Ponencia de clausura

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Tuberculosis elimination: lessons learned from yaws

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Control measures have massively reduced the incidence of many human infectious diseases but disease eradication has been proven a difficult goal, with just one human pathogen – smallpox – globally eradicated and three diseases currently targeted for eradication: polio, guinea worm and yaws. Several criteria are used to assess the eradicability of a disease:

- effective, practical interventions need to exist (such as strongly immunizing vaccines, highly efficacious and easy to administer drugs or simple behavior changes),
- practical diagnostic tools must be in place, with sufficient sensitivity to detect levels of infection that can lead to transmission,
- humans are essential for the life-cycle of the agent, which has no other animal reservoir and does not amplify in the environment.

The yaws eradication efforts provide valuable lessons to consider elimination of other infectious diseases such as Tuberculosis (TB). Yaws is caused by a spirochete, *Treponema pallidum* subsp. *pertenue,* transmitted by direct contact, while TB is an air-borne pathogen. Modelling for both diseases suggests that, to avert transmission, we need to identify and/or treat infected individuals before they develop the disease. This conference will discuss the challenges to achieve TB elimination in high-burden countries. We will scrutinise recognized control measures for yaws and other communicable diseases that could potentially curb the TB epidemic, including (i) active case-finding, (ii) interruption of transmission, (iii) containment of the reservoirs, (iv) increase resilience to diseases, and (v) management of resistant cases.

Aggressive strategies to treat all cases of a given disease constitute the first pillar of any elimination program. The yaws eradication programme consists of single-dose oral Mass Drug Administration (MDA) of single dose azithromycin to the entire population, pursuing high coverage of active cases, followed by resurveys to find residual cases. For yaws diagnostic confirmation in remote rural areas we use a point-of-care rapid strip test. An MDA strategy for TB is not feasible because of the need of a daily dose 6-month regimen for active drug-susceptible TB, therefore alternative strategies such as intensified active case detection are required. In addition, TB diagnostic tools, such as microscopy or Xpert MTB/RIF (Cepheid), require laboratory equipment and electricity which commonly do not exist in resource-limited settings.

Provision of treatment to prevent the establishment of a productive infection or progression of infection to disease is the second pillar of an elimination program. Latent yaws infection might last up to several decades; as a result, a large reservoir of infected human beings exists, among whom new cases might arise at any time (though recurrence commonly occurs within the 2 first years after the initial infection). To limit yaws transmission requires finding and offering treatment to a very high proportion of infected people. MDA of the entire population with high coverage

of latent cases is the most efficacious and cost-effective strategy to target latent yaws. In TB the risk of developing the disease is reduced by about 60-90% after receiving latent TB infection (LTBI) therapy, but at the community level the use of contact tracing alone is likely to detect only a small proportion of LTBI in high burden communities. New simplified weekly regimens for LTBI are advantageous and potentially could be used in MDA of the entire population as an alternative.

The absolute containment of any infectious source in the last-stage of an elimination program requires several activities which have been developed for yaws: (i) highly-sensitive and specific method for active detection of cases at very low levels using PCR on lesional swabs, (ii) improved surveillance strategies to reach remaining infections that will naturally tend to be in populations overlooked by interventions, (iii) highly-motivated staff, because the remaining foci of infection are the hardest to reach geographically, medically and socially. Such measures are also critical to stop TB transmission and are currently being used in low-burden countries.

Increased resilience to the disease may result from enhancing the immunity of susceptible individuals or from reducing susceptibility. There is no vaccine for the prevention of yaws or TB. For yaws, susceptibility to the disease can be reduced through supportive measures: health education, improvement in the standard of living and in personal hygiene, and provision of soap, water and clothing to children. Similarly, for TB there are a number of supportive measures that can reduce susceptibility to the disease: optimum HIV care, improved indoor air pollution, and reduced smoking, diabetes and malnutrition.

A major challenge of elimination programs using antibiotics is the emergence and spread of drug resistance that pose a threat to recent gains. Azithromycin resistance has been described in yaws; the risk of resistant mutant selection being low compared to the risk of transmission. A mitigation strategy to achieve cure and avoid dissemination of resistant strains is now in place consisting of biological surveillance using PCR assays and single dose injectable benzathine benzylpenicillin treatment. One of the most important barriers to TB elimination is the greatly complicated management of multi/extensively drug resistant tuberculosis (M/XDR-TB) alone or in association to HIV coinfection, that reduce treatment efficacy and increase the cost of treatment. As in yaws, a majority of MDR-TB is diagnosed among new cases (i.e. the majority are transmitted, not acquired, and there are well defined clonal MDR TB outbreaks). Therefore, besides improved adherence to limit generation of newly acquired drug resistance, TB prevention programs should consider MDR prophylactic treatment options that are effective in those harbouring MDR- latent TB strains.

In summary, while yaws seems eradicable even in the short term, the eradication of TB is unlikely in the coming years, mainly because the large reservoir (one fourth of the world's population is infected with TB), the lack of short, cheap and highly effective anti-TB and HIV regimens as well as better diagnostics, the lack of vaccine for prevention, and the insufficient ability to diagnose and treat drug-resistant TB.