Prevalence of drug-resistant tuberculosis in South Africa - Authors' reply

I consider that the reassuring conclusion of this manuscript should be mitigated and that further validation of the findings should be done using state-of-the-art laboratory methods, which are available in South Africa.

I declare no competing interests.

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1 Ismail NA, Mvusi L, Nannoo A, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. *Lancet Infect Dis* 2018; **18:** 779–87.
2 Van Deun A, Aung KJ, Hossain A, et al. Disputed *rpoB* mutations can frequently cause important rifampicin resistance among new tuberculosis patients. *Int J Tuberc Lung Dis* 2015; **19:** 185–90.
3 Andre E, Martin A. Isoniazid-resistant tuberculosis treatment with first-line drugs. *Lancet Infect Dis* 2017; **17:** 258–59.
4 Sanchez-Padilla E, Merker M, Beckert P, et al. Detection of drug-resistant tuberculosis by Xpert MTB/RIF in Swaziland. *N Engl J Med* 2015; **372:** 1181–82.

Nazir Ahmed Ismail and colleagues[1] investigated the prevalence of antituberculosis drug resistance in South Africa, during 2012–14, using a population normalised cross-sectional survey in nine of the country's provinces.[1] The study is commendable for its precision in the estimation of antituberculosis drug resistance on national and subnational categorical scales; the findings suggest the dire need for population matched national surveys in WHO high-burden countries,[2] and should focus on effective estimation, treatment, and monitoring of antidrug resistance in *Mycobacterium tuberculosis* strains.

India, China, and Russia, together account for almost half (around 47%) of the global burden of drug-resistant tuberculosis, whereas South Africa harbours the highest number of cases per capita of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis.[2] It will be a shortfall to WHO's End TB strategy and the UN's Sustainable Development Goals[3] if high-burden countries do not improve effectiveness in their national policies for tuberculosis control. The most recently available national drug-resistant tuberculosis survey in China[4] (of 33 provinces in 2007) identified 5·7% (n=3037) of new and 25·6% (n=892) of previously treated tuberculosis cases as MDR; 8% of these identified MDR cases are XDR. The latest South African survey reports that 2·1% (n=5423) of new and 4·6% (n=2210) of previously treated cases are MDR; the provincial MDR prevalence ranged from 1·6% to 5·1%; among reported MDR cases, 4·9% were XDR. Compared with 2001–02, the prevalence of rifampicin resistance has doubled in the 2012–14 survey, signifying the importance of regular surveys.

India has released the results of its first ever national antituberculosis drug resistance survey, which identifies prevalence of MDR tuberculosis in new and previously treated cases as 2·84% and 11·64%, respectively. Overall prevalence of MDR tuberculosis in India is 6·19%, of which 1·3% of cases are XDR;[5] the nationwide prevalence of resistance to any tuberculosis drug in new and previously treated cases is 28% and 36%, respectively. Although Russia is dauntingly expecting an upsurge in the numbers of cases of MDR tuberculosis and rifampicin-resistant tuberculosis (27% in new and 63% in previously treated cases), it has not released data from its national antituberculosis survey yet. The usefulness and effectiveness of surveys stand with the use of inclusion criteria of samples and normalisation of confounding variables. A Chinese survey sourced samples from both private and public healthcare systems[4] and an African survey did not define the sample inclusion criteria well;[1] an Indian survey did not include any samples from private tuberculosis clinics, which treat huge proportions of tuberculosis patients that are left unreported.[6] To achieve the goals of the WHO END-TB strategy, all high-burden countries should do nationwide antituberculosis resistance surveys that are normalised for confounding variables.

I declare no competing interests.

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1 Ismail NM, Mvusi L, Nanoo A, et al. Prevalence of drug-resistant tuberculosis and imputed burden in South Africa: a national and sub-national cross-sectional survey. *Lancet Infect Dis* 2018; **18:** 779–87.
2 WHO. Global tuberculosis report 2017. Geneva: World Health Organization, 2017.
3 UN Development Programme. Sustainable developmental goals. http://www.undp.org/content/undp/en/home/sustainable-development-goals.html (accessed April 24, 2017).
4 Zhao Y, Xu S, Wang L, et al. National survey of drug-resistant tuberculosis in China. *N Engl J Med* 2012; **366:** 2161–70.
5 Prasad J, Kumar P, Ramachandran R, et al. Report of the first national anti-tuberculosis drug resistance survey: India 2014–16. https://tbcindia.gov.in/showfile.php?lid=3315 (accessed April 24, 2017).
6 Arinaminpathy N, Batra D, Khaparde S, et al. The number of privately treated tuberculosis cases in India: an estimation from drug sales data. *Lancet Infect Dis* 2016; **16:** 1255–60.

Authors' reply

Unlike in southeast Asian countries where the private sector is substantially involved in the care of individuals with tuberculosis,[1] in South Africa the majority of individuals (84%) do not have private medical insurance and use public health facilities, including 91% of black Africans,[2] who are also disproportionately affected by tuberculosis. Furthermore, even among those with private medical insurance, the management of tuberculosis is generally undertaken in public health facilities in South Africa and funded by the government at no cost to the patients. Thus, although Ranjeet Singh Mahla's concern is that the absence of including sampling from the private sector might have biased our results, we believe that our sampling is representative of

tuberculosis cases in South Africa. We, however, concur that WHO's End TB strategy and the UN's Sustainable Development Goals have ambitious targets and reaching these would be hampered if high burden countries do not improve the effectiveness of their national policies for tuberculosis control, which should be based on robust epidemiological data.

In addition to the doubling in prevalence of rifampicin resistance observed, equally important was the increase thereof among new cases implying primary transmission of rifampicin-resistant strains. This highlights the importance of applying the Xpert MTB/RIF assay as the primary diagnostic tool for tuberculosis, irrespective of treatment history.

Although our study does illustrate the value of repeat surveys to monitor for the prevalence of drug-resistant tuberculosis, such surveys are complex, costly, and the data generally only available 2–3 years after the survery is done. Future surveys should also probably make use of next generation molecular tools instead of culture. Furthermore, if programmes are to be agile in their response to drug-resistant tuberculosis, structured routine surveillance is preferred allowing trend analysis, mapping geographical burden of disease, and achieving granularity at low levels to inform a response; all of which are now being implemented in South Africa.[3]

Although we note the suggestion by Emmanuel André that the absence of investigation for the Ile491Phe *rpoB* mutation in isoniazid-resistant isolates from our survey could have under-represented whether these isolates were in fact multi-drug resistant tuberculosis, we believe that such under-representation is unlikely, as the prevalence of isoniazid mono-resistant tuberculosis observed was similar to that reported elsewhere globally.[4] Furthermore, the high prevalence (30%) of the Ile491Phe mutation observed in the 2009 drug resistance survery in Swaziland, has not been observed elsewhere.[5,6] Also, as part of a separate WHO multicountry study using isolates from the survey, whole-genome sequencing was done on 1535 isolates from two provinces in South Africa (KwaZulu Natal, which neighbours Swaziland, and Gauteng) and there were minimal differences in the prevalence of rifampicin resistance based on phenotypic (5·7%) and sequencing data (5·5%),[5] and the prevalence of Ile491Phe mutation was less than 0·1% (one out of 1535), and identified phenotypically. Since the publication of our results, we have further analysed 92 of the isoniazid mono-resistant isolates that had whole-genome sequencing, and sequenced another 48 isoniazid mono-resistant survey strains from the Mpumalanga and North-West province, none of which had the Ile491Phe mutation.[7]

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1 Sulis G, Pai M. Missing tuberculosis patients in the private sector: business as usual will not deliver results. *Public Health Action* 2017; **7:** 80–81.
2 Statistics South Africa. Use of health facilities and levels of selected health conditions in South Africa: findings from the General Household Survey, 2013. http://www.statssa.gov.za/publications/Report-03-00-05/Report-03-00-052011.pdf (accessed June 14, 2018).
3 National Institute for Communicable Diseases. Microbiologically confirmed tuberculosis 2004–15, South Africa. 2017. http://www.nicd.ac.za/index.php/centres/centre-for-tuberculosis/public-health-surveillance/surveillance-of-microbiologically-confirmed-tb/ (accessed June 14, 2018).
4 WHO. Global TB Report. Geneva: World Health Organization, 2017.
5 Zignol M, Cabibbe AM, Dean AS, et al. Genetic sequencing for surveillance of drug resistance in tuberculosis in highly endemic countries: a multi-country population-based surveillance study. *Lancet Infect Dis* 2018; **18:** 675–83.
6 Walker TM, Kohl TA, Omar SV, et al. Whole-genome sequencing for prediction of *Mycobacterium tuberculosis* drug susceptibility and resistance: a retrospective cohort study. *Lancet Infect Dis* 2015; **15:** 1193–202.
7 Omar SV, Ismail F, Joseph L , et al. Prevalence of the rifampicin resistant determinant at codon 491 in South Africa, undetected by commercial phenotypic and genotypic methods-FIDSSA 2017 Congress abstracts. *South Afr J Infect Dis* 2017; **32** (suppl)**:** 38–119.