

Paul D. van Helden*

Robin M. Warren

Thomas C. Victor

Gian van der Spuy

Madalene Richardson

Eileen Hoal-van Helden

Dept of Medical Biochemistry,

University of Stellenbosch Medical School,

PO Box 19063, Tygerberg 7505, South Africa.

*e-mail: pvh@sun.ac.za

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Strain families of *Mycobacterium tuberculosis*

Response from Bifani *et al.*

The letter by van Helden *et al.* highlights two main points regarding our recent review article: (1) an explanation for the W-Beijing strain family's widespread dissemination and an emphasis on the importance of other strain families; and (2) the limited clinical evidence supporting the notion that W-Beijing family strains are better adapted to infect and cause human disease. The central thesis of our article was to underline and present the global dissemination, based on extensive reporting from the literature, of one particular *Mycobacterium tuberculosis* strain family.

As with most prevalent infectious diseases, there could be several reasons for the global spread of the W-Beijing family strains, including human migration, host population susceptibility and the genetic fitness of the pathogen. The nature of these factors is multifactorial; for example, transitory or permanent movement of a person(s) could indeed, as pointed out by van Helden *et al.*, be owing to specific economic routes, natural disasters or political conflicts. The high prevalence of W-Beijing family strains noted in Cape Town is certainly consistent with our hypothesis. However, we must be cautious before drawing any conclusions regarding the route or specific reason(s) for dissemination based on anecdotal evidence without a more systematic anthropological and/or historical analysis.

Our conclusions on the prevalence of the W-Beijing family are based on several studies primarily conducted in the Asian continent (including the former Soviet Union). Although not conclusive, the diversity and prevalence of the W-Beijing family in the cases from Asia do provide clues regarding the origins of this strain. Whether its prevalence is remarkable and/or (non-) exceptional does not obviate the observations that most *M. tuberculosis* genotyping laboratories worldwide have representatives of this strain family in their collection and that this strain has been documented to cause disease globally (see Table 1 in our review). However, we do concur with van Helden *et al.* in acknowledging the presence and importance of other large strain families. In our review, we note that the Haarlem family strain has also been widely reported. Although secondary genotyping data have supported the Haarlem family's genetic relatedness, we agree that more-extensive molecular characterization is required for these and other prevalent strain families.

The extensive studies on the W-Beijing family strains are the consequence of their prevalence in diverse geographical and epidemiological settings, and whether this is owing to publicity, dominance in certain regions or ease of strain identification is irrelevant. However, it was not the contention of our article that the W-Beijing strains represent the only or the most important *M. tuberculosis* family globally, but rather to highlight key characteristics that have been used to identify members of this family and summarize the diverse epidemiological settings where these strains have been reported. We agree

with the contention of van Helden *et al.* regarding the lack of substantial data supporting the W-Beijing family's spread owing to widespread *Mycobacterium bovis* Bacille Calmette–Guérin (BCG) immunization. In this regard, we noted in our review the spread of the W-Beijing strains in BCG-naïve populations in the USA, which argues against selective pressure induced by mass vaccination.

As van Helden and colleagues pointed out, *in vivo M. tuberculosis* studies measuring growth rates or specific host-immune responses have presented inconsistent conclusions. Therefore, we believe that as yet there are no definitive factors to account for the success or fitness of this strain family. There are several plausible explanations to account for the large extent of clustering seen in disease cases involving this group. The spread of this group in the diverse US population that has been exposed to large heterogeneous *M. tuberculosis* isolates (mainly owing to immigration) is suggestive of some, as-yet-undetermined, genotypic and/or phenotypic properties lending a specific biological advantage. However, it is possible, albeit unlikely, that the success of this strain family is simply the result of a founder effect.

Much can be learned by investigating the global dissemination of important strain families, as studies on the W-Beijing family strains have shown. Combining the advances in gene-chip technologies and sequencing methods (such as direct comparison of single nucleotide polymorphisms between clinical isolates) with current molecular epidemiological techniques will greatly aid in our understanding of why certain genotypic backgrounds of *M. tuberculosis* have successfully disseminated and caused disease worldwide.

Pablo J. Bifani

U447-Mécanismes Moléculaires de la Pathogénie Bactérienne, Institut Pasteur de Lille-IBL, 1, rue du Professor Calmette, BP 245-59019, Lille cedex, France.

Barun Mathema

Natalia E. Kurepina

Barry N. Kreiswirth*

PHRI TB Center, Public Health Research Institute, 455 First Ave, New York, NY10016, USA.

*e-mail: barry@phri.org

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