BIOTHERAPEUTICS QUARTERLY

Diagnostic and Pharmaceutical News for You and Your Medical Practice

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TYENNE® (tocilizumab-aazg) Injection

Date of Approval: March 5, 2024
Company: Fresenius Kabi USA, LLC
Treatment for: Rheumatoid Arthritis, Giant Cell Arteritis, Polyarticular Juvenile Idiopathic Arthritis, Juvenile Idiopathic Arthritis
Tyenne (tocilizumab-aazg) is an interleukin-6 (IL-6) receptor antagonist biosimilar to Actemra used for treatment of rheumatoid arthritis, giant cell arteritis, polyarticular juvenile idiopathic arthritis, and systemic juvenile idiopathic arthritis

TEVIMBRA® (tislelizumab-jsgr) Injection

Date of Approval: March 13, 2024
Company: BeiGene, Ltd.
Treatment for: Esophageal Carcinoma
Tevimbra (tislelizumab-jsgr) is a humanized immunoglobulin G4 (IgG4) anti-programmed cell death protein 1 (PD-1) monoclonal antibody indicated for the treatment of adult patients with unresectable or metastatic esophageal squamous cell carcinoma after prior systemic chemotherapy that did not include a PD-(L)1 inhibitor.

REZDIFFRA™ (resmetirom) Tablets

Date of Approval: March 14, 2024
Company: Madrigal Pharmaceuticals, Inc.
Treatment for: Nonalcoholic Steatohepatitis
Rezdiffra (resmetirom) is a thyroid hormone receptor-beta (THR-beta) agonist indicated in conjunction with diet and exercise for the treatment of adults with noncirrhotic nonalcoholic steatohepatitis (NASH) with moderate to advanced liver fibrosis (consistent with stages F2 to F3 fibrosis).

TRYVIO™ (aprocitentan) Tablets

Date of Approval: March 19, 2024
Company: Idorsia, Ltd.
Treatment for: High Blood Pressure
Tryvio (aprocitentan) is an endothelin receptor antagonist (ERA) for the combination treatment of hypertension that is not adequately controlled with other drugs.

WINREVAIR™ (sotatercept) for Injection

Date of Approval: March 26, 2024
Company: Merck
Treatment for: Pulmonary Arterial Hypertension
Winrevair (sotatercept) is an activin signaling inhibitor used for the treatment of adults with pulmonary arterial hypertension.

National Institutes of Health
Turning Discovery Into Health

March 6, 2024

Altered brain connections in youth with ADHD

At a Glance

- Youth with ADHD have elevated brain activity connecting the frontal cortex with the information processing centers deep in the brain.
- Understanding the brain regions involved in ADHD symptoms could help point toward directions for new approaches to treatment.

People living with attention-deficit/hyperactivity disorder, or ADHD, can struggle with focus and self-control. The condition's symptoms may interfere with daily functioning in both children and adults. ADHD can make it hard for kids to succeed in school, and for adults to thrive in the workforce and in personal relationships.

ADHD is a brain condition that requires a professional diagnosis to help guide treatment. Drugs that increase the levels of certain chemicals in the brain help some people with ADHD. But they don't work for everyone, and can have unacceptable side effects.

To design better treatments for ADHD, scientists need to understand more about how the brain works in people with the condition. Researchers have wondered if differences in the neural connections between the brain's frontal cortex, which sits in the front of the brain, and regions deep within the brain, called subcortical regions, may underlie some symptoms of ADHD. The frontal cortex plays a role in attention and control of unwanted behaviors. The subcortical regions are involved in learning, movement, reward, and emotion.

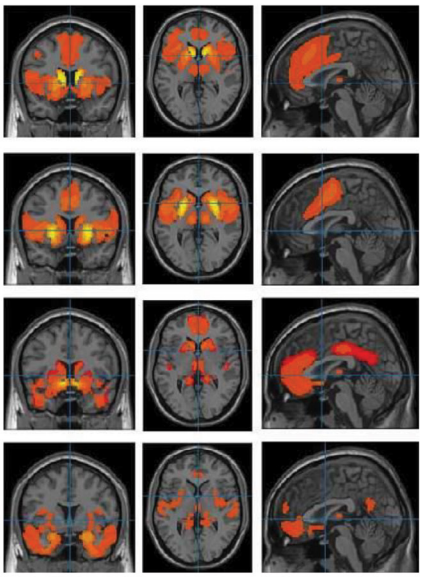

Image highlighting the parts of brain regions that were found to be highly connected with the frontal cortex in youths with ADHD. Regions shown, from top row to bottom, are the caudate, putamen, nucleus accumbens, and amygdala.*Norman et al, American Journal of Psychiatry*

Previous studies used a type of brain imaging called functional magnetic resonance imaging (fMRI) to look for such connections in children with symptoms of ADHD. fMRI can measure changes in brain activity in real time. But these studies have been small and returned conflicting results.

An NIH research team re-analyzed fMRI images collected in six previous studies. Altogether, those studies had obtained fMRI images from more than 1,696 youths with ADHD, aged 6 to 18, as well as almost 7,000 without the condition. In addition to using a large number of images, the researchers strictly defined the brain areas being measured. This allowed for more accurate comparisons between individual fMRI scans. Results were published March 13, 2024, in the *American Journal of Psychiatry*.

The team found that the brains of youth with ADHD had more activity between several subcortical regions and the frontal cortex than those in youth without the condition. The brains of youth with ADHD also showed greater connection between the frontal cortex and part of the brain called the amygdala. The amygdala helps process emotions and had been suspected to play a role in ADHD.

These results were seen regardless of children's sex, age, race or ethnicity, socioeconomic status, or estimated intelligence. The differences in brain connectivity also didn't appear to be affected by the presence or absence of other mental health problems, such as anxiety or depression. However, the differences found by the researchers were small and likely capture only part of the processes involved in ADHD.

"The findings from this study help further our understanding of the brain processes contributing to ADHD symptoms. Such understanding is a first step in thinking of new ways to help those who find the symptoms cause difficulties in day-to-day life," says Dr. Philip Shaw, who helped lead the study. "But these brain changes are only part of the story. ADHD is a complex condition, and many other changes in brain connectivity will play a role."

Related Links

- Children's Sleep Linked to Brain Development
- Brain Differences in Youth Linked to Increased Waist Size
- Dopamine Affects How Brain Decides Whether a Goal is Worth the Effort
- An Expanded Map of the Human Brain
- Mapping Brain Circuits Involved in Attention
- Focusing on ADHD: Attention Deficit Hyperactivity Disorder
- Keeping Up in School? Identifying Learning Problems
- Attention-Deficit/Hyperactivity Disorder (ADHD)
- Adolescent Brain Cognitive Development (ABCD) Study(link is external)

References: Subcortico-Cortical Dysconnectivity in ADHD: A Voxel-Wise Mega-Analysis Across Multiple Cohorts. Norman LJ, Sudre G, Price J, Shaw P. *Am J Psychiatry*. 2024 Mar 13:appiajp20230026. doi: 10.1176/appi.ajp.20230026. Online ahead of print. PMID: 38476041.

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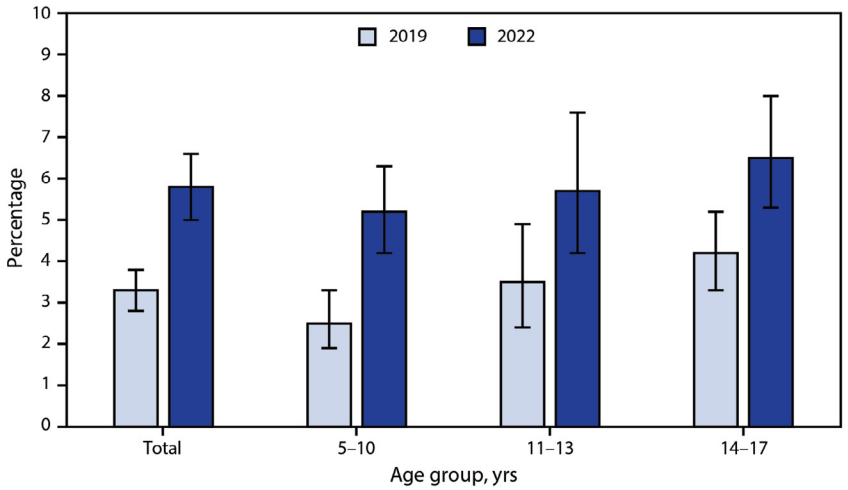
Source: https://www.nih.gov/news-events/nih-research-matters/altered-brain-connections-youth-adhd

QuickStats

FROM THE NATIONAL CENTER FOR HEALTH STATISTICS

Percentage* of Children and Adolescents Aged 5–17 Years Who Had Chronic School Absenteeism Due to Illness, Injury, or Disability During the Past 12 Months,† by Age Group and Year — National Health Interview Survey,§ United States, 2019 and 2022



* With 95% CIs indicated by error bars.
† Based on a response of ≥15 days to the survey question, "During the past 12 months, about how many days of school did (Sample Child) miss school because they had an illness, injury, or disability?"
§ Estimates are based on household interviews of a sample of the civilian, noninstitutionalized U.S. population.

The percentage of children and adolescents aged 5–17 years who had chronic school absenteeism during the past 12 months was higher in 2022 (5.8%) than in 2019 (3.3%). From 2019 to 2022, the percentage of children who had chronic school absenteeism increased for each age group. The percentage of children who had chronic school absenteeism increased with increasing age in 2019; no significant differences by age occurred in 2022.

Source: National Health Interview Survey, 2019 and 2022. https://www.cdc.gov/nchs/nhis.htm

Reported by: Lindsey I. Black, MPH, lblack1@cdc.gov; Nazik Elgaddal, MS.

Tuberculosis — United States, 2023

Paula M. Williams, DrPH[1,2]; Robert H. Pratt[2]; William L. Walker, DVM, PhD[2]; Sandy F. Price[2]; Rebekah J. Stewart, MSN, MPH[2]; Pei-Jean I. Feng, MPH[2]

Abstract

After 27 years of declining U.S. tuberculosis (TB) case counts, the number of TB cases declined considerably in 2020, coinciding with the COVID-19 pandemic. For this analysis, TB case counts were obtained from the National TB Surveillance System. U.S. Census Bureau population estimates were used to calculate rates overall, by jurisdiction, birth origin, race and ethnicity, and age group. Since 2020, TB case counts and rates have increased each year. During 2023, a total of 9,615 TB cases were provisionally reported by the 50 U.S. states and the District of Columbia (DC), representing an increase of 1,295 cases (16%) as compared with 2022. The rate in 2023 (2.9 per 100,000 persons) also increased compared with that in 2022 (2.5). Forty states and DC reported increases in 2023 in both case counts and rates. National case counts increased among all age groups and among both U.S.-born and non-U.S.–born persons. Although TB incidence in the United States is among the lowest in the world and most U.S. residents are at minimal risk, TB continues to cause substantial global morbidity and mortality. This postpandemic increase in U.S. cases highlights the importance of continuing to engage communities with higher TB rates and their medical providers in TB elimination efforts and strengthening the capacity in public health programs to carry out critical disease control and prevention strategies.

Introduction

Despite being both preventable and curable, tuberculosis (TB) remains one of the world's leading infectious disease killers (*1*). The United States has one of the lowest TB rates globally (*1*) and has a goal of eliminating TB (elimination defined as less than one case per 1 million population) by 2035 (*2*). During 1995–2014, health departments and CDC TB control efforts prevented as many as 300,000 persons from developing TB disease and averted up to $14.5 billion in costs (*3*). After 27 years of declining U.S. TB cases, the number of TB cases declined considerably in 2020 to 7,171, coinciding with the COVID-19 pandemic (*4*); however, TB case counts and rates increased in 2021 and 2022. This report provides provisional TB surveillance data for 2023 in the United States.

Methods

Tuberculosis Case Counts and Incidence

The 50 U.S. states and DC report each TB case that meets the Council of State and Territorial Epidemiologists' surveillance case definition* to CDC's National Tuberculosis Surveillance System (NTSS).† National case counts, along with counts by jurisdiction, birth origin,§ race and ethnicity, and age group, were obtained from NTSS. National and jurisdictional TB rates per 100,000 persons were calculated using the midyear U.S. Census Bureau population estimates,¶ and rates by birth origin (i.e., U.S.-born versus non-U.S.–born), race and ethnicity, and age group were calculated using the Current Population Survey** midyear estimates. Percentage changes in TB case counts and rates for 2023 compared with 2022 were calculated overall and by jurisdiction and demographic characteristics. Annual number and rate of TB cases are reported by birth origin for 2013 through 2023. SAS software (version 9.4; SAS Institute) was used for all analyses. This activity was reviewed by CDC, deemed not research, and was conducted consistent with applicable federal law and CDC policy.††

Population Characteristics

Self-reported race and ethnicity were categorized according to federal guidelines.§§ Persons of Hispanic or Latino (Hispanic) origin might be of any race but are categorized as Hispanic; all racial groups are non-Hispanic. Non-Hispanic persons who reported more than one race were categorized as "multiple race."

* https://ndc.services.cdc.gov/case-definitions/tuberculosis-2009
† This report is limited to National Tuberculosis Surveillance System data verified as of February 17, 2024. Updated data will be available in CDC's annual TB surveillance report later in 2024.
§ Persons born in the United States or certain U.S. territories or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.
¶ Short-term projections from the monthly population estimates by age, sex, and race and ethnicity were used for the 2023 population. Vintage 2022 Estimates were used for 2023 and 2022, and Vintage 2010 Estimates were used for 2013–2019. https://www.census.gov/programs-surveys/popest/data/tables.html
** https://www.census.gov/programs-surveys/cps.html
†† 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.
§§ https://www.census.gov/topics/population/race/about.html

Results

Tuberculosis Incidence by Jurisdiction

In 2023, the 50 U.S. states and DC provisionally reported 9,615 TB cases, an increase of 1,295 cases (16%) compared with the 8,320 cases reported in 2022, an 8% increase compared with the 2019 prepandemic case count (8,895), and the highest number of cases reported since 2013 (9,556) (Figure). Overall, the U.S. TB rate increased by 15%, from 2.5 per 100,000 persons in 2022 to 2.9 in 2023 (Table 1). Forty states and DC reported an increase in both case counts and rates compared with those in 2022. As in 2022, California reported the highest number of cases in 2023 (2,113), and Alaska reported the highest rate (10.6). Eight states and DC reported TB rates higher than the national rate of 2.9 per 100,000 in 2023.

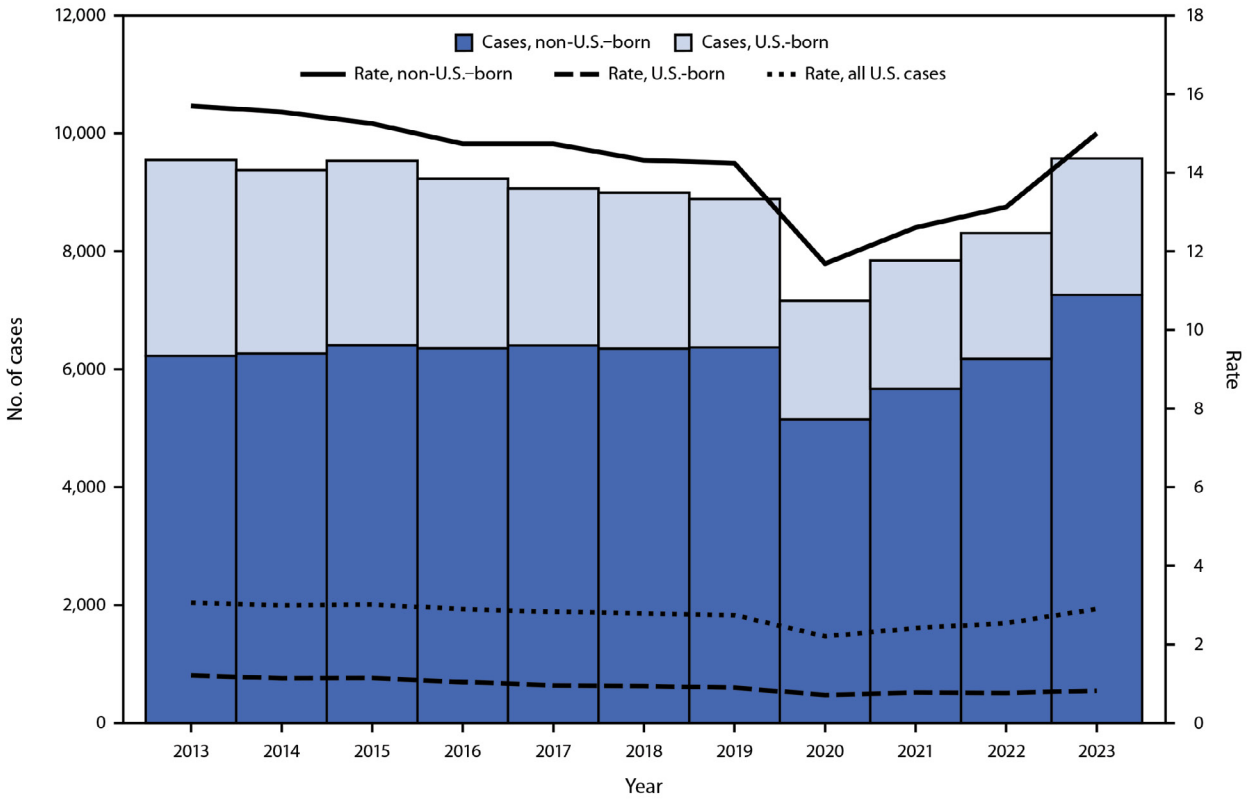
Tuberculosis Incidence by Demographic Characteristics

In 2023, among 9,573 TB cases in persons for whom birth origin was known, 7,259 (76%) occurred among non-U.S.–born persons, an 18% increase compared with the 6,177 such cases reported in 2022 (Table 2). The number of cases in U.S.-born persons in 2023 increased 9%, from 2,131 in 2022 to 2,314.¶¶ The rate increased among non-U.S.–born persons from 13.1 in 2022 to 15.0 in 2023, and the rate among U.S.-born persons remained at 0.8 cases per 100,000 persons.

Among U.S.-born persons with TB, 33% (753) identified as Black or African American (Black), 27% (614) as Hispanic, 26% (591) as White, 6% (130) as Asian, 5% (106) as American

¶¶ Proportions using birth origin are calculated excluding 12 cases in 2022 and 42 cases in 2023 for which birth origin was missing or unknown.

FIGURE. Annual number* and rate† of cases of tuberculosis disease, by birth origin§ — United States, 2013–2023



* Case counts are based on data from the National Tuberculosis Surveillance System as of February 17, 2024.
† Annual tuberculosis rate is calculated as cases per 100,000 persons. The Current Population Survey provides the population denominators used to calculate tuberculosis rate according to birth origin. https://www.census.gov/programs-surveys/cps.html (Accessed February 2, 2024).
§ Persons born in the United States or certain U.S. territories or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born. Persons for whom birth origin was unknown (range = 7 [2013] to 42 [2023]) are not included in this figure.

TABLE 1. Tuberculosis case counts and rate, by jurisdiction — United States, 2022 and 2023

Jurisdiction	No. of cases*		% Change 2022 to 2023§	TB rate†		% Change 2022 to 2023§
	2022	2023		2022	2023	
All	**8,320**	**9,615**	16	**2.5**	**2.9**	15
Alabama	65	92	42	1.3	1.8	41
Alaska	95	78	−18	13	10.6	−18
Arizona	154	202	31	2.1	2.7	30
Arkansas	68	83	22	2.2	2.7	21
California	1,842	2,113	15	4.7	5.4	15
Colorado	57	89	56	1.0	1.5	55
Connecticut	67	66	−1	1.9	1.8	−2
Delaware	13	21	62	1.3	2.0	60
District of Columbia	15	26	73	2.2	3.8	71
Florida	535	624	17	2.4	2.8	15
Georgia	261	248	−5	2.4	2.2	−6
Hawaii	100	116	16	6.9	8.1	16
Idaho	11	15	36	0.6	0.8	35
Illinois	298	353	18	2.4	2.8	19
Indiana	99	130	31	1.4	1.9	31
Iowa	60	67	12	1.9	2.1	11
Kansas	52	46	−12	1.8	1.6	−12
Kentucky	70	75	7	1.6	1.7	7
Louisiana	95	97	2	2.1	2.1	2
Maine	17	26	53	1.2	1.9	52
Maryland	157	198	26	2.5	3.2	26
Massachusetts	154	224	45	2.2	3.2	45
Michigan	120	149	24	1.2	1.5	24
Minnesota	132	160	21	2.3	2.8	21
Mississippi	53	41	−23	1.8	1.4	−23
Missouri	71	72	1	1.1	1.2	1
Montana	6	8	33	0.5	0.7	32
Nebraska	29	33	14	1.5	1.7	13
Nevada	62	86	39	2.0	2.7	38
New Hampshire	11	14	27	0.8	1.0	27
New Jersey	289	330	14	3.1	3.6	14
New Mexico	30	41	37	1.4	1.9	37
New York	709	894	26	3.6	4.6	27
North Carolina	164	215	31	1.5	2.0	29
North Dakota	10	9	−10	1.3	1.1	−11
Ohio	146	193	32	1.2	1.6	32
Oklahoma	77	66	−14	1.9	1.6	−15
Oregon	73	78	7	1.7	1.8	7
Pennsylvania	173	216	25	1.3	1.7	25
Rhode Island	17	27	59	1.6	2.5	59
South Carolina	101	90	−11	1.9	1.7	−12
South Dakota	10	14	40	1.1	1.5	39
Tennessee	106	118	11	1.5	1.7	10
Texas	1,100	1,235	12	3.7	4.0	11
Utah	33	34	3	1.0	1.0	2
Vermont	3	3	0	0.5	0.5	0
Virginia	195	207	6	2.2	2.4	6
Washington	251	222	−12	3.2	2.8	−12
West Virginia	11	15	36	0.6	0.8	37
Wisconsin	52	54	4	0.9	0.9	3
Wyoming	1	2	100	0.2	0.3	99

* Case counts are based on data reported to the National Tuberculosis Surveillance System as of February 17, 2024.
† Annual tuberculosis rate is calculated as cases per 100,000 persons using midyear population estimates from the U.S. Census Bureau. Short-term projections from the monthly population estimates by age, sex, and race and ethnicity were used for the 2023 population. Vintage 2022 estimates were used for 2022 and 2023. https://www.census.gov/programs-surveys/popest/data/tables.html
§ Percentage change in rate was calculated with unrounded numbers.

TABLE 2. Characteristics of persons with tuberculosis — United States, 2022 and 2023

Characteristic	No. of cases* (%)		% Change 2022 to 2023§	TB rate†		% Change 2022 to 2023§
	2022	2023		2022	2023	
Overall	**8,320**	**9,615**	**16**	**2.5**	**2.9**	**15**
Age group,¶ yrs						
0–4	199 (2)	233 (2)	17	1.1	1.3	17
5–14	163 (2)	231 (2)	42	0.4	0.6	45
15–24	844 (10)	1,017 (11)	21	2.0	2.3	16
25–44	2,450 (29)	3,001 (31)	22	2.8	3.4	21
45–64	2,416 (29)	2,597 (27)	7	2.9	3.2	9
≥65	2,248 (27)	2,530 (26)	13	4.0	4.3	9
Race and ethnicity						
U.S.-born,††,§§**	2,131 (26)	2,314 (24)	9	0.8	0.8	8
American Indian or Alaska Native	113 (5)	106 (5)	−6	4.5	4.1	−9
Asian	142 (7)	130 (6)	−8	1.7	1.5	−12
Black or African American	672 (32)	753 (33)	12	1.9	2.1	12
Native Hawaiian or other Pacific Islander	51 (2)	62 (3)	22	6.4	7.7	20
White	569 (27)	591 (26)	4	0.3	0.3	4
Hispanic or Latino	542 (25)	614 (27)	13	1.3	1.5	11
Multiple races	20 (1)	18 (1)	−10	0.3	0.2	−14
Non-U.S.–born,§§,¶¶**	6,177 (74)	7,259 (76)	18	13.1	15.0	14
American Indian or Alaska Native***	0 (—)	6 (1)	—	0.0	12.3	—
Asian	2,739 (44)	2,804 (39)	2	22.9	22.5	−2
Black or African American	650 (11)	922 (13)	42	14.2	18.2	28
Native Hawaiian or other Pacific Islander	105 (2)	115 (2)	10	28.4	36.6	29
White	274 (4)	300 (4)	9	3.4	3.7	10
Hispanic or Latino	2,278 (37)	2,876 (40)	26	10.5	12.9	23
Multiple races	68 (1)	64 (1)	−6	28.3	25.8	−9

Abbreviation: TB = tuberculosis.

* Case counts are based on data reported to the National Tuberculosis Surveillance System as of February 17, 2024.

† Annual tuberculosis rate is calculated as cases per 100,000 persons using midyear population estimates from the U.S. Census Bureau. Short-term projections from the monthly population estimates by age, sex, and race and ethnicity were used for the 2023 population. Vintage 2022 estimates were used for 2022 and 2023. https://www.census.gov/programs-surveys/popest/data/tables.html

§ Percentage change in rate was calculated with unrounded numbers.

¶ Age was missing or unknown for zero cases in 2022 and six cases in 2023.

** Persons born in the United States or certain U.S. territories or elsewhere to at least one U.S. citizen parent are categorized as U.S.-born. All other persons are categorized as non-U.S.–born.

†† Birth origin was missing or unknown for 12 cases in 2022 and 42 cases in 2023.

§§ Race and ethnicity was missing or unknown for 22 cases in 2022 and 40 cases in 2023 among U.S.-born persons.

¶¶ Race and ethnicity was missing or unknown for 63 cases in 2022 and 172 cases in 2023 among non-U.S.–born persons.

*** No TB cases reported among American Indian or Alaska Native persons in 2022.

Indian or Alaska Native, 3% (62) as Native Hawaiian or other Pacific Islander, and 1% (18) as multiple race. Among U.S.-born persons, the rate of TB in 2023 compared with 2022 increased 20% (11 cases) among Native Hawaiian or other Pacific Islander, 12% (81 cases) among Black, 11% (72 cases) among Hispanic, and 4% (22 cases) among White persons, and the rate declined 9% (–7 cases) among American Indian or Alaska Native, and 12% (–12 cases) among Asian persons. Among non-U.S.–born persons with TB, 40% (2,876) identified as Hispanic, 39% (2,804) as Asian, 13% (922) as Black, 4% (300) as White, 2% (115) as Native Hawaiian or other Pacific Islander, 1% (64) as multiple race, and 0.1% (six) as American Indian or Alaska Native persons. Among non-U.S.–born persons, the TB rate in 2023 compared with 2022 increased 29% (10 cases) among Native Hawaiian or other Pacific Islander, 28% (272 cases) among Black, 23% (598 cases) among Hispanic, and 10% (26) among White persons, among non-U.S.–born Asian persons, the rate declined 2% (65 cases).***

TB incidence increased in every age group in 2023 compared with 2022, with the largest relative increase among children aged 5–14 years (68 cases, corresponding to a 42% increase in case count and a 45% increase in rate). Among the 83% (8,013) of persons with TB in 2023 for whom HIV status was known, 5% were coinfected with TB and HIV.

Discussion

Provisional national surveillance data show that TB case counts and rates have increased since the COVID-19 pandemic, returning to the number of cases last observed in 2013 (*4*). Increases occurred in every age group and all except

*** Percentage change is calculated from unrounded numbers. For demographic groups with small populations (e.g., non-U.S.–born American Indian or Alaska Native), changes in rates should be interpreted cautiously because of the increased volatility of these rates.

10 U.S. states. Case counts increased among both U.S.-born and non-U.S.–born persons, with the most substantial increase, 18%, among non-U.S.–born persons (1,082 cases).

The United States has one of the lowest TB rates in the world (*1*) and most U.S. residents are at minimal risk for TB (*2,4*). The overall epidemiology of TB continues to reflect persistent disparities by birth origin, and race and ethnicity in the United States. TB rates in 2023 were highest among non-U.S.–born persons which is consistent with prepandemic trends. Among U.S.-born persons, rates remained <1.0 overall but were highest among those who identified as Native Hawaiian or other Pacific Islander, American Indian or Alaska Native, or Black.

Approximately 85% of TB cases in the United States are attributed to reactivation of latent TB infection (LTBI) rather than recent transmission (*2,4*). Therefore, sustained transmission of TB in the United States leading to outbreaks is uncommon. Essential TB elimination activities include TB testing among populations at risk and treating persons with LTBI or TB disease. To prevent transmission and reduce morbidity, TB disease must be detected quickly; effective treatment must be initiated promptly; and all exposed persons identified, evaluated, and treated if infected (*5*). This approach led to a 66% reduction in TB cases and 73% reduction in the TB rate in the United States in the first 25 years of implementation (*4*).

TB prevention and control interventions are primarily conducted by staff members in state and local public health programs. The decades-long downward trend in TB in the United States and the high TB disease treatment completion rates (*4*) underscore the success of these TB programs. However, during the COVID-19 pandemic, TB programs were severely taxed with many staff members and activities diverted to the COVID-19 response (*6*). Timely diagnosis and treatment of TB disease also suffered because of pandemic-related disruptions in health care access and health care workers focusing on identifying persons with COVID-19, who often have symptoms similar to those of pulmonary TB (*7*). These factors, along with changes in migration volume (*8*), probably contributed to the decrease in the number of cases observed in 2020, and to the subsequent rise in case counts and rates since 2020. Identification of TB cases possibly increased after the pandemic because of renewed attention to infectious diseases other than COVID-19.

The number of persons who received a new TB diagnosis has also risen globally. In 2022, the World Health Organization reported a second consecutive year of increasing TB case counts, with the global estimate of TB cases equaling that of 2016 (*1*). TB is not the only preventable communicable disease resurging after the COVID-19 pandemic. For example, influenza (*9*) and measles (*10*) have also experienced postpandemic surges. Setbacks to TB elimination in the United States illustrate the power of pandemics and other large-scale crises to have long-lasting effects on public health, a phenomenon also observed at the onset of the HIV epidemic when the number of TB cases increased after 3 decades of decline (*4*). Renewed progress toward TB elimination will require strengthened capacity of public health programs to carry out critical TB control and prevention strategies and engagement of providers and affected communities in TB elimination efforts. In addition, because most TB cases in the United States occur among non-U.S.–born persons, collaboration of public health entities in the United States with international partners is important to reduce TB morbidity globally.

Summary

What is already known about this topic?

For years, the United States has had one of the lowest tuberculosis (TB) rates in the world. In the first year of the COVID-19 pandemic, reported TB case counts dropped substantially, followed by increasing case counts every year since 2020.

What is added by this report?

During 2023, tuberculosis case counts increased among all age groups, among U.S-born and non-U.S.–born persons, and in most reporting jurisdictions. Overall, cases increased from 8,320 in 2022 to 9,615 in 2023, an increase of 1,295 cases. The rate also increased from 2.5 per 100,000 persons in 2022 to 2.9 in 2023.

What are the implications for public health practice?

Continued progress toward TB elimination will require strong public health systems that are capable of maintaining essential disease prevention and control activities and prepared to withstand the next pandemic or other large-scale crisis.

Limitations

The findings in this report are subject to at least two limitations. First, this analysis is limited to provisional surveillance data for 2023, and case counts might change before CDC's annual TB surveillance report is published. Second, rates are based on midyear population estimates from the U.S. Census Bureau that are subject to ongoing refinement.

Implications for Public Health Practice

The U.S. TB case count increases in 2023 underscores the ongoing global TB-associated morbidity and mortality. Renewed progress toward TB elimination will require strong public health systems both domestically and globally that are responsive to health disparities, capable of maintaining essential disease prevention and control activities, and prepared to withstand the next pandemic or other large-scale crisis.

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Tuberculosis Preventive Treatment Update — U.S. President's Emergency Plan for AIDS Relief, 36 Countries, 2016–2023

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Abstract

Tuberculosis (TB) is the leading cause of death among persons with HIV. In 2022, an estimated 167,000 TB-related deaths occurred globally among persons with HIV. TB preventive treatment (TPT) helps prevent TB disease and is recommended for persons at high risk for developing TB, including those with HIV. TPT, when taken with antiretroviral treatment (ART), can reduce TB-attributable deaths among persons with HIV. In 2018, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) program committed to offer one course of TPT to all eligible clients receiving ART. This analysis describes trends in TPT initiation and completion among PEPFAR-supported programs in 36 countries in Africa, Central and South America, and Asia during fiscal years (FYs) 2017–2023. Overall, TPT initiation rates peaked in FY19, a possible sign of programmatic saturation. TPT initiation among clients who had been on ART <6 months reached 59%, and overall completion rates up to 87% were reported. Approximately 13 million persons with HIV have completed TPT since FY17, but widespread adoption of shorter regimens, patient-centered approaches, and electronic medical record systems might be needed to ensure full TPT coverage. Through PEPFAR's partnership with national HIV programs, TPT has become the standard of care for persons with HIV.

Introduction

In 2022, an estimated 167,000 persons living with HIV experienced tuberculosis (TB)–related deaths globally, making TB the leading cause of death in this group (*1*). World Health Organization–recommended TB preventive treatment (TPT) regimens (*2*) reduce the risk for TB disease and TB-attributable deaths among persons with HIV.† TPT is recommended for persons living with HIV once active TB disease has been ruled out, even when latent TB infection status is unknown (*2*). TPT has historically consisted of once-daily isoniazid for 6 or 9 months; shorter 1- and 3-month rifapentine-based regimens are now available (*2*). At the 2018 United Nations General Assembly High-Level Meeting (UNHLM) on TB, member countries agreed to provide TPT to 6 million persons with HIV by 2022.§ In alignment with this announcement, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) committed to offer at least one course of TPT to all eligible clients receiving antiretroviral treatment (ART), including pregnant women.¶ This report summarizes PEPFAR's global progress on providing TPT to all ART clients in PEPFAR-supported programs, a cohort that includes approximately 19 million persons with HIV.

* These authors contributed equally to this report.

† https://www.cdc.gov/globalhivtb/who-we-are/success-stories/success-story-pages/scaling-tpt-ethiopia.html

§ https://www.who.int/publications/m/item/political-declaration-of-the-un-general-assembly-high-level-meeting-on-the-fight-against-tuberculosis

¶ https://na.usembassy.gov/wp-content/uploads/sites/132/PEPFAR-COP18-Guidance_FINAL-1.pdf

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

Methods

Data were collected through PEPFAR monitoring, evaluation, and reporting indicators.** Data were collected at 6-month intervals and disaggregated by age group (<15 and ≥15 years), sex, and HIV treatment status (<6 months on ART [ART-naive] and ≥6 months on ART [ART-experienced]). Semiannualized TPT initiation and completion rates were calculated among persons on ART in 36 PEPFAR-supported programs that reported TPT data at any time during fiscal years (FYs) 17–23.†† Initiation rates were calculated through FY23 quarter (Q) 2, and completion rates were calculated through FY23 Q4. TPT initiation rates were calculated as the number of TPT initiations in a 6-month period divided by the number of ART clients on treatment at the end of that period. Analysis of TPT initiation rates among ART-naive clients included only those initiating TPT within 6 months of ART initiation. TPT completion rates were calculated as the number of TPT completions in a 6-month period divided by the number of TPT initiations in the previous reporting period. TPT initiation and completion rates were aggregated across all PEPFAR-supported programs. Mann-Whitney-U tests ($\alpha = 0.05$) were used to assess stratum-specific differences in TPT initiation and completion rates. Data were analyzed using R software (version 4.3.2; R Foundation). This activity was reviewed by CDC, deemed not research, and conducted consistent with applicable federal law and CDC policy.§§

Results

Tuberculosis Preventive Treatment Initiation

The number of PEPFAR-supported countries that reported TPT data more than doubled during the analytic period (17 in FY17 and 36 in FY21). Overall, 16,832,651¶¶ TPT initiations were reported during FY17–23. The number of persons who initiated TPT increased by an average of 26% between each semiannual period during FY17–19 (Table). In the following semiannual period (FY20 Q2), the number of persons who initiated TPT decreased by 12%. TPT initiations began increasing again after FY20 Q2 and reached an all-time high in FY21 Q4 (1,802,814). Since then, the number of persons initiating TPT per year has declined. The overall increase in TPT initiations until FY20 was also reflected in

** https://help.datim.org/hc/article_attachments/10003735798420

†† The U.S. government FY runs October–September. In alignment with the PEPFAR reporting calendar, Q2 for semiannual metrics represents October–March of the following calendar year, and Q4 covers April–September.

§§ 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

¶¶ This value includes 555,936 TPT initiations that were reported in FY17 Q2 but occurred in FY16, in accordance with PEPFAR's standard indicator definition for TPT. To calculate TPT initiation rates, the number of TPT initiations must be aligned with the number of persons on ART in the previous reporting period. TPT initiations reported in FY17 Q2 were included in total counts, but initiation rates for that period were not calculated because the denominator (number of persons on ART) was outside the temporal scope of this report.

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TABLE. Tuberculosis preventive treatment initiations* among persons with HIV — 36 U.S. President's Emergency Plan for AIDS Relief–supported countries, October 2016–March 2023

Semiannual period†	Date range	Persons on ART	Persons on ART initiating TPT, no. (%)	Persons newly on ART	Persons newly on ART initiating TPT, no. (%)
FY17 Q2	Oct 2016–Mar 2017	11,726,101	654,161 (6)	—	—
FY17 Q4	Apr–Sep 2017	13,245,470	562,345 (4)	—	—
FY18 Q2	Oct 2017–Mar 2018	13,235,513	750,282 (6)	—	—
FY18 Q4	Apr–Sep 2018	14,769,349	750,431 (5)	1,437,294	243,744 (17)
FY19 Q2	Oct 2018–Mar 2019	13,433,062	1,192,952 (9)	1,236,576	308,431 (25)
FY19 Q4	Apr–Sep 2019	15,686,915	1,784,375 (11)	1,426,483	449,964 (32)
FY20 Q2	Oct 2019–Mar 2020	15,480,007	1,577,641 (10)	1,287,300	529,323 (41)
FY20 Q4	Apr–Sep 2020	17,383,890	1,651,619 (10)	1,194,562	579,085 (48)
FY21 Q2	Oct 2020–Mar 2021	17,248,709	1,750,779 (10)	1,173,027	615,747 (52)
FY21 Q4	Apr–Sep 2021	17,931,849	1,802,814 (10)	1,107,204	643,338 (58)
FY22 Q2	Oct 2021–Mar 2022	18,573,343	1,473,871 (8)	1,041,786	609,569 (59)
FY22 Q4	Apr–Sep 2022	19,238,096	1,311,024 (7)	1,007,261	591,548 (59)
FY23 Q2	Oct 2022–Mar 2023	19,472,835	1,014,421 (5)	934,074	494,023 (53)

Abbreviations: ART = antiretroviral treatment; FY = fiscal year; PEPFAR = U.S. President's Emergency Plan for AIDS Relief; Q = quarter; TPT = tuberculosis preventive treatment.

* TPT initiation rates were calculated as the number of TPT initiations in a 6-month period divided by the number of ART clients on treatment at the end of that period. Analysis of TPT initiation rates among ART-naive (newly on ART) clients include only those initiating TPT within 6 months of ART initiation. TPT initiations are reported in the period after the 6-month period when they occur. TPT initiations reported in FY17 Q2 were included in total counts but initiation rates for that period were not calculated, because the denominator (number of persons on ART) was outside the temporal scope of this report.

† The U.S. government FY runs October–September. In alignment with the PEPFAR reporting calendar, Q2 for semiannual metrics represents October–March of the following calendar year, and Q4 covers April to September.

initiation rates. During FY17–18, the semiannualized TPT initiation rates among all persons receiving ART (ART-naive and -experienced) ranged between 4% and 6% (Table). The TPT initiation rate peaked in FY19 Q4 (11%) and has since declined to 5% as of FY23 Q2. By contrast, the TPT initiation rate among ART-naive clients rose through FY22 Q4, from 17% in FY18 Q4 to 59% in FY22 Q4, before dropping to 53% in the most recent period assessed.

Tuberculosis Preventive Treatment Completion

Overall, 13,323,186 persons with HIV have completed TPT in PEPFAR-supported programs that report TPT data. TPT completion rates steadily increased from 56% in FY18 Q2 to 87% in FY23 Q2, before dropping to 86% in FY23 Q4 (Figure 1).

Differences by Sex, Age, and HIV Treatment Status

No statistically significant differences existed in overall TPT initiation or completion rates between sex and age groups (Figure 2). Among ART-naive clients, initiation rates were lower among those aged <15 years than among those aged ≥15 years (32% and 51%, respectively; p = 0.04). TPT completion rates were lower among ART-naive clients compared with ART-experienced clients (79% and 86%, respectively; p<0.01).

Discussion

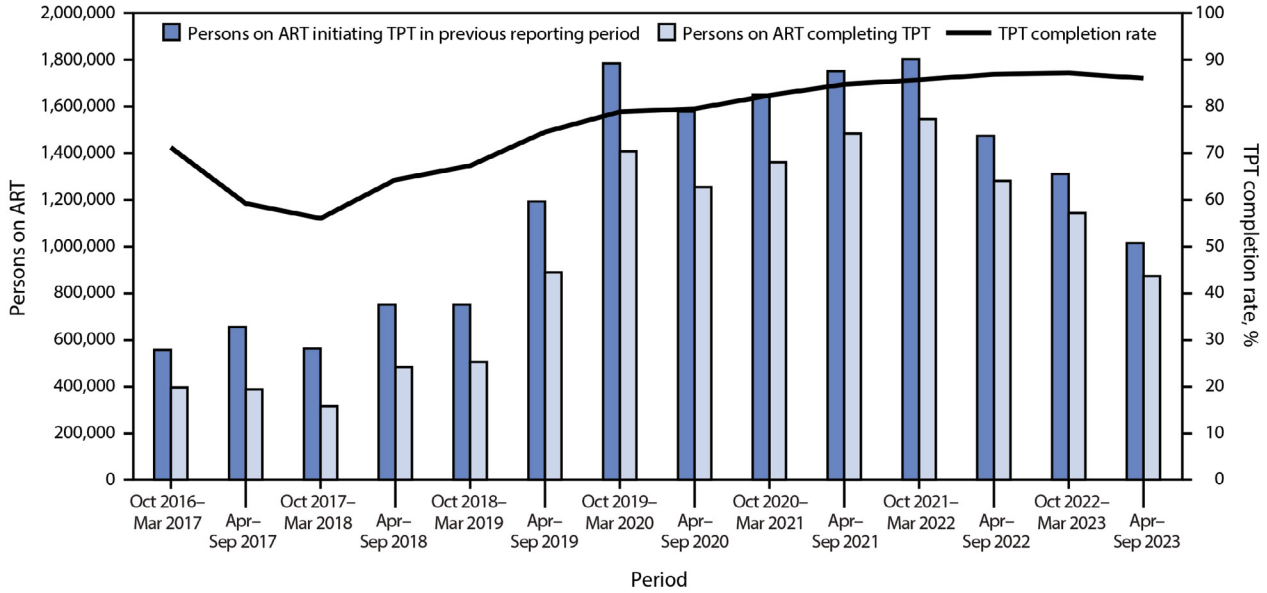
PEPFAR has supported the widespread integration of TPT as part of the HIV standard of care. As a result, approximately 13 million persons with HIV have completed TPT. These TPT completions meaningfully contributed to the 2018 UNHLM target for TPT among persons with HIV, the only UNHLM target achieved (*1*).

TPT initiation rates among ART-naive clients help monitor adoption of TPT into routine practice and are expected to be higher than initiation rates among ART-experienced clients, who might have already completed a course of TPT. Trends in overall initiations provide insight into TPT scale-up over time because climbing initiation rates would be expected when programs are rolling out TPT to the existing patient population. Declining overall TPT initiation rates over time might suggest programmatic saturation, in which all eligible ART clients have already received TPT. Importantly, PEPFAR program data cannot be used to directly measure saturation because these data are not person-level, and TPT completion was not collected before FY17.

Although overall TPT initiation rates trended downward, the percentage of ART-naive clients who received TPT increased. These trends might be indicative of a prioritization of TPT provision for those newly initiated on ART. At the country level, TPT coverage might vary by clinical guidance, eligibility, or supply chain mechanisms. Initiation rates were similar by age and sex, suggesting these factors did not play a major role in TPT initiation overall. However, lower initiation rates were noted among younger ART-naive clients compared with those aged ≥15 years.

Findings from this analysis were consistent with other reports that found lower TPT completion rates among ART-naive clients (*3*). Lower TPT completion rates have been found to be associated with perceived stigma (*4*), which might be higher among those recently diagnosed with HIV (*5*). High levels of

FIGURE 1. Tuberculosis preventive treatment completions* among persons on antiretroviral treatment — 36 U.S. President's Emergency Plan for AIDS Relief–supported countries, October 2016–September 2023



Abbreviations: ART = antiretroviral treatment; TPT = tuberculosis preventive treatment.
* TPT completion rates were calculated as the number of TPT completions in a 6-month period divided by the number of TPT initiations in the previous reporting period.

stigma related specifically to TPT have also been documented (*6*), and other barriers to TPT completion such as pill burden (*7*), lack of health education, and distance to health facilities (*8*) can affect ART-naive clients differently.

Limitations

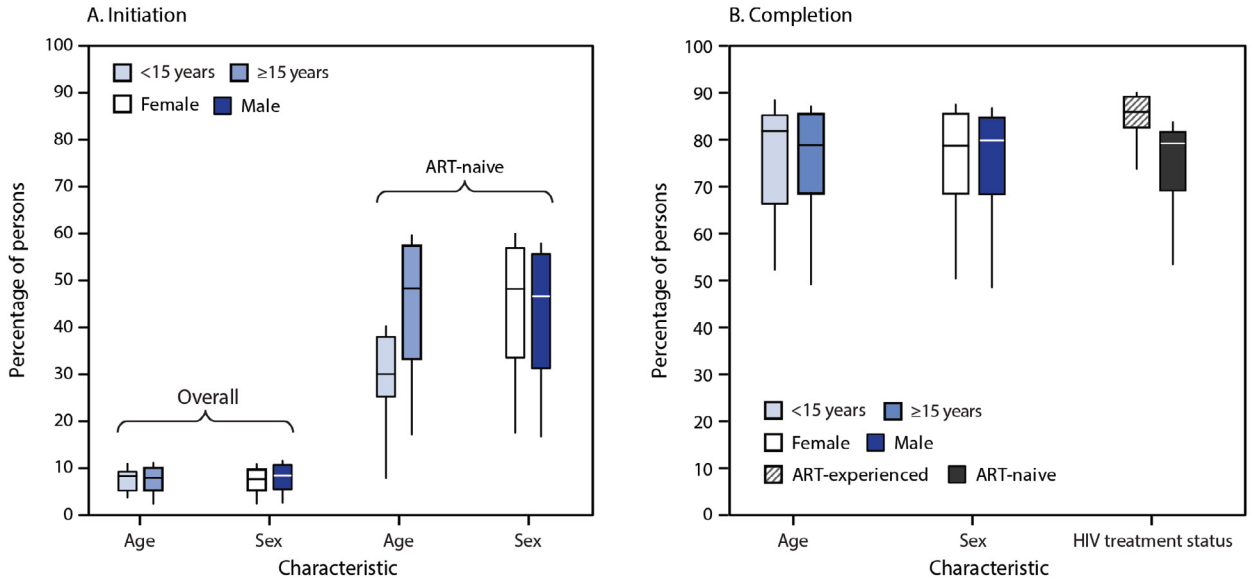
The findings in this report are subject to at least four limitations. First, PEPFAR-wide results represent a diverse range of settings and populations, and the number of countries reporting TPT data varied over time.*** As a result, aggregated values might not reflect trends in individual countries or subnational units, and trends over time are not representative of a true cohort. Second, because TPT completion is often measured on the basis of pill dispensation and self-report rather than direct observation or biomarker monitoring, completion rates might be overestimated. Third, the data used for this analysis were collected in a programmatic setting for monitoring purposes. Data quality might fall short of the accuracy and precision of data collected for clinical studies or in other research settings. Finally, no person-level data were available, and data were reported in broad age bands (<15 and ≥15 years), precluding more specific analyses.

*** Because of ongoing data quality assessments, data from one country that has historically reported a large number of TPT completions were not included in the most recent period assessed (FY23 Q4).

Implications for Public Health Practice

The steady increase in TPT completion rates suggests substantial improvements in HIV and TB service delivery, monitoring, and reporting practices. However, opportunities remain to ensure full TPT coverage and maximize the impact of TPT in reducing TB morbidity and mortality. An ongoing need exists to ensure all ART-naive clients receive the requisite support to access and complete a full course of TPT. Patient-level electronic medical record systems could be developed and expanded to better identify underserved geographic areas and subpopulations and to monitor outcomes over time. Offering patient-centered approaches to treatment delivery can help make health care access a positive and convenient experience for clients by aligning service delivery with their preferences and needs (*9*). Increasing access to short-course regimens for all could improve completion rates (*2*), and ensuring availability of pediatric TPT formulations might increase coverage among persons with HIV aged <15 years. Promoting the use of digital adherence tools, such as mobile telephone applications and electronic sensor-enabled pill boxes (*10*), could help support clients throughout the course of treatment. Finally, further population-level analyses could help determine whether TPT implementation has been associated with reductions in TB incidence and TB-attributable deaths in settings where broad TPT coverage was achieved. Importantly, lessons learned from

FIGURE 2. Differences* in tuberculosis preventive treatment initiation (A)† and completion (B)§ rates among persons on antiretroviral treatment, by age, sex, and HIV treatment status¶ — 36 U.S. President's Emergency Plan for AIDS Relief–supported countries, October 2016–September 2023**



Abbreviations: ART = antiretroviral treatment; TPT = tuberculosis preventive treatment.

* Mann-Whitney-U test (α = 0.05) assessed stratum-specific differences in TPT initiation and completion rates.

† TPT initiation rates were calculated as the number of TPT initiations in a 6-month period divided by the number of ART clients on treatment at the end of that period. Analysis of TPT initiation rates among ART-naive clients include only those initiating TPT within 6 months of ART initiation. P-values for differences by characteristic were age (overall): p = 0.72; sex (overall): p = 0.48; age (ART-naive): p = 0.04; and sex (ART-naive): p = 0.53.

§ TPT completion rates were calculated as the number of TPT completions in a 6-month period divided by the number of TPT initiations in the previous reporting period. P-values for differences by characteristic were age: p = 0.98; sex: p = 0.98; and HIV treatment status: p<0.01.

¶ Persons who initiated TPT within 6 months of ART initiation were included in the analysis of TPT initiation rates among ART-naive clients; those on ART for ≥6 months when initiating TPT were ART-experienced.

** Whiskers display the full range of values for each metric. Boxes display IQRs, with median values indicated by a horizontal line within the box.

Summary

What is already known about this topic?

Tuberculosis (TB) is the leading cause of death among persons with HIV. TB preventive treatment (TPT), combined with antiretroviral treatment (ART), reduces TB-attributable deaths among persons with HIV. In 2018, the U.S. President's Emergency Plan for AIDS Relief (PEPFAR) committed to offer TPT to eligible ART clients.

What is added by this report?

During October 2016–October 2023, approximately 13 million ART clients completed TPT in 36 countries. PEPFAR-supported programs achieved TPT completion rates up to 87%; initiation rates among clients who had been on ART <6 months (ART-naive) reached 59%.

What are the implications for public health practice?

Continued efforts are needed to maximize TPT coverage, especially for ART-naive clients. Short-course regimens, patient-centered care, and modernized medical record systems might help accomplish this goal.

TPT implementation in PEPFAR-supported programs might prove useful for TPT provision among other populations at risk, including household contacts of persons with TB.

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Performance of a single-use, rapid, point-of-care PCR device for the detection of *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis*: a cross-sectional study

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Summary

Background Timely detection and treatment are important for the control of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis*. The objective of this study was to measure the performance of the Visby Medical Sexual Health Test, a single-use, point-of-care PCR device.

Methods Women aged 14 years and older who presented consecutively to ten clinical sites across seven US states were enrolled for a cross-sectional, single-visit study. Patients who consented to participate, and who had not used any exclusionary products in the genital area in the previous 48 h, provided self-collected vaginal swabs for testing with the investigational device. Untrained operators received the specimens and ran the device using the guide provided. Specimens had to be run within 2 h of collection to be considered valid. For comparison, patient-infected status was derived by testing clinician-collected vaginal specimens with the Hologic Aptima Combo 2 Assay and Aptima *Trichomonas vaginalis* Assay, as well as the BD ProbeTec CT/GC Q^x Amplified DNA Assay and BD ProbeTec *Trichomonas vaginalis* Q^x Assay. If the results of those assays did not match, the BD MAX CT/GC/TV was used as a tiebreaker. The primary outcomes were the sensitivity and specificity of the investigational device for the detection of *C trachomatis*, *N gonorrhoeae*, and *T vaginalis* compared with patient-infected status.

Findings Between Feb 25, 2019, and Jan 6, 2020, 1585 participants aged between 14 years and 80 years (mean 34·8 [SD 14·2]) were enrolled. 1555 participants had tests run with the investigational device, of whom 1532 (98·5%) had a valid result on either the first or repeat test. Among the patients with evaluable results (including a determinate patient-infected status), the device had a sensitivity of 97·6% (95% CI 93·2–99·2) and specificity of 98·3% (97·5–98·9) for *C trachomatis* (n=1457), sensitivity of 97·4% (86·5–99·5) and specificity of 99·4% (98·9–99·7) for *N gonorrhoeae* (n=1468), and sensitivity of 99·2% (95·5–99·9) and specificity of 96·9% (95·8–97·7) for *T vaginalis* (n=1449).

Interpretation This innovative, rapid, easy-to-use, single-use, point-of-care device to detect *C trachomatis*, *N gonorrhoeae*, and *T vaginalis* infections showed excellent sensitivity and specificity, and could represent an important advance in the development of rapid diagnostics for sexually transmitted infections and other infectious diseases.

Funding Division of Microbiology and Infectious Diseases, National Institute of Allergy and Infectious Diseases.

Introduction

Nucleic acid amplification tests (NAATs) are the standard for quality clinical services to detect *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and *Trichomonas vaginalis* infections in the genital tract.[1] However, most NAATs require complex laboratory instrumentation, which limits the immediacy of diagnosis and treatment decisions. As a result, standard practices can err by treating some individuals who are not infected if antibiotics are given empirically for syndromic management, or by not treating infected individuals lost to follow-up when the results are available.[2,3] A diagnostic test that could be done at the point of care for curable sexually transmitted infections (STIs) could alleviate inappropriate antibiotic use, treat everyone that presents with an infection, and reduce the anxiety of waiting for test results for patients. In fact, accurate, rapid, point-of-care tests have been identified to be one of the innovations needed to regain traction against increasing rates of STIs.[4–6]

The challenge in developing point-of-care STI tests for *C trachomatis*, *N gonorrhoeae*, and *T vaginalis* in women is that, until 2019, the most compact and rapid tests were immunoassay lateral-flow devices, which rarely achieved clinical sensitivity over 90%—with a few exceptions, such as the OSOM Trichomonas Rapid Test (Sekisui Diagnostics) and the aQcare Chlamydia TRF kit (Medisensor).[7] The most robust advance in point-of-care STI testing in women was compact NAAT technology that can be used at the point of care, such as the Cepheid CT/NG Xpert rapid PCR test.[8] These instruments can run one to many

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Research in context

Evidence before this study

We searched PubMed for articles published up to April 3, 2020 using the search terms "point of care", "sexually transmitted infections", "*Chlamydia trachomatis*", "*Neisseria gonorrhoeae*", and "*Trichomonas vaginalis*". The most recent review of point-of-care testing, from 2016, found 33 publications with 13 articles evaluating test performance. This review showed that sensitive and specific point-of-care tests are available for *C trachomatis*, *N gonorrhoeae*, and *T vaginalis*, but only one of these (the Cepheid GeneXpert system) used nucleic acid amplification methods that provide the highest sensitivity. Since then, one additional test (binx io) has also been reported. However, the Cepheid GeneXpert and binx io use desktop machines that have a higher complexity of operation, require regular maintenance, do not detect *T vaginalis*, can do only one run at a time, and take longer than most patients are willing to wait to produce results.

Added value of this study

This study establishes a new class of diagnostic device, based on nucleic acid amplification, that is single-use, rapid (results in <30 min), and simple to use. This device runs a self-collected vaginal sample to provide an in-clinic accurate diagnostic test for *N gonorrhoeae*, *C trachomatis*, and *T vaginalis*. The device is potentially the new gold standard for point-of-care tests for infectious diseases such as sexually transmitted infections (STIs) and influenza and coronavirus infections, in which rapid turnaround is key. The findings show that the sensitivity and specificity of a true point-of-care test can be the same as those of a laboratory-based test.

Implications of all the available evidence

The development of rapid point-of-care tests for STIs and other infectious diseases represents an important need in medicine and public health. For the public health control of STIs, the implications for such a device are an advancement to treating everyone who needs treatment and avoiding unnecessary speculative treatment, as well as minimising time to treatment, which will reduce transmission and complications.

samples and give results in less than 90 min; however, that turnaround time is not within a typical clinical visit, and the tests are fairly expensive and require a stable electricity supply. Newer, table-top platforms retaining high sensitivity and specificity for *N gonorrhoeae* and *C trachomatis* (none are available for *T vaginalis*) have reduced the time to results to 30 min, closer to the 20 min that most patients find acceptable.[9,10]

Through the first quarter of 2020, no point-of-care tests that were close to receiving clearance by the US Food & Drug Administration (FDA) were able to detect all common STIs at the point of service with an easy-to-use, self-contained system that can deliver results in under 30 min.[6] The Visby Medical Sexual Health Test (Visby Medical, San Jose, CA, USA) is an innovative, single-use, rapid, nucleic acid-based diagnostic test for the detection of *N gonorrhoeae*, *C trachomatis*, and *T vaginalis* infections. This test can be done at the point of care without complex instrumentation and give a result in less than 30 min. We aimed to assess the performance of the Visby Medical Sexual Health Test for the detection of *N gonorrhoeae*, *C trachomatis*, and *T vaginalis* from self-collected vaginal specimens.

Methods

Study design, setting, and participants

We did a cross-sectional, single-visit study of women aged 14 years and older at ten clinics across seven US states. Sites included STI clinics, student health clinics, primary care clinics, academic clinical research centres, and private clinical research organisations located in the states of California, Florida, Illinois, Maryland, Mississippi, Nevada, and Pennsylvania.

We offered enrolment to consecutively presenting women who were either symptomatic or asymptomatic. Participant inclusion criteria were as follows: willing and able to give voluntary written informed consent (or parent or legal guardian consent for minors); female at birth (including pregnant and breastfeeding women); age 14 years or older at the time of enrolment; able to read and understand the procedural information provided for the study; and able and willing to follow all study procedures, including self-collection of one vaginal swab and permitting a licensed health-care provider to collect three additional vaginal swabs.

Exclusion criteria included the following: having a medical condition, serious intercurrent illness, or other circumstance that, in the investigator's judgment, could jeopardise the woman's safety or could interfere with study procedures; previous enrolment in this study; and use of antiperspirants, deodorants, or certain vaginal products (douches, washes, lubricants, wipes, moisturisers, or feminine hygiene sprays) in the genital area within 48 h before enrolment.

This study included collaboration between the device manufacturer (Visby Medical), the National Institute of Allergy and Infectious Diseases of the US National Institutes of Health (NIH), and the STAR STI Clinical Trial Group. The study was approved by a combination of a central institutional review board and local institutional review boards as required by the sites.

Investigational device

The Visby Medical Sexual Health Test device (figure 1) is a single-use, disposable, fully integrated, rapid, compact instrument containing a PCR-based assay for the

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qualitative detection and differentiation of DNA from *N gonorrhoeae*, *C trachomatis*, and *T vaginalis*. The device is intended to detect *N gonorrhoeae*, *C trachomatis*, and *T vaginalis* DNA in a variety of environments without the need for complex off-board sample processing or instrumentation.

The device is meant to be used by any clinic personnel using the quick-start instructions: input sample, activate device, and visually read colorimetric results in less than 30 min. A patient vaginal swab self-collection kit with transport media is provided with the product. The patient-collected swab sample is placed into a vial containing collection medium. A health-care professional then uses a transfer pipette to transfer 650 µL of the sample-containing media into the device input port. The transfer pipette automatically meters the sample volume needed for the device. Buttons 1, 2, and 3 are pressed in succession. After button 3 is pressed and the device is plugged in, a white LED light turns on indicating the reaction is in progress. At this point, the remaining device operation is automatic, including pathogen lysis and DNA release, PCR amplification, and detection of amplified products. When the reaction is complete, the LED light turns green indicating to the user that the results are ready. The results should be read within 2 h. If the sample is positive, a colorimetric change (from white to purple) is visible in the appropriate spot for the pathogen. If the test run is valid, results for all three organisms are readable.

The Sexual Health Test contains all the reagents and instrumentation required to run a single PCR-based test. The device stores buffers and reagents on board for release at the correct time. Printed circuit boards control temperature and time the movement of the motors and liquid flow. Sample processing occurs on the device using a combination of heat and chemical lysis to release pathogen DNA. The inactivated sample is mixed with lyophilised PCR reagents and then amplified by continuous-flow PCR using a serpentine-shaped, plastic-moulded, fluidic circuit that allows rapid heating and cooling. Biotin-labelled PCR primers specifically amplify *N gonorrhoeae*, *C trachomatis*, and *T vaginalis* genes. A detection flow cell has oligonucleotide capture probes that hybridise to the amplified pathogenic target (appendix p 1). A colorimetric signal is generated on the flow cell when horseradish peroxidase-linked streptavidin binds biotin-labelled amplicon and capture-probe pairs and catalyses the conversion of 3,3′,5,5′-tetramethylbenzidine, resulting in a purple precipitate. The presence of target pathogen in the sample thus leads to a white-to-purple colour change on the detection flow cell.

A control non-pathogenic *Neisseria* species is lyophilised and present in the lysis chamber of the device and serves as the positive internal process control. Lyophilised PCR primers that amplify the *Neisseria* spp internal control are included with primers for *N gonorrhoeae*, *C trachomatis*, and *T vaginalis*. The test is thereby monitored for effective sample preparation, PCR amplification, and detection. If all elements in the Sexual Health Test function properly, the positive control spot will produce a purple colour. The test is considered valid if there is a purple signal in the control window and a green check mark is visible on the test that indicates the test ran without error.

Figure 1: Visby Medical Sexual Health Test

Study procedures

Consecutive participants who met the enrolment criteria were asked to provide consent, assessed for clinical symptoms of infection, and asked about recent medication and topical vaginal product use. Participants were then provided with the manufacturer's self-collection instructions and urogenital specimen collection kit containing a swab and transport media, which they used to self-collect a vaginal specimen. An untrained operator received each specimen and ran the device using the provided operators' guide, without coaching or instruction. According to the protocol, the test needed to be run within 2 h of collection. If the result was invalid (no signal in control window) or an error occurred (no green check indicating that device operated correctly), a second test would be run, also within 2 h of collection. Meanwhile, a licensed health-care provider would collect three randomly ordered vaginal swabs (to account for the possible effect of collection order on the comparator assay performance). The study health-care provider recorded any signs of infection. Swabs were stored and transported per manufacturer guidelines for vaginal collection and testing, and specimen collection was standardised for all study sites.

See Online for appendix

Three comparator systems were used for control procedures: the Aptima Combo 2 Assay[11] and Aptima *Trichomonas vaginalis* Assay (Hologic, San Diego, CA, USA),[12] the BD ProbeTec CT/GC Q^{x} Amplified DNA

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	Participants (n=1585)
Sex	
Female	1585 (100·0%)
Ethnicity	
Not Hispanic or Latino	1168 (73·7%)
Hispanic or Latino	310 (19·6%)
Unknown	107 (6·8%)
Race	
American Indian or Alaska Native	12 (0·8%)
Asian	86 (5·4%)
Native Hawaiian or other Pacific Islander	6 (0·4%)
Black or African American	876 (55·3%)
White	414 (26·1%)
Multi-racial	70 (4·4%)
Unknown	121 (7·6%)
Age, years	
14–17	9 (0·6%)
18–25	564 (35·6%)
26–35	366 (23·1%)
36–45	225 (14·2%)
46–55	225 (14·2%)
>55	196 (12·4%)
Mean (SD)	34·8 (14·2)
Study site	
University of California San Diego Antiviral Research Center (San Diego, CA)	186 (11·7%)
Stroger Hospital of Cook County—CORE (Chicago, IL)	243 (15·3%)
San Francisco Department of Public Health (San Francisco, CA)	71 (4·5%)
Philadelphia Department of Public Health (Philadelphia, PA)	281 (17·7%)
University of Mississippi Medical Center (Jackson, MS)	62 (3·9%)
Florida International University (Miami, FL)	279 (17·6%)
AXIS Clinical Trials (Los Angeles, CA)	375 (23·7%)
Johns Hopkins University Rangos (Baltimore, MD)	16 (1·0%)
South Florida Clinical Trials (Hialeah, FL)	12 (0·8%)
Impact Clinical Trial (Las Vegas, NV)	60 (3·8%)

Data are n (%), unless otherwise specified.

Table 1: **Characteristics of enrolled study participants**

Assay[13] and BD ProbeTec *Trichomonas vaginalis* Q^{x} Assay (BD Molecular Diagnostics, Franklin Lakes, NJ, USA),[14] and the BD MAX CT/GC/TV (BD Molecular Diagnostics, Franklin Lakes, NJ, USA),[15] assuring three distinct nucleic acid amplification targets for each organism. The Aptima *Trichomonas vaginalis* Assay is not FDA-cleared for self-collected vaginal specimens, so all patient-infected status comparators were clinician-collected for consistency.

One reference laboratory (Molecular Testing Labs, Vancouver, WA, USA) processed and tested all of the comparator assays for the study. The laboratory conducted quality control and quality assurance procedures according to the manufacturers' recommendations and in compliance with the College of American Pathology. Trained laboratory staff processed swabs, tested the specimens, and interpreted the results according to each manufacturer's instructions on the respective FDA-cleared assays. For inclusion in the analysis, specimens were required to have the test initiated within the stability window stated by the manufacturer. For initial equivocal, invalid, or otherwise indeterminate results, tests were repeated once, per manufacturer recommendations, before being classified as positive, negative, equivocal, or invalid or unresolved. Laboratory testing staff were masked to clinical information and the investigational device results.

To assess patient-infected status, all participants had their specimens tested by the Aptima and BD ProbeTec systems. If there was discordance between those two results then the BD MAX CT/GC/TV result was used as a tiebreaker. Possible outcomes for patient-infected status by organism included infected, not infected, and indeterminate, with definitions determined a priori in the study protocol. Agreement between two of the three comparator assay results was required to determine a positive or negative patient-infected status. If there was no match between at least two comparator results, the status was considered indeterminate.

Participants were categorised as symptomatic if they responded affirmatively to whether they had any of the following symptoms on the clinical symptoms assessment case report form: unusual vaginal discharge, vaginal irritation (itching, burning, or soreness), lower abdominal or pelvic pain, painful urination, increased urinary frequency, abnormal bleeding or spotting, or pain or bleeding with sex or intercourse. Otherwise, the participant was classified as asymptomatic.

Statistical methods

The analytic population were those who were confirmed to have met the selection criteria and had specimens collected and run according to protocol. If results were missing from the Sexual Health Test, the data were not included in the analysis. If the patient-infected status was indeterminate or results were missing from the comparators that were required to determine a patient-infected status for an organism (ie, either the Aptima or Probetec result for any case, or the BD MAX CT/GC/TV result when a tiebreaker was needed), then the results for the organism without a valid positive or negative result for patient-infected status for that participant were excluded from the analysis.

For each organism, we calculated the sensitivity, specificity, accuracy (total agreement), positive predictive value, and negative predictive value of the investigational device against the patient-infected status, with 95% Wilson CIs.[16] The study was designed with a target sample size to achieve 120 positive cases of *C trachomatis*, 120 of *T vaginalis*, and 45 of *N gonorrhoeae* infections.

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The sample size was determined by the numbers required for a sensitivity of 95% with a lower confidence bound of 90% for *C trachomatis* and *N gonorrhoeae* and 85% for *T vaginalis*. The sample size was also to meet a specificity of at least 95% with a lower bound of 90%. In sub-analyses test characteristics were determined for those who were symptomatic and asymptomatic.

Analyses and figure and table generation were done with SAS version 9.4 or above.

This study is registered with ClinicalTrials.gov (NCT03852316).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Feb 25 2019, and Jan 6, 2020, 1585 women were enrolled in the study. Participants were aged between 14 years and 80 years (mean 34·8 [SD 14·2]), with broad demographic and geographical representation (table 1). Women who were pregnant or menstruating were included.

The Visby Medical Sexual Health Test was run for 1555 (98·1%) participants, of whom 1444 (92·9%) had a valid first test and a further 88 (5·7%) had valid results with a repeat test, for a total of 1532 (98·5% [95% CI 97·8–99·1]). Of those with a valid test result from the investigational device, 154 (10·1% [8·6–11·7]) were positive for *C trachomatis*, 50 (3·3% [2·5–4·3]) were positive for *N gonorrhoeae*, and 178 (11·6% [10·1–13·3]) were positive for *T vaginalis* (figure 2). In 1579 participants, the patient-infected status could be determined for at least one organism: 136 of 1579 participants were positive for *C trachomatis* (8·6% [7·3–10·1]), 44 of 1578 were positive for *N gonorrhoeae* (2·8% [2·0–3·6]), and 137 of 1579 were positive for *T vaginalis* (8·7% [7·4–10·2]). Subsequently, in addition to those with no valid result from the Visby Medical device, 75 patients were excluded from the *C trachomatis* analysis, 64 from the *N gonorrhoeae* analysis, and 83 from the *T vaginalis* analysis (figure 2), for reasons including the following: protocol deviations for study procedures (consenting error, incorrect collection of specimens, controls not done correctly before testing, testing outside the 2 h window, mislabelled specimen, non-completion of study visit), violation of study inclusion or exclusion criteria discovered after visit (one repeat participant and one participant with use of excluded product in the previous 48 h), no result available from

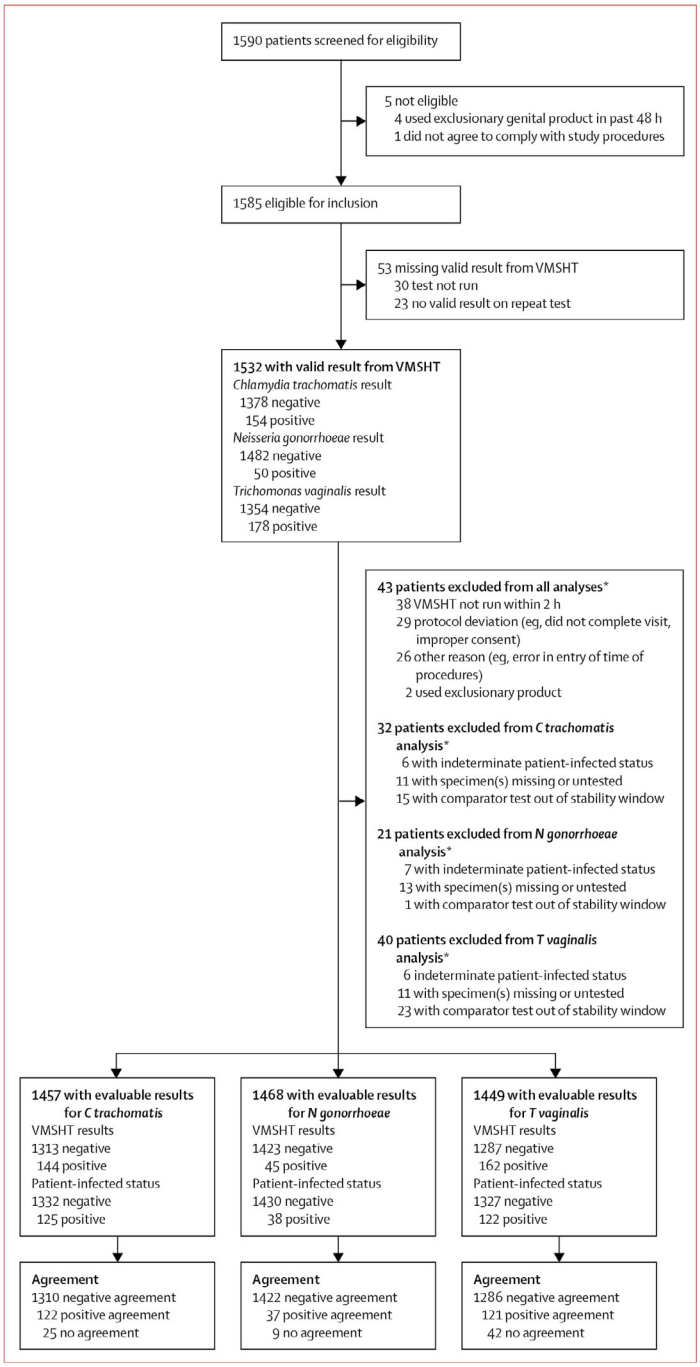

Figure 2: **Study flow diagram**
VMSHT=Visby Medical Sexual Health Test. *Some participants had multiple reasons for exclusion.

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	Patient-infected status designation, n			Sensitivity*	Specificity*	Accuracy*
	Positive	Negative	Total			
Result in symptomatic and asymptomatic patients						
C trachomatis (n=1457)	..	..	..	97·6% (93·2–99·2)	98·3% (97·5–98·9)	98·3% (97·5–98·8)
Positive	122	22	144	..	..	..
Negative	3	1310	1313	..	..	..
Total	125	1332	1457	..	..	..
N gonorrhoeae (n=1468)	..	..	..	97·4% (86·5–99·5)	99·4% (98·9–99·7)	99·4% (98·8–99·7)
Positive	37	8	45	..	..	..
Negative	1	1422	1423	..	..	..
Total	38	1430	1468	..	..	..
T vaginalis (n=1449)	..	..	..	99·2% (95·5–99·9)	96·9% (95·8–97·7)	97·1% (96·1–97·8)
Positive	121	41	162	..	..	..
Negative	1	1286	1287	..	..	..
Total	122	1327	1449	..	..	..
Result in symptomatic patients						
C trachomatis (n=735)	..	..	..	98·7% (93·0–99·8)	97·7% (96·3–98·6)	97·8% (96·5–98·7)
Positive	76	15	91	..	..	..
Negative	1	643	644	..	..	..
Total	77	658	735	..	..	..
N gonorrhoeae (n=746)	..	..	..	100·0% (83·9–100·0)	99·4% (98·6–99·8)	99·5% (98·6–99·8)
Positive	20	4	24	..	..	..
Negative	0	722	722	..	..	..
Total	20	726	746	..	..	..
T vaginalis (n=734)	..	..	..	98·6% (92·6–99·8)	95·8% (93·9–97·1)	96·0% (94·4–97·2)
Positive	72	28	100	..	..	..
Negative	1	633	634	..	..	..
Total	73	661	734	..	..	..
Result in asymptomatic patients						
C trachomatis (n=722)	..	..	..	95·8% (86·0–98·8)	99·0% (97·9–99·5)	98·8% (97·6–99·3)
Positive	46	7	53	..	..	..
Negative	2	667	669	..	..	..
Total	48	674	722	..	..	..
N gonorrhoeae (n=722)	..	..	..	94·4% (74·2–99·0)	99·4% (98·5–99·8)	99·3% (98·4–99·7)
Positive	17	4	21	..	..	..
Negative	1	700	701	..	..	..
Total	18	704	722	..	..	..
T vaginalis (n=715)	..	..	..	100·0% (92·7–100·0)	98·0% (96·7–98·9)	98·2% (96·9–98·9)
Positive	49	13	62	..	..	..
Negative	0	653	653	..	..	..
Total	49	666	715	..	..	..

The denominator for estimates is based on participants in the evaluable population for the specified organism.
*As determined by patient-infected status designation; data are % (95% Wilson CI).

Table 2: Test performance of Visby Medical Sexual Health Test for the detection of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis*, by organism and symptomatic status

investigational device (device not run or all runs within testing window were invalid or had an error), or no result for patient-infected status (lacking two comparators in agreement for any reason). In the final evaluable results, there were 1457 (93·7%) available for *C trachomatis*, 1468 (94·4%) for *N gonorrhoeae*, and 1449 (93·2%) for *T vaginalis*.

Table 2 shows the diagnostic performance measures for the investigational device by organism when compared with patient-infected status. The device had a sensitivity of 97·6% (95% CI 93·2–99·2) and a specificity of 98·3% (95% CI 97·5–98·9) for *C trachomatis*, sensitivity of 97·4% (86·5–99·5) and specificity of 99·4% (98·9–99·7) for *N gonorrhoeae*, and sensitivity of 99·2% (95·5–99·9) and specificity of 96·9% (95·8–97·7) for *T vaginalis*. Similar sensitivity and specificity were found for all organisms when the analysis was stratified by symptomatic and asymptomatic status (table 2). For all evaluable results, the Visby Medical Sexual Health Test had an overall accuracy (agreement with patient-infected status) in 98·3% (97·5–98·8) of results for *C trachomatis*, 99·4% (98·8–99·7) for *N gonorrhoeae*, and 97·1% (95% CI 96·1- 97·8) for *T vaginalis*.

Table 3 shows the agreement with each comparator. Positive agreement with the investigational device was highest for the Hologic Aptima and BD MAX assays for *N gonorrhoeae* and *C trachomatis*, and with the BD ProbeTec and BD MAX assays for *T vaginalis*. Positive predictive values and negative predictive values across a range of prespecified hypothetical prevalences of interest, adjusting the study specific values via Bayes' rule, are shown in table 4.

A second Sexual Health Test was done if the first was invalid and the specimen was still within the 2 h window. The first test was invalid in 111 (7·1%) of 1555 patients, and 23 (1·5%) patients had invalid tests on both the first and second runs (appendix p 2).

Of 27 operators, four left the study before they completed a user survey. Of the 23 who completed the survey on usability, in which they were asked about ease of use (appendix p 3), all operators responded that they would agree or strongly agree that "It was easy to set up the device", "The instructions for the device were easy to follow", and "Overall, it was easy to run the device". For the question "It was easy to see and understand the test results", 21 (91%) operators responded that they agreed or strongly agreed, and two (9%) were neutral.

Discussion

The results of this study showed that a single-use rapid device to detect *N gonorrhoeae*, *C trachomatis*, and *T vaginalis* from a self-collected vaginal specimen in women was highly accurate when performed by clinic staff without laboratory training. The device also delivered a valid test result for 98·5% of the samples provided. Results from this study were used to support a regulatory submission and Clinical Laboratory

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Improvement Act (CLIA) waiver submission to the FDA for the first rapid, simple, molecular, point-of-care testing device for STIs. This represents a major step forward for the detection of STIs that could result in more timely and accurate patient care, improved control of these infections, and a reduction in STI complications.[17] Widespread use of the rapid device would allow for treatment decisions in real time. Such use has been shown to improve appropriate treatment and reduce unnecessary antibiotic exposure.[18,19] Given the rising burden of STIs, a simple point-of-care device with those characteristics is highly desirable.[20] This device is the first to apply the advances in molecular and microfluidic technology towards true point-of-care, highly accurate, and rapid testing that can be applied to many prevalent infectious diseases globally.[21]

Compared with the Visby Medical Sexual Health Test, other point-of-care test systems—such as the binx io and GeneXpert—require samples to be placed in a desktop PCR instrument that once loaded will run for 30–45 min or longer.[8,22,23] The Visby Medical device is compact, transportable, scalable and, because it is single-use, does not require maintenance. Samples for one or many patients can be run sequentially as patients are seen in real time. Although other technologies are in development,[6,24] this device could be the first to be cleared for such use. The Visby Medical Sexual Health Test meets many of the desirable characteristics defined by WHO for a point-of-care device: sensitive, specific, user-friendly, rapid, robust, equipment-free, and deliverable to end users.[17] Most importantly, we observed excellent sensitivity and specificity when compared with the patient-infected status reference for the detection of *N gonorrhoeae*, *C trachomatis*, and *T vaginalis*. Our findings are similar to published estimates of the performance for NAATs for STIs.[12,14,15,25,26] The closest examples of true point-of-care PCR tests are the binx io and GenXpert, which have been investigated in studies of self-collected vaginal specimens, although neither covers all three of the organisms covered by the Visby Medical device. The binx io device had a sensitivity of 96·1% and specificity of 97·7% for the detection of *C trachomatis* (n=51).[9] The GeneXpert had a sensitivity of 98·7% and a specificity of 99·4% for *C trachomatis* (n=79), and a sensitivity of 100·0% and a specificity of 99·9% for *N gonorrhoeae* (n=22).[8]

In the current study, operators of the Visby Medical device were untrained and used the enclosed quick-start instructions to operate the test. They found the test easy to use and were successful in operating the tests. These results suggest that the test could meet CLIA-waiver requirements.

Strengths of this study include a diverse study population of participants from across different geographical and clinical sites. To minimise bias, all devices used to determine patient-infected status had different amplification targets and methodologies to avoid the results being systematically aligned.

	Visby Medical Sexual Health Test result, n			Positive agreement*	Negative agreement*	Accuracy*
	Positive	Negative	Total			
***C trachomatis* result**						
Hologic Aptima	..	..	..	97·6% (93·1–99·2)	98·2% (97·3–98·8)	98·1% (97·3–98·7)
Positive	120	3	123	..	..	..
Negative	24	1308	1332	..	..	..
Total	144	1332	1455	..	..	..
BD ProbeTec	..	..	..	92·3% (86·4–95·8)	98·2% (97·3–98·8)	97·7% (96·8–98·3)
Positive	120	10	130	..	..	..
Negative	24	1303	1327	..	..	..
Total	144	1313	1457	..	..	..
BD MAX	..	..	..	98·2% (90·6–99·7)	98·0% (96·3–98·9)	98·0% (95·8–97·7)
Positive	55	1	56	..	..	..
Negative	9	442	451	..	..	..
Total	64	443	507	..	..	..
***N gonorrhoeae* result**						
Hologic Aptima	..	..	..	97·3% (86·2–99·5)	99·4% (98·8–99·7)	99·3% (98·7–99·6)
Positive	36	1	37	..	..	..
Negative	9	1419	1428	..	..	..
Total	45	1420	1465	..	..	..
BD ProbeTec	..	..	..	83·3% (69·4–91·4)	99·3% (98·7–99·6)	98·8% (98·2–99·3)
Positive	35	7	42	..	..	..
Negative	10	1413	1423	..	..	..
Total	45	1420	1465	..	..	..
BD MAX	..	..	..	100·0% (83·2–100·0)	99·2% (98·0–99·7)	99·2% (98·0–99·7)
Positive	19	0	19	..	..	..
Negative	4	497	501	..	..	..
Total	23	497	520	..	..	..
***T vaginalis* result**						
Hologic Aptima	..	..	..	82·0% (75·1–87·3)	97·1% (96·1–97·9)	95·6% (94·4–96·6)
Positive	123	27	150	..	..	..
Negative	37	1259	1296	..	..	..
Total	160	1286	1446	..	..	..
BD ProbeTec	..	..	..	95·9% (90·8–98·2)	96·6% (95·5–97·5)	96·5% (95·5–97·4)
Positive	117	5	122	..	..	..
Negative	45	1282	1327	..	..	..
Total	162	1287	1449	..	..	..
BD MAX	..	..	..	100·0% (91·0–100·0)	96·6% (94·5–97·9)	96·8% (94·9–98·0)
Positive	39	0	39	..	..	..
Negative	16	448	464	..	..	..
Total	55	448	503	..	..	..

The denominator for estimates is based on participants in the evaluable population for the specified organism. BD Max was not run for every sample and was only used as a tiebreaker or, in some cases, was run if the sample was going to pass the testing window and the other comparator results were not completed. *Data are % (95% Wilson CI).

Table 3: **Performance of the Visby Medical Sexual Health Test for the detection of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis*, by organism, against each comparator device**

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	Positive predictive value	Negative predictive value
***Chlamydia trachomatis* prevalence**		
1%	37·4%	>99·9%
2%	54·7%	>99·9%
5%	75·7%	99·9%
10%	86·8%	99·7%
20%	93·7%	99·4%
***Neisseria gonorrhoeae* prevalence**		
1%	63·7%	>99·9%
2%	78·0%	>99·9%
5%	90·2%	99·9%
10%	95·1%	99·7%
20%	97·8%	99·3%
***Trichomonas vaginalis* prevalence**		
1%	24·5%	>99·9%
2%	39·6%	>99·9%
5%	62·8%	>99·9%
10%	78·1%	>99·9%
20%	88·9%	99·8%

Table 4: Estimates of positive predictive value and negative predictive value across a range of hypothetical prevalences, by organism

Weaknesses of the study include the moderate number of *N gonorrhoeae* cases, which might have affected the precision of the observed sensitivity. Finding a substantial number of *N gonorrhoeae* cases in women is a challenge, and we did attempt to go to higher prevalence areas and recall women who had tested positive for *N gonorrhoeae* in a clinic to come in for a study visit. Another weakness is that, because the patient-infected status composite reference method required at least two comparator assays to agree, limitations in the performance of the comparator assays had the potential to affect the observed device accuracy. The proportion of specimens that tested positive with the investigational device was higher than the proportion with a positive patient-infected status, and there were differences in agreement between devices, but not enough evidence to clearly support higher sensitivity of the investigational device. Only one false-negative result for *N gonorrhoeae* was recorded for the device when compared against patient-infected status, and in that case the stored device image revealed a probable misinterpretation by the operator when later reviewed by study staff. Additionally, because this study did not use self-collected specimens for the comparator assays but did for the test device, the positivity would also be biased in favour of the test device because self-collected specimens for women are more sensitive.[27]

To adopt the use of this or any point-of-care test for STIs, clinics will need to incorporate training and timing into their workflows. It will be important for clinicians to understand that positive predictive values of STI tests vary by organism, and that a positive value for an organism in a low prevalence setting (where positive predictive value is less than 90%) will require interpretation of the result within the context and possibly further confirmation by a second test. For usability, this technology will need to be validated with samples from all genders and anatomical sites.

In summary, this study evaluated a new, first-in-class, diagnostic point-of-care device for the detection of STIs in women. The Visby Medical Sexual Health Test had excellent agreement with other FDA-approved laboratory-based assays for the detection of *N gonorrhoeae*, *C trachomatis*, and *T vaginalis* and should be suitable for a CLIA-waived test environment. This device has major potential for the rapid detection of STIs in clinical settings.

Contributors

SRM, LA, AF, CAG, LH, LM, PM, SP, SS, ands CB ran the clinical trial sites. SRM, CBB, MS, TW, MRW, and JDK wrote and led clinical trial protocol development and implementation. MRW and DS were involved in statistical analysis. SRM, CBB, and JDK drafted the manuscript. All authors approved the final submitted version of the manuscript.

Declaration of interests

SRM, CBB, DS, LH, CB, SS, CAG, TW, AF, SP, MS, LM, and JDK received funds via grants or contracts from the NIH. SP has received funding from University of California San Francisco. MS has received personal fees from Visby Medical. CAG has received funding support from Cepheid, SpeeDx, Binx Health, Becton Dickinson, and Hologic. LM has received grant funding from Roche Molecular, Evofem, Janssen Pharmaceutical, Prosoft Clinical, GlaxoSmithKlein, and SpeeDx. JDK has received support from Danaher, Cepheid, and Hologic. SRM held financial interests in Pfizer, Bristol Myers Squibb, Geron, and Forty Seven; and has received grant funding from Gilead, Merck, the California Institute of Regenerative Medicine, and the California HIV/AIDS Research Program. All other authors declare no competing interests.

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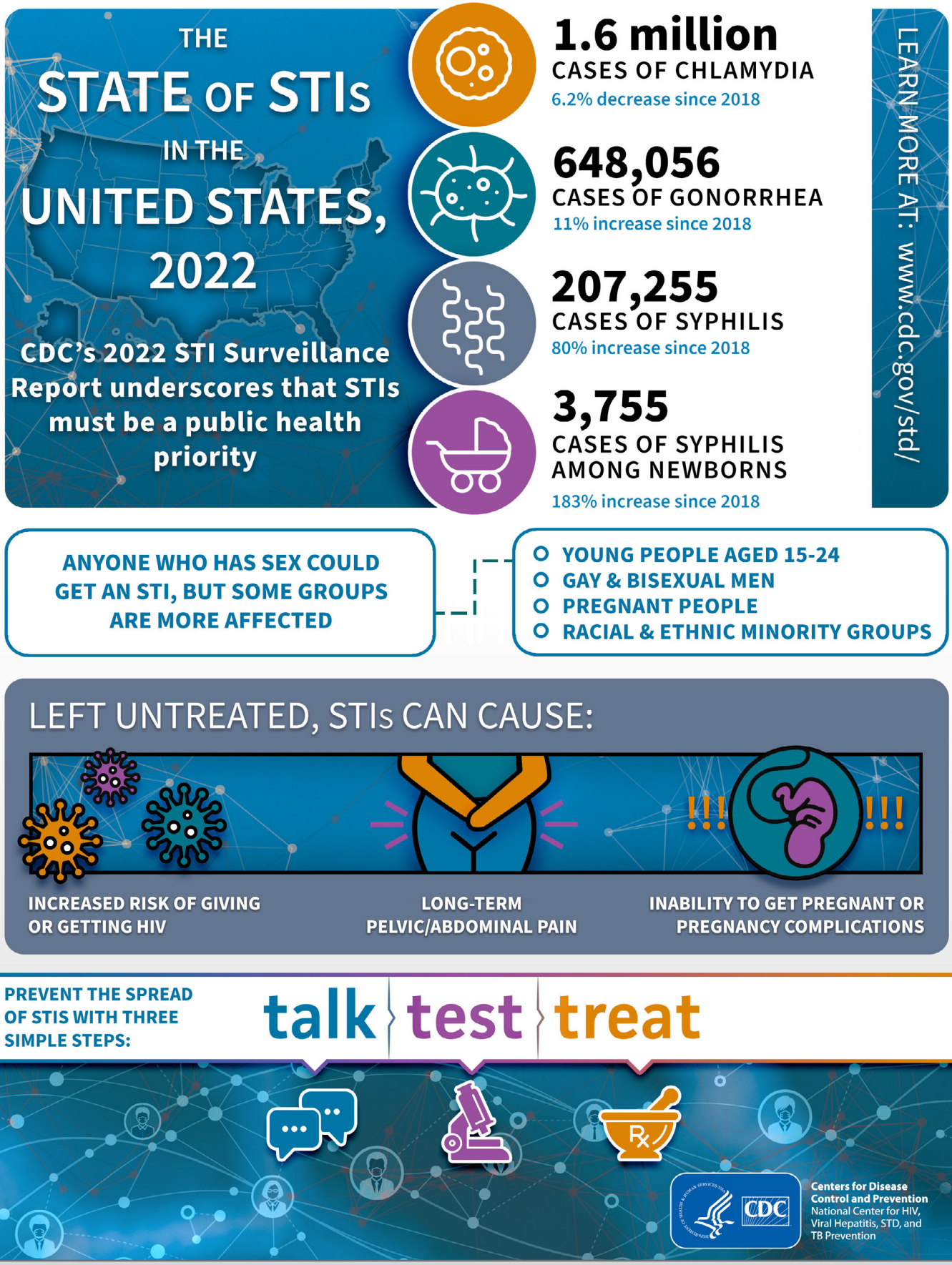
THE
STATE OF STIs
IN THE
UNITED STATES,
2022
CDC's 2022 STI Surveillance Report underscores that STIs must be a public health priority
1.6 million
CASES OF CHLAMYDIA
6.2% decrease since 2018
648,056
CASES OF GONORRHEA
11% increase since 2018
207,255
CASES OF SYPHILIS
80% increase since 2018
3,755
CASES OF SYPHILIS AMONG NEWBORNS
183% increase since 2018
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YOUNG PEOPLE AGED 15-24
GAY & BISEXUAL MEN
PREGNANT PEOPLE
RACIAL & ETHNIC MINORITY GROUPS
LEFT UNTREATED, STIs CAN CAUSE:
!!!
!!!
INCREASED RISK OF GIVING OR GETTING HIV
LONG-TERM PELVIC/ABDOMINAL PAIN
INABILITY TO GET PREGNANT OR PREGNANCY COMPLICATIONS
PREVENT THE SPREAD OF STIS WITH THREE SIMPLE STEPS:
talk
test
treat
Rx
CDC
Centers for Disease Control and Prevention
National Center for HIV, Viral Hepatitis, STD, and TB Prevention

Notes from the Field

Measles Outbreak — Cook County, Illinois, October–November 2023

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On October 10, 2023, the Cook County Department of Public Health (CCDPH) in Illinois was notified by hospital A, a large pediatric facility, of a suspected measles case in a child aged 2 years (patient A) who had immigrated from Yemen on September 29 and who had no history of receipt of measles, mumps, and rubella (MMR) vaccine. The child visited hospital A's emergency department (ED) on October 5 with fever, cough, and coryza and, after receipt of negative COVID-19, influenza, and respiratory syncytial virus test results, received a diagnosis of an unspecified viral illness. On October 8, the child visited hospital B's ED with worsening respiratory symptoms and received a positive rhinovirus/enterovirus test result on a respiratory pathogen panel, after which the child was transferred to hospital A and admitted for respiratory distress related to bronchiolitis and underlying reactive airway disease. The next day, while hospitalized, the child developed a maculopapular rash. On October 10, the child's family reported contact with a person with clinically diagnosed measles before U.S. arrival.* Measles was confirmed by real-time reverse transcription–polymerase chain reaction (RT-PCR) testing on October 11; the child was discharged the same day.

Investigation and Outcomes

During the child's October 5–11 health care encounters, 247 health care workers† and 177 patients and patient companions§ were considered to have been exposed, including 13 children aged <1 year, five immunosuppressed children, and one child aged >1 year with no history of MMR vaccination. Among these 19 children, two received a dose of MMR vaccine within 72 hours of the exposure, and 13 received immune globulin.

The index patient's household contacts included two siblings with no history of MMR vaccination and with serologic testing indicating measles susceptibility. One sibling, aged 4 years, (patient B) arrived in the United States at the same time as the index patient (September 29). The second sibling, aged 9 years, (patient C) had arrived in the United States in January 2023. Both siblings developed measles while in quarantine with rash onsets on October 22 (patient B) and November 1 (patient C). Patient B also reported fever, cough, coryza, and conjunctivitis; patient C also reported fever. Neither child was hospitalized, although patient B required an ED visit at hospital A for supportive care. On October 17, exposure notification letters were delivered to all residents in the apartment building where the index patient lived.

On October 30, hospital A notified CCDPH of another child, aged 2 years, (patient D) who had been evaluated in an ED early that morning with fever, cough, and coryza, then discharged. The family of that child lived in the same 2-story apartment building as the index patient, but on a different floor. Patient D had no history of MMR vaccine; the child's parents reported objections to MMR vaccine based on personal beliefs and perceptions about vaccine side effects. Measles was confirmed in this child by RT-PCR testing on October 30; rash onset occurred on November 1. The families of patients A–C and patient D had different cultural backgrounds from one another and spoke different primary languages; both families independently reported no contact with the other family. Their apartment units did not have shared ventilation; however, laundry facilities and building entrances were shared.

On October 31, testing was also performed for a sibling of patient D, a child aged 1 year (patient E), also with no history of MMR vaccine, who had isolated coryza and who attended a child care facility¶ on October 30 while symptomatic; a nasopharyngeal swab collected in the home confirmed measles by RT-PCR testing. Attendees and staff members of the child care facility were notified the same day. One child aged 2 months received immune globulin, one child aged 11 months received

* The patient with clinically diagnosed measles was an extended family member of a similar age as the index patient. The exposure occurred in Yemen on September 24 or 25.

† All health care workers had either received 2 doses of MMR vaccine or had titers documenting immunity. One health care worker who had received 3 MMR vaccine doses was considered susceptible based on titer results; this worker was excluded from work and monitored for 21 days, during which time measles did not develop.

§ Immunity status was verified for 174 exposed patients and patient companions; three patients were lost to follow-up. Among the 174 patients with available information, 105 (60%) had documented proof of immunity (including two patients who received MMR vaccine within 72 hours of exposure). The remaining 69 (40%) persons were offered postexposure prophylaxis, if eligible; advised to quarantine (not attend work, school, or a child care facility); and were monitored for 21 days. None developed measles.

¶ Illinois state law mandates age-appropriate MMR vaccination for children attending schools and child care facilities; however, families with religious objections can obtain an exemption. None of the children in the family of the index patient were attending school or a child care facility at the time of the investigation. The director of the child care facility attended by patients D and E reported that a religious exemption form had been submitted for both unvaccinated children; however, despite multiple requests from CCDPH, copies of these forms were not provided.

1 dose of MMR vaccine, and 11 children who had received their first MMR vaccine dose received an early second dose as post-exposure prophylaxis.** Fever in patient E did not occur until November 6, and rash did not appear until November 9, which was 9 days after the positive RT-PCR test result and child care facility notification.†† Measles testing is indicated for susceptible contacts of measles cases when the contact has prodromal symptoms (i.e., fever, cough, coryza, or conjunctivitis); however, isolated coryza experienced by this patient at the time of specimen collection might not have been related to measles. Because testing for measles before fever onset is not typically performed, an accurate infectious period for this patient was difficult to ascertain. Patient E's symptoms resolved without requiring emergency care or hospitalization. This activity was reviewed by CDC, deemed not research, and was conducted consistent with applicable federal law and CDC policy.§§

Preliminary Conclusions and Actions

In this community outbreak, five children developed measles. Although all patients were eligible to have received MMR vaccine before their exposures, none had been vaccinated because of cultural barriers, limited access to care, and vaccine refusal. Whereas previous measles outbreaks in the United States have primarily occurred in underimmunized communities with highly interconnected social networks (*1*), neither of the affected families described in this report was part of a similar close-knit social community, and vaccination coverage data for the patients' sociocultural groups were not available. Public health responses have typically required tailored approaches that include developing culturally appropriate education materials, securing translation services, and building relationships with community leaders (*2*). These efforts are time-consuming and costly, with a median cost per measles patient of approximately $33,000 during 2004–2017 (*3*). This outbreak is a reminder that measles is highly contagious, and transmission can occur between children who are not social contacts. Outbreaks might become more common as global measles cases continue to rise (*4*) and the number of children with exemptions to childhood vaccines increases (*5*). Clinicians should consider measles in susceptible patients with febrile rash illness and clinically compatible measles symptoms. All eligible children and susceptible adults should receive 2 appropriately spaced doses of MMR vaccine to prevent measles and measles outbreaks.¶¶

** MMR vaccine was administered within 72 hours after exposure; immune globulin was administered within 6 days after exposure.

†† Measles patients are typically considered infectious from 4 days before through 4 days after rash onset.

§§ 45 C.F.R. part 46.102(l)(2), 21 C.F.R. part 56; 42 U.S.C. Sect. 241(d); 5 U.S.C. Sect. 552a; 44 U.S.C. Sect. 3501 et seq.

¶¶ https://www.cdc.gov/vaccines/vpd/mmr/public/

Summary

What is already known about this topic?

Measles is a highly contagious vaccine-preventable disease. In the United States, 2 doses of measles, mumps, and rubella (MMR) vaccine are recommended for all children aged 12–15 months and 4–6 years.

What is added by this report?

During October 5–November 1, 2023, five measles cases occurred in unvaccinated, vaccine-eligible children aged 1–9 years who lived in the same apartment building but did not socialize with one another. During the outbreak, approximately 400 persons were exposed to measles, including 13 children aged <1 year.

What are the implications for public health practice?

Two doses of appropriately spaced MMR vaccine are recommended for all children and other susceptible persons to prevent measles cases and outbreaks.

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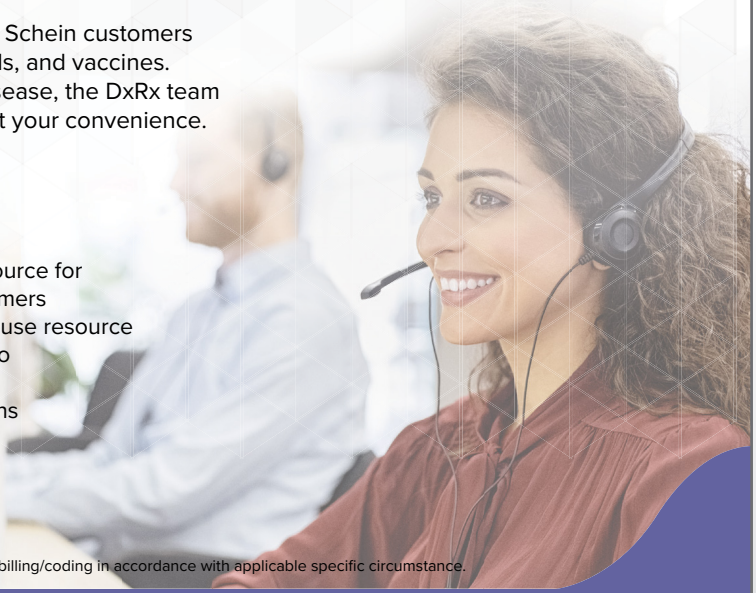
DxRx can answer questions related to:

- Latest updates on supply issues
- Indications and usage as provided on package inserts
- Brand-to-generic comparisons
- CPT® and J codes*
- Product storage requirements
- ACIP recommendations for vaccinations
- Flu vaccine and flu-related topics

Benefits:

- Complimentary resource for Henry Schein customers
- Easy-to-access and use resource
- E-mail for answers to pharmaceutical and vaccination questions



*For informational purposes only.
Source: www.reimbursementcodes.com or www.cms.gov. Customer is responsible for verification of billing/coding in accordance with applicable specific circumstance.

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This is an official CDC HEALTH ADVISORY

HAN HEALTH ALERT NETWORK

Increase in Global and Domestic Measles Cases and Outbreaks: Ensure Children in the United States and Those Traveling Internationally 6 Months and Older are Current on MMR Vaccination

March 18, 2024, 12:30 PM ET
CDCHAN-00504

Summary

The Centers for Disease Control and Prevention (CDC) is issuing this Health Alert Network (HAN) Health Advisory to inform clinicians and public health officials of an increase in global and U.S. measles cases and to provide guidance on measles prevention for all international travelers aged ≥6 months and all children aged ≥12 months who do not plan to travel internationally. Measles (rubeola) is highly contagious; one person infected with measles can infect 9 out of 10 unvaccinated individuals with whom they come in close contact. From January 1 to March 14, 2024, CDC has been notified of 58 confirmed U.S. cases of measles across 17 jurisdictions, including seven outbreaks in seven jurisdictions compared to 58 total cases and four outbreaks reported the entire year in 2023. Among the 58 cases reported in 2024, 54 (93%) were linked to international travel. Most cases reported in 2024 have been among children aged 12 months and older who had not received measles-mumps-rubella (MMR) vaccine. Many countries, including travel destinations such as Austria, the Philippines, Romania, and the United Kingdom, are experiencing measles outbreaks. To prevent measles infection and reduce the risk of community transmission from importation, all U.S. residents traveling internationally, regardless of destination, should be current on their MMR vaccinations. Healthcare providers should ensure children are current on routine immunizations, including MMR. Given currently high population immunity against measles in most U.S. communities, the risk of widescale spread is low. However, pockets of low coverage leave some communities at higher risk for outbreaks.

Background

Measles is a highly contagious viral illness and can cause severe health complications, including pneumonia, encephalitis (inflammation of the brain), and death, especially in unvaccinated persons. Measles typically begins with a prodrome of fever, cough, coryza (runny nose), and conjunctivitis (pink eye), lasting 2 to 4 days before rash onset. The incubation period for measles from exposure to fever is usually about 10 days (range 7 to 12 days), while rash onset is typically visible around 14 days (range 7 to 21 days) after initial exposure. The virus is transmitted through direct contact with infectious droplets or by airborne spread when an infected person breathes, coughs, or sneezes, and can remain infectious in the air and on surfaces for up to 2

hours after an infected person leaves an area. Individuals infected with measles are contagious from 4 days before the rash starts through 4 days afterward.

Declines in measles vaccination rates globally have increased the risk of measles outbreaks worldwide, including in the United States. Measles cases continue to be brought into the United States by travelers who are infected while in other countries. As a result, domestic measles outbreaks have been reported in most years, even following the declaration of U.S. measles elimination in 2000. Most importations come from unvaccinated U.S. residents.

Measles is almost entirely preventable through vaccination. MMR vaccines are safe and highly effective, with two doses being 97% effective against measles (one dose is 93% effective). When more than 95% of people in a community are vaccinated (coverage >95%) most people are protected through community immunity (herd immunity). However, vaccination coverage among U.S. kindergartners has decreased from 95.2% during the 2019–2020 school year to 93.1% in the 2022–2023 school year, leaving approximately 250,000 kindergartners susceptible to measles each year over the last three years. Thirty-six states plus the District of Columbia (DC) had less than 95% MMR coverage among kindergartners during the 2022–2023 school year. Of states with less than 95% MMR coverage, ten reported more than 5% of kindergartners had medical and nonmedical exemptions, highlighting the importance of targeted efforts at increasing vaccine confidence and access.

Recommendations for Healthcare Providers

- Schools, early childhood education providers, and healthcare providers should work to ensure students are current with MMR vaccine.
    - Children who are not traveling internationally should receive their first dose of MMR at age 12 to 15 months and their second dose at 4 to 6 years.
- All U.S. residents older than age 6 months without evidence of immunity who are planning to travel internationally should receive MMR vaccine prior to departure.
    - Infants aged 6 through 11 months should receive one dose of MMR vaccine before departure. Infants who receive a dose of MMR vaccine before their first birthday should receive two more doses of MMR vaccine, the first of which should be administered when the child is age 12 through 15 months and the second at least 28 days later.
    - Children aged 12 months or older should receive two doses of MMR vaccine, separated by at least 28 days.
    - Teenagers and adults without evidence of measles immunity should receive two doses of MMR vaccine separated by at least 28 days.
- At least one of the following is considered evidence of measles immunity for international travelers: 1) birth before 1957, 2) documented administration of two doses of live measles virus vaccine (MMR, MMRV, or other measles-containing vaccine), or 3) laboratory (serologic) proof of immunity or laboratory confirmation of disease.

- Consider measles as a diagnosis in anyone with fever (≥101°F or 38.3°C) and a generalized maculopapular rash with cough, coryza, or conjunctivitis who has recently been abroad, especially in countries with ongoing outbreaks. When considering measles, then:
    - **Isolate:** Do not allow patients with suspected measles to remain in the waiting room or other common areas of a healthcare facility; isolate patients with suspected measles immediately, ideally in a single-patient airborne infection isolation room (AIIR) if available, or in a private room with a closed door until an AIIR is available. Healthcare providers should be adequately protected against measles and should adhere to standard and airborne precautions when evaluating suspect cases, regardless of their vaccination status. Healthcare providers without evidence of immunity should be excluded from work from day 5 after the first exposure until day 21 following their last exposure. Offer testing outside of facilities to avoid transmission in healthcare settings. Call ahead to ensure immediate isolation for patients referred to hospitals for a higher level of care.
    - **Notify:** Immediately notify state, tribal, local, or territorial health departments (24-hour Epi On Call contact list) about any suspected case of measles to ensure rapid testing and investigation. States report measles cases to CDC.
    - **Test:** Follow CDC's testing recommendations and collect either a nasopharyngeal swab, throat swab, and/or urine for reverse transcription polymerase chain reaction (RT-PCR) and a blood specimen for serology from all patients with clinical features compatible with measles. RT-PCR is available at many state public health laboratories, through the APHL Vaccine Preventable Disease Reference Centers, and at CDC. Given potential shortages in IgM test kits, providers should be vigilant in contacting their state or local health department for guidance on testing.
    - **Manage:** In coordination with local or state health departments, provide appropriate measles post-exposure prophylaxis (PEP) as soon as possible after exposure to close contacts without evidence of immunity, either with MMR (within 72 hours) or immunoglobulin (within 6 days). The choice of PEP is based on elapsed time from exposure or medical contraindications to vaccination.

Recommendations for Health Departments

Measles is an immediately notifiable disease. State, tribal, local, and territorial health departments have the lead in disease investigations and should report measles cases and outbreaks within 24 hours through the state health department to CDC (measlesreport@cdc.gov) and through NNDSS.

- Establish measles case reporting from healthcare facilities, providers, and laboratories to public health authorities.
- If measles is identified, conduct active surveillance for additional (secondary) cases and facilitate transportation of specimens immediately to confirm diagnosis.
- Record and report details about cases of measles, including adherence to recommended precautions and facility location(s) of index and secondary cases.
- Enhance outreach and communications to under-vaccinated communities through trusted messengers.

Recommendations for Parents and International Travelers

- Even if not traveling, ensure that children receive all recommended doses of MMR vaccine. Two doses of MMR vaccine provide better protection (97%) against measles than one dose (93%). Getting MMR vaccine is much safer than getting measles, mumps, or rubella.

- Anyone who is not protected against measles is at risk of getting infected when they travel internationally. Before international travel, check your destination and CDC's Global Measles Travel Health Notice for more travel health advice, including where measles outbreaks have been reported.
- Parents traveling internationally with children should consult with their child's healthcare provider to ensure that they are current with their MMR vaccinations at least 2 weeks before travel. Infants aged 6 to 11 months should have one documented dose and children aged 12 months and older should have two documented doses of MMR vaccine before international travel. Depending on where you are going and what activities you plan, other vaccines may be recommended too.
- After international travel, watch for signs and symptoms of measles for 3 weeks after returning to the United States. If you or your child gets sick with a rash and a high fever, call your healthcare provider. Tell them you traveled to another country and whether you or your child have received MMR vaccine.

For More Information

- Parents and International Travelers
  - Measles Vaccines for Children | CDC
  - Plan for Travel – Measles | CDC
  - Global Measles Situation | CDC
- Health Departments and Public Health Professionals
  - Measles: Information for Public Health Professionals | CDC
  - CDC Measles Toolkit for Health Departments
  - Partnering for Vaccine Equity | CDC
  - Vaccine Preventable Diseases | APHL
- Healthcare Providers
  - Measles One-Pager for Healthcare Providers | Project Firstline and AAP
  - Immunization Schedules | CDC
  - Safety Information for Measles, Mumps, Rubella (MMR) Vaccines | CDC
  - For Healthcare Professionals – Diagnosing and Treating Measles | CDC
  - Interim Measles Infection Prevention Recommendations in Healthcare Settings | CDC
  - Measles – Vaccine Preventable Diseases Surveillance Manual | CDC
  - Rubeola / Measles | CDC Yellow Book 2024
  - Measles Lab Tools | CDC
  - Measles Serology | CDC
  - Measles Specimen Collection, Storage, and Shipment | CDC
  - Test Directory | Submitting Specimens to CDC | Infectious Diseases Laboratories | CDC

- Webinar Thursday, August 17, 2023 – We Must Maintain Measles Elimination in the United States: Measles Clinical Presentation, Diagnosis, and Prevention (cdc.gov) (Free CE)

The Centers for Disease Control and Prevention (CDC) protects people's health and safety by preventing and controlling diseases and injuries; enhances health decisions by providing credible information on critical health issues; and promotes healthy living through strong partnerships with local, national and international organizations.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

HAN Message Types

- **Health Alert:** Conveys the highest level of importance about a public health incident.
- **Health Advisory:** Provides important information about a public health incident.
- **Health Update:** Provides updated information about a public health incident.

###

This message was distributed to state and local health officers, state and local epidemiologists, state and local laboratory directors, public information officers, HAN coordinators, and clinician organizations.

###

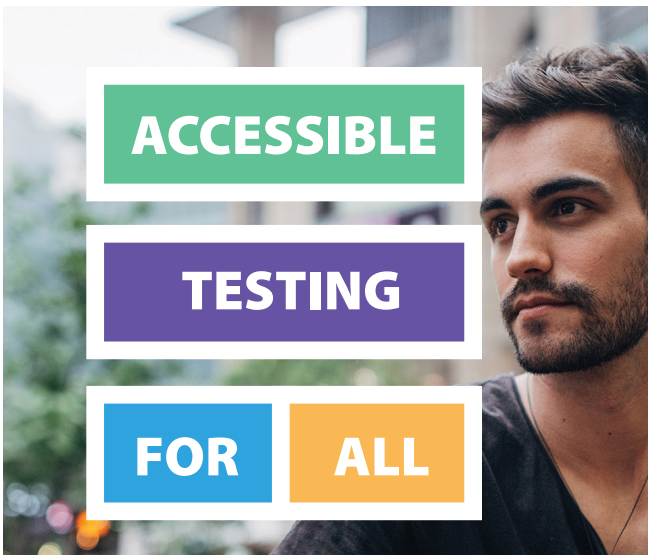
Additional Resources

- HAN Archive By Year
- HAN Types
- Sign Up for HAN Email Updates
- HAN Jurisdictions

Last Reviewed: March 14, 2024
Source: Center for Preparedness and Response (CPR)

CALL TO ORDER FLU VACCINE TODAY!

Everyone 6 months and older should get a flu vaccine every season with rare exceptions. Children younger than 5 years old—especially those younger than 2—are at high risk of developing serious flu-related complications. A flu vaccine offers the best defense against flu and its potentially serious consequences and can also reduce the spread of flu to others. Source: CDC.gov



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