European shortage of purified protein derivative and its impact on tuberculosis screening practices

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ABSTRACT

Setting & Objective
In June 2014 we became aware that shortages of purified protein derivative (PPD), the test substance used for tuberculin skin tests (TST), had occurred in several European healthcare institutions providing care for children with TB. To establish the extent of the shortage a survey was performed.

Design
Survey conducted over a 1-month-period (June to July 2014) among Paediatric Tuberculosis Network European Trials Group (ptbnet) members.

Results
Thirty-five physicians from 23 European countries contributed data. The most commonly used PPD product was RT23 (Statens Serum Institut; n=22; 63%). Twenty-one (60%) participants reported that their institution was experiencing a PPD shortage. The majority (n=17; 81%) of those reporting a shortage were using RT23. Thirteen (37%) participants reported changes in screening practices resulting from the shortage, including sourcing PPD from alternative manufacturers, restricting remaining supplies to patients at greatest risk, or replacing TST with IGRA testing.

Conclusions
The data show that a PPD shortage affecting multiple European countries occurred in 2014. The shortage resulted in changes in TB screening capabilities and practices, potentially compromising patient care, as well as public health efforts. Appropriate actions to prevent future PPD shortages should be explored urgently by public health agencies and key stakeholders.
Introduction

Since the early 20th century purified protein derivative (PPD), a heterogeneous mixture of mycobacterial peptides, has been used as the test substance for the tuberculin skin test (TST). The TST was the only available test for the detection of latent TB infection (LTBI), until interferon-gamma release assays (IGRA) became commercially available in 2002. In clinical practice the TST is also commonly used to support the presumptive diagnosis of active TB. There are data suggesting that IGRA perform worse in children compared with adults, and consequently many specialists recommend a dual testing approach in children using both TST and IGRA in parallel to increase overall sensitivity. Notably, the latest guidelines of the American Academy of Pediatrics Committee on Infectious Diseases recommend that for LTBI screening in children younger than 5 years of age TST should be used in preference to IGRA. The 2015 World Health Organization guidelines for the management of latent tuberculosis infection state that in low- and middle-income countries IGRA should not replace TST for LTBI screening irrespective of the patient’s age.

Contact tracing to identify individuals with LTBI who may benefit from preventive therapy is a key strategy of TB control programs in most countries with low TB prevalence. The vast majority of those countries continue to use TST rather than IGRA for this purpose, and are therefore reliant on a stable supply of PPD. Worldwide only a limited number of manufacturers produce PPD for clinical use. Therefore, significant PPD supply shortages at one manufacturer are likely to affect the market on a global scale.

In June 2014, a message highlighting issues with the supply of PPD in Austria was posted on the mailing list of the Paediatric Tuberculosis Network European Trials Group (ptbnet). In the following 48 hours several other network members reported that they were experiencing similar issues. These events prompted us to conduct a structured survey within the network.

The survey reported here aimed to capture data on the extent of the PPD shortage at specialist centers providing care for children with TB across Europe, and to establish the impact of this shortage on TB screening practices at those centers.
Material and Methods

The survey was conducted over a 1-month-period (11th June to 11th July 2014) among the members of ptbnet. The network comprises clinicians, public health professionals and researchers with a special interest in paediatric TB (for further details see: http://www.tb-net.org/index.php/ptbnet). At the time the survey was conducted ptbnet had a total of 97 members, based in 25 European countries; each of these countries has a designated ptbnet country representative.

All ptbnet members were invited by email to participate in the survey, and asked to provide information regarding the following: i) the PPD preparation used in their healthcare institution, ii) whether there was a shortage of PPD in their healthcare institution at that time, iii) the date of the onset of the PPD shortage (if shortage present), iv) details regarding the stock and supply of PPD at that time, and v) any changes in TB testing practices resulting from the PPD shortage (if shortage present).

Members were sent reminders to participate in the survey via group email two weeks after initiation of the survey. In addition, targeted emails were sent to the ptbnet country representatives asking them to provide the data requested. All replies were collated into an Excel database hosted on a secure internet server. In instances where replies lacked sufficient detail respondents were contacted via email and asked to provide clarification by one of the authors (M.T.).

Ethical approval

According to current UK National Research Ethics Service (NRES) regulations, research involving healthcare staff participating in research by virtue of their professional role does not require Research Ethics Committee review (Governance Arrangements for Research Ethics Committees, paragraph 2.3.13). Participation in this survey was voluntary, and participants were aware that the results may be published. In addition, all participants consented to their data being published.
Results

A total of 35 physicians involved in TB screening programs and/or providing care for children with TB from 23 European countries contributed contemporary data, which are summarised in Table 1. No replies were received from two European countries that have ptbnet members (Denmark and Malta).

The most commonly used PPD product in the healthcare institutions represented by the participants was RT23 (Statens Serum Institut (SSI), Copenhagen, Denmark; n=22; 63%), followed by Tubertest (Sanofi Pasteur, Lyon, France; n=6; 17%), PPD Tuberculin mammalian (BulBio, Sofia, Bulgaria; n=6; 17%), and PPD Tuberculin (St. Petersburg Institute of Vaccines and Sera (SPIVS), St. Petersburg, Russia; n=1; 3%). There were no within-country variations in the PPD product used, as shown in Table 1.

Twenty-one (60%) participants reported that their institution was currently experiencing a shortage of PPD. Shortages were reported from a total of 14 countries (Austria, Belgium, Croatia, Czech Republic, Germany, Greece, Hungary, Italy, Lithuania, Spain, Sweden, Switzerland, Ukraine, United Kingdom). The majority of those reporting a PPD shortage were using RT23 (SSI; n=17; 81%) at their healthcare institution; only four of the participants who were using RT23 (based in Finland, Germany, Portugal, and Slovenia) reported that they were not experiencing a current shortage. Fewer participants reported shortages of Tubertest (Sanofi Pasteur; n=2; 10%), PPD Tuberculin mammalian (BulBio; n=1; 5%), and PPD Tuberculin (SPIVS; n=1; 5%). The last was reported by a participant from the Ukraine who highlighted that the shortage was persisting since 2011, and that a Ukrainian company (Biolik JSC) was planning to commence production of PPD in the near future. A Romanian participant reported recently having changed from procuring PPD from a national manufacturer (Cantacuzino Institute for Serum and Vaccines, Bukarest, Romania) to importing PPD from Bulgaria (produced by BulBio).
Five (14%) participants (based in Spain, Sweden and the Ukraine) reported that there were no stocks of PPD currently available at their healthcare institution. An additional 10 (29%) participants reported that current stocks at their institution were ‘limited’ or ‘very limited’; a further seven (20%) reported supply issues.

Thirteen (62%) of the 21 participants who reported a shortage of PPD additionally reported changes in TB screening practices resulting from the shortage. Some had started the process of sourcing PPD from alternative manufacturers (including all Spanish survey participants), or were considering this option (Table 1). Others had changed their testing strategies, restricting their limited remaining PPD supplies to patients at greatest risk, or had entirely replaced TST with IGRA testing as a result of the PPD shortage.
The results from this survey show that a significant PPD shortage affecting healthcare institutions providing care for children with TB in a considerable number of European countries occurred in the second half of 2014. Some institutions experienced critical shortages while others had no remaining stocks of PPD at all. The great majority of institutions experiencing a PPD shortage were using RT23 produced by SSI.

Our data also highlight that this PPD shortage had a significant impact on TB screening capabilities and practices. Importantly, this shortage struck healthcare providers without appropriate warning. Companies supplying PPD and public health agencies alike failed to prepare end-users for the shortfall of available product. As a result, alternative supplies were not in place in many settings, jeopardizing TB control efforts in several European countries.

Interestingly, Public Health England (previously U.K. Health Protection Agency) announced in April 2014 that PPD was available, but that only orders restricted to one pack (containing 10 vials of RT23) per week could be accepted. No explanation for this change in policy was provided. It is worth noting that the U.K. already experienced a PPD shortage in 2003, when Evans Vaccines, at that time the only licensed PPD manufacturer in the U.K., had production problems and PPD had to be sourced from SSI as an interim measure.

The recent PPD shortage affecting Europe is not an isolated incident. In April 2013 the U.S. Centers for Disease Control and Prevention (CDC) announced a national shortage of PPD caused by production problems with Tubersol manufactured by Sanofi Pasteur, one of only two Food and Drug Administration licensed PPD products. The CDC advised the use of the other licensed product, Aplisol, produced by JHP Pharmaceuticals. However, the company only had ‘a restricted quantity’ at that time, and Aplisol shortages had already been reported by several TB control officials by the time of that announcement. According to the chronology outlined in a CDC publication in December 2013, the issues with Tubersol began in late 2012, and continued until October 2013 when the product returned to market. In August 2013, 29 of 52 U.S. jurisdictions reported a shortage of at least one of the two PPD products in health departments ‘to the extent that routine activities were being threatened or
had been curtailed. Canada also experienced a PPD shortage, which evolved in late 2012. 

The impact of this recent European PPD shortage on public health will be difficult to measure, as it will be impossible to determine how many patients did not receive preventive treatment and therefore subsequently developed active TB, as a direct result of PPD being unavailable for TB screening. Children will be at particular risk, due to the suboptimal performance of IGRA in young patients, and the fact that without preventive treatment young children are at far higher risk of progressing from LTBI to active TB compared with adults.

Although messages posted via the ptbnet mailing list indicate that the PPD shortages reported here had resolved in most healthcare institutions by the first quarter of 2015, more recent messages (last quarter of 2015) have highlighted renewed shortages in Croatia and Germany. It is probable that the current shortages are at least in part related to the migration crisis Europe is currently experiencing, which results in more TST tests being performed than previously. For example, a German consensus statement has recently emphasised the need to screen all refugee children and adolescents for TB irrespective of the TB incidence in their country of origin, and recommended that a TST should preferably be used in children below 5 years of age for this purpose. Our network has recently highlighted the importance of TB screening in migrants from high TB prevalence countries arriving in Europe, and emphasised that screening should not solely focus on the detection of cases with active TB, but also include identification and preventive treatment of individuals with LTBI.

The ongoing PPD supply issues, which have been highlighted in a number of recent national public health agency publications and even by the popular press, raise a number of important questions relevant to physicians, public health officials, and policy makers. Considering the importance of functioning TB control programs for public health, it would appear critical that PPD production and supplies are monitored by a supra-national agency, such as the European Centre for Disease Prevention and Control or the World Health Organization. These agencies could also maintain backup supplies for use during critical shortages, as is already the case for certain vaccines.
Manufacturers should be encouraged to put reliable systems into place to prevent such shortages and communicate production issues early. We believe that timely open dialogue and concerted action involving all key stakeholders is required to ensure the uninterrupted supply of a test reagent that remains crucial to public health.

The key limitations of this survey lie in the fact that the number of participants was relatively small, and the fact that we were unable to obtain data from several European countries. However, by using an established network of European paediatric TB specialists and specifically targeting its country representatives we were able to capture reliable, real-time data from a total of 23 European countries. All survey participants were based in paediatric healthcare settings, and it therefore remains uncertain if adult healthcare institutions in the countries captured by this survey were affected to the same extent. Finally, the majority of participants were based in University or University-affiliated healthcare institutions, and the data may therefore not be representative of the situation in regional hospitals at that time.

**Conclusions**

The data from this survey show that a PPD shortage affecting healthcare institutions in multiple European countries occurred in the summer of 2014. In several healthcare institutions providing care for children with TB this shortage resulted in changes in TB screening policies, potentially compromising patient care on an individual patient level, as well as public health efforts on national levels. Appropriate mechanisms to prevent future PPD shortages should be explored urgently by public health agencies and key stakeholders.
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Potential conflicts of interest
All authors – none.

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31. Deutsches Zentralkomitee zur Bekämpfung der Tuberkulose. Lieferengpass
Tuberkulin PPD RT 23 SSI: Empfehlungen zum Einsatz anderer diagnostischer
Table 1. Results of the Paediatric Tuberculosis Network European Trials Group survey regarding the availability of purified protein derivative.

<table>
<thead>
<tr>
<th>Country</th>
<th>National TB prevalence*</th>
<th>Healthcare Institution / Academic Institution / Organisation</th>
<th>PPD preparation used (manufacturer)</th>
<th>PPD shortage</th>
<th>Onset of PPD shortage</th>
<th>PPD stock and supply</th>
<th>Change in TB testing strategy resulting from PPD shortage</th>
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<td>Austria</td>
<td>9.8/100.000</td>
<td>Wilhelminenspital Vienna</td>
<td>RT23 (SSI)</td>
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<td>no</td>
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<td>no</td>
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<td>yes</td>
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<td>yes</td>
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</tbody>
</table>

Abbreviations: N/A – not applicable; PHE – Public Health England; PPD – purified protein derivative; SPIVS - St. Petersburg Institute of Vaccines and Sera; SSI – Statens Serum Institut