PPI use is known to be an excellent marker of frailty and ill health[3] and even well-designed non-interventional studies will struggle to account for this effect by adjusting for covariates. This may explain the numerous PPI–disease associations reported in observational studies.[3]

We do not believe that 'well-designed, high-quality studies with larger study cohorts' will lead to reproducible conclusions, as suggested by Song et al.[1] Where there is no robust comparator available, reliable inference requires a more rigorous approach. Options would include large randomised controlled trials undertaken in settings with a very high burden of TB disease (possibly not feasible). Alternatively, Mendelian randomisation studies describing the association between genetically predicted achlorhydria and TB disease could be considered.[4]

In assessing the risks associated with PPI use, clinicians should be cautious about claims made using observational data and remember that the discontinuation of PPIs can cause harm in some patients.[5]

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Using a geographic information system as a management tool for tuberculosis control

In recent years, free and highly performant software for geographic information systems (GIS) has become increasingly available. At the same time, smartphones have become omnipresent. Among their many options is the possibility to capture accurate geographic coordinates. We believe that GIS could become a useful tool not only in research but also in the management of tuberculosis (TB) control programmes. As an example, we describe an intitiative from the Comoros where mapping of TB patients at the village level has been added to the routine recording and reporting system.

The Comores are a small island nation north of Madagascar (Figure, Panel 1), with a total population of approximately 800 000. The country has a well-organised TB control programme, with excellent treatment success rates (91% cure rate among new smear-positive patients registered over the period 2014–2018). However, there is an apparent deficit in case detection. In 2017, 130 TB cases were notified, equivalent to a TB treatment coverage rate of 46% using the World Health Organization (WHO) incidence estimate of 35 per 100 000 population.[1] Based on the 'Global Burden of Disease Study, 2015' (GBD), which estimates the annual incidence rate for the Comoros at 80/100 000 (probability interval 70–92), the treatment coverage rate could be as low as 20%.[2]

On the main island of Grande Comore, home to 50% of the population, case detection rates are higher than those on the other islands. The island measures approximately 65 km from north to south and 24 km from west to east and has seven health districts, each with its own district health centre. Smear microscopy for TB is performed in the capital city Moroni, located in the centre of the west coast of the island and home to 15% of its population, and in Mitsamiouli in the north. In 2016, an additional microscopy centre was opened in Foumbouni, on the south-east coast. More recently a GeneXpert system (Cepheid, Sunnyvale, CA, USA) was set up in Moroni.[3]

Routine TB patient data such as type of patient, type of disease, initial sputum smear results, results of follow-up sputum examinations and treatment outcomes, are entered in an MS Access database (MicroSoft, Redmond, WA, USA). A series of queries was added to this database, which allow us to generate reports on new cases and relapses, as well as reports on treatment outcomes. For each patient, village or town of residence is recorded from a standardised list. To the table containing this list of 201 towns/villages in Grande Comore, we added geographical coordinates and 2017 population estimates. We then created an additional query that provides numbers of TB patients per village, with the geographic coordinates of the village, for any chosen period. These data can be exported and plotted on a map, for which we used Quantum GIS (QGIS), a free GIS software package.[4]

Over the 2014–2018 period, in Grande Comore a

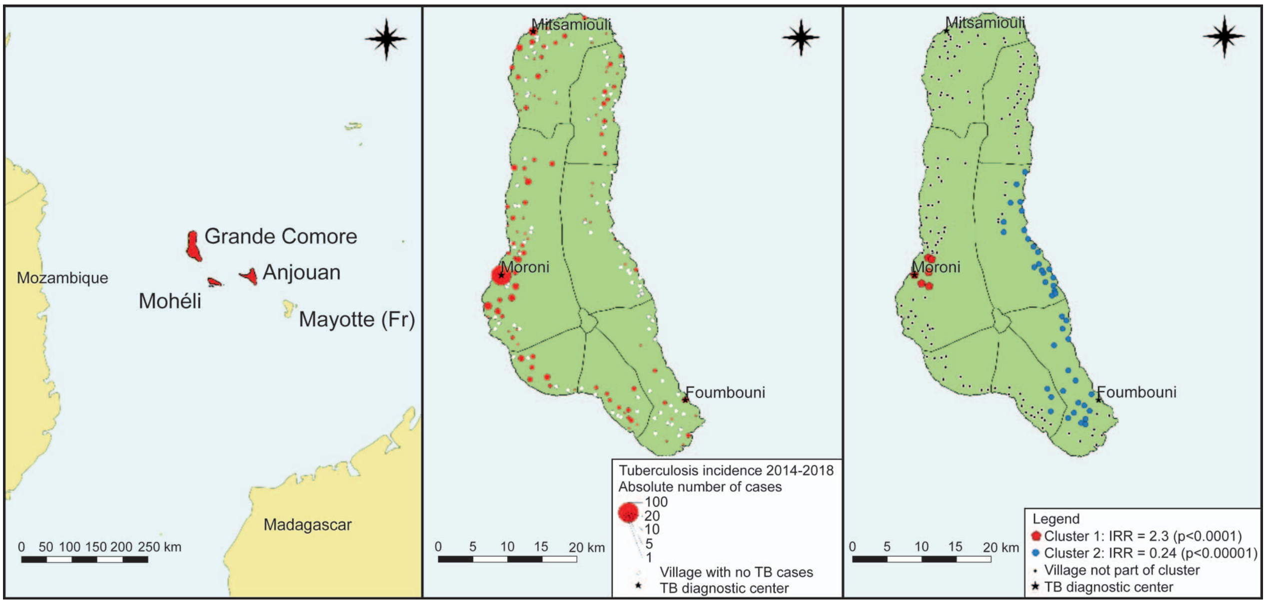

Figure Panel 1: The Comoros; Panel 2: Map of the distribution of tuberculosis cases by village on Grande Comore (2014–2018); Panel 3: High- and low case detection rate clusters based on Kulldorff's spatial scan statistical analysis. TB = tuberculosis; IRR = incidence rate ratio.

total of 374 new TB cases were reported, 272 pulmonary cases, 175 of whom (64%) were smear-positive and 102 extrapulmonary cases. We extracted these data through the designated query in the MS Access database and plotted these on a map in QGIS (Figure, Panel 2). The surface of the red dots shown on the map is proportional to the absolute number of cases in that location over the 5-year period.

At first glance, we observed high numbers of cases around the capital city, Moroni, on the west of the island, and few cases on the east side. To confirm our observations, taking into account the population sizes of the villages, we fitted a purely spatial Poisson model using Kulldorff's spatial scan statistic.[5] This software, which is also freely available, groups together clusters of villages that are in geographic proximity and calculates incidence rates inside and outside such clusters. It retains clusters with high or low incidence rate ratios using the villages outside the cluster as reference and also provides associated P values. We retained only clusters with a $P < 0.05$. One high-incidence cluster centred around the capital city, Moroni, and one low-incidence cluster on the south-western part of the island were identified (Figure, Panel 3). The high-incidence cluster included 120 cases of TB within a combined population size of 71 874, resulting in a relative risk of 2.3 ($P < 0.0001$). The low detection rate cluster is made up of 43 villages with a total population of 62 042. In this cluster, only 15 cases of TB had been reported over the 5-year period, resulting in a relative risk of 0.24 ($P < 0.00001$). The direct surroundings of the other two diagnostic centres, Mitsamiouli and Foumbouni, were not part of any high case notification clusters. The surrounding areas of Foumbouni were even part of the low case notification cluster.

We thus observed a major difference in TB case notification rates between the city of Moroni plus some nearby villages and a cluster of villages on the east side of the island. Stochasticity may play a role, given the relatively small population sizes, but by grouping together data over a 5-year period our estimates became fairly stable and are highly unlikely to be due to chance variations. Our analysis based on Kulldorff's spatial scan statistic thus confirmed what has already been suspected based on the projection of crude case finding figures on a map.

As Behr et al. convincingly demonstrate in their recent paper, most TB cases are due to recent (re)infections, with disease rarely occurring more than 2 years after infection.[6] This would further strengthen the rationale for identifying clusters of high incidence to allow for targeted control measures aiming to interrupt ongoing transmission to be implemented. However, the interpretation of the significance of such clusters requires some caution. With an overall case detection rate for Grande Comore of just above 50% of the WHO estimate, high-incidence clusters may merely reflect better accessibility to diagnostic services and the main concern should be the low-incidence clusters. In and around the city of Moroni, the case detection rate is 95% of the WHO incidence estimate; in the more remote villages it is only 14%. Two studies from Ethiopia by Dangisso et al. and Shaweno et al. show a similar pattern of low case notification in areas with poor geographical access to health services.[7,8]

Caution is also required when concluding that case notification in Moroni and surroundings is adequate, since according to the GBD estimate it could still be as low as 41%. Given the uncertainty on incidence estimates, the apparent under detection and heterogeneity observed and the relatively small population size, a prevalence survey to estimate the extent of underreporting and guide future TB control efforts seems a logical next step.

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