Coupling genomic epidemiology to a refined contact tracing in tuberculosis: Now or Never

Acoplar la epidemiología genómica a un estudio de contactos refinado en tuberculosis: ahora o nunca

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Surveillance of tuberculosis (TB) transmission, specially in large cities, is undoubtedly a challenge. Molecular epidemiology studies carried out in different populations of this type[1-5] identify very complex transmission patterns, not exclusively linked to the most obvious transmission environments (households, workplaces) and with cross-involvement of autochthonous and migrant cases, given the growing presence of the latter in the population of different megacities, who come in search of better opportunities, theoretically, for life.

The epidemiological difficulty of tracing the routes of TB transmission is also the consequence of the particular idiosyncrasy of this disease, in which the spectrum and clinical course develop in a range of manifestations spanning long periods, even years, between exposure and disease. This makes it extremely difficult to identify the source of infection by means of conventional, epidemiological strategies (conventional contact tracing CCT)) based on the search for disease in the patient's living environment, which inevitably only provides a "partial picture" of the prolonged and complex phenomenon of transmission of this disease.

The aforementioned difficulty in accurately tracing the dynamics of TB transmission in socio-epidemiologically complex populations makes it necessary to continuously optimise the way in which we approach epidemiological surveillance. Molecular/genomic epidemiology on a population-based/universal and systematic basis over time has helped to advance our understanding of the particular complexity of TB transmission[1,6]. It has allowed to improve CCT by interrogating not only the patients but the *M. tuberculosis* strains involved (enhanced CT [ECT]). However, the ECT improvements achieved through the integration of molecular/genomic are still insufficient.

In this regard, improvement efforts must be symmetrical in the two axes on which any control programme aiming at optimisation must rest: i) the accurate and rapid identification of transmission clusters derived from strain characterisation and ii) the refined investigation of the epidemiological links between cases grouped in these clusters.

Progress in increasing laboratory discrimination between *M. tuberculosis* strains in order to define clusters with maximum precision is useless if it is not accompanied by an equivalent effort to improve the information we obtain from TB cases and their contacts to understand where and how TB transmission occurs. *Vice versa*, it is not possible to improve case and contact investigation if we don´t exploit the undoubted guidance that comes from studying the association between cases in clusters.

The implementation of genomic epidemiology strategies in clinical practice, as an innovative tool for TB transmission control, requires the involvement of all those involved in diagnosis, patient care, and transmission control; to which must be added a genomic analysis node capable of providing the team with information in a format that is easily interpretable and anticipated at the time of diagnosis, to allow intervention. This complexity of

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coordination is perhaps the reason why its implementation has not yet become widespread.

Almeria is a key node in our territory in terms of the continuous implementation, over more than two decades, of analytical and strategic advances, parallel in both axes, laboratory and CCT. Throughout this time of joint work between microbiologists, clinicians and epidemiologists, sequential milestones have been achieved: (i) the integration of molecular epidemiology into the CCT to jointly analyse the association between clusters and epidemiological links, helping to identify unsuspected transmission settings[4], (ii) the implementation of a new scheme to perform the genotypic analysis directly on clinical specimens[7] or iii) the integration of molecular information on clusters in the official report generated by the microbiology laboratory, accessible to all professionals involved in the control of this disease.

This synergistic, balanced and continuous progress has led to the proposal and evaluation of a new twist in the search for maximum optimisation of TB transmission surveillance. This new model is based on i) the characterisation, not molecular but genomic, of the clusters, in a rapid manner, when it is still useful for the CT and ii) the involvement of community health workers (CHWs) in the ECT, for a detailed study of the transmission contexts revealed by the clusters, as they make it possible to eliminate the linguistic, cultural and trust barriers, which are so limiting in obtaining relevant information in the epidemiological investigation.

This tandem activity provides extremely useful information to optimise how and where control resources are directed, depending on the nature of each cluster. Thus, through advanced genomic characterisation it is possible to label new cases not only as belonging to clusters, but through the analysis of genomic relationships between strains we can categorise new cases as more likely (i) due to recent exposures or (ii) resulting from reactivations of past exposures. This discrimination is highly relevant to define control strategies according to the nature of each cluster, allowing us to prioritise control efforts to those environments truly associated with active transmissions, which are responsible for the appearance of new secondary cases. In parallel, the work of CHWs is key to understanding the links identified between cases belonging to each new cluster, as well as to identifying the transmission environment associated with it, the only way to effectively target control resources to these active transmission environments. All these innovations should be included in the EndTB strategy from WHO, to help to gain its goals.

The genomic study of new clusters, interpreted within a refined ECT, supported by CHWs, has also made it possible to reveal situations of great epidemiological complexity, which would not have been suspected with conventional strategies. In this sense, it was possible to break down the dichotomy of possibilities behind a new migrant TB case (reactivation of exposures in the country of origin vs. new infection acquired in the host country after arrival). The study of a group of migrants recently arrived in Andalusia, after a long-term extremely hard journey from different countries in the Horn of Africa, in an integrated manner with the study of other migrants from the same countries of origin, resident in other European countries, allowed a third option to be added to the two dichotomous interpretations mentioned above, namely transmission along the same migratory journey, shared by migrants from different African countries[8].

Among all the complex transmission realities uncovered by the association between genomic analysis and refined ECT, the identification of a large and long-lasting *M. caprae* zoonosis, which had gone unnoticed for two decades[9], responsible for TB cases that had been managed in the usual way, with the consequent effort in unnecessary CT, prophylaxis and stigma, and most seriously, the lack of control of infected animal foci that continued to cause cases. A detailed study of some of the migrant cases involved in this zoonotic event allowed, thanks to the thoroughness of the investigation facilitated by the CHWs, to identify new interfaces of exposure to infected animals different from the professional livestock-related settings usually considered. In particular, the refined ECT, integrated with the joint work with the veterinary authorities, following the One Health postulates, made it possible to identify the existence of irregular herds probably responsible for exposures in migrant greenhouse workers, with no professional activity in relation to livestock farming.

The work experience in genomic epidemiology in TB has been decisive in ensuring an effective response in many of the nodes involved in the surveillance of the different SARS-CoV-2 variants throughout the COVID-19 pandemic. This has been the case both in countries with a longer track record in genomic surveillance of MTB, such as the UK, and in Spain. Much of the initial efforts to provide a genomic surveillance capability in COVID-19 relied on groups that had already used this analytical language for TB. Following these initial efforts, it was possible to extend the expertise and analytical capacity to a larger network of nodes and thus strengthen the effectiveness of population-based surveillance for this emerging pathogen. To ensure the activity of this network in our country, an unprecedented effort was made to provide a wide selection of laboratories with sequencing equipment and training for genomic analysis. This has provided us with a unique potential to replicate the dynamics of advanced genomic surveillance that was activated during the

pandemic, now taking advantage of these resources and capacities to improve the control of highly relevant diseases such as TB. The usefulness of integrating genomic analysis to accurately reorientate CCT and thus increase its efficiency and ultimately transmission control has already been fully demonstrated. All that is needed is a political decision by the authorities responsible for public health to devote the same resources to the other major cause of death from a single infectious agent, TB.

It would be paradoxical, and enormously unfair, that after the generosity, dedication and effort of a large part of the community of professionals and researchers dedicated to TB analysis and surveillance, in leading and supporting surveillance in COVID, both from the laboratory and epidemiology axes, it would now be clumsy and unfair to miss a unique opportunity to take advantage of these resources to ensure the expansion of an optimised model of TB surveillance.

One of the few positive aspects of the pandemic that we have been able to extract from it is that it has definitively put an end to the consideration that there are surveillance and control strategies that should be restricted to research projects, without the need to include them in Public Health control programmes. The pandemic has fortunately blurred these artificial, and false, boundaries between research and the care environments, demonstrating in a resounding way that advanced genomic epidemiology strategies have been essential for the systematic and routine surveillance of this new disease.

The question now is: are we going to stand passively and watch a whole active network of genomic analysis and training dedicated exclusively at surveillance for SARS-CoV-2, and maybe other seasonal respiratory viruses? It is critical that we do not miss a unique, historic opportunity to exploit these valuable resources by facilitating the expansion of advanced TB surveillance models across our territory. It is time to consider them what they should have always been, essential resources for integration into TB surveillance and control programmes in the public health setting. It is Now or never!!!!

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