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From the authors:

We would like to thank A.W.J. Bossink and colleagues for their comments.

With regard to Epstein–Barr virus (EBV) serostatus, our laboratory has a diagnostic interest in EBV serology and our experience would indicate that for the age ranges in our published study [1] (*i.e.* both patients and controls) there will be 100% seropositivity for EBV. In Northern Ireland (UK), 60% of 10 yr olds are seropositive; in adults, this figure rises to >95% (unpublished data; P.V. Coyle, Regional Virus Laboratory, Belfast Health and Social Care Trust, Belfast, UK; personal communication).

Regarding the possible contamination of sputum samples with EBV DNA present in saliva, we have found that there is good correlation between EBV in lower and upper respiratory tract specimens, which is not consistent with contamination. We and other labs see little evidence of latent EBV when testing whole blood or white blood cells, making the presence of B-cells in sputum unlikely to be a confounding factor.

On the point of PCR being unable to differentiate between DNA derived from active viral replication or latent infection, as we were not detecting latency in B-cells (as previously noted) and as EBV causes a productive infection in epithelial cells, it follows current knowledge [2, 3] that we were measuring active viral replication. This also makes the determination of the number of B-cells in the sputum irrelevant.

The final issue regarding potential dilution of specimens with hypertonic saline is unlikely to be significant as previously published work has shown that induced sputum separated from saliva is similar to lower respiratory secretions expectorated spontaneously [4]. In the setting of our previously published study [1], any dilutional effect was negligible within the context of an assay determining viral load over six logarithms.

We would also like thank W.B. Grant for his comments in relation to vitamin D and chronic obstructive pulmonary disease. These comments raise several interesting points in this area and highlight the need for further prospective studies in this group of patients.

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STATEMENT OF INTEREST

None declared.

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Extensively drug-resistant tuberculosis: is its definition correct?

To the Editors:

Two articles by MIGLIORI and co-workers [1, 2], which recently appeared in the *European Respiratory Journal (ERJ)*, may support the idea that the current definition of extremely drug-resistant tuberculosis (XDR-TB) [3, 4] is not the most adequate.

In recent years, XDR-TB has become a major concern as it leads to incurable TB in a significant proportion of patients [4, 5]. XDR-TB was first defined in March 2006 as multidrug-resistant TB (MDR-TB; resistance to isoniazid and rifampicin) plus resistance to at least three of the six second-line anti-TB drug groups (fluoroquinolones, aminoglycosides, polypeptides,

thioamides, cycloserine and para-aminosalicylic acid (PAS)) [6]. However, this definition permits the possibility of susceptibility to fluoroquinolones and aminoglycosides (kanamycin, amikacin) and/or polypeptides (capreomycin) in some XDR-TB patients, meaning much higher success rates could be achieved if such drugs were used. Amongst second-line drugs, only the fluoroquinolones and injectables (aminoglycosides and polypeptides) have bactericidal activity and could be considered very effective. Fluoroquinolones and injectables therefore seem to represent the same as isoniazid and rifampicin amongst the first-line drugs. Acknowledgement of the fact that the success of treatment with second-line drugs depends on the use of fluoroquinolones and injectables (aminoglycosides and polypeptides), in addition to the fact that susceptibility testing to these drugs produces more reliable and reproducible results, prompted a modification of the definition of XDR-TB. Currently, XDR-TB is defined as MDR-TB plus resistance to fluoroquinolones and to at least to one of the second-line injectables (kanamycin, amikacin and capreomycin) [3, 4].

Although two recent studies have shown that the current definition of XDR-TB is predictive of a poorer clinical outcome than MDR-TB [1, 7], this definition may still be inappropriate even though it is clearly better than the first. This is particularly so because, in special cases, it allows the use of some first-line drugs and/or one of the injectables (kanamycin, amikacin or capreomycin).

The current definition permits the possibility of susceptibility to ethambutol and/or pyrazinamide, which, although rare, could be present in any given case. In a recent study, MIGLIORI *et al.* [1] presented the unfavourable outcome of MDR-TB cases resistant to all first-line drugs compared with other MDR-TB

cases in which there was susceptibility to ethambutol, pyrazinamide or streptomycin. Table 1 shows that the role of pyrazinamide was a very important in three studies and that a success rate of >90% was achieved with pyrazinamide plus ethionamide and cycloserine [8–10, 15].

The current XDR-TB definition also allows the use of one of the injectables (kanamycin, amikacin or capreomycin) along with ethionamide, cycloserine and PAS, thereby reaching a possible cure rate of >80% [15], as can be observed in four of the studies presented in table 1 [11–14]. The possibility of success in an XDR-TB patient using an injectable and all of the second-line drugs could therefore be very close to that achieved in patients with MDR-TB and without XDR-TB (for example, in MDR-TB patients with susceptibility to all of the injectables) [15]. In their more recent study, MIGLIORI *et al.* [2] evidenced the favourable outcome of XDR-TB patients with susceptibility to capreomycin, the least frequently used injectable in the world, and, for this reason, susceptibility is possible in many patients with resistance to kanamycin and/or amikacin.

For all of these reasons, the most accurate definition of extensively drug-resistant tuberculosis would be cases with resistance to all first-line drugs (not only those defining multidrug-resistant tuberculosis) and to fluoroquinolones and all of the injectables (not just to one), the two most potent second-line drugs groups. Usually, these patients have a possible treatment success rate of <50% and clearly stand apart from exclusively multidrug-resistant tuberculosis patients. If the current extensively drug-resistant tuberculosis definition is maintained, we will shortly be in need of a new definition for those cases, thus constituting a new level of difficulty in antituberculosis treatment for which the best classification would be XXDR (extensively extensively drug-resistant tuberculosis).

TABLE 1 Outcome of tuberculosis patients resistant to isoniazid, streptomycin and para-aminosalicylic acid (PAS), treated with only three drugs[#] in the pre-rifampicin and pre-fluoroquinolone period

First author [ref.]	Country	Period of study	Subjects [†] n	Follow-up period	Drugs regimen ⁺	Cured/completed treatment	Efficacy of regimen [§]	Died	Defaulters/withdrew/lost ^{††}	Failures/nonresponders ^{###}
TOUSEK [8]	CZ	1959–1962	55	2 yrs	Z, Eth, Cs	45 (82)	96		8 (14)	2 (4)
ZIERSKI [9]	PL	1958–1962	32	9 months	Z, Eth, Cs	31 (97)	97			1 (3)
SOMNER [10]	UK	1960–1962	22	5 yrs	Z, Eth Cs	20 (91)	100	1 (4.5)	1 (4.5)	
FISCHER [11]	USA	1960–1962	146	4 yrs	Z, Kn, Eth, Cs, S, Vi, Cm, E, PAS	122 (83)	88	27 (18)		37 (25)
KASS [12]	USA	1960–1962	74	4 yrs	Z, Kn, Eth, Cs, E, Cm, Th	58 (79)	81			16 (21)
PINES [13]	UK	1961–1963	12	2 yrs	Z, Eth, Cs, Vi, Th	9 (75)	90	2 (17)		1 (8)
KASS [14]	USA	1962–1964	24	277 days	Z, Kn, Eth, Cs, Eth, Cs, E, Cm, Th	23 (96)	96			1 (4)

Data presented as n (%) or %, unless otherwise stated. Z: pyrazinamide; Eth: ethionamide; Cs: cycloserine; Kn: kanamycin; S: Streptomycin; Vi: viomycin; Cm: capreomycin; E: ethambutol; Th: thioacetazone. [#]: with or without one injectable; [†]: multidrug-resistant tuberculosis patients with known outcome in the study; ⁺: each subject took only three of these drugs; [§]: those who were cured/completed treatment divided by those who were cured/completed treatment plus failures/nonresponders; ^{††}: patients not taking drugs regularly are included; ^{###}: including relapses known in patients cured previously. Reproduced and modified from [15] with permission from the publisher.

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STATEMENT OF INTEREST

None declared.

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An ecological analysis of incidence of tuberculosis and *per capita* gross domestic product

To the Editor:

In 2006, an estimated 9 million new cases of tuberculosis (TB) emerged worldwide [1]. Of these, only 1% occurred in the European Union and North America combined, while Africa and South-East Asia contributed >65%. Among the 22 high-burden countries, 17 were in Africa, 16 of which were in the lowest quartile in terms of *per capita* gross domestic product (GDP). Since 2001, the fight against poverty has been a major theme in the World Health Organization's (WHO) "Stop TB" strategy. Indeed, poverty "fuels" TB by facilitating transmission through crowded working and living conditions, it may increase the risk of progression to disease through malnutrition, and imposes barriers to accessing health services.

The aim of the present analysis was to explore and illustrate the relationship between the incidence of TB and an indicator of standard of living (*per capita* GDP) using WHO and World Bank estimates.

The *per capita* GDP, *i.e.* total market value of all final goods and services produced within a given country in a given period of time, is often used as an indicator of standard of living. The advantages are that it is measured frequently, widely used and easily accessible information, and that technical definitions for estimating GDP are relatively consistent between countries.

The World Bank publishes yearly estimates of *per capita* GDP per country [2]. Similarly, the WHO provides annual estimates for TB incidence for each country by WHO region [2]. Of the 211 WHO member states and 177 countries with reports by the World Bank, there were 171 pairs with information on both GDP and TB. For uniformity of the denominator, United Nations population estimates for 2004 [3] were used to obtain *per capita* figures for GDP and TB, respectively.

The choice of the same denominator permitted a direct regression on the numerators (rather than on rates), using population size as a weight. Linear regression on the logarithm