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Surprisingly Low Levels of Measles Immunity in Persons With HIV: A Seroprevalence Survey in a United States HIV Clinic

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Background. Measles outbreaks have become increasingly common due to deteriorating vaccination rates, fluctuating herd immunity, and varying antibody decline. Limited knowledge exists regarding prevalence and risk factors associated with measles seronegativity among persons with HIV (PWH).

Methods. This was a cross-sectional study conducted at an academic HIV clinic in Omaha, Nebraska. Participants were screened for the presence of measles IgG antibody. Demographic and clinical information was obtained through electronic medical record review. Simple and multivariable logistic regressions were performed to identify risk factors for measles seronegativity.

Results. Three hundred fifty-one participants were enrolled, with a measles seroprevalence rate of 70.3%. The mean age (range) was 48 (20–74) years, 77% were male, and 53% were Caucasian. The mean CD4 nadir (range) was 334 (1–1675) cells/mm³. At the time of testing, 86% and 87% of the seronegative and seropositive participants had an HIV RNA <50 copies/mL, respectively. Younger age was significantly associated with measles seronegativity ($P = .003$), as was birth year after 1957 ($P = .021$). Prior history of measles infection was associated with seropositivity ($P = .011$). All other risk factors evaluated, including written documentation of adequate vaccination, were not associated with seronegativity.

Conclusions. Our study demonstrates a measles seroprevalence rate that is remarkably lower than previously reported in PWH (92%), and, more importantly, is considerably lower than the rate needed to maintain herd immunity (95%). With higher than expected seronegativity and absence of notable risk factors aside from age, our findings support expanded measles immunity screening for PWH who are at risk of measles exposure.

Keywords. immunity; HIV; measles; seroprevalence.

Measles outbreaks continue to occur year after year in the United States, even after the disease was declared eliminated in the year 2000. In 2019, there were 1282 cases in 31 different states, the highest number of cases seen since 1992 [1]. This resurgence has also been demonstrated in numerous countries throughout the world, leading to increased endemic outbreaks and elevated risk for travel-related infections [2]. This is due in large part to overall declining vaccination rates related to rising spread of vaccine safety misinformation coupled with concerns for vaccination failure [3–5]. Transmission in the general population within the United States has been primarily linked to failure to vaccinate rather than failure of the vaccine

itself. Failure to vaccinate often leads to small unvaccinated subgroups, which can cause fluctuating herd immunity within the total population. It is not surprising that failure to vaccinate is a problem given that multiple international organizations such as the World Health Organization (WHO) and Strategic Advisory Group of Experts (SAGE) note vaccine hesitancy to be on the rise [6–8]. The Centers for Disease Control and Prevention (CDC) currently recommends a 2-dose measles, mumps, and rubella (MMR) vaccine beginning around 1 year of age. The MMR vaccine became widely available in 1963 with widespread infection rates before vaccine availability, so birth before 1957 is thought to provide presumptive immunity [9].

The increases in incidence of measles in the United States and globally are a serious public health concern due to the disease's highly contagious droplet spread and potentially severe complications. Typically, those affected by the disease will develop fever, rash, and upper respiratory infectious symptoms, but some develop severe respiratory and neurologic complications leading to death [9, 10]. Due to immune dysfunction, persons with HIV (PWH) who contract measles can present atypically and experience higher rates of measles-associated morbidity and mortality [11–13]. Furthermore, studies have

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shown decreased immunogenicity of measles-containing vaccines among children and adults with HIV as well as waning seropositivity over time despite antiretroviral therapy (ART) [10, 14–16].

Given the highly infectious nature of measles, population immunity rates of at least 93%–95% are needed to achieve herd immunity [17]. Studies in the general population have demonstrated immunity rates around 92% [18]. A recent systematic review reported a measles seroprevalence of 92% among adolescents and adults with HIV, but the US-based studies included in the review were either very small, published before combination ART (CART), or retrospective in nature (and thus included serology data collected before CART), so little is known about current seroprevalence rates among PWH in the United States [19].

With fluctuating herd immunity, variations in antibody decline, and decreasing vaccination rates leading to increased incidence of measles in the United States, PWH are at risk for contracting measles due to ongoing outbreaks. Given this as well as the potential for severe complications associated with measles infection in PWH, further studies are needed in this population. The goal of this study was to determine the current seroprevalence of and risk factors for measles seronegativity among PWH.

METHODS

Study Population

This was a cross-sectional study conducted at an academic HIV clinic in Omaha, Nebraska. All adult patients with HIV (≥ 19 years of age) presenting to the clinic from November 2019 through January 2020 were invited to participate. Patients were eligible to participate if they were willing to undergo serologic testing at the time of their appointment or if they had previously been tested for measles immunity within the last 6 months.

Patient Consent Statement

This study was approved by the Institutional Review Board of the University of Nebraska Medical Center (IRB #556-19-EP). All participants provided written informed consent.

Data Collection

Participants who enrolled had serology collected at the time of their regularly scheduled clinic visit. Measles immunity was determined by use of a multiplex flow immunoassay to detect measles IgG. An antibody index level of ≤ 1.0 indicated no significant level of detectable measles antibody and was considered seronegative. An antibody index of ≥ 1.1 was considered seropositive, which was concordant with manufacturer-established interpretive criteria.

Demographic (age, sex) and clinical information (body mass index [BMI], most recent HIV RNA and CD4 counts, CD4 nadir, route of HIV transmission, history of opportunistic infections, history of malignancy, and history of immunosuppressant

medications) was obtained through electronic medical record (EMR) review. Participants also completed a questionnaire at the time of their visit in order to document their country of origin, race/ethnicity, and recall of prior measles vaccination and/or infection. If available, immunization records were obtained through review of either the Nebraska or Iowa statewide immunization database as well as through EMR review. Study data were collected and managed using REDCap electronic data capture tools hosted at our facility.

Statistical Analysis

Simple (single-predictor) and multivariable logistic regression models were used to identify risk factors among sociodemographic and clinical characteristics associated with the outcome measles seronegativity. All measures with simple logistic regression model *P* values $< .20$ were included in the multivariable model. Statistical analyses were completed using STATA, version 16.1 (College Station, TX, USA).

RESULTS

A total of 351 participants were enrolled in this study. The overall study population characteristics are shown in Table 1. The mean age (range) was 48 (20–74) years, with 12% born before 1957. Participants were 77% male and 53% Caucasian. The majority (81%) were born within the United States. The mean CD4 nadir (range) was 334 (1–1675) cells/mm³. At the time of testing, 86% and 87% of the seronegative and seropositive participants had an HIV RNA < 50 copies/mL, respectively. The most common route of HIV transmission was via sex (52%), followed by unknown exposure (41%) and sharing needles/syringes (5%).

Overall, the measles seroprevalence rate in our study population was low at 70.3%. Younger age was significantly associated with measles seronegativity (median age, 45 years seronegative vs 49 years seropositive; odds ratio [OR], 0.97; *P* = .003). There was a significantly lower proportion of participants born before 1957 in the seronegative group (6% vs 15%; OR, 0.51; *P* = .021). However, there were only 43 total participants included in the study born before 1957, with 6 (14%) found to be seronegative. A history of prior measles infection was also associated with seroprevalence, with 24% of the seropositive participants reporting prior infection compared with only 12% of the seronegative participants (*P* = .011). No other risk factors assessed including sex, race/ethnicity, body mass index, country of origin, CD4 nadir < 200 , history of opportunistic infections, history of malignancy, route of HIV transmission, duration of HIV disease, and use of immunosuppressant medications were found to be associated with seronegativity. Patient recall of measles immunization was higher than the actual documentation of vaccination among both groups, but self-reported vaccination history was not associated with immunity (61% seronegative vs 64% seropositive; *P* = .408). Nearly one-third of participants

Table 1. Overall Patient Demographic and Clinical Characteristics

Characteristic		n = 351, No. (%), Mean ± SD, or Mean (Range)
Age, y		48 (20–74)
Born before 1957		43 (12)
Sex	Male	271 (77)
	Female	80 (23)
Race/ethnicity	Non-Hispanic White	185 (53)
	Non-Hispanic Black	98 (28)
	Other	68 (19)
Country of origin	United States	283 (81)
	Mexico	21 (6)
	Other	47 (13)
Body mass index, kg/m ²	Underweight (9–18)	5 (1)
	Normal weight (19–24)	81 (23)
	Overweight (25–29)	127 (36)
	Obese (30–39)	114 (32)
	Extremely obese (40–65)	24 (7)
HIV disease duration, y		14 ± 9
Most recent HIV RNA, copies/mL	<50	303 (86)
	50–199	16 (5)
	≥200	32 (9)
Most recent CD4, cells/μL	0–199	16 (5)
	≥200	335 (95)
CD4 nadir <200		226 (64)
History of opportunistic infections		74 (21)
History of malignancy		13 (4)
History of immunosuppressant medications		20 (6)
Route of HIV transmission	Sex	184 (52)
	Sharing needles/syringes	18 (5)
	Mother to child	4 (1)
	Blood transfusions	1 (0)
	Unknown	144 (41)
Written documentation of prior measles immunization		43 (13)
Verbal report of prior measles immunization		220 (63)
Prior measles infection		
	Documented	2 (1)
	Verbal only	69 (20)
	No history	273 (78)
	Unsure	7 (2)

in each group denied any history of measles immunization at any time (30% in the seronegative group and 31% in the seropositive group), and the remainder did not know (10% vs 6%, respectively). Overall, written documentation of measles immunization was poor (Table 2). Following multivariable adjustment, younger age was still trending toward, but was not quite a significant predictor of, seronegativity (OR, 0.98; $P = .083$) (Table 3). However, in a sensitivity analysis that also controlled for race, sex, and BMI, younger age was again a significant predictor of seronegativity (OR, 0.98; $P = .040$).

DISCUSSION

Our cross-sectional study of a large group of PWH demonstrated a very low seroprevalence rate of 70.3%, which is much

lower than the rates reported in most previously published studies, with the exception of 2 very small studies from 2008 and 2011 that reported seroprevalence rates of 67.5% and 67% in 21 and 16 PWH, respectively [20, 21].

Measles remains one of the leading causes of vaccine-preventable illnesses, with increasing resurgence seen worldwide [22]. Seroprevalence data can aid in measles eradication as they identify immunity gaps and allow for public health officials to target these gaps with additional efforts [23]. It should be noted, however, that seroprevalence studies are resource-intensive and difficult to make nationally representative. Several prevalence studies in the early 1990s reported measles seropositivity in adult PWH from 90% to 99% [16, 24–26]. The average age in these studies was 35 years, which is younger than the average age in our study, and there are some data to support waning

Table 2. Simple Logistic Regression Models for Seronegativity

Characteristic	Seronegative (n = 104), No. (%) or Mean ± SD	Seropositive (n = 247), No. (%) or Mean ± SD	PValue	Odds Ratio (95% CI)
Age, y	45 ± 12	49 ± 12	.003	0.97 (0.95–0.99)
Born before 1957	6 (6)	37 (15)	.021	0.35 (0.14–0.85)
Female sex	21 (20)	59 (24)	.452	0.81 (0.46–1.41)
BMI >25 kg/m ²	79 (76)	186 (75)	.896	1.04 (0.61–1.77)
Race				
Non-Hispanic White	61 (59)	124 (50)	Ref.	Ref.
Non-Hispanic Black	23 (22)	75 (30)	.098	0.62 (0.36–1.09)
Other	20 (19)	48 (19)	.591	0.85 (0.46–1.55)
Country of origin outside US	19 (18)	49 (20)	.735	0.90 (0.50–1.63)
CD4 nadir <200	42 (40)	83 (34)	.227	1.34 (0.83–2.15)
History of opportunistic infections	26 (25)	48 (19)	.245	1.38 (0.80–2.38)
History of malignancy	6 (6)	7 (3)	.193	2.10 (0.69–6.41)
Immunosuppressant medications	8 (8)	12 (5)	.300	1.63 (0.65–4.12)
Duration of HIV, y	13 ± 9	14 ± 9	.546	0.99 (0.97–1.02)
HIV transmission via ^a				
Sex	56 (54)	128 (52)	Ref.	Ref.
Needle/syringe sharing	5 (5)	13 (5)	.815	0.88 (0.30–2.59)
Mother to child	3 (3)	1 (0)	.099	6.86 (0.70–67.59)
Unknown	40 (38)	104 (42)	.600	0.88 (0.54–1.42)
Documented measles immunization	19 (18)	27 (11)	.066	1.82 (0.96–3.45)
Patient recall of measles immunization	63 (61)	157 (64)	.598	0.88 (0.55–1.41)
Prior measles infection (documented or verbal)	12 (12)	59 (24)	.011	0.42 (0.21–0.82)

Abbreviation: BMI, body mass index.

^aReceiving blood transfusion not included as only 1 patient reported that method.

immunity over time, which is important to consider given an increasing prevalence of aging PWH [27]. Furthermore, in several reports, participants who were born before 1957 made up a significant proportion of the study population (43%–66%), which could account for the overall higher seroprevalence seen [24–26]. A larger and more current study from New York City reported a measles seroprevalence rate of 85% but was limited by its retrospective design [28]. The authors reported on serology collected between 1998 and 2011, so these results do not reflect current rates of immunity and thus do not account for waning immunity over time.

Both the CDC and state health departments recommend measles vaccination for PWH who do not have evidence of measles immunity or severe immunosuppression [9, 29].

Table 3. Multiple Logistic Regression Model for Seronegativity (n = 344^a)

	PValue	Odds Ratio (95% CI)
Age	.083	0.98 (0.96–1.00)
History of malignancy	.125	2.46 (0.78–7.80)
Documented measles immunization	.318	1.40 (0.72–2.72)
Prior measles infection (documented or verbal)	.127	0.57 (0.27–1.18)

^aSeven persons who were “unsure” of prior measles infection were counted as missing and removed through listwise deletion; “Born before 1957” was not included in the multivariable model as “Age” is strongly correlated with this indicator variable.

Although the WHO recommendations support the administration of an additional dose of measles-containing vaccines for children with HIV on ART following immune reconstitution, they do not recommend the routine administration of an additional dose of a measles-containing vaccine in adults with HIV. However, the data to support the WHO recommendation in adults with HIV are based on a limited number of studies in both adolescents and adults from varying time periods from around the world that show no difference in seroprevalence rates among adolescents and adults with and without HIV [19]. Measles serology is not routinely collected in PWH, so knowing which patients are at risk for seronegativity and thus stand to benefit from vaccination could help providers apply the guidelines to their practices. Response to measles vaccination is not completely known in PWH, as outlined by Loevinsohn et al. In 6 studies comprised of 109 measles-seronegative patients, measles immunogenicity postvaccination ranged from 0% to 56%. The studies were dated from 1993 to 2016, with a trend toward higher immunogenicity rates in studies conducted after the introduction of combination ART [19]. Additionally, Fieberkohn and colleagues found that a third dose of MMR vaccine did not result in a significant improvement in seroprevalence in an HIV-negative population. Finally, although some data suggest that waning immunity contributes to reduced vaccine

efficacy [30], most people with waning antibodies have an anamnestic response to repeat vaccination, which suggests ongoing immunity [31]. In summary, more data are needed to determine whether waning immunity in PWH is associated with increased susceptibility to infection and whether repeat vaccination in seronegative PWH would result in increased seroprevalence. As demonstrated in previous studies, we found younger age, particularly birth after 1957, to be associated with measles seronegativity [25, 26, 28]. It is important to note that not all persons born before 1957 demonstrated immunity, however. CDC guidelines currently report birth before 1957 as acceptable presumptive evidence of measles immunity, but our findings suggest that this may not hold true in all PWH given that 14% of patients born after 1957 did not have immunity. Previously reported risk factors for seronegativity included history of oral hairy leukoplakia [25, 26] and a longer duration of HIV diagnosis [28], but these risk factors were not reproducible in our study.

Although prior history of measles infection was associated with seropositivity, there was no correlation between written documentation of vaccination and immunity. Written documentation of measles immunization and patient recall of either infection or vaccination were poor in both the seropositive and seronegative groups. With poor reporting of vaccination status, it is difficult to determine if seronegative status relates to failure to vaccinate, vaccine failure, or waning immunity over time, which can limit risk factor analysis. There has been documented decline in measles antibodies postvaccination of about 3% per year in the general population, with 1 study noting variations of up to a 9.7% decline annually [27]. Vaccination failure is also an increasing concern, as HIV alone can be a cause of waning immunity postvaccination. Vaccination failure has been documented in children with HIV, leaving them more vulnerable as they age [32–34]. One study from Zambia compared HIV-infected youth with non-HIV-infected youth and found that at least 25% of HIV-infected youth were seronegative, significantly more than only 8% in non-HIV-infected youth [34].

Further prospective, multicenter seroprevalence data would be beneficial as our study is limited to a single center in Omaha, Nebraska, and thus limits the generalizability to larger institutions or states with more diverse patient populations. Long-term studies looking at response to re-vaccination and measles seroprevalence over time would also be beneficial.

In summary, with rising measles outbreaks year after year, identifying immunity gaps is now imperative to measles elimination. Our study demonstrates a measles seroprevalence rate of 70.3%, which is remarkably lower than the rate reported in prior studies of both the general population and PWH (92%), and, more importantly, is significantly lower than the rate needed to maintain herd immunity (95%). With higher than expected seronegativity and absence of notable risk factors aside from age, it is difficult to predict which PWH would benefit

from measles seroprevalence surveillance. Our findings thus support expanded measles immunity screening for all PWH who are at risk of measles exposure.

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