MESA: Investigando brotes y aumentos de transmisión de TB en tiempos de COVID

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QFT-Plus and new IGRAs in Pediatrics

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The microbiological diagnosis of tuberculosis (TB) in children remains challenging, mainly as children typically have paucibacillary disease[1]. Consequently, pediatricians frequently have to rely on immune-based tests, such as the tuberculin skin test (TST) and interferon-gamma release assays (IGRAs), to support a presumptive diagnosis of TB. However, TST has a number of well-documented limitations, including suboptimal specificity[2]. On the other hand, IGRAs have become widely available for clinical use in referral centers, being more specific than the TST, although they were found to lack the ability to distinguish between latent TB infection (LTBI) and TB disease and to have suboptimal sensitivity in patients with TB disease[3].

In 2016, the latest generation QFT assay, QuantiFERON-TB Gold Plus (QFT-Plus) (QIAGEN+, Germantown, Maryland, USA) was released. In contrast to its predecessor, the QFT-GIT assay, QFT-Plus antigen tubes only contain ESAT-6 and CFP-10 as stimulatory *Mycobacterium tuberculosis* antigens, but not TB7.7. Furthermore, QFT-Plus assays have a newly added second antigen tube (TB2) containing shorter ESAT-6 and CFP-10 peptides, aimed at eliciting CD8 +T cell responses, in addition to the first antigen tube (TB1), which contains longer peptides directed at CD4 +T cells[4]. An improved sensitivity in active TB with this new IGRA was claimed by the pharmaceutical company to justify this change. However, data regarding the performance of this assay in the pediatric population remain scarce. Therefore, we aimed to determine, firstly, the performance of QFT-Plus in a large cohort of children and adolescents at risk of TB in a low-burden setting[5], and secondly, the performance of QFT-Plus, compared with previous generation of IGRAs and the TST, in children with TB in Europe[6]. For the first objective, we designed a cross-sectional and multicentric study at health-care institutions participating in the Spanish Pediatric TB Research Network (pTBRed), including patients <18 years who had a QFT-Plus performed between September 2016 and June 2020. For the second objective, we launched a multicenter and ambispective cohort study within the pediatric TB Network European Trials Group (ptbnet), comprising more than three-hundred members, among all the TB cases <18 years-of-age diagnosed between January 2009 and December 2019.

Of 1.726 patients included in the first study[5], 260 (15,1%) underwent testing during contact tracing, 288 (16,7%) on clinical/radiological suspicion of TB disease, 649 (37,6%) for migrant screening, and 529 (30,6%) prior to initiation of immunosuppressive treatment. Overall, the sensitivity of QFT-Plus for TB (n=189) and for LTBI (n=195) was 83,6% and 68,2%, respectively. The agreement between QFT-Plus TB1 and TB2 antigen tubes was excellent (98,9%, κ=0,961). Only five (2,5%) patients with TB had discordance between TB1 and TB2 results. Indeterminate assay results (n=54, 3,1%) were associated with young age, lymphopenia and elevated C reactive protein concentrations. QFT-Plus performed very similarly to previous IGRAs, and the second antigen tube (TB2) did not significantly increase the assay sensitivity in the diagnosis of active TB.

In the second study[6], with 1.001 TB cases from 16 countries, QFT-Plus was performed in 358, QFT-GIT in 600, T-SPOT.TB in 58 and TST in 636 cases. The overall test sensitivities were of 83,8% (95%CI: 80,2-87,8%) for QFT-Plus, 85,5% (95%CI: 82,7-88,3%) for QFT-GIT, 77,6% (95%CI: 66,9-88,3%) for T-SPOT.TB and 83,3% (95%CI: 83,3-86,2%) for TST (cut-off ≥10 mm). Therefore, QFT-Plus does not perform better than previous generation of IGRAs (QFT-GIT) or the TST in children with TB disease. Additionally, tests performed worse in CNS and miliary TB, and in immunocompromised children. We can conclude that none of the tests evaluated had sufficiently high sensitivity to be used as a rule-out test in children with suspected TB.

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Experiencia del primer programa de estudio de contactos de TB en una zona rural de Angola

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Introducción

La detección activa de casos en determinadas poblaciones de alto riesgo, que incluye el rastreo de contactos, es de vital importancia para lograr el objetivo de acabar con la Tuberculosis (TB) en 2035[1]. Angola figura entre los 30 países del mundo con mayor carga de TB y TB multirresistente (TB-MDR), con una incidencia estimada en 2020 de 350 casos por cada 100.000 habitantes[2]. El protocolo de actuación del Programa Nacional de Lucha Contra la Tuberculosis (PNLCT) presenta información incierta y poco adaptada a la realidad sobre la búsqueda activa de casos, especialmente entre los contactos de pacientes con TB. En 2015 se instauró el primer programa de rastreo de contactos de TB en el Hospital Nossa Senhora da Paz (HNSP), municipio de Cubal, Angola. El HNSP, institución privada con participación sanitaria nacional, es el centro de referencia para el diagnóstico y tratamiento de la TB del municipio. Desde 2007 mantiene una estrecha colaboración con el Hospital Universitario Vall d'Hebron (HUVH) de Barcelona mediante el desplazamiento de sanitarios, formación e investigación.

Material y métodos

Siguiendo las recomendaciones de la OMS, se consideraron contactos todas aquellas personas convivientes y/o con contacto próximo y prolongado en espacios cerrados los 3 meses previos al inicio del tratamiento del caso índice[3]. Hasta 2016, el programa estuvo centrado en aquellos contactos de pacientes con baciloscopia positiva, contactos de TB-MDR, contactos VIH positivos y niños menores de 5 años, a partir de entonces, se incluyeron también aquellos contactos de pacientes con baciloscopia negativa. El rastreo inicial se realizó mediante la evaluación de síntomas (tos de cualquier duración, expectoración, hemoptisis, fiebre o sudoración nocturna), exploración física y radiografía de tórax. En caso de sospecha clínica o radiológica, se solicitaba baciloscopia de esputo o de aspirado nasogástrico. Además, y a pesar de no poder evaluar la infección tuberculosa latente (ITL) por falta de test de Mantoux o IGRAs, se ofrecía tratamiento preventivo de TB a todos aquellos contactos de pacientes con TB (no MDR) menores de 5 años o VIH positivos tras descartar enfermedad activa. Es importante destacar que la visita y la realización de la baciloscopia se ofrecían de forma gratuita, pero no la realización de otras pruebas como la radiografía de tórax o la ecografía torácica dado el carácter concertado de la institución. En diciembre de 2021, y a través de un proyecto financiado por el HUVH, se incluyó el diagnóstico molecular mediante Xpert MTB/rif (Cepheid, Sunnyvale, CA) al programa de contactos y la realización de la radiografía de tórax de forma gratuita.

Resultados

Desde marzo de 2015 hasta septiembre de 2022, se notificaron 6.354 casos de Tuberculosis (TB) en el municipio de Cubal, 695 de los cuales clasificados como multirresistentes (MDR) por fracaso terapéutico previo o confirmación molecular. Durante este período, se valoraron 1.978 contactos de 980 casos índice (15,4% del total de casos notificados) con una media (DE) de 1,4 (± 1,7) contactos por caso. Un 22,9% (224) de los casos índice estaban clasificados como MDR, un 70,8% (1401) tenían una baciloscopia positiva inicial y un 7,1% (141) eran casos pediátricos.

Un 74% (1.465) de los contactos eran familiares de primer grado de los casos índices. La mediana (RIQ) de edad de los contactos fue de 13 [5-29] años, 1.223 (61,8%) eran mujeres, 550 (27,8%) tenían menos de 5 años de edad y 437 (22,1%) eran contactos de un caso de TB-MDR. Aproximadamente un 70% (1.379) de los contactos eran del municipio de Cubal.

Un 45,2% (859) de los contactos presentaba al menos uno de los 5 síntomas utilizados para el *screening* inicial. La duración de los síntomas se registró en 542 (63,1%) contactos; 27 (5%) explicaban una duración de más de 6 meses, 171 (31,5%) entre 1 y 6 meses y 344 (63,5%) menos de 1 mes. Un 16,9% (92) de estos contactos presentaba una auscultación pulmonar patológica. Únicamente 329 (16,6%) contactos realizaron la radiografía de tórax como parte del cribaje. Esta se interpretó como patológica en 129 (39,2%) casos.

Finalmente, se inició tratamiento para TB en 200 (10,1%) contactos, 146 (73%) de ellos < 15 años y 112 (56%) ≥ 5 años. Solo se obtuvo confirmación microbiológica en 74 (37%) casos. Cuarenta y ocho (64,9%) mediante baciloscopia y 26 (35,1%) mediante Xpert MTB/rif. Treinta y ocho (19%) contactos iniciaron un esquema de segunda línea y únicamente se confirmó la resistencia a rifampicina mediante Xpert MTB/rif de forma inicial en 4 (10,5%) de ellos. En cuanto a la infección tuberculosa latente, 59 contactos iniciaron tratamiento preventivo, 38 (64,4%) de los cuales menores de 5 años y 3 (5,1%) con infección por VIH. Únicamente 38 (6,9%) de los 550 contactos menores de 5 años iniciaron tratamiento preventivo de ITL. El resto de contactos que inició tratamiento preventivo fue por criterio médico no claramente definido en los registros.

Conclusiones

La participación en el programa de contactos fue baja teniendo en cuenta el número de casos notificados en Cubal y la media de contactos evaluados por caso índice. En contraposición, se inició tratamiento en un alto porcentaje (10%) de contactos, mayoritariamente de forma empírica. El inicio de tratamiento preventivo de ITL en menores de 5 años fue bajo (6,9%).

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Quantifying bacterial load in sputum of pulmonary tuberculosis by Xpert MTB/RIF to monitor infectivity of tuberculosis among household members

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Introduction

Tuberculosis (TB) is a bacterial disease that causes 1,5 million deaths per year and to reduce disease impact exposure to the bacteria, early identification of infected persons and adequate preventive therapy to limit progression from latent tuberculosis infection (LTBI) to active TB disease, is crucial. Classically, TB disease is diagnosed through direct visualization of the bacteria with staining-assisted microscopy techniques, of which acid fast bacilli (AFB) smearing is most known, through culture or through nucleid acid amplification tests (NAAT). A specific real-time polymerase chain reaction (rt-PCR) called Xpert MTB/RIF, which later evolved to Xpert MTB/RIF Ultra, has been developed for TB. Respectively microscopic grading, time to positivity (TTP) and cycle threshold (CT) value of PCR can be used to quantify the bacterial load [1,2]. The amount of bacteria in a sputum sample is associated with increased infectivity[3,4]. This study investigated if the Xpert MTB/RIF quantified bacterial load in sputum samples of pulmonary TB patients was correlated with the infection ratio of the TB patients causing LTBI in their households.

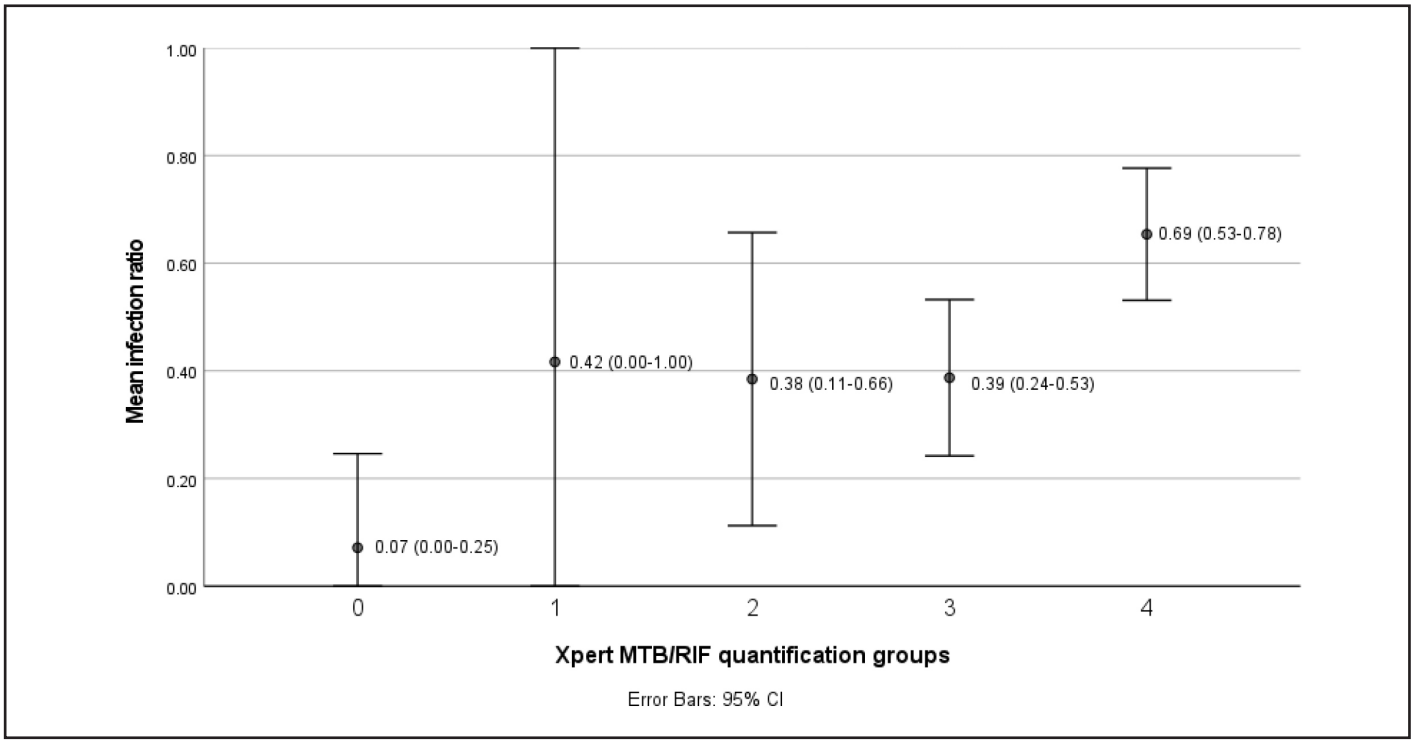
Methodology

In this retrospective cohort study the quantification results of pulmonary TB patients of 16 years or older from Vall d'Hebron University Hospital (VHUH) between 2010 and 2021 were correlated with the number of LTBI among households found in the contact tracing program. Patients from whom Xpert MTB/RIF on sputum was not used in diagnosis were excluded for analysis of the primary objective. Patients that had no contact tracing investigation or had 0 household members were excluded. The bacterial load detected by PCR was categorized in 4 groups. The Ct value of Xpert MTB/RIF and Xpert MTB/RIF Ultra were calibrated to represent a similar bacterial load in each quantification group. Contacts were detected through the Barcelona TB control program (PGTB) performed by Agencia Salud Pública de Barcelona and preventive medicine department of VHUH. Contacts were considered infected if they had a positive tuberculosis skin test (TST), or interferon gamma release assay (IGRA), or through clinical ruling by a medical expert. The proportion of household contacts that was infected of the total number of household contacts of the pulmonary TB patient was the infection ratio, which were grouped in 4 categories (0-25%; 26-50%; 51-75%; 76-100%). Comparing the Xpert MTB/RIF quantification groups with the grouped infection ratio was done through a chi-squared test and comparison of the mean infection ratio per Xpert MTB/RIF quantification group was done through ANOVA test.

Results

Between 2010 and 2021, 1.305 TB patients were identified, of who 911 had pulmonary TB or a combination of extra-pulmonary and pulmonary TB. We excluded 833 patients because: contact tracing was not accessible (364), no Xpert MTB/RIF on sputum available (451), no household members (15) or because younger than 16 years old[3]. We used 78 TB index patients for analysis. They had 771 listed contacts of which 319 (41,4%) were household members. 126 (39,5%) of them were diagnosed with LTBI. Another 14 cases were detected with of active TB disease, the majority (64,3%) being younger than 17. Categorisation of bacterial load in sputum was as follow. Seven patients had no bacteria detected in the sputum. Three patients were categorized to group 1 (very low: 28< Ct ≤38), 12 patients were categorized to group 2 (low: 22< Ct ≤28), 30 patients to group 3 (medium: 16< Ct ≤22) and 26 patients to group 4 (high: Ct ≤16). Categorisation on infection ratio gave the following results. 31 patients infected 0-25% of their household. 21 patients infected 26-50% of their household. 6 patients infected 51-75% of their household. 20 patients infected 76-100% of their household.

Figure 1. Mean infection ratio per Xpert MTB/RIF quantification groups.



The Xpert MTB/RIF quantification groups are significantly correlated with the grouped infection ratio, with patients in higher quantification groups infecting larger proportions of the family (p-value: 0,013). Mean infection ratio increased significantly over the Xpert MTB/RIF quantification groups (p value: 0,002), as is shown in Figure 1. Among Xpert MTB/RIF negative sputum samples there was still transmission of disease.

Xpert MTB/RIF ct results were correlated with the bacilloscopic grading. Besides, the presence of pulmonary cavities are correlated with increased infectivity (p value: 0,018).

Discussion

According to our study, household members of pulmonary TB patients with high bacterial load are more at risk to be infected than household members of pulmonary TB patients with low bacterial load, and patients with pulmonary TB and negative Xpert MTB/RIF result, may still result in an infection ratio among household members. The observation that TB transmission to younger household members results in active TB disease rather than LTBI stresses the importance of close contact screening, specially when a vulnerable, like paediatric, population is involved. Due to the retrospective study design data collection and merging process was complex and decreased the useful sample size, which reduces the power of the correlation. Nevertheless, has this study has shown that the role of Xpert MTB/RIF quantification can be elaborated, replacing or supporting AFB smear grading as proxy of bacterial load for identification of the most infectious patients and thus be of aid in contact tracing programs. However, contact investigation should also rely on other factors such as house conditions, overcrowding, diagnostic delay (increase exposure time) or contact susceptibility. Xpert MTB/RIF can be applied as a useful tool in places with limited resources in the hard decision to decide when or where to allocate contact tracing investigation.

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