ECDC GUIDANCE

Programmatic latent tuberculosis control in the European Union and candidate countries - Draft conclusions

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Background and Rationale

- The WHO's End TB strategy aims at a 90% reduction of TB incidence and 95% reduction of mortality by 2035. The control of latent tuberculosis infection (LTBI) is an important step towards TB elimination.

- The ECDC guidance aims at

- *"providing EU/EEA Member States and candidate countries with support for implementation of programmatic LTBI control in national TB programmes"*

Guidance topics

Target population
In which populations will LTBI control measures lead to the largest benefit?

Diagnosis of LTBI
What is the most optimal and reliable diagnostic test or combination of tests for LTBI?

LTBI treatment
What is the most optimal regimen for LTBI treatment?

Programmatic issues
What is the best approach for programmatic LTBI control?

- Case detection (screening, contact tracing)
- Treatment related interventions (treatment adherence, adverse events)
- Education
- Implementation
- Program Monitoring & Evaluation

Process and Methodology

2013

- Inventory of expert opinions - workshop at ECDC
- Scoping and identifying questions

2014-16

- Evidence collection, appraisal and synthesis
- WHO/ ECDC commissioned systematic reviews (SRs) carried out
- Economic modelling work from Erasmus MC
- Review of reviews and evidence synthesis from Pallas

2016

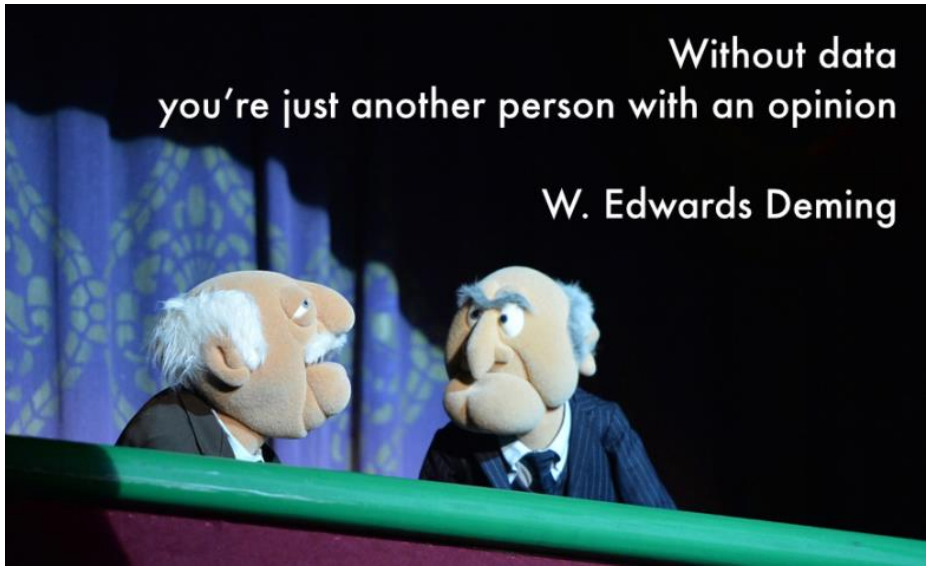
- *Ad hoc* scientific expert panel at ECDC
- Delphi process to develop guidance

2016-17

- Further Delphi by email and phone consultation with *ad hoc* scientific panel

Evidence collection

- Pallas Evidence synthesis from
  - Commissioned Systematic reviews
  - Non-commissioned systematic reviews
- Erasmus MC cost-effectiveness modelling work
- National and international guidelines
- Expert views and experience



Topic	Questions	Non commissioned SRs	Commissioned SRs
Risk of LTBI	LTBI infection risk LTBI progression risk • Clinical risk groups • Population risk groups • Vulnerable groups • Occupational risk groups	Diel, 2012; Campbell, 2016; Campbell, 2015; Fox, 2013; Triasih, 2012; Schepisi, 2015; Shah, 2014; Kotila 2016; Vinkeles Melchers, 2013; Patra, 2015; Freeman, 2010	Govindasamy, 2014 Sotgiu, 2014 Girardi, 2014
Diagnosis of LTBI	TST and IGRAs Effectiveness, cost-effectiveness and acceptability	Campbell, 2015; Auguste, 2016; Nienhaus, 2011; Abarca-Tomos, 2013;	Kik, 2014 Van't Hoog, 2014
Treatment of LTBI	Efficacy, toxicity, cost-effectiveness, acceptability	Stagg, 2014; Sharma, 2013; Ai, 2015; Ayele, 2015; Chavan, 2011; Diel, 2015; Abarca Tomos, 2013; Langendam, 2013	Zenner, 2016 Den Boon, 2014 Girardi, 2014 Den Boon, 2016 Girardi, 2014 Sandgren, 2016 Stuurman, 2016
Programmatic issues in LTBI control	Effectiveness, cost-effectiveness, access to groups, barriers and interventions modifying screening and treatment uptake and completion, M&E, integration into existing programmes	Aldridge, 2014; Campbell, 2015; Uyei, 2011; Schepisi, 2015; Kotila, 2016; Triasih, 2012; Fox, 2013; Shah, 2014; Nienhaus, 2011; Vinkeles-Melchers, 2013 ; Lutge, 2015; M'Imunya, 2012; Lutge, 2015; Abarca Tomas, 2013; Alsdurf, 2016; Uyei, 2011; Legido-Quigley, 2013	Girardi, 2014 Stuurman, 2016 Sotgiu, 2015

Overview of research questions and systematic reviews for guidance

Quality of evidence

	Definition	Included study designs	AMSTAR
No evidence	No evidence or clear conclusions from any studies	- No studies included	Not applicable
Weak evidence	No strong evidence from high quality studies. Only tentative evidence from moderate quality studies or clear evidence from low quality studies	- RCTs - Cohort/case-control studies - Cost-effectiveness studies - Cross-sectional studies - Outbreak studies - No study design reported	Low to high quality review
Moderate evidence	Tentative evidence from multiple high quality studies, or clear evidence from one high quality study or multiple medium quality studies, with minimal inconsistencies across all studies	- Largely RCTs; and/or - Largely cohort/ case-control studies; and/or - Largely cost-effectiveness studies	Moderate to high quality review
Strong evidence	Clear conclusions from multiple high quality studies	- Largely RCTs included	High quality review

So… what is in the draft guidance then?

Target groups for programmatic LTBI control

- Advisable for all **people living with HIV** (regardless of CD4 cell counts, viral loads, ART status or belonging to other risk groups).

- Advisable for **severely immunocompromised persons**
  - including patients initiating **immunosuppressive drugs** (such as tumour necrosis factor (TNF)-alpha inhibitors);
  - **patients preparing for transplantations;**
  - patients who have diseases that affect the immunological status (e.g. **end stage renal diseases and preparing for dialysis**).

- Advisable for persons with **silicosis**.

Target groups for programmatic LTBI control

- Advisable for **all close contacts** of persons with infectious pulmonary TB.
- **Specific migrant populations** can be considered for programmatic LTBI control
  - Depends on epidemiological situation in host country and characteristics of the migrants such as TB incidence in country of origin, migration route, type of migrant and time since migration.
- Could be considered for **prisoners, homeless persons and drug users**
  - Depends on the epidemiological situation of TB in the country and in the specific risk group settings and feasibility.
- **Could be considered for healthcare workers,** but should be focused at HCWs at higher risk of TB
  - Those working in settings with a high risk of TB transmission, and HCWs identified in a contact investigation.

Diagnosis of LTBI

- Both TST and IGRA can be used for diagnosing LTBI.
- Choice of test depends on circumstances and practicalities.

Target groups	Preferred test	Reason
Children under 5 years of age	TST	Children's immune system, difficulty drawing blood, little data on performance of IGRAs in young children.
Vulnerable and hard-to-reach populations	IGRA	No need for a second visit to read the test result.
Immunocompromised patients (including PLHIV)	Combination of TST and IGRA	LTBI tests are less sensitive in immunocompromised individuals. In order not to miss infected individuals, a more inclusive approach is advisable.
Migrant populations	IGRA or TST acceptable. IGRA for large numbers	No need for a second visit to read the test result.
BCG-vaccinated individuals	IGRA	TST may be affected by prior vaccination with BCG

Treatment of LTBI

- Effective treatments for LTBI are
  - **Isoniazid (INH) (6-9 months)**
  - **Rifapentine (RPT) + INH (3 months)**
  - **INH + rifampicin (RIF) (3-4 months)**
  - **RIF (3-4 months)**

- Short-course RIF containing regimens appear to be less toxic compared with INH
  - Shorter LTBI treatment regimens and treatments with less frequent administration are preferred over longer LTBI treatments regimens
  - Careful clinical **monitoring and follow-up** of individuals who are prescribed LTBI treatment is advisable in order to detect drug-related adverse events

- MDR-TB and XDR-TB **contacts** identified as having LTBI
  - Advisable to provide information and health education and observe clinically
  - Not sufficient evidence to recommend preventive Rx - conduct an individual risk assessment before deciding

Programmatic issues - themes

Identification of population groups

Training and education

Access to population groups

Incentives and enablers

Which test

barriers

Which treatment

Combination with other health programmes

The cascade of care in diagnosis and treatment of latent tuberculosis infection: a systematic review and meta-analysis

Hannah Alsdurf, Philip C Hill, Alberto Matteelli, Haileyesus Getahun, Dick Menzies

Initiation and completion rates for latent tuberculosis infection treatment: a systematic review

Andreas Sandgren[1], Marije Vonk Noordegraaf-Schouten[2], Femke van Kessel[2], Anke Stuurma Anouk Oordt-Speets[2] and Marieke J. van der Werf[3*]

Scarce evidence, many questions not addressed, mainly primary studies observational studies

Programmatic issues: optimising LTBI screening

- Screening of vulnerable populations can be facilitated by ensuring that **health services** are **accessible** for specific risk groups.

- **Good rapport with well trained HCWs** can support contact investigations.

- **Integration of LTBI control** into existing TB and other health and social care programs and services, is likely to be beneficial.

Programmatic issues: optimising LTBI treatment adherence

- **Directly observed therapy (DOT)** improves treatment completion in individuals at risk of non-adherence.

- **Culturally appropriate "patient-centred" case management** can improve treatment initiation and completion, especially in individuals from vulnerable groups.

- To support screening uptake and completion some **incentives and enablers** may help.

  But the usage and effectiveness of these depends on specific target groups and resources in different settings and countries

Programmatic issues: optimising LTBI control

- **Training of healthcare workers** on LTBI could be effective in improving target populations' willingness to be diagnosed and treated for LTBI.

- **Patient counselling and education** could be effective in improving adherence and completion rate in certain population groups.

Monitoring and evaluation

- The implementation of programmatic LTBI control and targeting it to specific populations should be **monitored and evaluated using the WHO monitoring and evaluation indicators**.

Knowledge gaps

- The level of evidence of included literature is generally low

- More good quality comparative studies are needed for all areas considered in the guidance, particularly in the following areas

  - Programmatic aspects of LTBI control, specifically regarding the effectiveness and impact of programmatic LTBI control
  - Interventions to improve uptake and adherence
  - Understanding of LTBI tests including distinguishing remote infection and re-infection
  - Cost and cost-effectiveness data, data on population sizes of risk groups, data on overlap and transmission between these groups, and precise data on risk of TB in risk groups.

Thank you!!

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