Early Detection and Integrated Management of Tuberculosis in Europe

PJ-03-2015
Early diagnosis of tuberculosis

D3.1
External Evaluation Plan for the project

WP 3 – Evaluation

Due date of deliverable	Month 6 – 2 November 2016
Actual submission date	06/12/2016
Start date of project	3 May 2016
Duration	36 months
Lead beneficiary	UCL
Last editor	Charlotte Jackson
Contributors	UCL, KI
Dissemination level	*Public*

This project E-DETECT TB has received funding from the European Union's Health Programme (2014-2020) under grant agreement N°709624.

History of the changes

Version	Date	Released by	Comments
1.0	24-10-2016	Charlotte Jackson (UCL)	First Draft circulated to the consortium for input
1.1	17-11-2016	Pauline Chetail (UCL)	Formatting and collation of KI's comments
1.2	18-11-2016	Charlotte Jackson (UCL)	Incorporation of A-MD's comments and additional comments from KI

Table of contents

1. Introduction

1.1. Background information on E-DETECT TB

The E-DETECT Tuberculosis (TB) consortium is a European Commission co-funded group which brings together world leading TB experts in national public health agencies (Sweden, United Kingdom, the Netherlands, Italy and Romania), with industry (Delft diagnostics) and major academic centres (UCL, Karolinska, SMI, OSR, UNIBS). The composition of the consortium also reflects the incidence of TB in different European countries.

The overall objective of the consortium is to contribute to a decline, and the eventual elimination of TB, in the EU. Specific objectives include:

1. To ensure early diagnosis in vulnerable populations- defined as homeless individuals, Roma, those with a history of drug use within the community, and prisoners- in two high incidence European countries (Romania and Bulgaria). This will be done by an outreach mobile digital x-ray screening van equipped with automated x-ray reading equipment and rapid molecular diagnostics. (Work Package [WP] 4)
2. To evaluate approaches to consolidate migrant TB detection and improve European **cross-border management** by:
    a. producing new feasibility data on early detection and care integration in individuals arriving via the Mediterranean sea in Italy using innovative molecular testing at immigration (WP6).
    b. collating, analysing and evaluating multi country data on TB in migrants to low incidence countries to inform effective strategies for early diagnosis of active and latent TB in low incidence EU countries (WP6).
3. To support the development of action plans in member states by taking best practice approaches from countries where E-DETECT TB partners have developed national and international strategies and evidence from this project and providing a framework, in collaboration with ECDC, to support the adaptation and implementation of these measures across other EU member states (WP7).

Successful delivery of all programmes should contribute to a reduction in EU TB incidence; in particular:

- **Outreach activity in Romania and Bulgaria is expected to lead to the early detection and treatment of active TB.** Patients detected early and successfully treated will benefit from an increase in quality of life, including being able to return to the work place, and provide for dependents where required. Those prevented from being secondarily infected will each gain between 0.14 to 1.55 quality adjusted life years (estimated based on published TB quality of life studies in Europe). There will also be a projected increase of 10% in patients placed on treatment for TB and MDR TB who would otherwise not have been found, and a consequent rise of 20% in those completing treatment due to better patient support. This has a cost implication for the health system, but also considerable benefits to the individuals by reducing premature mortality (from nearly 10% to under 5%) and to society in decreasing further spread substantially. Due to the high proportion (25%) of TB cases within the EU in Romania, a substantial impact of E-DETECT TB would be to accelerate the current slow decline.
- **Implement and evaluate migrant TB detection in Italy and early diagnosis of active and latent TB in migrants in low incidence countries.** In this setting, further decline of TB incidence can only be achieved by intervention in migrant populations who account for the majority of new TB notifications. Lessons would be identified that are applicable to low incidence countries with a high migrant TB burden in the EU. The screening of migrants immediately on arrival will have a direct effect of early diagnosis on the migrants we plan to screen in Italy leading to an increase in quality of life with an estimated gain of 0.05 quality adjusted life years per person diagnosed early and nearly 1 quality adjusted life year per case prevented. The work programme in Italy will help identify the optimal strategy for targeting vulnerable migrants arriving via the Mediterranean Sea, with particular emphasis on strengthening of cross-border interventions.
- **Creating a database containing information on active and latent TB cases, in migrants from low incidence countries.** This will allow the identification of the best approach for screening all migrants and how this might best be targeted to the groups at highest risk. Appropriate screening in migrants successfully delivered in low incidence countries will have a considerable impact on European TB trends. Particular outcomes from database analysis will include an understanding of which population sub-groups to screen, where and with which technology. Furthermore, the lessons learnt from analysis of the database generated by this study will be applicable to all EU Member States with a high TB burden in migrants, and eventually globally.
- **Strengthening national TB programmes**. Completion of this work stream should result in an improved understanding of the differences and commonalities of national TB strategies and action plans across the EU. Furthermore, it will lead to a better understanding of barriers and facilitators to implementing national TB action plans and thus the development of a document describing the best approach to develop novel, future strategies.

1.2. Deliverable objectives

The evaluation work package (WP3) has been developed to serve to broadly integrate other work packages by assessing progress towards meeting project objectives and drawing together key quantitative and qualitative analysis of all work packages. It will therefore both serve to evaluate the E-DETECT programme, and the success of the outreach activities in Romania (WP4) and the migrant screening initiative in Italy (WP5) as well as the value of various approaches for screening for latent and active TB (WP5).

2. The Evaluation of E-DETECT TB

Purpose

To determine if E-DETECT has delivered all designated components of the grant to time and to a high quality. We will utilise a structure, process and outputs and outcomes model to outline whether the intervention has achieved its stated objectives.

Methods

Independent assessment comparing the outputs of each WP, including when they were delivered, to those described in the original grant proposal, including an assessment of quality.

An up-to-date Gantt chart for the project will be obtained and a hierarchy of deliverables created, together with a standardised framework of assessment for fitness for purpose. Each deliverable within a WP will be assessed as to timeliness and quality by the Evaluation Team. Should any deliverables be delayed or of lower quality than expected, reasons for this will be explored through discussions with the consortium members responsible for their delivery.

Key outcome(s)

WP deliverables met.

Outputs

Report to funders covering all WPs.

2.1. Evaluation of early case detection in Romania (WP4)

Purpose

Determine the effectiveness and cost-effectiveness of the mobile screening radiography unit in Romania.

Epidemiological methods

WP4 has been tasked with collecting the following data for the evaluation:

- Among those screened we will describe the number of people eligible for screening and number screened, by risk category, age and sex.
- To allow a description of the population, we will collect data from all detected active TB cases, including resistance to rifampicin, smear status, symptoms reported at the time of screening, and average delay from start of symptoms to treatment onset.
- We will also collect comparable data on cases with active TB diagnosed by the national TB programme prior to the intervention and during the intervention period who would otherwise have been detected by the van. This will include all cases with risk factors that fall within the criteria for screening.
- Results of human versus computer-read chest xrays in terms of detecting radiographic abnormalities and GeneXpert versus liquid culture diagnoses of *Mycobacterium tuberculosis* infection and rifampicin resistance.
- Whether referred patients start TB treatment, attended their appointments and what dates and type of supervision was given for treatment. This will be linked to national surveillance information to determine treatment completion. The delay from start of symptoms to treatment onset.

The following analyses will be undertaken:

- Structure-process-output-outcome mapping of the service.
- Descriptive analysis of the number of people eligible for screening versus the number screened.
- Prevalence of CAD4TB radiographic changes due to TB in different risk groups and how this changes during the work package.
- Prevalence of confirmed TB disease and rifampicin resistance and how this changes during the work package.

- Using liquid culture as the gold standard, the relative sensitivity and specificity of the CAD4TB system and human read chest xrays, respectively, for detecting bacteriologically confirmed TB. The accuracy of CAD4TB will be compared to that of human readers in order to determine if automated reading can detect relevant radiographic abnormalities with the same accuracy as human readers. The use of CAD4TB as an aid for human readers, feasibility, acceptability, cost, and cost-effectiveness will also be assessed. Using liquid culture as the gold standard, the relative sensitivity and specificity of GeneXpert both for the detection of *Mycobacterium tuberculosis* and rifampicin resistance, and the relative prevalence of confirmed disease.
- Analysis of risk factors, TB symptoms and chest xray findings using logistic regression to test the hypothesis that passively identified cases are more likely to be smear positive and have more severe disease on diagnosis than actively identified cases and to compare treatment uptake and outcomes in passively and actively identified cases after controlling for potential confounders (such as treatment delivery mode).
- The average delay from start of symptom and diagnosis, respectively, to treatment onset.

Key outcome(s)

- The number of individuals detected with active TB (assuming prevalence of 600 per 100,000 in year 1 and 400 per 100,000 in year 2 of screening), by risk category.
- Number of individuals placed on appropriate treatment for drug sensitive and drug resistant TB.
- Number of patients completing treatment.
- The proportion of individuals placed on effective treatment within 1 week.
- Difference in diagnostic delay between intervention detected cases and other detected cases
- Difference in smear positivity between intervention detected cases and other detected cases
- Difference in treatment completion between intervention detected cases and other detected cases.
- Sensitivity and specificity of CAD4TB and human read xray.

Health economics

Undertake an economic evaluation of the programme to assess value for money. Our approach will follow the approach used in recent mathematical and health economic models in the UK to assess latent TB screening and active case finding (NICE). We will calculate QALYs and costs over up to a 50 year time horizon from a health care provider perspective, applying discount rates of between 3% and 10%. A probabilistic sensitivity analysis will be conducted using the distribution of the estimated

values of the main variables of interest. Health utilities will be informed by published studies and our European Commission funded studies on tuberculosis screening in Europe and published reviews of latent and active TB detection and treatment. The cost per case averted will be calculated in addition to the cost per QALY gained, cost per case detected and the expected total cost and cost effectiveness of delivery at scale.

OUTPUTS

Report documenting the effectiveness and cost-effectiveness of the mobile screening service.

2.2. Evaluation of migrant screening in Italy (WP5)

PURPOSE

Determine the effectiveness and cost-effectiveness of screening migrants for active and latent TB in Italy.

EPIDEMIOLOGICAL METHODS

WP5 has been tasked with collecting the following data for the evaluation:

- The number of people eligible for screening and number screened (for both active and latent TB), including their demographic information.
- The screening results.
- Treatment uptake and completion.

The following analyses will be undertaken:

- Structure-process-output-outcome mapping of the service.
- Uptake of latent and active TB screening and treatment by country of origin, place of screening (temporary or settled), and immigrant status.
- The prevalence of detected active and latent TB by country of origin, place of screening, and immigrant status.
- Multivariable statistical analysis to determine the factors associated with uptake of screening and positive results.

HEALTH ECONOMICS

Undertake an economic analysis to determine which strategy offers the best value (the yield and costs of screening using different screening algorithms).

A similar approach to WP4 will be employed for estimating the cost-effectiveness of migrant screening. Incremental cost-effectiveness ratios will be calculated for QALYs gained, cases detected and cases averted.

KEY OUTCOME(S)

Number of cases of TB detected among temporary migrants

OUTPUTS

Report documenting the effectiveness and cost-effectiveness of the mobile screening service.

2.3. Analysis of active and latent TB screening data to inform migrant health

WP5 also includes the collation of data from multiple countries to allow the investigation of the best approaches for screening migrants for active and latent TB infection (LTBI). The databases to be used include:

1. a collation of standardised programmatic latent TB data to investigate uptake and yield of screening and factors associated with better yield and treatment initiation and completion. This will include a descriptive comparison on uptake and yield of the pooled datasets on latent TB (including site of screening, country of origin, immigration status, age and sex). Data from the UK, Netherlands, Sweden and Italy as well as any other EU country willing to participate will be collated.
2. access to ECDC held data on active TB notifications in Europe and the use of country of birth/citizenship variable to investigate the risk groups at the highest risk of tuberculosis and where screening might improve early detection of TB and prevent subsequent progression among those with latent TB.
3. a collation of research databases involving cohorts where latent TB tests have been used to assess progression to active TB.

These analyses will require a data sharing agreement, the establishment of a central database and data analysis plan which will outline descriptive and analytical statistical methods to address each question.

Health economics

In selected countries, undertake an economic analysis to determine which strategy, including prioritization of risks groups to screen and treat for LTBI, offers the best value. Data on screening yield in different groups will be used to model the cost-effectiveness of migrant LTBI screening, using a similar approach to WP3 and WP4.

Key outcome(s)

- Number of people screened, by country of origin, age and sex
- Number of LTBI detected
- Number started on treatment and completed treatment (from selected countries where data are available)

Outputs

A multi-country database on LTBI screening of migrants

Report documenting the screening coverage and yield in different groups.

3. Outputs

A final publication will be prepared which guides and supports each Member State TB control programme in developing a national TB action or strategy in terms of the effectiveness and cost effectiveness of the interventions evaluated in this programme of work.

4. Evaluation Group

The evaluation will be jointly undertaken by two Centres within the Institute for Global Health at University College London (UCL): the Centre for Infectious Disease Epidemiology (CIDE) and the Centre for Global Health Economics. The Centre for Infectious Disease Epidemiology also hosts the coordination work package; the Centre for Global Health Economics is independent of CIDE. The evaluation team will also include other universities in the consortium (Karolinska, Brescia, Milan) and public health organisations (KNCV, PHE, INMI).

The Centre for Global Health Economics, at IGH, comprises a team of experienced health economists (www.ighe.org), who regularly undertake the economic analyses of complex, large-scale trials. Analyses commonly include assessing the cost effectiveness and equity impact of interventions, and understanding the fiscal space for sustainable and scalable programme delivery. The health economics team is currently involved in a variety of projects in South East Asia, Sub-Saharan Africa, Middle East, Central Asia and Eastern Europe. These projects include interventions focused on improving maternal and child survival, reducing maternal and child under nutrition, allocative efficiency of HIV and TB responses/resources, improving access to HIV and sexual reproductive health care, and reducing the prevalence of non-communicable disease, in particular, diabetes.

The Centre for Infectious Disease Epidemiology at IGH is a world leading centre on the epidemiology, prevention and treatment of infections including tuberculosis, hepatitides, HIV, and other common problems such as antimicrobial resistance and vaccine preventable diseases particularly among vulnerable populations. The Centre includes epidemiologists, public health experts, data scientists, modellers, clinicians and nursing staff with experience of tuberculosis in Europe within academia and industry as well as leadership of national programmes.