



## Commentary

## Flies and Yaws: Molecular Studies Provide New Insight



Lola V. Stamm Ph.D.

Department of Epidemiology, Program in Infectious Diseases, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC 27599-7435, United States

## ARTICLE INFO

## Article history:

Received 17 August 2016

Accepted 18 August 2016

Available online 20 August 2016

Yaws is caused by infection with *Treponema pallidum* subspecies *pertenue* (*TPE*), a spirochete that is very closely related to *T. pallidum* subsp. *pallidum* (*TPA*), the etiologic agent of syphilis (Giacani & Lukehart, 2014; Stamm, 2015). Whereas syphilis is a sexually transmitted disease with a global distribution, yaws is transmitted by direct contact of broken skin with active lesions and primarily affects children who live in poor rural communities in humid, tropical areas of Africa, Southeast Asia and the Pacific Islands. Both syphilis and yaws are chronic, multi-stage diseases that can cause destructive lesions of skin, bone and cartilage. Control of these diseases is based on interrupting transmission through the identification and treatment of cases and their contacts. Because of the antigenic similarity of the *T. pallidum* (*TP*) subsp., serological tests that are used for diagnosis of syphilis are also used for diagnosis of yaws, although these tests cannot differentiate the two diseases. However, molecular differentiation of the *TP* subsp. is possible via PCR amplification of polymorphic genomic loci coupled with DNA sequencing (Giacani & Lukehart, 2014).

In 2012, the World Health Organization (WHO) launched a yaws eradication program based on mass azithromycin treatment of individuals in endemic communities followed by clinical and serological surveys to detect and treat remaining cases and their contacts (Giacani & Lukehart, 2014; Stamm, 2015). An earlier WHO campaign conducted in the mid-20th century reduced the number of yaws cases by nearly 95%. However, yaws was not eradicated and when local efforts to prevent new cases failed, yaws resurged.

To date, smallpox is the only infectious disease of humans that has been eradicated. A biological factor that favored smallpox eradication is the lack of a nonhuman reservoir. In contrast to smallpox, a yaws-like disease has been documented in various species of nonhuman primates (NHPs) that reside in areas of Africa where yaws may be present in humans (Knauf et al., 2013; Fribourg-Blanc & Mollaret, 1969; Knauf et al., 2012). Knauf et al. reported a disease that caused skin lesions in baboons at Lake Manyara National Park (LMNP) in Tanzania (Knauf et al.,

2012). These investigators demonstrated the presence of *TP* in the affected baboons' tissues using immunohistochemistry and showed with molecular techniques that the spirochetal agent is very closely related to *TPE*. Although humans can be experimentally infected with a baboon *TP* strain (i.e., Fribourg-Blanc) (Smith et al., 1971) that is highly similar to *TPE*, it is unclear if baboons can serve as a reservoir for human infection and, if so, how yaws could be transmitted from baboons to humans. Knauf et al. hypothesized that insects might function as a mechanical vector for interspecies transmission of *TP* in areas where there is a high prevalence of *TP*-induced skin ulcerations in NHPs (Knauf et al., 2013). The possibility that insects (i.e., flies) act as a vector for yaws merits renewed consideration based on the results of observational and experimental studies that were conducted several decades ago in the pre-molecular era. In 1907, Castellani, who identified *TPE* as the etiologic agent of yaws (Stamm, 2015), noted that non-biting flies "eagerly crowd" on the lesions of yaws patients and "sucking with avidity the secretion" may afterward alight on the broken skin of others, purportedly enabling the transmission of yaws (Castellani, 1907). Castellani demonstrated that *Musca domestica* flies that fed on yaws patients' lesions could transmit yaws to monkeys whose skin had been scarified. Later, Lamborn succeeded in transmitting yaws to a human using *M. sorbens* as the vector (Lamborn, 1936). In 1953, Satchell and Harrison reported that *M. sorbens* and *M. domestica* that fed on yaws lesions for 5 min or less picked up *TPE* on their mouthparts (Satchell, 1953). Microscopic analysis revealed that motile *TPE* were present for up to 2 h in the flies' crop, but that these spirochetes were rarely present in the flies' gut contents. Although the early studies of Castellani and Lamborn showed that flies can act as a vector for yaws in an experimental setting, confirmation of the role of flies as a vector for yaws in a natural setting remained elusive.

An essential criterion to incriminate flies in the transmission of yaws is the demonstration that flies from a yaws-endemic setting harbor viable *TPE*. In their study published in this issue of EBioMedicine, Knauf et al. report the results of molecular interrogation of wild-caught flies from LMNP and Tarangire National Park (TNP) for the presence of *TPE*-like strains (Knauf et al., 2016—in this issue). Knauf et al. detected *TP* DNA in 17–23.5% of 207 flies based on PCR amplification of two or more *TP* genomic loci. Interestingly, *M. sorbens*, which has been shown to transmit yaws in an experimental setting, was one of two fly species at both LMNP and TNP that was disproportionately PCR positive for *TP* DNA. Phylogenetic analysis of the polymorphic *tp0548* locus showed that 23 of 26 *TP* sequences from the flies cluster with sequences from human *TPE* strains and from baboon *TP* strains (i.e., Fribourg-Blanc and LMNP). Nineteen of the 23 *TP* sequences from the flies were identical

DOI of original article: <http://dx.doi.org/10.1016/j.ebiom.2016.07.033>.E-mail address: [lstamm@email.unc.edu](mailto:lstamm@email.unc.edu).<http://dx.doi.org/10.1016/j.ebiom.2016.08.028>2352–3964/© 2016 The Author. Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

to TPE-like sequences from the TP-infected LMNP baboons (Knauf et al., 2012). Furthermore, three TP sequences from the flies cluster with sequences from human TPA and *T. pallidum* subsp. *endemicum* (i.e., endemic syphilis) strains, suggesting that different TP subsp. are present in the baboon population or possibly that flies had contact with TP-infected humans.

The intriguing results of Knauf et al. could have important implications for yaws eradication efforts, but several questions remain (Knauf et al., 2016—in this issue). For example, what is the source of the fly-associated TP DNA (e.g., infected baboons or humans)? Are fly-associated TP viable and present in sufficient numbers for interspecies transmission? Do humans living in villages that border LMNP and TNP have clinical and/or serological evidence of yaws? If so, does fly control have an effect on the incidence/prevalence of yaws in these villages? Some of these questions may be difficult to address because of the fragile, not-yet-cultivable nature of the TP subsp. However, the use of molecular tools and epidemiological methods should facilitate further studies to elucidate the potential role of flies in the transmission of yaws. Clearly, a better understanding of yaws transmission is necessary for the development of suitable control strategies that are critical to achieve WHO's 2020 goal of yaws eradication.

## References

- Castellani, A., 1907. Experimental investigations on framboesia tropica (yaws). *J. Hyg.* 7 (4), 558–569.
- Fribourg-Blanc, A., Mollaret, H.H., 1969. Natural treponematoses of the African primate. *Primates Med.* 3, 113–121.
- Giacani, L., Lukehart, S.A., 2014. The endemic treponematoses. *Clin. Microbiol. Rev.* 27 (1), 89–115.
- Knauf, S., Batamuzi, E.K., Mlengeya, T., et al., 2012. *Treponema pallidum* infection in the wild baboons of east Africa: distribution and genetic characterization of the strains responsible. *PLoS One* 7 (2), e50882.
- Knauf, S., Liu, H., Harper, K.N., 2013. Treponemal infection in nonhuman primates as possible reservoir for human yaws. *Emerg. Infect. Dis.* 19 (12), 2058–2060.
- Knauf, S., Raphael, J., Mitja, O., et al., 2016. Isolation of *Treponema* DNA from necrophagous flies in a natural ecosystem. *EBioMed* 11, 85–90.
- Lamborn, W.A., 1936. The experimental transmission to man of *Treponema pertenu* by the fly *Musca sorbens* WD. *J. Trop. Med. Hyg.* 15 (39), 235–239.
- Satchell, G.H., Harrison II, R.A., 1953. Experimental observations on the possibility of transmission of yaws by wound-feeding Diptera in western Samoa. *Trans. R. Soc. Trop. Med. Hyg.* 42 (2), 148–153.
- Smith, J.L., David, N.J., Indgin, S., et al., 1971. Neuro-ophthalmological study of late yaws and pinta. II. The Caracas project. *Br. J. Vener. Dis.* 47 (4), 226–251.
- Stamm, L.V., 2015. Yaws: 110 years after Castellani's discovery of *Treponema pallidum* subspecies *pertenu*. *Am. J. Trop. Med. Hyg.* 93 (11), 4–6.