**Abstract:** Rapid emergence of syphilis and oral sexual behaviors has focused attention on oral syphilis, and published reports of cases with oral syphilis have increased in the recent decades. We performed a systematic literature review by searching articles from PubMed, EMBASE, and Google Scholar, looking for case reports or series that would potentially have the clinical characteristics and outcomes for each individual case with oral syphilis. A total of 145 cases with the infection, from 95 studies, were identified to include in our review. Two main clinical phenotypes (ulcerative lesions and mucous patches) appeared to be of particular relevance to oral manifestations. A solitary ulcer was mostly manifested as the lesion of primary syphilis (91.7%) preferentially located on the upper lip, tongue, palate, and buccal mucosa. The most affected anatomical site in the patients with single location involved was the tongue (37.5%), followed by the lips (29.5%), palates (19.3%), and buccal mucosa (6.8%). It is concluded that oral syphilis has its predominant clinical phenotypes although it can manifest in diverse manners.

Syphilis is still a major global health issue with an important burden of disease, particularly in low-income countries, in which its prevalence is highest. The incidence of syphilis has increased during the last decades in many high-income countries particularly because of outbreaks of the disease among gay, bisexual, and other men who have sex with men (GBMSM). Syphilis presents in 3 stages denoted as primary, secondary, and tertiary syphilis. A person with primary or secondary syphilis who has a sore or a rash can pass the infection to others. The primary lesion appears at the site of infection, mainly occurring on the external genitals, vagina, anus, or rectum, and secondary syphilis can result in systemic spread of the spirochetes beyond the primary infection site to affect many organs mostly presenting with dermatologic, rheumatologic, neurologic, and ocular signs. Because of the changing sexual habits particularly among GBMSM, presentation of oral manifestations may rise. In recent decades, an increasing number of cases with oral syphilis have been reported. In addition, along with increasing practice of fellatio in sexual behaviors particularly among GBMSM, the mouth can be the initial site of the infection. In this study, we conducted a systematic review through collecting, analyzing, and summarizing the clinical findings related to oral manifestations of early syphilis in adults from peer-reviewed studies published worldwide.

**MATERIALS AND METHODS**

**Search Strategies**

The guidelines for the preferred reporting items for systematic reviews and meta-analyses statement (PRISMA) were adhered to in this systematic review. Electronic literature search was in databases of MEDLINE (via PubMed), EMBASE, Google Scholar to identify the studies matching the following combinations of MeSH Terms (syphilis OR *Treponema pallidum* OR *T. pallidum*) and keywords (oral OR mouth OR tongue OR lip) for identifying articles published between January 1, 2000, and January 31, 2021. References and citations of the identified articles were further searched manually for additional relevant studies.

**Eligibility Criteria**

English published case reports or series reporting information of clinical manifestations related to syphilis in oral cavity (mouth), or on tongue or lip were included in this systematic review. Only cases with adult (acquired) syphilis were included, and cases with congenital or tertiary syphilis were excluded. Narrative reviews, commentaries, epidemiological survey articles, and conference abstracts were excluded.

**Literature Screening**

The literature screening was based on a 2-step process. First, titles and abstracts of all identified citations were downloaded and
preliminarily reviewed for inclusion to full text review. Second, full texts were assessed for eligibility according to the abovementioned inclusion and exclusion criteria. The PRISMA flowchart (Fig. 1) illustrates a summary of the literature search and screening strategies.

**Data Extraction and Management**

Extracted data from each of the included case reports consisted of the publication information, demographic and behavioral variables of the patient, duration of symptoms, human immunodeficiency virus (HIV) infection status, clinical presentations, serological testing for syphilis, pathological findings, stage of syphilis, and treatment regimen and outcome. Extracted data from the included case series consisted of the number of cases in addition to the abovementioned data.

**Data Analysis**

The extracted information was synthesized qualitatively or quantitatively. The details of the cases were classified to create categories that would facilitate comparison between the classifications. Pooled descriptive analyses were conducted for the initial data analysis. The prespecified subgroups were compared using \( \chi^2 \) test for categorical covariates and \( t \) test for continuous covariates. Statistical significance was defined as a \( P \) value of 0.05 or less. All analyses were performed using SPSS, version 22 (IBM SPSS, Chicago, IL) and MedCalc, version 11.1 (MedCalc, Mariakerke, Belgium).

**RESULTS**

**Literature Selection**

We identified a total of 5571 publications including 413 from PubMed, 2379 from EMBASE, 2775 from Google Scholar, and 4 from reference lists of identified articles. After 800 duplicated and 4491 irrelevant articles were excluded, 280 articles were assessed through a full-text review for eligibility. Among these 280 articles, 185 were further excluded. The most common reasons for exclusion were (1) conference abstracts or posters (n = 44); (2) articles not in English (n = 41); (3) irrelevant studies (n = 29); or (4) narrative review or comment articles (n = 20). Fifteen, 13, and 12 articles were excluded because they were relevant to epidemiology surveys, pharyngeal and tertiary or congenital syphilis, respectively. Five studies were excluded because it lacked information of clinical manifestations. Of the 95 studies finally included in the systematic review (79 case reports and 16 case series) report a total of 145 cases, Figure 1. Of the 145 included cases, 33.1% were reported from countries in South America, 7.6% from North America, 37.2% from Europe, and 22.1% from Asia.

**Sociodemographic and Behavior Information**

Among the 145 cases, 97 (66.9%) were men, with a significantly higher male proportion reported in North America or Europe (≥80%) than South America or Asia (<60%; \( \chi^2 = 12.39, P = 0.006; \) Table S1, http://links.lww.com/OLQ/A736). Age ranged from 17 to 83 years, with a mean and standard deviation of 37.3 and 21.2.
13.3 years. The cases reported from North America or Europe (40.0 ± 12.6) were elder than those from South America or Asia (35.1 ± 13.6; \( t = 2.24, P = 0.03 \)). Male cases (39.6 ± 14.0 years) were also elder than female cases (32.5 ± 10.5 years; \( t = 3.06, P = 0.003 \)). Among 28 male cases that reported their sexual orientation, 21 admitted a homosexual or bisexual behavior and majority (85.7%) of them were reported from Europe or North America (\( \chi^2 = 14.56, P = 0.002 \); Table S1, http://links.lww.com/OLQ/A736). Less than half of the reported cases (58, 40.0%) were assessed for risk of sexual behaviors, and less than one fourth (34, 23.4%) provided information on oral sex behaviors.

**Diagnosis of Syphilis**

Syphilis diagnosis was essentially based on serological assays to detect treponemal (TP) and non-TP (NTP) antibodies. Majority of the reported cases were diagnosed using serological reactivity for both NTP and TP (126, 80.0%). Among them, 4.8% (7) and 16.6% (24) cases were tested for specific IgG and IgM. The median titer was 1:64 (range: 1:4 to >1:2048) in 91 cases for NTP. In addition, 2.1% (3) cases were diagnosed by darkfield microscopy and 6.9% (10) with TP-PCR. Among 81 cases reporting NTP . In addition, 2.1% (3) cases were diagnosed by darkfield microscopy. The median activity for both NTP and TP (126, 80.0%). Among them, 4.8% (7) cases were diagnosed by serological reactivity for both NTP and TP (126, 80.0%). Among them, 4.8% (7) and 16.6% (24) cases were tested for specific IgG and IgM.

**TABLE 1. Distribution of Clinical Manifestations Related to Syphilis by Anatomical Site of Oral Cavity**

| Lesions by Clinical Manifestation, n (%) | No. Cases | Ulcer | Mucous Patch | Nodule | Lesions by Clinical Manifestation, n (%) | No. Cases | Ulcer | Mucous Patch | Nodule |
|-----------------------------------------|-----------|-------|--------------|--------|-----------------------------------------|-----------|-------|--------------|--------|
| Anatomic location                        |           |       |              |        |                                         |           |       |              |        |
| Tongue                                  | 62 (42.8) | 31 (50.0) | 27 (43.5) | 4 (6.5) | 33 (37.5)                              | 21 (63.6) | 9 (27.3) | 3 (9.1)     |
| Lip                                     | 24 (16.0) | 16 (66.7) | 8 (33.3) | 0       | 13 (14.8)                              | 11 (84.6) | 2 (15.4) | 0            |
| Lower lip                               | 15 (40.5) | 20 (54.1) | 2 (5.4) | 16 (18.2) | 8 (50.0)                              | 6 (37.5)  | 2 (12.5) |              |
| Nonspecific                             | 7 (4.8)   | 3 (42.8) | 4 (57.1) | 0       | 1 (1.1)                               | 0         | 1 (100.0) | 0            |
| Lip—total†                              | 26 (29.5) | 18 (69.2) | 6 (23.1) | 2 (7.7) |                                         |           |       |              |        |
| Palate                                  | 19 (13.1) | 8 (42.1) | 10 (52.6) | 1 (5.3) | 6 (6.8)                                | 4 (66.7)  | 1 (16.7) | 1 (16.7)     |
| Hard palate                             | 10 (45.5) | 4 (80.0)  | 0       | 0       | 5 (25.0)                              | 2 (100.0) | 0       | 0            |
| Non-specific                            | 16 (11.0) | 8 (50.0)  | 8 (50.0) | 0       | 6 (6.8)                                | 4 (66.7)  | 2 (33.3) | 0            |
| Palate—total†                           | 17 (19.3) | 11 (64.7) | 5 (29.4) | 1 (5.9) |                                         |           |       |              |        |
| Buccal mucosa                           | 12 (19.3) | 13 (22.2) | 28 (47.1) | 1 (1.7) | 6 (6.8)                                | 4 (66.7)  | 2 (33.3) | 0            |
| Commissure                              | 13 (9.0)  | 8 (61.5) | 5 (38.5) | 0       | 4 (32.5)                              | 3 (75.0)  | 1 (25.0) | 0            |
| Tonsil                                  | 6 (4.1)   | 2 (33.3) | 4 (80.0) | 0       | 0                                     | 0         | 0       | 0            |
| Uvula                                   | 5 (3.4)   | 1 (20.0) | 4 (80.0) | 0       | 0                                     | 0         | 0       | 0            |
| Vestibular                              | 4 (28.6)  | 2 (50.0) | 2 (50.0) | 0       | 1 (100.0)                             | 0         | 0       | 0            |
| Lingual frenulum                        | 3 (21.4)  | 2 (66.7) | 1 (33.3) | 0       | 0                                     | 0         | 0       | 0            |
| Gingiva/gum                             | 3 (21.4)  | 1 (33.3) | 2 (66.7) | 0       | 1 (100.0)                             | 0         | 0       | 0            |
| Floor of mouth                          | 2 (1.4)   | 1 (50.0) | 0       | 1 (50.0) | 0                                     | 0         | 0       | 0            |
| Stage of syphilis                       |           |       |              |        |                                         |           |       |              |        |
| Primary                                 | 29 (20.0) | —     | —           | —      | 24 (27.3)                              | 22 (91.7) | 2 (8.3) | 0            |
| Secondary                               | 91 (62.8) | —     | —           | —      | 46 (52.3)                              | 23 (50.0) | 18 (39.1) | 5 (10.9)    |
| Early (no staging)                      | 20 (13.8) | —     | —           | —      | 13 (14.8)                              | 9 (69.2)  | 4 (30.8) | 0            |
| Primary and secondary                   | 5 (3.4)   | —     | —           | —      | 5 (57)                                | 4 (80.0)  | 0       | 1 (20.0)    |
| Total†                                  | 145       | —     | —           | —      | 88                                     | 58 (65.9) | 24 (27.3) | 6 (6.8)     |

*Ulcer includes chancre, and ulcerative or erosive lesion; mucous plaque includes mucous patch, reddish patch or whitish patch, and plaque; nodule includes nodular, popular or papillomatous lesion.

†The sum of cases with lesions in anatomical sites may be larger than the total number of the included cases (n = 145) because some cases may have more than one location with the lesion.

**Clinical Manifestations**

Of the cases with information of whether the lesions were only isolated in oral cavity, more than half (55/95; 57.9%) were accompanied with extraoral manifestations, particularly among cases with secondary syphilis (\( P = 0.001 \); Table S2, http://links.lww.com/OLQ/A736). They mostly involved the skin, palm, and genital mucosa. The clinical manifestations by anatomical site are summarized in Table 1. Of the 145 reported cases, the tongue was mostly affected (62, 42.8%) followed by lips (58, 40.0%) and palates (49, 33.8%). Single anatomical site was involved in 60.7% (88) cases, and multiple sites were in half of cases with secondary syphilis (49.5%). Among the cases with single site involved, 2 main clinical phenotypes appeared to be of particular relevance to oral manifestations: ulcerative lesions (58, 65.9%) and mucous patches (24, 27.3%). Nodular, popular, or papillomatous lesion alone was rarely presented as a single clinical symptom (6, 6.8%). The distributions of clinical signs on lips or palates were generally not different across anatomical sites but the patients with ulcerative lesions were more likely to be diagnosed as primary syphilis, whereas patients with secondary syphilis were more likely to have mucous patches (\( \chi^2 = 16.21, P = 0.013 \)). The sites affected were not significantly different between men and women, although the upper lip seemed more influenced than the lower in men (60.0% vs 26.7%), whereas the inverse happened in women (45.5% vs 27.3%), Table 2.
The tongue was more likely to be affected among older cases as compared with other anatomical sites ($\chi^2 = 19.17, P = 0.024$; Table 2).

### Histopathological Findings

Around half of the included cases (70, 48.3%) undertook the histopathological examination. The histologic findings were generally nonspecific, indicating the epithelial changes and inflammatory infiltrations with mainly plasma cells (62.9%), as well as other inflammatory cells, such as lymphocytes, and histocytes. Immunohistochemistry was conducted among 10 cases to identify the spirochete histologically.

### Treatment Regimens and Outcomes

Majority of the cases (138, 95.2%) reported a treatment regimen. Among them, intramuscular injection of benzathine penicillin G (BPG) at 2.4 or 1.2 million units per week for 1 to 4 weeks was used in most cases (92.0%). Three cases were treated with intramuscular injection of benzathine procaine penicillin in an aim to prevent the potential of developing neurosyphilis and 4 cases (2.9%) were treated with amoxicillin. Other regimens used in cases who were allergic to penicillin included lin G (BPG) at 2.4 or 1.2 million units per week for 1 to 4 weeks in 94.6% cases and additional 4.5% obtained partial remission, complete or significant remission of the oral symptoms was observed in 9.5% cases.

Table 2). Of the 112 cases reporting clinical outcomes of the treatment, complete or significant remission of the oral symptoms was observed in 94.6% cases and additional 4.5% obtained partial remission. One case treated with oral azithromycin did not obtain a clinical remission.

### DISCUSSION

Although the case with oral syphilis was reported by literature as early as in 1904, there were relatively few case reports published before 2000, most of which were reported in 1950s. However, such cases have been appeared increasingly in the recent 2 decades probably due to an increasing behavior related to exposure of oral cavity to the infections. Oral sex involves using the mouth, lips, or tongue to stimulate the penis (fellatio), vagina (cunnilingus), or anus (anilingus) of a sex partner. It has been noted that oral sex has become increasingly common among homosexual populations. However, oral sex is also prevalent among heterosexual populations. A questionnaire survey among 2116 men and 2140 women in the United States indicated that majority of men (85.4%) and women (83.2%) had performed oral sex. An online survey among 899 heterosexual university students who reported on their sexual activities in their most recent sexual encounter indicated that over two thirds of participants reported their involvement of either giving or receiving oral sex, or both of these activities.

Theoretically, transmission of HIV is possible if an HIV-positive man ejaculates in his partner’s mouth during oral sex, but the risk of getting or transmitting HIV from oral sex (0%–0.04% transmission probability per sexual act) is still much lower than with anal or vaginal sex. However, this risk is relatively high for syphilis transmission (1.0% transmission probability per act) during primary and secondary syphilis, particularly in the mouth with oral ulcers, or genital sores. Oral syphilitic lesions have become the most common extragenital signs of the infection. However, the large spectrum of their clinical appearances can make the diagnosis a challenge for the oral health care (OHC) providers, such as stomatologists, odontologists, or dentists, leading to a delay in diagnosis or misdiagnosis.

Oral lesions are usually stated by patients as the reason for seeking medical care, whereas OHC providers are usually the first to examine the lesions. An oral lesion may be the first or the only sign of the infection and is usually not firstly considered as syphilis for confirming the diagnosis. Oral manifestations of syphilis may mimic many disease processes and be clinically unspecific. Early detection of the primary infection varied across the regions as indicated in our study. Countries in Europe and North America may have better access of patients to health care and efficient facilities to make a detection of primary infection. In contrast, this detection may be delayed in most of resource-limited settings. The proportion of primary syphilis in our study (<10%) is consistent to that found in a recent epidemiological study in Brazil. Based on our systematic review, 2 main clinical phenotypes of oral manifestations (ulcerative or erosive lesions and mucous patches) were identified to be of particular relevance to oral syphilis. It was reported that the upper lip was more commonly affected than the lower in men, whereas the opposite occurs in women, which was explained by probably reflecting the anatomy involved with fellatio and cunnilingus. Our study echoes this observation but the gender-specific anatomical preference is not statistically significant.
Serologic tests are still essential in making the diagnosis of oral syphilis. Two types of serologic tests (TP and NTP tests) should be used for the diagnosis. However, there were still 13.8% cases who undertook only NTP test partly because of unavailability or unaffordability of TP tests. It is known that the sensitivity of the NTP tests, such as rapid plasma reagin and venereal disease research laboratory is relatively low (estimated 78%–86%) for detecting primary syphilis infection.109 If only NTP test is used, around 15% to 25% of primary syphilis cases could be missed. A recent study indicates that the rapid TP testing with oral fluid specimen (eg, saliva) has shown a high sensitivity for identifying infection of syphilis, particularly for the active infection with high NTP antibody (eg, rapid plasma reagin) titer of 1:8 or greater to achieve a sensitivity of 92%.106 This oral fluid-based test may be useful for screening of syphilis in patients in the OHC settings because majority of the cases reported to have oral syphilis (98.9%, 90/91) had a NTP titer of 1:8 or greater. Although dark-field microscopic examination was conducted in some of reported cases, this method is usually not recommended for examination of oral lesions since another TP organism is normally present in the oral cavity and can confuse diagnosis.111 Biopsies of oral lesions are occasionally the first examination requested by the health providers, but histopathologic findings are not always helpful because of they are usually considered nonspecific. However, a study indicates that combination of plasma cell arteritis and plasma cell neuritis may be specific enough to direct the clinician toward a diagnosis of syphilis prior to clinical confirmation.112 Diagnosis of oral syphilis may also be aided by detailed examination of sexual and/or social lifestyles of a patient and of any of the available sexual partner. However, information on risk behaviors was collected or reported in only one third of the reported cases, and the sexual orientation or oral sex behavior was even less reported. Penicillin is still highly effective for treatment of syphilis and BPG has been widely recommended by the guidelines of World Health Organization and many countries as the first-line regimen for treatment of early syphilis.113,114 There are not specific recommendations for treatment of oral syphilis in these guidelines. However, unlike HIV infections in which oral lesions could be used as an indicator of the disease severity because of its effects on CD4+ T-cell count and increased viral load,115 oral lesions are not considered as a risk factor of the disease severity.116 Therefore, oral syphilis at the early stage can be treated with the same recommended regimens as those for cutaneous-genital syphilis. A good response indicated by clinical remissions was observed in all cases treated with the first-line or alternative regimens except 1 case treated with azithromycin probably due to resistance to this drug.117 Although our systematic review indicates a similar clinical response of parenteral penicillin with other regimens, quite a few reported cases were treated with nonpenicillin regimens. Therefore, BPG is still the first-line recommendation for early syphilis including oral syphilis. However, shortages of BPG have been reported by many high-morbidity countries,118 as well as some developed countries, including Japan.119 In clinical practice, presumptive or empirical therapy for syphilis may be worthwhile to consider in cases with a strong suspicion for oral syphilis and unavailability of serological testing. The expedient response to treatment could confirm the diagnosis.

Our systematic review has several strengths. The review represents the first systematic analysis of reported cases with oral syphilis in which the extensive literature searches and a synthesized analysis of all the available reports was conducted. Moreover, it included relatively large number of cases and may be among the first studies focused on subgroup and comparative analyses, which is impossible for any small number of cases, as well as the case series study design to perform. However, several limitations inherent in this review should be highlighted, although many of them are inherently related to the nature of case reports or series design. First, although our literature searches may be comprehensive enough to capture the case reports and series published during the recent 2 decades, only articles in English were included in the review, potentially resulting in selection bias. Second, reporting and/or publication bias resulting in the potential incompleteness of the evidence is also a concern. For example, a disproportionate number of cases with isolated lesions were more likely to be submitted as case reports for publication by dentists, whereas those cases with extraoral (cutaneous) manifestations could be managed by dermatologists who might not report these cases as oral syphilis. Third, potential heterogeneity across the included studies in terms of definitions of stage-specific cases, clinical manifestations, and laboratory assays may limit us to make a correct synthesis of these data. Finally, this review sought to retrospectively evaluate the data from each of published cases. Despite these limitations, the findings from our review can provide important insights into the clinical features, as well as case management of oral syphilis for dermatovenerologist and oral care providers.

In conclusion, our systematic review indicates the need to include syphilis in the differential of oral ulcers, mucous patches, as well as other lesions, in the OHC settings. Further multicenter prospective observational studies or retrospective chart reviews using a uniform study protocol may be required to provide a substantial basis for characterizing this disease. In addition, a specific guideline on management of oral syphilis, as well as a training program, may be helpful for improving the capacity of OHC providers to respond to rapid emergence of syphilis.

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For further references, please see “Supplemental References,” http://links.lww.com/OLQ/A736.