Western Pacific	1.22 (0.05, 29.96)
Africa	6.27 (0.31, 128.00)
Americas	Ref.

HBV, hepatitis B virus; HCC, hepatocellular carcinoma; IAHBc, Isolated anti-hepatitis B core.
Note: Maximum iterations = 250; maximum beta step size = 5; maximum step halving = 5; Log-Likelihood Convergence Criterion = 0.00001; Beta Change Convergence Criterion = 0.000.

vaccination status, health insurance, having a regular primary care provider, and seeing a health care provider in the past year.

3. Discussion

This study assessed the prevalence of anti-HBc, specifically iAHBc, among high-risk individuals who immigrated to the Greater Philadelphia area through a cross-sectional analysis. Many community-based HBV screening campaigns only test HBsAg and anti-HBs, which could result in many people with prior exposure to HBV or individuals with underlying infections being missed, especially among older individuals and the first-generation African and Western-Pacific populations. Our results support the need to include anti-HBc in HBV screening, as recommended in the updated CDC guidelines.

By including anti-HBc as an indicator of exposure, these data also indicate higher rates of HBV exposure within the African immigrant community, especially among those from West Africa. Philadelphia's African community has increased odds of having iAHBc compared to individuals born in America. Additional HCV and HIV testing are needed in individuals screened as iAHBc, due to the increased risk associated with OBI. Resource-limited communities in Africa are not routinely screened for HBV or are screened with rapid testing or point-of-care HBsAg kits.[20] However, point-of-care kits are generally not as accurate as laboratory-based tests and do not test for those with a past infection, those at risk of reactivation, and those with HIV, HCV, or HBsAg mutation who are at risk of an OBI.[20]

Exposure to HBV is known to be higher in the Chinese and Korean immigrant communities.[4,21] However, our data imply that those from the Western Pacific do not have increased odds of having an iAHBc above those born in America and subsequently less risk of OBI compared to those from Africa. Such a decreased risk of OBI would be expected to decrease the risk of HCC, yet the incidence of HCC among Asian Americans was 10.6 per 100,000 individuals in 2020, higher than compared to non-Hispanic Black individuals at 9.5 per 100,000 individuals. Future work is needed to understand the risk of HCC in OBI by geographic region.[25]

Having a primary care physician and health insurance is not associated with a decreased odds of iAHBc in this high-risk population. The protective effect of health insurance on health outcomes and improvement in health care access is well established.[22,23] This finding might suggest that individuals are being missed within the clinical setting due to inadequate screening. However, this finding could also be due to wide confidence intervals in the data, as reporting a prior vaccination history was also not protective for screening as having iAHBc. Additionally, most of those who had an immunized serology reported not being

vaccinated, but this may be due to failure to recall if they were vaccinated or to understand the question.

This study is the first to assess the prevalence and odds of iAHBc within Philadelphia among individuals at high risk for HBV. A prior study in 2020 of high-risk individuals in Philadelphia showed the prevalence of the protective anti-HBs to be 59% and the prevalence of the HBsAg, indicating an active infection, to be 7.9%.[19] The prior study's prevalence remains consistent with our findings of 58% with anti-HBs. The prevalence of those currently infected with HBV is again similar at 6.8%. Notably, more first-generation adults from Africa were sampled compared to the prior study, but the proportion of those with HBsAg and anti-HBs are still similar.

Our study's findings for the prevalence of iAHBc within a high-risk group were expectedly higher than the estimated national average of 0.8%, as it includes individuals at low risk for HBV.[13] A community-based study on iAHBc in a high-risk population in New Jersey studied the high-risk population of Korean-Americans who were tested between 2009 and 2015 and showed results consistent with the findings in this study.[24] Our findings similarly indicate an increase in the prevalence of iAHBc with age, showing that for every 1-year increase in age, the odds of having iAHBc increase by 1.03. Additionally, the prevalence of iAHBc in the prior study was reported as 10.9%, only slightly higher than our population prevalence of 7%.[24] However, within Pennsylvania's first-generation Korean-American population strata, the prevalence of iAHBc is 15%. This difference could be due to the low sample counts or the prior study having both first-generation and second-generation Korean-Americans. These comparisons may indicate that our findings have external validity despite the low sample size of those with iAHBc.

These results also support the most recent screening recommendations published by the CDC on March 10th, 2023.[9] The recommendations are for all adults to be screened once per lifetime and all pregnant persons during each pregnancy, preferably in the first trimester, with the triple panel of HBsAg, anti-HBs, and total anti-HBc during the initial screening.[9] The new recommendations may help increase access to screening within underserved communities and can help identify persons with an active or occult infection to help facilitate appropriate linkage to care.

4. Limitations

This study faced important limitations. This study is not generalizable to the population of Philadelphia as a whole, as the study was limited to adults considered at high risk for HBV infection. Primarily, iAHBc is a rare event with a prevalence of 7% (n = 13) in this population (n = 177). The rarity of the serological result causes wide confidence intervals due to the sample size. Additional studies with a larger sample size are necessary to increase the validity of these findings. In particular, the study's sample size of the Southeast Asian community was much smaller compared to the African and Western-Pacific communities; an acute HBV infection cannot be ruled out in those with iAHBc since this could be due to the window period, underestimating those with an acute infection and overestimating those with an OBI. Further testing would be needed to verify the proportion of OBI, as HBV DNA testing was not performed in this study population.

Additionally, in some instances, a translator was us, which could have resulted in underreporting of risk factors. The data analysis using the Firth logistic regression has limitations, notably, the large confidence intervals associated with the odds ratios. While we do not think this impacted the findings, it is important to note. These data may have been skewed due to prior knowledge of one's results using Pearson's Chi-square, although some expected counts were less than 5 (20.156, 12 degrees of freedom, p = 0.064) due to the low sample size and rarity of iAHBc. Those with a prior negative result most often had a prior infection that has since resolved. However, this finding does not significantly impact our conclusion as most participants reported that they were not screened before or did not know if they were screened before.

Declaration of competing interest

Catherine Freeland: Hepatitis B Foundation receives research and program grants from Gilead Sciences, GSK, BMS, Antios and VBI Vaccines. Catherine Freeland has served on patient advisory committees for GSK and Gilead Sciences.

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Chari Cohen: Hepatitis B Foundation receives research and program grants from Gilead Sciences, GSK, BMS, Antios and VBI Vaccines. Chari Cohen serves on patient advisory committees for GSK and Gilead Sciences.

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Data availability

Data will be made available on request.

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Appendix A. Supplementary data

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