The global epidemiology of Haemophilus ducreyi infections is poorly documented because of difficulties in confirming microbiological diagnoses. We evaluated published data on the proportion of genital and nongenital skin ulcers caused by H. ducreyi before and after introduction of syndromic management for genital ulcer disease (GUD). Before 2000, the proportion of GUD caused by H. ducreyi ranged from 0.0% to 69.0% (35 studies in 25 countries). After 2000, the proportion ranged from 0.0% to 15.0% (14 studies in 13 countries). In contrast, H. ducreyi has been recently identified as a causative agent of skin ulcers in children in the tropical regions; proportions ranged from 9.0% to 60.0% (6 studies in 4 countries). We conclude that, although there has been a sustained reduction in the proportion of GUD caused by H. ducreyi, this bacterium is increasingly recognized as a major cause of nongenital cutaneous ulcers.
**Haemophilus ducreyi**, a fastidious gram-negative bacterium, is the causative agent of chancroid, a genital ulcer disease (GUD). The organism is usually spread during sexual intercourse through microabrasions, and the disease usually manifests as multiple painful superficial ulcers associated with inguinal lymphadenitis (1). As a result of the painful nature of the lesions, patients usually seek immediate treatment, and asymptomatic carriage is therefore uncommon (2). In addition to causing GUD, *H. ducreyi* has been found in several recent studies to be a major cause of chronic skin ulceration in children from developing countries (3–6).

The global epidemiology of chancroid is poorly documented, and it is not included in World Health Organization estimates of the global incidence of curable sexually transmitted infections (STIs). There are some key challenges in interpreting data on the epidemiology of *H. ducreyi* as a causative agent of GUD. First, genital herpes cases are easily misdiagnosed as chancroid on clinical examination. Thus, reports based only on clinical diagnosis can be erroneous. Second, laboratory culture is technically difficult, and the highly sensitive and specific nucleic acid amplification tests, such as PCR, are rarely available outside national reference laboratories or specialized STI research settings, which makes it difficult to confirm clinical diagnoses.

Determination of the true global incidence of chancroid is made more difficult by widespread adoption of syndromic management for bacterial GUD (i.e., treatment with antimicrobial drugs effective against syphilis and chancroid) without microbiological confirmation in many countries. Therefore, countries often report only the total number of GUD cases. In addition, identification of GUD etiology is rarely conducted in resource-poor countries to validate syndromic management for which chancroid could also be common.

Earlier studies of tropical skin ulcers did not generally test for *H. ducreyi*, with the exception of a small number of case reports (7–11). There are major limitations in describing the prevalence of causative agents in tropical skin lesions that typically occur in children in rural areas where there is no access to laboratory facilities. Pathogens such as *Fusobacterium fusiforme*, *Staphylococcus aureus*, and *Streptococcus pyogenes* have been reported from Gram staining of exudative material collected from tropical ulcers (12). However, cultures or PCR testing for definitive identification of fastidious pathogens involved has not been traditionally conducted. The purpose of this study was to improve our understanding of the epidemiology of *H. ducreyi* infection through a systematic review of published data on the proportion of genital and skin ulcers caused by this bacterium.

**Methods**

**Search Strategy and Selection Criteria**
A systematic review was conducted to identify all relevant studies that examined the etiology of GUD and nongenital skin ulcers involving *H. ducreyi*. We searched the National Library of Medicine through PubMed for “*H. ducreyi*,” “chancroid,” “genital ulcer,” OR “skin ulceration” AND “proportion” OR “prevalence.” The search was limited to studies published during January 1, 1980–December 31, 2014. In addition, we searched references of identified articles and other databases for other articles, and we reviewed abstracts, titles, and selected studies potentially containing information on chancroid epidemiology. We contacted researchers who were working with *H. ducreyi* to identify unpublished literature for inclusion. No language restrictions were set for searches.

The decision tree for inclusion or exclusion of articles is shown in Figure 1. We included studies if the proportion of etiologic agents in genital ulcers and nongenital skin ulcers, including *H. ducreyi*, was confirmed by laboratory techniques. Clinical diagnosis of chancroid is often based on the appearance of the ulcer, which is characteristically painful, purulent, and deep with ragged, undermined edges (Figure 2). However, because the appearance of these ulcers is similar to ulcers caused by other bacteria, clinical diagnosis can be nonspecific or insensitive and often requires laboratory confirmation (1). In addition, microscopy identification of typical morphologic features and serologic detection lack sensitivity and specificity (13,14). Thus, we only considered the following diagnostic methods as providing acceptable evidence of *H. ducreyi* infection: 1) isolation and identification by culture; or 2) PCR/real-time PCR.

**Data Extraction and Synthesis**
For all qualifying studies, extracted data included study country, year of study, diagnostic test used for confirmation, total number of *H. ducreyi*-positive cases, and sample size. Descriptive analyses of extracted data were conducted, and the number of *H. ducreyi*-confirmed cases was divided by the total number of cases to calculate the proportion of cases caused by *H. ducreyi*. Studies qualifying for data extraction were grouped into 2 categories: studies conducted before 2000 and studies after 2000. This date separates studies before and after widespread implementation of syndromic management of GUD. Study sites were also plotted by geographic region. No quantitative meta-analysis was undertaken.

**Results**
We identified 277 records in which we found 46 articles describing 49 studies on GUD that met our inclusion...
Epidemiology of Haemophilus ducreyi Infections

277 unique articles identified by database research

177 articles excluded after review of abstract:
5 duplicate
3 repeated data
27 reviews
11 only data on other GUDs
35 on other STIs
17 on immunology or genetics
15 metaanalysis
13 on diagnostic tools
31 on treatment and control

Full text review of 90 articles of genital lesions plus 10 on nongenital lesions

45 articles excluded after review of full text:
6 repeated data from other papers
39 did not use diagnostic tools that met our criteria

55 articles included in qualitative analyses (describing 60 studies)
46 articles on chancroid (describing 49 studies)
9 articles on skin ulcers (describing 9 studies)
2 unpublished studies on skin ulcers

Figure 1. Procedure for selecting eligible references on the epidemiology of Haemophilus ducreyi as a causative agent of genital ulcers. GUDs, genital ulcer disease; STI, sexually transmitted infections.

Figure 2. Ulcers caused by infection with Haemophilus ducreyi. A, B) Genital ulcers in adult patients from Ghana (provided by David Mabey). C, D) Skin ulcers in children from Papua New Guinea (provided by Oriol Mitjà).
Laboratory confirmation of chancroid by PCR or culture was reported in 33 (67%) and 16 (32%) of the 49 studies, respectively. Of 16 studies that used culture, 7 (43%) used Mueller-Hinton agar with a nutritional supplement (e.g., IsoVitalex; Becton Dickinson, Franklin Lakes, NJ, USA), 1% used hemoglobin, and 5 (31%) used chocolate agar–based media; the remaining studies used other culture media. Five (31%) of 16 studies incubated agar plates at low temperatures (33°C–35°C), and 2 (12%) incubated plates at 36°C. Remaining articles did not specify incubating temperature.

Different PCR primer targets were used to amplify DNA sequences, including the 16S rRNA gene, the groEL gene, and the hemolysin gene. In addition to herpes simplex virus (HSV) PCR, 23 studies used a multiplex PCR that could simultaneously detect the 3 major causes of GUD (H. ducreyi, Treponema pallidum, and HSV types 1 and 2) (15). Studies encompassed 33 countries: 17 in Africa, 4 in Southeast Asia, 3 in Europe, 2 in the Middle East, 3 in South America, and 2 in the Caribbean, 1 in the United States, and 1 in Australia.

### Incidence of Chancroid

Of 49 studies on chancroid analyzed, 35 were published during 1980–1999 (Table 1) and 14 during 2000–2014 (Table 2). In general, data showed a clear decrease in the proportion of chancroid during 1980–2014 in all areas analyzed (Figure 3).

### Table 1. Characteristics of 35 studies of genital ulcers caused by *Haemophilus ducreyi*, 1980–1999*

<table>
<thead>
<tr>
<th>Area, reference†</th>
<th>Country</th>
<th>Year of study</th>
<th>Diagnostic method</th>
<th>No. patients with GUD</th>
<th>No. cases <em>H. ducreyi</em> infection</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Africa</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Paz-Bailey et al. (16)</td>
<td>Botswana</td>
<td>1993</td>
<td>Culture</td>
<td>108</td>
<td>27</td>
<td>25.0 (17.7–33.9)</td>
</tr>
<tr>
<td>Steen (17)</td>
<td>Côte d'Ivoire</td>
<td>1996</td>
<td>PCR</td>
<td>NA</td>
<td>NA</td>
<td>47</td>
</tr>
<tr>
<td>Mabey et al. (18)</td>
<td>Gambia</td>
<td>1987</td>
<td>Culture</td>
<td>104</td>
<td>54</td>
<td>51.9 (42.4–61.2)</td>
</tr>
<tr>
<td>Hawkes et al. (19)</td>
<td>Gambia</td>
<td>1995</td>
<td>M-PCR</td>
<td>18</td>
<td>8</td>
<td>44.4 (24.5–66.2)</td>
</tr>
<tr>
<td>Nsanze et al. (20)</td>
<td>Kenya</td>
<td>1980</td>
<td>Culture</td>
<td>97</td>
<td>60</td>
<td>61.8 (51.9–70.9)</td>
</tr>
<tr>
<td>Kaul et al. (21)</td>
<td>Kenya</td>
<td>1997</td>
<td>Culture</td>
<td>189</td>
<td>54</td>
<td>28.5 (22.6–35.3)</td>
</tr>
<tr>
<td>Morse et al. (22)</td>
<td>Lesotho</td>
<td>1994</td>
<td>M-PCR</td>
<td>105</td>
<td>55</td>
<td>53.3 (43.8–62.6)</td>
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<tr>
<td>Harms et al. (23)</td>
<td>Madagascar</td>
<td>1992</td>
<td>Culture</td>
<td>12</td>
<td>61</td>
<td>19.8 (11.6–31.3)</td>
</tr>
<tr>
<td>Behets et al. (24)</td>
<td>Madagascar</td>
<td>1997</td>
<td>M-PCR</td>
<td>196</td>
<td>64</td>
<td>32.6 (26.4–39.5)</td>
</tr>
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<td>Behets et al. (25)</td>
<td>Malawi</td>
<td>1995</td>
<td>M-PCR</td>
<td>778</td>
<td>204</td>
<td>26.2 (23.2–29.4)</td>
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<tr>
<td>Hoyo et al. (26)</td>
<td>Malawi</td>
<td>1999</td>
<td>M-PCR</td>
<td>137</td>
<td>41</td>
<td>29.0 (22.8–36.0)</td>
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<tr>
<td>Bogaerts et al. (27)</td>
<td>Rwanda</td>
<td>1992</td>
<td>Culture</td>
<td>395</td>
<td>115</td>
<td>29.1 (24.8–33.7)</td>
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<td>Totten et al. (28)</td>
<td>Senegal</td>
<td>1992</td>
<td>PCR</td>
<td>39</td>
<td>22</td>
<td>56.4 (40.9–70.7)</td>
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<tr>
<td>Crewe-Brown et al. (29)</td>
<td>South Africa</td>
<td>1981</td>
<td>Culture</td>
<td>100</td>
<td>45</td>
<td>45 (35.5–54.7)</td>
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<tr>
<td>Dangor et al. (30)</td>
<td>South Africa</td>
<td>1989</td>
<td>Culture</td>
<td>240</td>
<td>164</td>
<td>68.3 (62.2–73.8)</td>
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<tr>
<td>Chen et al. (31)</td>
<td>South Africa</td>
<td>1994</td>
<td>M-PCR</td>
<td>538</td>
<td>171</td>
<td>31.7 (27.9–35.8)</td>
</tr>
<tr>
<td>Lai et al. (32)</td>
<td>South Africa</td>
<td>1994</td>
<td>M-PCR</td>
<td>160</td>
<td>232</td>
<td>68.9 (62.7–74.5)</td>
</tr>
<tr>
<td>Meheus et al. (33)</td>
<td>Swaziland</td>
<td>1979</td>
<td>Culture</td>
<td>155</td>
<td>68</td>
<td>43.9 (38.3–51.7)</td>
</tr>
<tr>
<td>Ahmed et al. (34)</td>
<td>Tanzania</td>
<td>1999</td>
<td>PCR</td>
<td>102</td>
<td>12</td>
<td>11.7 (6.8–19.4)</td>
</tr>
<tr>
<td>Le Bacq et al. (35)</td>
<td>Zimbabwe</td>
<td>1991</td>
<td>Culture</td>
<td>30</td>
<td>22</td>
<td>24.4 (16.7–34.2)</td>
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<td><strong>Asia</strong></td>
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<tr>
<td>Wang et al. (36)</td>
<td>China</td>
<td>1999</td>
<td>M-PCR</td>
<td>96</td>
<td>0</td>
<td>0.0 (0.0–3.8)</td>
</tr>
<tr>
<td>Risbud et al. (37)</td>
<td>India</td>
<td>1994</td>
<td>M-PCR</td>
<td>302</td>
<td>84</td>
<td>27.8 (23.0–33.1)</td>
</tr>
<tr>
<td>Rajan et al. (38)</td>
<td>Singapore</td>
<td>1983</td>
<td>Culture</td>
<td>670</td>
<td>56</td>
<td>8.3 (6.4–10.7)</td>
</tr>
<tr>
<td>Beyrer et al. (39)</td>
<td>Thailand</td>
<td>1996</td>
<td>M-PCR</td>
<td>38</td>
<td>0</td>
<td>0.0 (0.0–9.1)</td>
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<tr>
<td><strong>North America</strong></td>
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<td></td>
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<td></td>
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<tr>
<td>Dillon et al. (40)</td>
<td>United States</td>
<td>1990</td>
<td>Culture</td>
<td>82</td>
<td>27</td>
<td>32.9 (23.7–43.6)</td>
</tr>
<tr>
<td>Merz et al. (41)</td>
<td>United States</td>
<td>1995</td>
<td>M-PCR</td>
<td>143</td>
<td>56</td>
<td>39.1 (23.1–47.3)</td>
</tr>
<tr>
<td>Merz et al. (42)</td>
<td>United States</td>
<td>1996</td>
<td>M-PCR</td>
<td>516</td>
<td>16</td>
<td>3.1 (1.9–4.9)</td>
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<tr>
<td><strong>South America</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sanchez et al. (43)</td>
<td>Peru</td>
<td>1995</td>
<td>M-PCR</td>
<td>61</td>
<td>3</td>
<td>4.9 (1.6–13.4)</td>
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<tr>
<td><strong>Caribbean</strong></td>
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<tr>
<td>Sanchez et al. (44)</td>
<td>Dominican Republic</td>
<td>1996</td>
<td>M-PCR</td>
<td>81</td>
<td>21</td>
<td>25.9 (17.6–36.4)</td>
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<tr>
<td>Behets et al. (45)</td>
<td>Jamaica</td>
<td>1996</td>
<td>M-PCR</td>
<td>304</td>
<td>72</td>
<td>23.6 (19.2–28.7)</td>
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<tr>
<td>Bauwens et al. (46)</td>
<td>Bahamas</td>
<td>1992</td>
<td>PCR</td>
<td>47</td>
<td>7</td>
<td>14.8 (7.4–27.6)</td>
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<td><strong>Middle East</strong></td>
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<tr>
<td>Madani et al. (47)</td>
<td>Saudi Arabia</td>
<td>1999</td>
<td>Culture</td>
<td>3,679</td>
<td>78</td>
<td>2.1 (1.7–2.5)</td>
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<tr>
<td><strong>Europe</strong></td>
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</tr>
<tr>
<td>Kyrriakis et al. (48)</td>
<td>Greece</td>
<td>1996</td>
<td>Culture</td>
<td>695</td>
<td>32</td>
<td>4.6 (3.2–6.4)</td>
</tr>
<tr>
<td>Bruisten et al. (49)</td>
<td>The Netherlands</td>
<td>1996</td>
<td>M-PCR</td>
<td>388</td>
<td>3</td>
<td>0.8 (0.2–2.3)</td>
</tr>
</tbody>
</table>

*GUD, genital ulcer disease; NA, not available; M-PCR, multiplex PCR.
During 1980–1999, the proportion of genital ulcers caused by *H. ducreyi* in these studies ranged from 0.0% in Thailand and China to 68.9% in South Africa (Table 1). Eleven (31.4%) studies reported high proportions (>40%) of cases of infection with *H. ducreyi*. All of these studies were conducted in countries in Africa (Côte d’Ivoire, Gambia, Kenya, Lesotho, Senegal, South Africa, and Swaziland). Slightly lower proportions (20%–40% of cases) were observed in 15 (42%) studies: 10 in countries in Africa, 2 in the United States during localized outbreaks, 1 in Jamaica, 1 in the Dominican Republic, and 1 in India.

Only a few countries reported low proportions (<10%) of genital ulcers infected with *H. ducreyi*, including Singapore (8.3%), Peru (5%), Greece (4.6%), the Netherlands (0.9%), United States (3.1%), and Saudi Arabia (2.1%). The study in Saudi Arabia was conducted during 1995–1999; a total of 27,490 patients were examined for STIs. Chancroid was diagnosed by culture and was reported as the least common STI during this survey. The only studies that reported no cases of chancroid were conducted in Thailand in 1996 and China in 1999; both studies used multiplex PCR for detection of GUD cases.

During 2000–2014, the proportion of *H. ducreyi* infections was low (<10%) in all studies analyzed, except for 1 study in Malawi (15%) (Table 2). Studies in 5 countries (Kenya, Namibia, Zambia, Brazil, and Australia) did not report any cases of infection with *H. ducreyi*. Other studies reporting proportions of infections <10% were conducted in Botswana, Mozambique, South Africa, Uganda, Pakistan, and France. No reports were found for studies in North America, Southeast Asia, or the Caribbean.

### Nongenital Skin Infections with *H. ducreyi*

During 1988–2010, several case reports described 4 children and 4 adults with nonsexually transmitted infections with *H. ducreyi* that manifested as lower leg lesions but no genital lesions. The reported case-patients were travelers who had been to Fiji (7), Samoa (8), Vanuatu (9), or Papua New Guinea (10).

### Figure 3.

New Guinea (10) (Table 3). Outside the south Pacific region, a 5-year-old refugee from Sudan who had lower leg ulceration was also given a diagnosis of infection with *H. ducreyi* (11).

A cohort study conducted in Papua New Guinea in 2014 showed evidence that *H. ducreyi* is a major cause of chronic skin ulceration; *H. ducreyi* DNA was identified by PCR in 60.0% of skin lesions in children (3). Similar studies in other areas reported laboratory-confirmed skin ulcers in children caused by *H. ducreyi* in Papua New Guinea (6), Solomon Islands (4), Vanuatu (C.Y. Chen, pers. comm.), and Ghana (5) (Table 3).

### Discussion

Our review confirmed 2 major findings. First, reduction in the proportion of genital ulcers caused by *H. ducreyi* has been sustained for the past decade and a half. Second, there is increasing evidence that *H. ducreyi* is a common and newly recognized causative agent of chronic skin ulceration in children from developing countries.

In the 1990s, the global prevalence of chancroid was estimated to be 7 million (17). Chancroid was one of the most prevalent GUDs, particularly in resource-poor countries in Africa, Asia, Latin America, and the Caribbean (1; reference 51 in online Technical Appendix). Recommendations to introduce syndromic management for treatment of GUD caused by bacteria were published by the World Health Organization in 1991 and fully implemented by 2000 (reference 61 in online Technical Appendix). Since that time, global incidence of GUDs, particularly chancroid, has decreased substantially, and genital herpes viruses (HSV-1 and HSV-2) have become the predominant cause of GUD (reference 53 in online Technical Appendix). Currently in Europe and the United States, chancroid is restricted to rare sporadic cases. Transmission of *H. ducreyi* remains ongoing in only a few countries that have limited access to health services (2,6).

Our data show marked decreases in the proportion of GUD caused by *H. ducreyi* in several countries. Spinola et al. reported similar conclusions obtained from 25 PCR-based studies (reference 62 in online Technical Appendix). For example, in Botswana (16), Kenya, (20), and South Africa (29), the proportion of GUD caused by *H. ducreyi* decreased from 25%–69% to negligible (0.0%–1.2%) levels (16; references 48,52 in online Technical Appendix). Studies in Zambia (reference 56 in online Technical Appendix), Namibia (reference 51 in online Technical Appendix), and China (36) did not report any cases of chancroid during 2000–2009. A study in Thailand reported elimination of chancroid by introduction of a condom use program in the 1990s (reference 63 in online Technical Appendix). Similar decreases have been reported from Cambodia and Sri Lanka, with rapid elimination of chancroid and congenital syphilis in most settings (reference 63 in online Technical Appendix). However, these findings should be interpreted with caution because, given the short duration of infectivity, even a low prevalence of *H. ducreyi* in a population with GUD implies that a reservoir of infected persons with a high rate of sex partners is present.

Recent research has identified *H. ducreyi* as a previously unrecognized cause of nongenital skin ulcers in tropical areas. In 2013–2015, six studies in Papua New Guinea (3,6), the Solomon Islands (4), Vanuatu (C.Y. Chen et al., pers. comm.), and Ghana (5; C.Y. Chen et al., pers. comm.) showed that a high proportion of laboratory-confirmed skin ulcers were caused by *H. ducreyi*. Nearly half of the 690 enrolled patients with ulcers in these 6 studies had *H. ducreyi* detectable by PCR, whereas other bacteria, such as *T. pallidum* subsp. *pertenue*, the causative agent of yaws, were detected in 25% of patients.

These cases of infection with *H. ducreyi* confirmed by molecular analysis suggest that clinicians should be more aware of this newly recognized bacterium in skin ulcers of persons in tropical areas. In the context of new efforts to eradicate yaws, mass treatment with azithromycin in
Papua New Guinea reduced the absolute prevalence of ulcers not caused by yaws, which were mainly caused by *H. ducreyi*, from 2.7% to 0.6% (prevalence ratio 0.23, 95% CI 0.18–0.29) at 12 months after treatment (6). However, persistence of *H. ducreyi* at low levels after mass treatment in Papua New Guinea (3) and Ghana (5) suggest that 1 round of mass treatment might not be successful in eradicating *H. ducreyi* skin ulcers.

Our review has several limitations. First, the increase in HSV-related GUD as a result of immunosuppression by HIV infection would result in a decrease in the proportion of chancroid among all GUD case-patients. Second, the lack of sequential studies performed in similar clinical settings at multiple time points precludes an optimal interpretation of the apparent decrease. Third, results might be affected by poor-quality data from many developing countries and might be inflated by publication bias. Fourth, PCR is more sensitive than culture. Therefore, increasing diagnostic yield might have partially masked the scale of the decrease in *H. ducreyi* as a cause of GUD.

In summary, we observed a quantitative and sustained reduction in cases of chancroid as a result of antimicrobial drug syndromic management and major social changes. In addition, data from several research groups indicate that *H. ducreyi* can cause nongenital skin lesions in persons residing in different regions. Further studies of this newly described pathogen skin disease association are required, and appropriate policies are needed that include the routine practice of managing tropical skin ulcers.

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Ms. González-Beiras is a predoctoral fellow at Instituto de Higiene e Medicina Tropical, Lisbon, Portugal. Her primary research interests are strategies for elimination of neglected tropical diseases.

References

Neurocysticercosis—a Parasitic Brain Infection

Dr. Seth O’Neal discusses his article on the economic burden of neurocysticercosis, which is a brain infection caused by Taenia solium larval cysts

http://www2.cdc.gov/podcasts/player.asp?f=8638194
Epidemiology of *Haemophilus ducreyi* Infections

Technical Appendix

References


