



Early Detection and Integrated Management of Tuberculosis in Europe

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Early diagnosis of tuberculosis

E-DETECT (EARLY DETECTION AND INTEGRATED MANAGEMENT OF TUBERCULOSIS IN EUROPE)

Work Package 4.1:

Screening Roma population and clients of the methadone replacement clinic in Plovdiv, Bulgaria (14 – 18 October 2019)

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D4.1

Feasibility screening in Bulgaria

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Key word list

Tuberculosis, Mobile X-ray Unit, screening, Roma, Bulgaria

Definitions and acronyms

Acronyms	Definitions
TB	Tuberculosis
MRU	Mobile X-ray Unit
WHO	World Health Organization
ECDC	European Centre for Disease Control and Prevention
E-DETECT	Early Detection and Integrated Management Of Tuberculosis In Europe
EU	European Union
MDR-TB	Multi-Drug Resistant Tuberculosis
NTP	National TB Programme
CAD4TB	Computer-Aided Detection for Tuberculosis
UK	United Kingdom
NTPR	National TB Programme of Romania
KNCV	Royal Dutch Tuberculosis Foundation
UCL	University College of London
NGO	Non-Government Organisation
CXR	Chest X-ray

1. Introduction

For the general objectives of E-DETECT-TB we refer to deliverable D1.2, the Work Package 1 interim report of January 2018.

This deliverable (D4.1) describes the pilot study planned under Work Package 4: to demonstrate the feasibility of the active case finding approach implemented in Romania in another EU Member State (Bulgaria). Bulgaria is a country in transition from a high to intermediate TB incidence and is experiencing high TB rates among certain population subgroups. In WHO Euro/ECDC country review reports, the opportunity to enhance screening activities has been highlighted for those countries. For details of existing active case-finding initiatives and outcomes in Bulgaria 2010 – 2018 we refer to the Annex.

1.1. Specific Objectives Work Package 4

1.1.1. Early case finding

- 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 Romania and in a feasibility pilot in Bulgaria. This will be done by an outreach mobile digital x-ray screening van equipped with automated x-ray reading equipment (CAD4TB; DELFT Imaging Systems) and rapid molecular diagnostics. (GeneXpert)

1.1.2. Care integration

- To strengthen care integration using an outreach strategy within the same vulnerable populations in Romania providing a one-stop “shop” (clinic), which brings together all required procedures, social support to vulnerable groups, peer support, and close links to the national TB programme to ensure treatment completion

1.2. Actions to achieve the objectives of Work Package 4:

1.2.1. Equip MXU

4.1: Equip mobile digital radiography unit (MXU)

1.2.2. Training of staff

4.2: Training of the staff to implement the screening activities: including a kick-off meeting in Romania and further training in London

1.2.3. Screening vulnerable populations

4.3: Screening of the vulnerable populations (project months 7-30). Selection of populations, settings and cities will be guided by data from the TB surveillance system on the prevalence in risk groups, settings and geographical areas.

1.2.4. Quality control

4.4: Quality control with possible adaptation of the diagnostic methods and algorithm. This includes quality control procedures to assess the CAD4TB method through double reading by Romanian radiologists/chest physicians and Dutch experts and bacteriological quality control

1.2.5. Care integration

4.5: Strengthened care integration in vulnerable populations in Romania: Develop, agree and implement on the pathway and point of care for referred cases and treat TB patients in the screening programme under the conditions of the NTP Romania. In addition, peers will support the diagnosed patients to complete treatment successfully.

1.2.6. Pilot project Plovdiv, Bulgaria

4.6: Implement a feasibility study / pilot TB screening project in Plovdiv/Bulgaria: organise a kick-off meeting in Bulgaria to share screening practices in Romania, UK and the Netherlands. Implement a pilot TB screening project in high-risk settings in Plovdiv / Bulgaria for one week and evaluate it in WP 3.

1.3. General context Deliverable 4.1

1.3.1. Deliverable

D4.1: Feasibility study/pilot screening in Plovdiv / Bulgaria, and report.

1.3.2. Background

WHO recommends systematic screening for active TB in subpopulations that have poor access to health care, such as people living in urban slums, homeless people and other vulnerable groups.

1.3.2.1. Aim

A pilot screening activity will be done in the last year of the E-DETECT project in Bulgaria to assess the feasibility of running the same activity in another EU country than Romania.

1.3.2.2. Location

In consultation with the National TB Programme of Bulgaria and the National Institute of Infectious Diseases the venue of screening was determined to be in Plovdiv, the second largest city of Bulgaria (375 000 inhabitants, of which an estimated 50 000 belong to the Roma population, mainly living in the Stolipinovo district). In the Stolipinovo district is also a methadone substitution facility situated, serving approximately 100 (former) IV drug users. In Stolipinovo operates a strong Non-Government Organisation (NGO) “Roma Foundation” for social and medical support to the Roma population, who has agreed to assist during the pilot project. The city is located 125 kilometres from Sofia. It is served by a regional TB Clinic¹, (40 beds and out-patient services), served by a chest physician, a medical microbiologist and TB nurses, who agreed to be the back-up for clinical follow-up during or after the five screening days, as well as perform the reading of the chest X-rays made during the pilot project. Parking facilities and 3-phase electricity supply are available.

¹ The TB Clinic is part of the Department of Pulmonary Diseases and Phthisiology at University Hospital, Plovdiv

1.3.3. Deliverable objective 1

To pilot the feasibility of implementing an outreach service with a mobile x-ray screening van for early diagnosis of TB, combined with social support to ensure care integration, in Bulgaria

2. Methodological approach

2.1.1. Implementation

The NGO serving the Roma population planned to perform pre-screening triage to identify individuals in the Roma populations with symptoms compatible with active TB. However, due to the postponement of the activity from September to October the triage could not take place. We planned to offer the x-ray screening to eligible persons between 17.00 – 20.00 hours, as many of them were thought not to be present during daytime due to work or other activities. After the first day of screening this time frame was adjusted to 15.00 – 18.00 hours in an attempt to increase the attendance. The clients of the methadone replacement clinic were screened in the morning of the last day of screening. We planned to have sputum collected from individuals with high CAD4TB scores (>50/60) and that would be collected outside of the MXU during screening and transported to the microbiology department of the Plovdiv TB Clinic. The cartridges for the GeneXpert machine were provided by the Bulgarian NTP. Chest X-rays were made available digitally to the Plovdiv TB Clinic for reading, i.e. through the Thirona Cloud server of DELFT.

2.1.2. Inclusion criteria

Roma population and clients of the methadone replacement clinic Plovdiv ≥ 18 years

2.1.3. Targeted number of screened individuals per project day:

100 individuals

2.1.4. Participants

The feasibility study / pilot screening was performed by a medical microbiologist and former director of the National Institute for Infectious Diseases in Bulgaria (coordinator), a chest physician from the TB Clinic in Plovdiv, a medical microbiologist from the TB Clinic in Plovdiv, a radiographer from the Lung Hospital in Plovdiv the MXU team from Romania (driver, radiographer, economist/ logistical coordinator and economist/project coordinator), and a consultant TB physician from The Netherlands.

3. Summary of activities and research findings

3.1. Preparations

3.1.1. Permission and inspection

Before the pilot could be implemented permission was required from the Ministry of Health in Sofia and the Radiation Protection Section of the Nuclear Energy Department of Bulgaria. The necessary documents were provided by the Marius Nasta Institute in Bucharest, Romania, and translated in Bulgarian. The pilot study was postponed by one month (from the original date originally planned (18-22 September 2019), awaiting the necessary permission from the relevant Bulgarian authorities. Two weeks before the pilot was planned all necessary documents were received. On Monday morning 14th October 2019, day 1 of the pilot project, radiation measurements were performed in and around the Romanian MXU on location in Stolipinovo. These findings were satisfactory according to Bulgarian Radiation Protection Legislation. The MXU was also inspected and approved by officials of the Regional Health Inspectorate of Plovdiv.

3.1.1.1.

The Municipality of Plovdiv offered electricity to the MXU but the power cable had to cross the road unprotected against the passing cars. Therefore it was decided to use the MXU generator for power supply, also because the amount of fuel was considered sufficient to allow the MRU to function independently during the 5 days of the project.

3.2. Screening

3.2.1. Pre-screening

Pre-screening was not performed. The Roma NGO explained that the Stolipinovo area is divided in sectors, defined by Roma clan origin. Roma from different clans would not travel to another area. It was further explained that the NGO had planned for support in the week originally planned and because the pilot was postponed the NGO already had other commitments in the screening week. However, two English speaking educated persons from the Roma community were allocated to the MXU where they placed a table outside and registered the people before examination and translated the Cyrillic names in Latin based letters.

3.2.2. Procedures of screening in Stolipinovo

The Roma NGO had earlier indicated another location, better targeted to the more deprived individuals according to them, but the Plovdiv municipality had decided different, with the argument of providing electricity. The MXU was now parked in the less-deprived area of Stolipinovo, next to the Stolipinovo Health Centre (with a static X-ray device) and only screened passers-by and not belonging to the groups at highest risk for TB. Only 25-35 persons were screened per day although when screening was done in the afternoon instead of the evening, this resulted even less CXRs per session.

The day after screening the CXRs were read by the pulmonologist of the TB Policlinic of Plovdiv after successful set-up of the Thirona Cloud. Human reading results were recorded in an Excel file. A summary of the results is provided in the Table. Of interests, two individuals being told on Monday that their CXR would be discussed with the pulmonologist both returned the next day to inquire about the findings. One person received a referral note to the pulmonologist.

Lesson learned is that timing of the screening should be well-planned (e.g. in the summer more people will be back from abroad; more advocacy is needed (e.g. posters, local radio when available, churches); better targeted, e.g. informing the community that screening is aimed to symptomatic individuals preferably. Perhaps the initiative of TB screening with an MXU needs more time to be recognised, used and appreciated by certain TB risk groups in the Bulgarian population. However, mobile units are used to deliver various health services in these populations, e.g. by paediatricians and gynaecologists.

3.2.3. Numbers screened and outcome

Number of chest X-rays per day and outcomes of CAD4TBv.6 reading in detail

Day / CAD	0-10	11-20	21-30	31-40	41-50	51-60	61-70	71-80	81-90	91-100	TOTAL
14-10-2019	1	4	1	-	17	7	1	-	-	-	31
15-10-2019		4	3	7	9	3	-	-	-	-	26
16-10-2019	1	3	1	1	22	7	-	2	-	-	37
17-10-2019		6	2	1	9	9	-	-	-	1	28
18-10-2019	1	2	4	5	17	2	3	1	1	-	36
TOTAL	3	19	14	14	74	28	4	3	1	1	158

* One CXR with fault and CAD score of -1

** One CAD4TB score was 97 but appeared old TB 20 years ago, hospital admission for one year, at present no complaints; no cough, no sputum production

Number of chest X-rays per day and outcomes of human reading

Day	Number	Normal (0)	Suggestive TB (1)	Suggestive other pathology (2)	Other
14-10-2019	31	20	0	2	9
15-10-2019	26	24	0	0	2
16-10-2019	37	33	0	2	2
17-10-2019	27	21	0	2	4
18-10-2019	35	25	2	1	7
TOTAL	156	123	2	7	24

On the 4 days of community screening among Roma population in Stolipinovo no individual with radiological signs, compatible with probable or possible active intrathoracic TB was identified. One person with a CXR showing extensive abnormalities, compatible with fibrotic lesions after a previous episode of TB, was interviewed and was treated for TB 20 years ago and at present had no symptoms. The person will be followed-up by the pulmonologist. On review of the CXRs the next day the pulmonologist would attempt to obtain a sputum for bacteriological testing of one individual with a CAD score of 73 (CAD scores could not be seen on the viewing station on the X-ray control panel in the MXU but could be requested, in case of relevant abnormalities, by the TB physician in the MXU from the logistic coordinator as CAD scores did appear on his laptop). During screening, after reading the chest X-ray and a basic interview, no indication for sputum collection was found. Most abnormalities identified were not related to TB and not considered urgent.

On the last day of the screening (18-10-2019) the methadone clinic in Stolipinovo was visited. Apart from the clients also staff such as cleaners and security officers were screened. Of the 35 CXRs made, 27 were from clients. It was immediately clear that when reading these CXRs, that abnormalities and high (requested) CAD4TB scores were more common among the methadone users, compared to the Roma population screened in the community during the rest of the week.

Three sputa were taken in the day of screening the methadone centre, with CAD4TB scores >60. The results of the direct bacteriological tests (smear microscopy and GeneXpert) were negative for the three specimens.

3.2.4. Opinions of team

Due to language barriers and logistical procedures, it was not feasible to obtain opinions from clients about the screening initiative.

One of the Roma translators, assisting in registration, said that originally the Roma NGO had designated another location for the screening in Stolipinovo. However, the Municipality of Plovdiv wanted the MXU to be parked next to the health centre. He believed the original location would have been better, perhaps attracting people who could be more at risk for TB.

The radiographer worked for the first time in an MXU instead of a hospital and considered this intervention as a good initiative.

The chest-physician thought screening of the methadone users would be complimentary to other active case-finding activities in Bulgaria, as is not excluded that the risk groups of homeless persons and illicit drug users could be missed by the other case-finding activities. Apparently methadone clinics were screened at times previously but this intervention may have been abandoned.



4. Conclusions and future steps

4.1. Feasibility

Objective of this pilot study, early diagnosis using an outreach service with a mobile x-ray screening van combined with social support to ensure care integration in Bulgaria, proved feasible in Bulgaria.

Bulgaria already uses digital MXUs for screening among predominantly prisoners and the Roma population, but perhaps not in a structured way and employing technology such as CAD, teleradiology or molecular fast-track diagnostics such as GeneXpert close to the MXU. It is also not clear whether MXU activities in Bulgaria are embedded in NGO outreach programs, for pre-screening of targeted individuals, assisting to reach target populations and improve acceptability and accessibility, or providing social support after a diagnosis of TB has been made, in order to improve treatment initiation and completion. Bulgaria already has programs for NGO outreach activities in order to support TB case-finding.

4.2. Future steps

4.2.1. Possible spin-off of pilot project on the use of Bulgarian MXUs

4.2.1.1. *Renewed interest in integrating latest technologies for active TB case-finding*

A spin-off of this pilot study could be to renew interest in this technology and with advancing technical knowledge over the years, available international experience regarding various aspects of MRU screening, and demonstrated opportunities for cooperation, upgrade and integrate these MXUs into a coordinated and structured screening tool, connected to a national database, to screen identified TB risk groups, more specifically homeless persons and illicit drug users, in all regions of Bulgaria.

4.2.1.2. *Cross-sectional screening of facilities for homeless persons and illicit drug users*

The pilot study seems to indicate that the yield of active case-finding among homeless persons and illicit drug users could be higher compared to Roma community screening (higher CAD4TB scores and more abnormalities listed by human reading as suggestive for active intrathoracic TB among the clients of the methadone centre), although the screening did not take place among the possibly higher risk Roma population initially selected. In the context of and complementary to the data in Table 1 in the Annex, this observation could deserve further attention by attempts to provide the necessary evidence whether a TB problem in these risk groups is preventing Bulgaria from a faster reduction in the national burden of TB disease.

The existing MXUs could be used to screen the most important facilities for homeless persons and illicit drug users in Bulgaria, for example a one-week screening in Sofia and in the rest of Bulgaria, divided in three sectors, also one week per sector. Such an exercise should be carefully planned, with identification and prioritisation of facilities, communication with these facilities for assistance,

communication with possible NGOs for support, communication of back-up by local clinical, bacteriological, nursing and social workers, and other logistical issues. In analogy to the Open Doors initiative (see Annex) this intervention could be repeated every 6 months. In the rest of the year the MXUs remain available for other screening activities, such as prison, migrant or Roma community screening.

When the Bulgarian MXUs are not equipped with technology for teleradiology and/or software for interpretation of the chest X-rays, it could be considered that, at least initially, a, preferably experienced, TB physician joins the MXU to interpret the images from the X-ray station as initial reading, to give feedback to the clients of the results, or to initiate possible follow-up in case of any abnormalities, such as the collection of spot-sputum. A team for an MXU could then consist of a TB physician, local TB nurse or social worker, radiographer and driver (for more background see reference 1,4, 11-13, among others).

Such a nation-wide inventory could serve two purposes;

1. To provide data on TB prevalence among homeless persons and illicit drug users in facilities for these risk groups in Bulgaria
2. To reduce TB transmission and progression to active disease in individuals using these facilities.

The data can then be used to provide evidence (or absence of evidence) for upgrading the available MXUs for an active case-finding program targeting homeless persons and illicit drug users, when it appears that these risk groups are insufficiently reached by regular health care, NGO outreach activities (see Annex) or the Open Doors program.

4.3. Executive conclusion and recommendation

Active targeted case-finding using an outreach service with a mobile x-ray screening unit proved feasible in Bulgaria. Increased awareness of the intervention among the target groups could increase daily attendance and pre-screening the target population with questionnaires for relevant symptoms or pre-screening with Tuberculin Skin Tests could increase yield and reduce costs.

4.3.1. Recommendation

Bulgaria already has a decade of experience of active case-finding of TB case, involving digital MXUs, NGO outreach programs and hospital Open Doors initiatives, involving ten thousands of individuals screened, contributing a substantial proportion of TB cases annually notified in Bulgaria.

Although this feasibility project was too short and limited to provide robust data and no TB cases could be confirmed, the higher CAD4TB scores and more abnormalities listed by human reading as suggestive for active intrathoracic TB among the clients of the methadone centre could support a broader analysis of whether certain groups, such as homeless persons and illicit drug users, often described as those with highest risk for TB (apart from contact investigations) in other studies in EU

countries (see list of relevant references in section 6) are sufficiently covered by the existing active case-finding interventions. When a more comprehensive screening of these risk groups is considered beneficial and necessary from an individual and public health care point of view, existing interventions could be used and amalgamated into additional and complementary targeted screening initiative for homeless persons and illicit drug users, with existing (but possibly upgraded) MXUs, supported by NGO outreach workers, and backed up by the “Open Doors” TB clinics in all regions of Bulgaria.

5. Publications resulting from the work described

A publication of the pilot result is not anticipated.

It is planned in 2020, to organise a two-day TB conference in Bulgaria with funds from the E-DETECT TB project. Participants (approximately 50) are: Bulgarian district TB coordinators, representatives of Ministry of Health, representatives of major municipalities, representatives of regional health inspectorates, representatives of NGOs, and others. The purpose of the conference is an exchange of experience of TB screening in The Netherlands, the UK, Romania and Bulgaria, with the aim of strengthening active case-finding in Bulgaria.

6. Bibliographical references of selection of related literature

1. De Vries G, Van Hest R. From contact investigation to tuberculosis screening of drug addicts and homeless persons in Rotterdam. *Eur J Public Health* 2006; 16: 133-6.
2. Story A, Van Hest R, Hayward A. Tuberculosis and social exclusion. *BMJ* 2006; 333: 57-8.
3. Antoine D, Maguire H, Story A. Epidemiology and response to the growing problem of tuberculosis in London. *Eurosurveill* 2006;11:25-8.
4. De Vries G, Van Hest RA, Richardus JH. Impact of mobile radiographic screening on tuberculosis among drug users and homeless persons. *Am J Respir Crit Care Med* 2007; 176:201-7.
5. Story A, Murad S, Roberts W, Verheyen M, Hayward AC. Tuberculosis in London: the importance of homelessness, problem drug use and prison. *Thorax* 2007;62:667-71.
6. Van Hest NA, De Vries G, Smit F, Grant AG, Richardus JH. Estimating the coverage of tuberculosis screening among drug users and homeless persons with truncated models. *Epidemiol Infect* 2008;136:628-35.
7. Story A, Bothamley G, Hayward AC. Crack cocaine and infectious tuberculosis. *Emerg Infect Dis* 2008;14:1466-9.
8. Van Hest R, Story A. Controlul tuberculozei la persoanele fără locuință din Uniunea Europeană: mai mult decât simple cuvinte. (Tuberculosis control among homeless persons in the European Union: more than words alone). *Pneumologie* 2009; 58: 84-7.
9. Anderson C, Story A, Brown T, Drobniewski F. Tuberculosis in UK prisoners: a challenge for control. *J Epidemiol Community Health* 2010;64:373-6.
10. Abubakar I, Story A, Lipman M, Bothamley G, van Hest NAH, Andrews N, Watson JM, Hayward AC. Diagnostic accuracy of digital chest radiography for pulmonary tuberculosis in a UK urban population. *Eur Respir J* 2010;35: 689-92.
11. Jit M, Stagg H R, Aldridge R W, White P J, Abubakar I. Dedicated outreach service for hard to reach patients with tuberculosis in London: observational study and economic evaluation. *BMJ* 2011; 343: d5376.
12. Story A, Aldridge R W, Abubakar I, et al. Active case finding for pulmonary tuberculosis using mobile digital chest radiography: an observational study. *Int J Tuberc Lung Dis* 2012; 16: 1461–1467.
13. Zenner D, Southern J, Van Hest R, De Vries, Stagg HR, Antoine D, Abubakar I. Active case finding for tuberculosis among high-risk groups in low-incidence countries. *Int J Tuberc Lung Dis* 2013;17:573-584.
14. Van Hest NA, Aldridge R, De Vries G, Sandgren A, Hauer B, Hayward A, Arrazola de Oñate W, Haas W, Codecasa LR, Caylà JA, Story A, Antoine D, Gori A, Quabeck L, Jonsson J, Abubakar I. Tuberculosis control in big cities and urban risk groups in the European Union: a consensus statement. *Euro Surveill* 2014; 2014;19(9):pii=20728.
15. De Vries G, Aldridge RW, Cayla JA, Haas WH, Sandgren A, Van Hest NA, Abubakar I and the Tuberculosis Control in Big Cities and Urban Risk Groups in the European Union (EU) Working Group. Epidemiology of tuberculosis in big cities in the European Union and the European economic Area. *Euro Surveill* 2014;2014;19(9):pii=20726.
16. Lönnroth K, Migliori GB, Abubakar I, D'Ambrosio L, de Vries G, Diel R, Douglas P, Falzon D, Gaudreau M.A, Goletti D, González Ochoa E, LoBue P, Matteelli A, Njoo H, Solovic I, Story A, Talal Tayeb T, van den Werf M.J, Weil D, Zellweger JP, Raviglione MC. Towards tuberculosis elimination: an action framework for low-incidence countries. *Eur Respir J* 2015;45:928-52.

17. Hogeweg L, Sanchez C, Maduskar P, Philipsen R, Story A, Dawson R, Theron G, Dheda K, Peters-Bax L, van Ginneken B. Automatic detection of tuberculosis in chest radiographs using a combination of textural, focal, and shape abnormality analysis. *IEEE Trans Med Imaging* 2015
18. Van Hest R, de Vries G. Active tuberculosis case-finding among drug users and homeless persons: after the outbreak. *Eur Respir J* 2016;48:269-271;pii: ERJ-00284-2016. doi: 10.1183/13993003.00284-2016.
19. Anderson C, Anderson SR, Maguire H, Hayward AC, Story A. Tuberculosis in London: the convergence of clinical and social complexity. *Eur Respir J* 2016;48:1233-1236.
20. Aldridge RW, Story A, Hwang SW, Nordentoft M, Luchenski SA, Hartwell G, Tweed EJ, Lewer D, Katikireddi SV, Hayward AC. Morbidity and mortality in homeless individuals, prisoners, sex workers, and individuals with substance use disorders in high-income countries: a systematic review and meta-analysis. *Lancet* 2017 DOI: [http://dx.doi.org/10.1016/S0140-6736\(17\)31869-X](http://dx.doi.org/10.1016/S0140-6736(17)31869-X)
21. Abubakar I, Matteelli A, de Vries G, Zenner D, Cirillo DM, Lönnroth K, Popescu G, Barcellini L, Story A, Migliori GB. Towards tackling tuberculosis in vulnerable groups in the European Union: the E-DETECT TB consortium. *Eur Respir J* 2018;51. pii: 1702604. doi: 10.1183/13993003.02604-2017.
22. Gupta RK, Lipman M, Story A, de Vries G, van Hest R, Erkens C, Rangaka MX, Abubakar I. Active case-finding and treatment adherence in risk groups in the tuberculosis elimination era. *Int J Tuberc Lung Dis* 2018; 22:479-487.
23. Melendez J, Hogeweg L, Sánchez CI, Philipsen RHHM, Aldridge RW, Hayward AC, Abubakar I, van Ginneken B, Story A. Accuracy of an automated system for detection of tuberculosis on chest radiographs in high-risk screening. *Int J Tuberc Lung Dis*. 2018 ;22 :567-571. doi: 10.5588/ijtld.17.0492.
24. Aldridge RW, Hayward AC, Hemming S, Yates S, Ferenando G, Possas P, Garber E, Watson JM, Geretti AM, McHugh TD, Marc Lipman M, Story A. High prevalence of latent tuberculosis and blood borne virus infection in a UK homeless population. *Thorax* 2018 Jun;73(6):557-564. doi: 10.1136/thoraxjnl-2016-209579.
25. Yassine B, Taylor P, Story A. Fully automated lung segmentation from chest radiographs using SLICO superpixels. *Analog Integrated Circuits and Signal Processing* 2018. DOI 10.1007/s10470-018-1153-1
26. Golli AL, Nicu MF, Turcu F, Popescu M, Ciobanu-Mitrache L, Olteanu M. Tuberculosis remains a public health problem in Romania. *Int J Tuberc Lung Dis* 2019;23:226-231.
27. Gliddon HD, Shorten RJ, Hayward AC, Story A. A sputum sample processing method for community and mobile tuberculosis diagnosis using the Xpert MTB/RIF assay. *ERJ Open Research* 2019 5: 00165-2018; DOI: 10.1183/23120541.00165-2018

7. Annex

7.1.1. Alternative “active” case-finding interventions in Bulgaria 2010-2018

7.1.1.1. Pre-screening

In Bulgaria “pre-screening” is performed for many years by local NGOs, using questionnaires to identify individuals in the community with relevant symptoms. Symptomatic individuals can be directly referred to a local health centre or hospital for a CXR, or first a Tuberculin Skin Tests (TST) is given locally and only those who are TST-positive are referred for further examination, in order to make pre-screening possibly more targeted (Annex 1).

Table 1: Yield of NGO outreach active case-finding in Bulgaria 2010 – 2018

Compact Roma Populations (living in city areas; not mobile Roma)										
Year	2010	2011	2012	2013	2014	2015	2016	2017	2018	TOTAL
Number of persons from vulnerable groups interviewed for TB* risk	10.854	9.947	9.056	9.939	9.339	7.697	14.134	17.391	18835	107.192
Total number of medical examinations carried out on-site and in TB hospitals with the assistance of NGOs	3855	3150	3565	2093	2144	1704	5366	8827	7694	38.398
Number of people diagnosed with TB from those interviewed for the risk of TB	53	26	50	69	55	44	76	81	89	543
% TB + cases / N examined	1,4%	0,8%	1,4%	3,3%	2,6%	2,6%	1,4%	0,9%	1,2%	1,4%
Number of people diagnosed with LTBI** from those surveyed for TB risk	219	224	351	180	168	112	380	408	399	2.441
% LTBI cases / N examined	5,7%	7,1%	9,8%	8,6%	7,8%	6,6%	7,1%	4,6%	5,2%	6,4%
* TB = tuberculosis; ** LTBI = latent TB infection										
Other populations at risk (such as homeless persons, illicit drug users)										
Variables	2010	2011	2012	2013	2014	2015	2016	2017	2018	TOTAL
Number of persons from vulnerable groups interviewed for TB risk	5.119	2.171	2.365	4.337	5.015	3.857	5.717	6.193	4.884	39.658
Total number of medical examinations carried out on-site and in TB hospitals with the assistance of NGOs	3.068	908	1013	1814	2.042	1.466	1.667	2.464	1.878	16.320
Number of TB diagnosed with tuberculosis from those interviewed for the risk of TB	20	0	3	4	4	6	8	16	28	89
% TB + cases / N examined	0,7%	0,0%	0,3%	0,2%	0,2%	0,4%	0,5%	0,6%	1,5%	0,5%
Number of people diagnosed with LTBI from those surveyed for TB risk	109	30	14	23	36	29	73	114	154	582
% LTBI cases / N examined	3,6%	3,3%	1,4%	1,3%	1,8%	2,0%	4,4%	4,6%	8,2%	3,6%

* TB = tuberculosis; ** LTBI = latent TB infection

In 9 years' time through NGO outreach work in the Roma communities 543 individuals were diagnosed with TB, out of 38 398 individuals examined, translating into a TB prevalence rate of 1.400 per 100.000 individuals, much higher than the national TB rate in Bulgaria. Among other risk groups such as homeless persons and illicit drug users in 9 years' time 89 persons were diagnosed with TB out of 16 320 individuals examined, translating into a TB prevalence rate of 500 per 100.000 individuals. It is not clear whether these data overlap and whether other risk groups than homeless persons and illicit drug users were involved, with a low risk of TB, diluting the TB prevalence rate in the "other risk groups". The a priori assumption would rather be that among homeless persons and illicit drug users a higher TB prevalence rate would be expected compared to the general Roma community.

7.1.1.2. Open Doors Initiative

In Bulgaria there is another successful alternative program for examining individuals with symptoms and complaints of lung disease (in general, not specific for TB): the "Open Doors" initiative. Hospitals open their doors one week per three months for free examination of persons with possible lung disease, including TB. The yield of the "Open Doors" initiative for TB is also high, even higher compared to NGO outreach screening initiatives, with TB prevalence rates of 1.400 to 2.300 cases per 100.000 persons examined.

Table 2: Yield of Open Doors "active" case-finding in Bulgaria 2009 - 2018

OPEN DOOR CAMPAIGNS

		Number of consulted and examined by TB physicians	Number suspicious for TB	% of suspicious / examined	TB+ for treatment	% of TB + / examined	% of TB + / suspicious	Number of cases with LTBI	% LTBI/examined	% LTBI/suspicious
1	2009	7.920	2.458	31%	120	1,5%	4,9%	339	4,3%	13,8%
2	2010	13.149	4.649	35%	181	1,4%	3,9%	820	6,2%	17,6%
3	2011	12.528	4.022	32%	215	1,7%	5,3%	705	5,6%	17,5%
4	2012	7.578	2.493	33%	176	2,3%	7,1%	335	4,4%	13,4%
5	2013	3.814	579	15%	62	1,6%	10,7%	267	7,0%	46,1%
6	2014	5.591	1.229	22%	95	1,7%	7,7%	424	7,6%	34,5%
7	2015	1.487	233	16%	27	1,8%	11,6%	99	6,7%	42,5%
8	2016	7.083	1.480	21%	126	1,8%	8,5%	472	6,7%	31,9%
9	2017	7.765	1.761	23%	120	1,5%	6,8%	531	6,8%	30,2%
10	2018	6.935	1.386	20%	120	1,7%	8,7%	359	5,2%	25,9%
Total		73.850	20.290	27%	1.242	1,7%	6,1%	4.351	5,9%	21,4%

It cannot be excluded that there is an overlap between the yield of the Open doors campaigns and the NGO pre-screening campaigns reported earlier, as some of the examined individuals might be the result of NGO pre-screening referral and not self-referral due to the Open Doors intervention.

7.1.1.3. Targeted mobile X-ray screening

Bulgaria has 3 – 4 mobile X-ray units, located in different areas of the country and used for prison screening and ad hoc community / population screening by regional TB hospitals. Probably all these MXU's are digitalised but they might not be equipped by WIFI and teleradiology. They are not connected to a national database and not supplied with CAD software and the CXR's are read by local TB specialists. There is no GeneXpert machine inside the MXUs but it is assumed that quick examination of sputa can be performed in local or regional microbiology laboratories when arrangements are made, to allow for early detection of TB. It is unknown whether screening exercises by Bulgarian MXUs are supported by local NGOs. It seems the MXUs are mainly used to screen prisoners and Roma population. Migrant screening is performed occasionally since Bulgaria is not having a large migrant population and those seeking asylum in the EU usually do not stay for long in Bulgaria. It is unknown whether these MXUs are also used to screening homeless persons and illicit drug users, such as the clients of methadone replacement clinics or needle exchange posts. The yield of screening among migrants and Roma is low.

Table 3: Yield of MXU active case-finding in Bulgaria 2017 - 2018

Screening 2017 and 2018 by Bulgarian MXUs				
	Prisons	Migrants	Roma	TOTAL
Number of persons in a given group	3.781	575	10.631	14.987
Number of persons to be examined	3.825	575	12.131	16.531
Number of respondents	3.360	492	6.834	10.686
Number of persons with suspected TB diagnosis	103	3	44	150
	3,07%	0,61%	0,64%	1,40%
Number of persons with confirmed TB diagnosis	15	0	2	17
TB+ from tested	0,45%	0,00%	0,03%	0,16%
TB+ from suspects	14,56%	0,00%	4,55%	11,33%
Number with cancer	5	2	19	26
Count with another pathology	73	72	411	556
Number directed to other studies	125	43	215	383