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A framework to address multidrug-resistant tuberculosis in Pacific Island countries and territories

Background

Resistance to anti-tuberculosis (TB) drugs, and particularly the emergence of multidrug-resistant TB (MDR-TB), has become a major public health problem worldwide and an obstacle to effective global TB control. The development of MDR-TB, defined as TB with an isolate resistant to at least the two most effective TB drugs, isoniazid and rifampicin, results from poor treatment practices and failure to conform to World Health Organization (WHO) TB programme guidelines and the International Standards for TB Care, and underscores the importance of a patient-centred management approach that promotes adherence to lengthy treatment regimens.

Although available data indicate an overall low level of drug resistance in the Pacific Islands, excluding Papua New Guinea, alarmingly high levels in some Pacific Island countries and territories (PICTs), especially in Micronesia, have been observed. Chuuk State in the Federated States of Micronesia (FSM) reported two major MDR-TB outbreaks involving two separate isolates in 2008.

Most cases have been managed with laboratory support from the Pacific TB Laboratory Initiative (PATLAB) network and clinical support from external technical advisers. Major constraints have been the timely procurement of second-line drugs, long-term management of patients in isolation, training and education needs of staff, and reliance on PATLAB expertise.

Hence, one major recommendation of the Fourth Pacific Stop TB Meeting[1] (WHO 2008) was that technical partners (i.e. the Secretariat of the Pacific Community, SPC; Centers for Disease Control and Prevention, CDC; and WHO) should support the development of a framework of response to MDR-TB in the Pacific that will link the three critical aspects of case management of MDR- TB: laboratory services, technical and/or clinical support for case management, and the timely provision of second-line drugs.

To respond to this need, a working group comprising experts from these technical agencies and from PATLAB was established to develop the framework document.

Epidemiology of MDR-TB in PICTs

In 2008, the estimated number of MDR-TB cases in Papua New Guinea (primary and acquired) (95% confidence interval) was 600 (0 to 1,200). MDR-TB has been reported in Guam and the Commonwealth of the Northern Mariana Islands (CNMI) for several years. Many of the MDR-TB cases in these two countries were associated with migrant workers from countries with a high prevalence of MDR-TB.

Since early 2008, Chuuk State (one of the four states comprising FSM) has been confronted with two simultaneous outbreaks of MDR-TB. In total, 8 confirmed and 18 suspected MDR-TB cases have been identified; 7 patients died and 19 are currently receiving treatment (2010) with individualised treatment regimens tailored to the susceptibility results of the isolates. The first outbreak of MDR-TB

[1] Held in Brisbane, Australia from 11–14 March 2008.

in Chuuk was linked with an overseas source, a cluster of MDR-TB among migrants from Southeast Asia arriving in Saipan, CNMI. The second outbreak of MDR-TB in Chuuk was associated with the lack of quality directly observed treatment (DOT) in the local setting.

Between 2004 and 2009, six cases of MDR-TB were diagnosed in residents of the Republic of the Marshall Islands (RMI). The most recent case, found in 2008, was reported on Majuro Atoll. A contact investigation was conducted around this case in October 2009 and revealed four additional cases of MDR-TB (three probable and one confirmed), bringing the total number of MDR-TB cases occurring in the period January 2004 to November 2009 to ten.

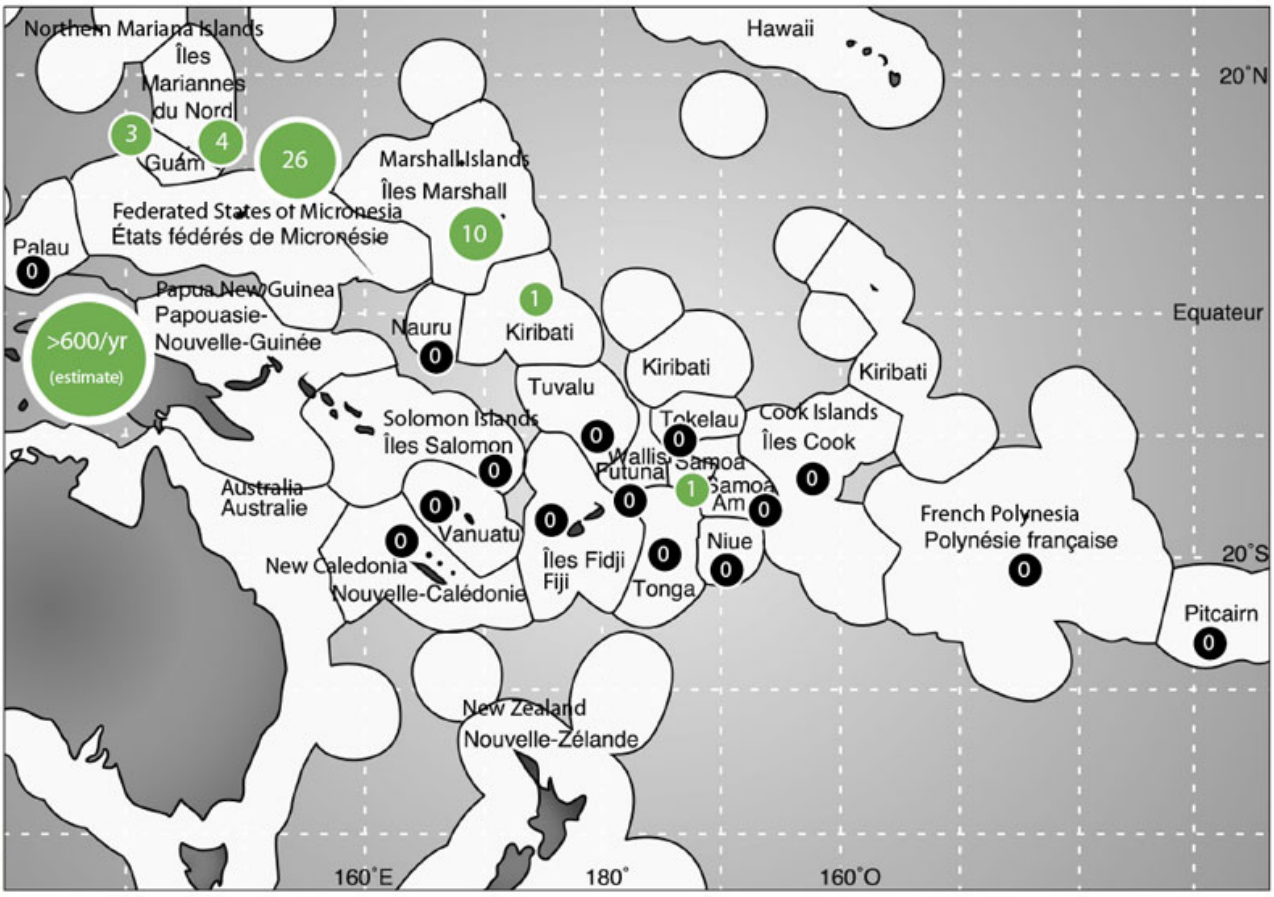

Figure 1. Number of reported MDR-TB cases by PICT (probable and confirmed) 2004–2009.

Kiribati also experienced its first case of MDR-TB in 2005 (the patient died during the first year of treatment). Samoa diagnosed its first MDR-TB case before 2000 and the second case in 2007. The second case was a migrant patient who had received TB treatment overseas before migrating to Samoa. The patient successfully completed treatment with second-line TB drugs in 2009.

The increasing number of MDR-TB cases reported, especially in Micronesian countries, is of concern, although many cases have not been confirmed. In addition, it is likely that there is under-reporting and under-detection of MDR-TB in the Pacific Islands due to the limited capacity of PICTs to perform culture and drug susceptibility testing (DST). Only the US-affiliated PICTs and French territories perform continuous drug resistance surveillance based on the routine testing of TB patients.

It is, therefore, necessary to expand MDR-TB surveillance to better understand the magnitude and trends of drug resistance and links with HIV, especially in high-priority PICTs where a high caseload is combined with increased potential for MDR-TB and for HIV (e.g. Kiribati and Solomon Islands).

Laboratory services for diagnosising MDR-TB in PICTs

Laboratories play a central role in patient care and surveillance; thus, provision of quality-assured services is critical. Sputum smear microscopy remains the sole means of local TB diagnosis in the majority of PICTs where there is a lack of routine collection and submission of specimens from MDR-TB suspects for culture and DST to confirm the diagnosis of MDR-TB. Data management systems for tracking laboratory results and monitoring response to treatment are limited as well.

PATLAB is a collaborative partnership between PICTs and mainland reference laboratories (Pacific TB reference laboratories, PTRLs), ensuring a sustained link between national TB laboratories and reference laboratories. PTRLs provide technical support to national TB programmes in PICTs, including smear, culture and DST for samples from patients considered to be high risk for having drug-resistant TB.

TB culture and DST should be performed in the following circumstances:

- **Failure or relapse after retreatment regimen with first-line drugs –** These patients have about an 80% likelihood of having MDR-TB if their treatment has been well supervised.
- **Symptomatic close contacts of a proven MDR-TB case –** Investigation of symptomatic children and HIV-positive contacts is especially important because these patient groups are at increased risk of progression to active disease.
- **Failure or relapse after new patient treatment regimen –** Most relapses and failures after treatment of a new patient will still be drug-susceptible.
- **Retreatment patients sputum smear positive at end of intensive phase (month 3).**
- **New patients sputum smear positive at end of month 3.**
- **All HIV-positive patients diagnosed with active TB –** Mortality rates from MDR-TB are high in HIV-positive cases unless detected early.

The PATLAB network needs to be prepared to process more specimens from MDR-TB suspects in PICTs, and to provide training and technical support for the stepwise development of new culture laboratories in PICTs in the coming years.

Molecular technologies such as the Hain MDR-TB test are potentially powerful tools for resource limited settings (Helb et al. 2010). These new diagnostic tools will require additional evaluation before application in TB laboratories in PICTs.

Ensuring uninterrupted supply of second-line drugs

Management of second-line drugs is complex, especially when individualised treatment regimens are used, as is the case in PICTs. Drugs are frequently changed as a result of adverse effects, delayed DST results, and poor response to treatment. National TB control programmes face several obstacles in the area of second-line drug procurement, including high costs and lack of local capacity for stringent quality assessment of drug manufacturers and their products. A fast-track application

to the Green Light Committee (GLC)[2] was developed for the Pacific Islands to ensure access to quality-assured second-line drugs. However, ensuring the timely procurement and delivery of these drugs remained a challenge anda mechanism of pre-empted procurement of second-line drugs was developed. This planned establishment of a buffer stock for second-line anti-tuberculosis drugs for treatment of up to 20 MDR-TB patients in PICTs has been approved by the GLC.

Developing a comprehensive framework for the management and care of MDR-TB

An appropriate treatment strategy consists of a rational method for designing the optimal treatment regimen, a patient-centred approach for delivering this regimen with direct observation, and a plan for monitoring and managing adverse drug reactions. Designing a regimen and monitoring MDR treatment must be done in consultation with someone who has experience using the drugs to treat MDR-TB and managing the cases; however, there is limited expertise in PICTs for MDR-TB management.

To assist PICTs, a TB treatment and support network has been established with the objective of providing expert clinical advice to national TB programme staff in 20 PICTs on all aspects of care, treatment, management and follow-up of MDR-TB cases. The TB treatment and support network comprises a listserv that is moderated by professional staff from SPC's TB Section. Expert consultants are available (by phone or email) to provide clinical advice on any case of TB, particularly MDR-TB.

Prioritise TB infection control

Policies and protocols for infection control and protection of healthcare workers, other patients, and visiting family members, when they exist, are not enforced or monitored closely in most PICT hospitals.

The framework outlines the specific measures to be taken when managing MDR-TB patients and provides a simple checklist.

Management of contacts

In view of the increasing concern with the transmission of MDR- and extremely drug-resistant (XDR)-TB, contact investigation may be a means of early identification of new cases of primary resistance. Early detection may prevent further transmission of resistant *Mycobacterium tuberculosis*.

There is no proven prevention treatment for infected contacts of MDR-TB cases. The use of second-line drugs for this purpose is controversial and not generally recommended by WHO.

The framework emphasises the need for all contacts to receive clinical monitoring and to be educated about their contact with an MDR-TB case and about the importance of seeking treatment urgently should they develop signs and symptoms of TB disease. Where resources are available, preventive treatment tailored to the source case isolate drug susceptibility pattern should be considered in close contacts with a high risk for progression to TB disease – particularly young children and the immune-suppressed.

The recommendations will be updated as more evidence to guide the treatment and management of MDR-TB contacts becomes available.

[2] A subgroup of the MDR-TB Working Group of the Stop TB Partnership, and an advisory body of WHO that promotes access to (and monitors the use of) quality-assured, life-saving MDR-TB treatment.

Standardised recording and reporting system

An appropriate recording and reporting system for MDR-TB is essential for evaluating programme performance and treatment effectiveness.

National TB programmes in most PICTs have implemented only the basic DOTS information system and do not have the set of forms necessary for proper recording of diagnosis, monitoring and care of MDR-TB. The framework recommends the performance indicators and the forms and registers that should be used by MDR-TB control programmes.

Conclusion

The framework is organised around the five components of the DOTS strategy as the underlying principles are the same. Its key components are the diagnosis of MDR-TB, an urgent response plan, management of MDR-TB cases and their contacts, infection control measures and monitoring and evaluation. The framework promotes a standardised and harmonised approach throughout PICTs, and takes into account the unique aspects of MDR-TB treatment and management in the Pacific Islands region.

The framework seeks to offer simple and clear guidance to national TB programme managers and public health officials from PICTs, referring to the more comprehensive WHO *Guidelines for the programmatic management of drug-resistant tuberculosis* and other reference documents for more details.

The framework document can be downloaded from the SPC webpage: http://www.spc.int/php/index.php?option=com_docman&task=cat_view&gid=53&Itemid=83

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