It’s back — nearly eliminated syphilis rates are increasing

While the world’s attention has been focused on the SARS-CoV-2 pandemic since early 2020, an “ancient” disease, also known as the great pretender because its symptoms can mimic many other diseases, continued to spread, reaching levels not seen in decades. Prior to the emergence of SARS-CoV-2, the United States was in the midst of a precipitous rise in syphilis, along with other common sexually transmitted infections. Since reaching a historic low in 2000 and 2001, the rate of primary and secondary syphilis has increased almost every year. Between 2014 and 2018, reported cases of primary and secondary syphilis rose 71%, and during 2018–2019 rose an additional 11.2%. Reported cases of congenital syphilis (infection of a fetus in utero) rose 185% between 2014 and 2018, during 2018–2019 rose an additional 41.4%, and continued to rise in 2020.

In response to the rising incidence of these STIs, the Department of Health and Human Services released the STI National Strategic Plan: 2021–2025. The plan outlined 5 high level goals and several specific objectives to address the rising prevalence of STIs in the United States. Achieving each goal, listed in Table 1, requires integration and coordination between relevant stakeholders, including patients, clinicians, public health authorities, laboratories and pharmaceutical and medical device developers.
Table 1. High Level Goals and Objectives of the STI National Strategic Plan

<table>
<thead>
<tr>
<th>Goal Focus</th>
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<tr>
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The availability of accurate diagnostics with clear interpretive guidance is important to fulfill the objectives of the STI National Strategic Plan: 2021–2025. Below, we summarize the current state of diagnostics for syphilis and the guidance for interpreting results.

**Syphilis**

Syphilis, caused by the bacterium *Treponema pallidum* (*T. pallidum*) has been divided into stages on the basis of clinical symptoms:

- **Primary syphilis:** classic single painless ulcer or chancre at the site of infection or multiple, atypical or painful lesions
- **Secondary syphilis:** skin rash, mucocutaneous lesions distant from the primary lesion, and lymphadenopathy
- **Latent syphilis:** absence of clinical symptoms, early latent is infection that occurred within the past 12 months, late latent is infection that occurred more than 12 months prior
- **Tertiary syphilis:** can affect multiple organ systems including the heart, brain nerves, eyes, livers, etc.

In 2019, there were 129,813 reported cases of syphilis in the U.S., including 38,992 cases of primary and secondary syphilis, the most infectious stages of the disease. All regions of the U.S. are experiencing increased rates of syphilis infection. The populations disproportionately impacted are men who have sex with men (MSM), pregnant people, and racial and ethnic minorities. While rates of primary and secondary syphilis are lower among women, rates have increased in recent years with a 178.6% increase noted during 2015–2019 suggesting an accelerating heterosexual syphilis epidemic. The increased rate in women is especially concerning as it is concurrent with a significant increase in the rate of congenital syphilis cases.

**Congenital Syphilis**

Concomitant with the increasing rates of syphilis in women of reproductive age, the rate of congenital syphilis reported in the U.S. has consistently increased since 2015 with 1,870 cases reported in 2019, and 2,022 cases reported in 2020. Congenital syphilis can result in significant negative outcomes including miscarriage, stillbirth, prematurity, low birth weight, or death shortly after birth. Babies born with congenital syphilis can experience deformed bones, severe anemia, jaundice, enlarged liver and spleen, blindness or deafness, and skin rashes.
Screening of pregnant women is recommended during the 1st and 3rd trimesters to identify and treat syphilis infections and prevent perinatal transmission. The second most common missed congenital syphilis prevention opportunity in 2019 was the lack of timely prenatal care and subsequent lack of timely syphilis testing.

Figure 3. Total syphilis — Rates of reported cases among women aged 15–44 by state, U.S.

Laboratory diagnosis of syphilis

The significant increases in reported cases of syphilis that have occurred within the last decade require bold initiatives to detect and treat STIs, including increasing the number of syphilis screenings performed.

Diagnosis of syphilis requires the use of reflexive testing algorithms including both treponemal antibody specific assays (e.g., EIA, TPPA) and non-treponemal antibody assays (e.g., RPR). Treponemal antibodies appear earlier than nontreponemal antibodies and can remain detectable for life, including after successful treatment. A positive treponemal screen test requires a nontreponemal test be performed to confirm diagnosis and guide patient management decisions. Nontreponemal tests are not specific for syphilis but can be used to monitor treatment efficacy. These assays can produce false positive results especially in pregnant women, recently vaccinated individuals, individuals with autoimmune conditions, and in older populations.

The syphilis testing algorithms include the reverse sequence algorithm and the traditional algorithm.
Women's Health

Reverse algorithm

The reverse algorithm can identify persons previously treated for syphilis, those with untreated or incompletely treated syphilis and those with false-positive nontreponemal results that can occur.

**Treponema pallidum Screening Cascade**

- **Negative**
  - Stop
  - No laboratory evidence of syphilis infection. If recent exposure is suspected, repeat testing in 2–4 weeks.

- **Positive/Equivocal**
  - Nontreponemal test: Qualitative RPR
    - Negative
    - Positive/Syphilis and non-treponemal antibodies detected. Consistent with current or past syphilis. RPR titers can be used to monitor treatment effectiveness.
    - Positive/Equivocal
      - Different treponemal test: TrepSure®
        - Positive/Equivocal
          - Treponemal antibodies detected; consistent with past or potential early syphilis infection. If past history of treatment reported, no further management is needed unless recent exposure suspected. If no past history of treatment, follow guidelines for treatment of latent syphilis. If recent exposure suspected, repeat testing in 2–4 weeks.
        - Negative
          - Possible false-positive result. Stop if low-risk patient. If syphilis is strongly suspected, retest in one month, or treat as late latent syphilis.
Traditional cascade

Syphilis is a treatable disease and negative outcomes can be avoided with timely diagnosis and treatment. The development of opportunities for direct to consumer and/or point of care testing for syphilis may help to remove barriers to testing in the future.

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Test Results</th>
<th>Actions</th>
</tr>
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<tbody>
<tr>
<td>Rapid Plasma Reagin (RPR) Test with Reflex to Treponema pallidum Ab</td>
<td>Non-reactive</td>
<td>No laboratory evidence of syphilis infection</td>
</tr>
<tr>
<td></td>
<td>Reactive</td>
<td>RPR, Quantitative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Reactive ≥1:1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treponemal antibody</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Negative</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Non-Treponemal antibodies detected. Syphilis unlikely; biological false positive possible.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Treponemal and Non-Treponemal antibodies detected. Consistent with past or current (potential early) syphilis.</td>
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Labcorp is proud to be at the forefront for offering a comprehensive suite of STI testing options. For more information on test options and how our STI portfolio can support the goals of the STI National Strategic Plan: 2021–2025, click here.

January Health Awareness Calendar

- Cervical Health Awareness Month
- National Birth Defects Prevention Month

References