

## **Diagnostic TPP for detection of a case of yaws and detection of azithromycin resistance.**

Yaws is a bacterial infection that is found across the tropics. More than 80 countries/territories are known to have previously reported or currently report cases of yaws.

### **Epidemiology**

Yaws is caused by infection with *Treponema pallidum* subsp. *pertenue*. The disease is now predominantly reported in West and Central Africa and the Pacific but has previously been endemic throughout the tropics<sup>1,2</sup>. Most cases of yaws are found in children. Transmission is believed to occur through skin-to-skin contact with infectious lesions of primary yaws. *T.p.* subsp. *pertenue* is closely related to *T.p.* subsp. *Pallidum*, the causative agent of syphilis, but unlike the latter is not transmitted through sexual contact or from mother to the developing foetus during pregnancy.

The clinical course of yaws starts with primary yaws, characterised by a single infectious lesion. If the individual is untreated, the initial lesion will heal but the infection will continue. This asymptomatic state is called latent yaws. The individual may then progress on to develop secondary yaws, during which time new infectious lesions occur. The patient may alternate between asymptomatic latent yaws and further episodes of secondary yaws for several years. If the patient remains untreated for a long time (>5–10 years), they may develop tertiary yaws. The lesions of tertiary yaws are destructive and disfiguring but not infectious.

### **Public Health Response**

Yaws has been targeted for eradication since the mid-20<sup>th</sup> Century. Previous efforts focused on the use of mass or targeted treatment with penicillin. Although these efforts reduced the prevalence of yaws by >90% they were ultimately not successful at achieving eradication<sup>1</sup>. In 2012, the World Health Organization (WHO) launched a new strategy—‘the Morges strategy’—based on mass treatment with azithromycin<sup>3</sup>. Central to this strategy is the identification of all endemic communities, followed by community mass treatment. Small scale pilots of implementation of this strategy have been conducted in several settings.

Once the number of yaws cases has fallen, ongoing case finding and treatment is required to identify and treat remaining cases and their close contacts. Once no further cases of yaws are detected, the programme switches to surveillance, including serological surveillance of children aged <5 years<sup>5</sup>.

As the aim of the programme is eradication, detection of single cases is important. This detection occurs in 2 scenarios: i) deciding whether to initiate a programme – in this setting finding a single yaws case is sufficient to declare a community endemic and needing treatment; and ii) surveillance after mass treatment – in this setting it is important to exclude that even a single suspected case is truly yaws and therefore that interventions can stop.

A major concern has been the identification of a small number of cases of yaws which have developed resistance to azithromycin<sup>4</sup>. Two mutations are known to confer resistance to azithromycin. Detection of phenotypic resistance is complicated by the inability to routinely culture *T. pallidum*, and therefore the focus of resistance detection is on a) identification of cases of clinical treatment failure, and b) identification of known mutations associated with resistance to azithromycin.

The 2021–2030 NTD roadmap has set a target of yaws eradication by 2030.

## Available Diagnostic Tools

To date, clinical examination combined with serological tests are the mainstay of yaws diagnosis. Serological tests can be performed either in a laboratory or in the field through lateral flow assays. Molecular diagnostic tests including PCR are commonly used in research and increasingly within programmes.

## Diagnostic Technical Advisory Group

WHO's Department of Control of Neglected Tropical Diseases (NTD) manages a diverse portfolio of twenty diseases, each with its own unique epidemiological and diagnostic challenges. It was decided by the Strategic and Technical Advisory Group (STAG), the principal advisory group to the Director-General of WHO on the control, elimination and eradication of NTDs, that a single WHO working group would help ensure that a unified approach could be used to identify and prioritize diagnostic needs, and to inform WHO strategies and guidance on the subject<sup>6</sup>.

The first meeting of the Diagnostic Technical Advisory Group (DTAG), an advisory group to the Department of Control of Neglected Tropical Diseases, was held in Geneva, Switzerland, on 30<sup>th</sup> and 31<sup>st</sup> October 2019.

DTAG members discussed priorities for the year ahead as well as how to manage the complexity of supporting the diagnostics agenda across the entirety of WHO's NTD portfolio. Recommendations were made, based on the understanding that they would be reviewed at the next meeting, as it had been made clear that all NTDs had diagnostic needs which would have to be addressed in due course.

One of the recommendations was that TPPs for diagnostics were needed to support emerging yaws control programmes.

## Purpose of the TPP

The purpose of this TPP is to lead to development of new diagnostic tools for 'detection of a case of yaws' and 'detection of an azithromycin-resistant case of yaws'.

For detection of a case of yaws, the tool or tools must be able to detect a single case of active yaws infection.

For detection of a case of azithromycin resistant yaws, – the tool or tools must be able to detect mutations known to be associated with azithromycin resistance in yaws.

## Bibliography

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- 3 The World Health Organisation. Eradication of yaws - the Morges Strategy. *Wkly Epidemiol Rec* 2012; **87**: 189–94.

4 Beale MA, Noguera-Julian M, Godornes C, *et al.* Yaws re-emergence and bacterial drug resistance selection after mass administration of azithromycin: a genomic epidemiology investigation. *Lancet Microbe* 2020; **1**: e263–71.

5 World Health Organization. Eradication of yaws – A guide for programme managers. World Health Organization, 2018 <http://www.who.int/yaws/resources/9789241512695/en/> (accessed Oct 17, 2018).

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