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Short Communication

Surveillance of adverse events in the treatment of drug-resistant tuberculosis: A global feasibility study

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ABSTRACT

The World Health Organization launched a global initiative, known as aDSM (active TB drug safety monitoring and management) to better describe the safety profile of new treatment regimens for drug-resistant tuberculosis (TB) in real-world settings. However, comprehensive surveillance is difficult to implement in several countries.

The aim of the aDSM project is to demonstrate the feasibility of implementing national aDSM registers and to describe the type and the frequency of adverse events (AEs) associated with exposure to the new anti-TB drugs.

Following a pilot study carried out in 2016, official involvement of TB reference centres/countries into the project was sought and cases treated with bedaquiline- and/or delamanid-containing regimens were consecutively recruited. AEs were prospectively collected ensuring potential attribution of the AE to a specific drug based on its known safety profile.

A total of 309 cases were fully reported from 41 centres in 27 countries (65% males; 268 treated with bedaquiline, 20 with delamanid, and 21 with both drugs) out of an estimated 781 cases the participating countries had committed to report by the first quarter of 2019.

The World Health Organization (WHO) seeks global evidence on the safety and tolerability of new treatment regimens for drug-resistant tuberculosis, including multidrug-resistant tuberculosis (MDR-TB) (Halleux et al., 2018).

The WHO launched a comprehensive approach, known as aDSM (active TB drug safety monitoring and management) (World Health Organization, 2015), proposing that national programmes implement 'active and systematic clinical and laboratory assessment of patients on treatment with new TB medicines, or novel MDR-TB or XDR (extensively drug-resistant)-TB regimens to detect, manage and report suspected or confirmed drug toxicities' (Halleux et al., 2018). This initiative is really important as, after more than 40 years without any new drug specifically licensed to manage TB, we finally have bedaquiline and delamanid (Borisov et al., 2017; Kim et al., 2018; Kuksa et al., 2017; Mohr et al. 2018; Pontali et al., 2017; Pontali et al., 2018; Pym et al., 2016).

Although some information on safety of the new drugs has been made available, more clinical details (to obtain through extensive surveillance of adverse events (AEs)) are required. This is particularly relevant in view of the potential bedaquiline, delamanid, clofazimine, and quinolones have to increase the QT interval (Pontali et al., 2017) and generate an arrhythmic event. Therefore, the real-time monitoring of anti-TB regimens is fully justified (Halleux et al., 2018; World Health Organization, 2015). Of course, although any kind of AE requires prompt clinical action, special attention is necessary on serious AEs, as they are potentially life-threatening. In particular, according to the WHO aDSM project serious AEs include death or a life-threatening experience, hospitalization or prolongation of hospitalization, persistent or significant disability, or congenital anomaly (Halleux et al., 2018; World Health Organization, 2015).

The WHO proposal to national programmes was to initiate regular monitoring of AEs, as well as collect and report information

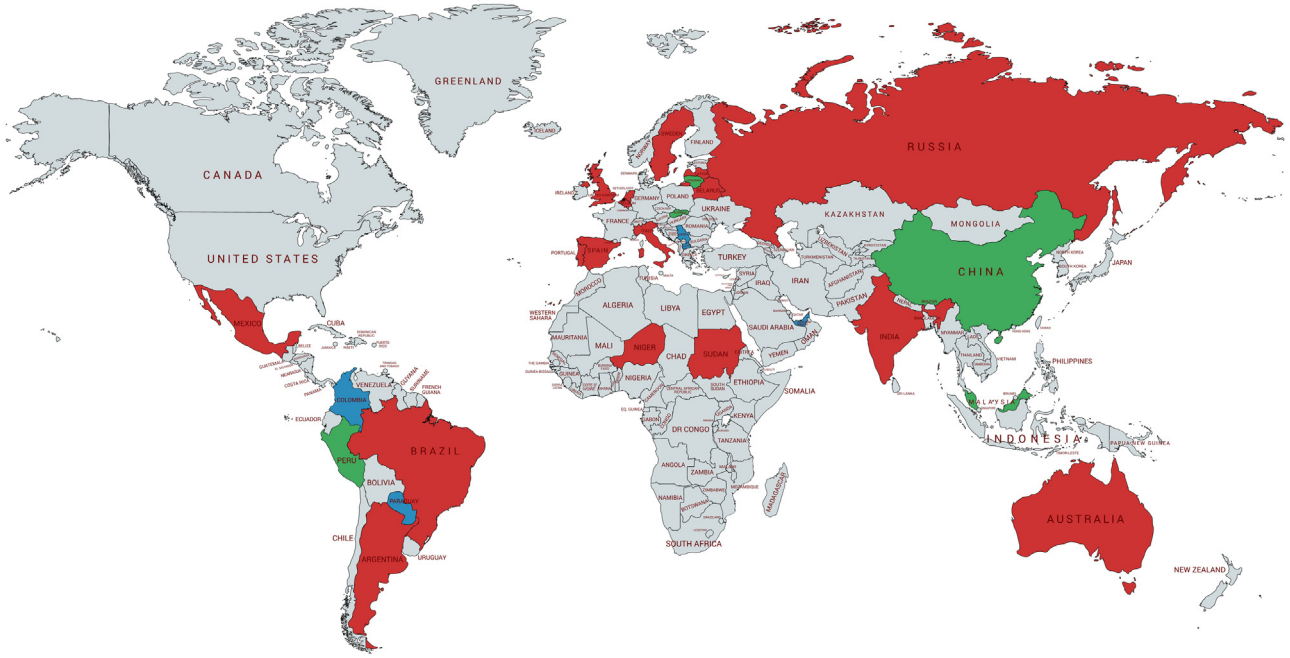

Figure 1. Map of the participating countries.
Red: Countries which regularly reported; Green: Countries in the process of reporting; Blue: Countries which activated active monitoring of adverse events with no cases yet treated with new drugs.

on bacteriological status at diagnosis (sputum smear, culture, drug resistance profile), bacteriological conversion/reversion (sputum smear and culture conversion rates) and treatment outcomes (Halleux et al., 2018). The surveillance methodology has been left to countries which were supposed to use electronic registers or existing electronic medical record systems (Halleux et al., 2018), complementing, rather than duplicating, national pharmacovigilance initiatives.

WHO also launched a global aDSM database to collect a standard set of variables including anonymised individual-level patient data on serious AEs (Halleux et al., 2018), and provided clear guidance on how to implement aDSM at a national level (World Health Organization, 2015).

National TB Programmes faced difficulties in implementing aDSM and contributing to the global database. Taking advantage of a newly implemented global network (Global Tuberculosis Network-GTN) (Borisov et al., 2017; Rossato Silva et al., 2018) a large aDSM project was launched to demonstrate the feasibility of implementing national aDSM registers. The GTN research addressed clinical centres with the goal of assessing the safety and tolerability profile, as well as the effectiveness of anti-TB drugs and regimens in MDR-TB patients treated with new drugs (bedaquiline, delamanid) worldwide. The WHO initiative is focused on National Tuberculosis Programmes in order to evaluate the safety of anti-TB regimens. The two initiatives are co-ordinated.

After a pilot study was implemented in 2016 in a few centres to assess the suitability of the project and its potential implementation, and following the approval of the coordinating centre's Ethics Committee (July 11th, 2017), the project was proposed to the clinical centres or national programmes participating in the network. Each centre or country signed a confidentiality and data-sharing agreement with the coordinating centre and obtained local Ethics Committee clearance as per legislation in force.

All consecutive cases for which bedaquiline and/or delamanid were prescribed since the moment the centre or country adhered to the project were enrolled. The AEs of any drug involved in the treatment regimen were prospectively collected, ensuring a probabilistic mechanism of causality assignment (e.g. attribution of the AE to a specific drug based on its evidence-based profile). The data collection form in an electronic format was based on the WHO-recommended template, although more clinical details were requested (World Health Organization, 2015).

Table 1
Participating countries and details on the cases reported.

Countries	Estimated cases[a] N	Estimated coverage[b] %	Cases enrolled N	Male N (%)	Cases treated with Bdq N (%)	Cases treated with Dlm N (%)	Cases treated with Bdq-Dlm or Dlm-Bdq consecutively N (%)	Cases treated with Bdq-Dlm in combination N (%)
EUROPE								
Belgium	3	60	3	2 (67)	3 (100)	0 (0)	0 (0)	0 (0)
Belarus[f]	113	80	27	17 (63)	20 (74)	7 (26)	0 (0)	0 (0)
Italy[g]	29	80	27	17 (63)	20 (74)	6 (25)	0 (0)	1 (4)
Latvia	30	100	30	18 (60)	20 (40)	3 (10)	1 (3)	6 (20)
Lithuania	170	100	Data uploading	–	–	–	–	–
Macedonia	No cases	100	–	–	–	–	–	–
Netherlands[f]	6	100	6	5 (83)	3 (50)	0 (0)	1 (17)	2 (33)
Portugal	1	100	1	1 (100)	0 (0)	1 (100)	0 (0)	0 (0)
Russian Federation[f]	257	100[c]	140	87 (62)	135 (96)	2 (1)	1 (0.7)	2 (1)
Serbia	No cases	100	–	–	–	–	–	–
Slovakia	1	100	1	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Spain[g]	9	100	1	0 (0)	1 (100)	0 (0)	0 (0)	0 (0)
Sweden	16	100	5	2 (40)	4 (80)	0 (0)	1 (20)[i]	0 (0)
United Kingdom	4	20	4	2 (50)	4 (100)	0 (0)	0 (0)	0 (0)
AFRICA								
Niger	21	100	13	13 (100)	10 (77)	0 (0)	0 (0)	3 (23)
Sudan	5	100	2	2 (100)	2 (100)	0 (0)	0 (0)	0 (0)
LATIN AMERICA								
Argentina	11	100	3	0 (0)	3 (100)	0 (0)	0 (0)	0 (0)
Brazil	33	100	26	22 (85)	26 (100)	0 (0)	0 (0)	0 (0)
Colombia	No cases	100	–	–	–	–	–	–
Mexico[f]	8	100	4	3 (75)	1 (25)	1 (25)	0 (0)	2 (50)
Paraguay	No cases	100	–	–	–	–	–	–
Peru	30	80	Data uploading	–	–	–	–	–
ASIA								
China[h]	5	100[d]	Data uploading	–	–	–	–	–
India	15	100[e]	10	5 (50)	9 (90)	0 (0)	1 (10)	0 (0)
Malaysia[h]	8	100	Data uploading	–	–	–	–	–
United Arab Emirates	No cases	–	–	–	–	–	–	–
OCEANIA								
Australia	6	100[e]	6	4 (67)	6 (100)	0 (0)	0 (0)	0 (0)
TOTAL 27	781	Range 20%–100%	309	200 (65)	268 (87)	20 (7)	5 (2)	16 (5)

[a] Cases estimated by countries to be fully reported by 1st quarter 2019.
[b] Countries' estimate of the national coverage of the aDSM project on new drugs.
[c] In the 2 Oblasts reporting.
[d] In the Province reporting.
[e] In the State reporting.
[f] 2 centres.
[g] 6 centres.
[h] 1 centre.
[i] Case with Dlm for 4 days only, not concomitant with Bdq.

This article reports on the initial results of the aDSM project.

As of January 31st 2019 (interim analysis), 41 centres in 27 countries (Figure 1, Table 1) provided aDSM information on new anti-TB drugs: 14 in Europe, 6 in Latin America, 4 in Asia, 2 in Africa, and 1 in Oceania. 5 countries participated in the aDSM project although no case has yet been treated with bedaquiline and/or delamanid.

This resulted in 100% coverage for the majority of the countries, while in some of them the actual coverage was lower. In the Russian Federation 2 Regions (Moscow and Arkhangelsk Oblasts) are represented with 100% coverage, as well as the Victoria State in Australia and the Zhejiang Province in China.

A total of 309 cases were fully reported from January 2016 to January 2019 (65% males; 268 treated with bedaquiline, 20 with delamanid and 21 with the two drugs prescribed in combination or consecutively) out of the estimated 781 cases the participating countries committed to report in the first quarter 2019.

The recruitment process in all continents was long and time-consuming, although the support and enthusiasm of the participating colleagues allowed for resolution of any existing problems. Several countries (including Sub-Saharan Africa) were asked to participate, but some centres decided to decline as the project is on a voluntary basis and the activity is perceived as 'difficult' 'or time-consuming' without provision for additional resources.

During the 'interim analysis', planned in the second quarter 2019, AEs will be analysed separately both per drug (bedaquiline, delamanid, linezolid, fluoroquinolones, clofazimine, etc.) and per 'severity' status.

To our knowledge, this is the first published evidence of a global aDSM project in the literature.

Conflict of interest statement

No competing interest declared.

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Ethical approval

Approval was not required.

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