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Breaking the paradigm: Optimized Case Finding multiplies tuberculosis detection among key populations in Ukraine

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Abstract
Introduction: In 2018, there were 3 million "missed" tuberculosis (TB) cases globally, much of which was disproportionally concentrated among key populations. To enhance TB case-finding, an Optimized Case Finding (OCF) strategy involving all contacts within the social network of an index TB case was introduced in five regions of Ukraine. We assessed TB detection and linkage to TB treatment using OCF in key populations.
Methodology: A cohort study using routine program data (July 2018 – March 2020). OCF empowers the index TB case to identify and refer up to eight close contacts within his/her social network for TB investigations.
Results: Of 726 index TB cases in key populations, 6,998 close contacts were referred for TB investigations and 275 were diagnosed with TB (183 drug-sensitive and 92 drug-resistant TB). The TB case detection rate was 3,930/100,000 and the Numbers Needed to Investigate to detect one TB case was 25. TB was most frequent among people who inject drugs and homeless groups. Compared to TB detection using routine household case finding within the general population (1,090/100,000), OCF was 3.6-fold more effective and when compared to passive case finding in the general population (60/100,000), OCF was 66 times more effective. 99% (273) of TB patients were linked to care and initiated TB treatment.
Conclusions: The OCF strategy among key populations is very effective in identifying TB cases and involving them for treatment through the recruitment of the contacts from the risk social networks. We advocate to scale-up this case finding strategy in Ukraine and beyond.

Key words: Key populations; Optimized Case Finding; Operational Research; SORT IT.

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Introduction

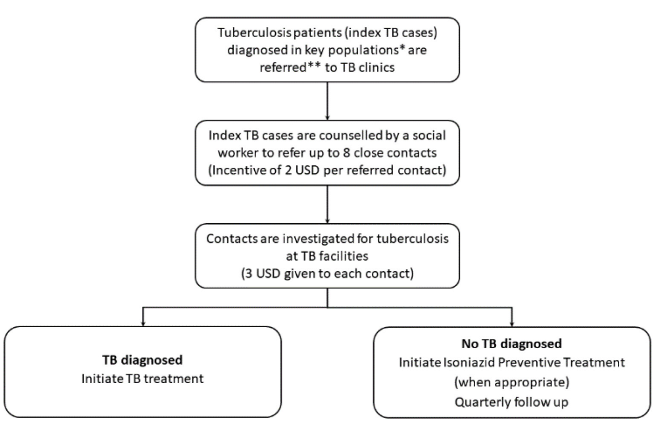
In 2018, there were still 10 million cases of tuberculosis (TB), 1.2 million deaths, and 3 million active TB cases missed by health systems (referred as "missed TB cases") globally [1].

Missed TB cases are disproportionally concentrated among vulnerable and key population groups that often do not have access to health [2-5]. These include socially marginalized individuals including people who inject drugs (PWID), displaced, homeless, Roma, and former prisoners. Many of them are human immunodeficiency virus (HIV) positive, use drugs, and live in cramped conditions with poor ventilation. These factors accentuate their risk for acquisition and transmission of TB [6]. People who use drugs are at increased risk of TB, with rates documented in the pre-AIDS era of over 10 times higher than among the general population. HIV further increases the risk of TB, and TB is a leading AIDS-defining illness and cause of mortality among people living with HIV who inject drugs. To attain the World Health Organization (WHO) End TB targets of 90% reduction in TB deaths and 80% reduction in TB incidence by 2030, a focus on vulnerable groups is urgently needed [7]. Two of the three targets in the End TB strategy and Stop TB Partnership Strategic Plan involve key populations. One of these targets aims to ensure that TB diagnostic and treatment services reach at least 90% of key populations, while the other target aims at a minimum of 90% treatment success [7]. Ukraine is one of the high-burden countries for multidrug-resistant TB and like elsewhere, "missed TB cases" are likely to be concentrated in vulnerable and key populations [2,7]. TB case finding in the country has relied on a "passive" approach where patients self-present to health facilities. However, vulnerable population groups who are often criminalized and/or socially marginalized are less likely to neither self-present nor be able to navigate to access the desired healthcare services in the system. It is thus important to think of an "active" case-finding approach for this group.

Based on experience from an Optimized Case Finding (OCF) for HIV [8,9], which uses Social Network Strategy for HIV Testing Recruitment that has demonstrated its effectiveness for HIV detection among key populations, the Alliance for Public Health (APH) in Ukraine adapted a similar active strategy for TB case finding in key population groups. This strategy goes beyond household case finding and includes all kinds of contacts within the social network of key populations. Fundamentally, the OCF strategy empowers the index TB case to refer up to eight close contacts for TB investigations (Figure 1). It is unique in that the onus is placed on the TB index case to decide on the closest contacts within his/her social network and then refer them. This starkly contrasts with the usual contact tracing strategy which is practically limited to immediate household contacts.

Finding ways of improving the detection of TB among key populations is important and aligns well with the Sustainable Development Goal (SDG) of achieving Universal Health Coverage for TB and the WHO Flagship Initiative "Find.Treat.All. #EndTB" [10]. A PubMed search revealed no previous studies that have described the adaptation of the OCF experience to TB case finding in key populations and linkage to care. Hence, we undertook this study aiming to describe the strategy of TB OCF among key populations and assess the resulting TB detection rate and the linkage to TB treatment.

Figure 1. Optimized Case Finding for tuberculosis among key population groups in Ukraine



*Includes people who inject drugs, ex-prisoners, homeless, the Roma population and internally displaced persons; **Referred by harm reduction programs and from medical facilities.

Among contacts of index TB cases referred for TB investigations using an OCF strategy, our specific objectives were to determine the:

- Number of contacts of index TB cases investigated and diagnosed with TB;
- Number Needed to Investigate (NNI) to detect one TB case in contacts;
- Socio-demographic characteristics of TB among index cases and contacts;
- TB cases detected per 100,000 contacts through OCF compared to other routine case finding strategies;
- Number (and proportion) started on TB treatment among those diagnosed with TB.

Methodology

Study design

A retrospective cohort study using routine program data.

Study Setting

Ukraine is the largest country in Eastern Europe with a population of 42 million people. It is bordered by Poland, Slovakia, Hungary, Romania, Moldova, Russia, and Belarus. There are an estimated 800,000 people from key population groups, 324,300 being PWID. The TB incidence rate is 80 (52-115) per 100,000. The APH in Ukraine is a principal recipient of the Global Fund and PEPFAR country grants. APH coordinates, supervises and monitors HIV prevention and care activities including TB care and harm reduction services for key populations. These services are conducted by over 100 partnering non-governmental organizations (NGOs) in the country who work in close collaboration with the Public Health Services of Ukraine.

Tuberculosis management

The management of TB is according to national and WHO guidelines [11]. Both drug-sensitive and drug-resistant TB are managed at specialized TB clinics available at secondary and tertiary levels, while primary healthcare center involvement in TB is still limited. The Public Health Center of Ukraine provides organizational and technical guidance for the implementation of TB care. A national electronic database of TB was introduced in 2012 (the eTB-manager). In Ukraine, the routine strategies for TB case finding include: a) passive case finding for the general population where individuals are expected to self-present to heath facilities when they have symptoms suggestive of TB and b) active household case finding where household contacts of index cases are screened for TB. OCF is an active case-finding strategy for key population groups that were introduced by the APH.

Optimized Case Finding for tuberculosis

Figure 1 illustrates the OCF strategy. In brief, patients diagnosed with TB can originate from key population groups who are referred from NGO, run HIV/TB and harm reduction programs or health facilities. These individuals are considered as Index TB cases. Key population groups include PWID, ex-prisoners (persons within 2 years after being released from prison), homeless, the Roma population, and internally displaced persons. Each index case is counseled by a social worker who provides information on how and where to refer up to eight contacts for TB investigation. The period for a contact to be referred is up to three months before the index case being diagnosed.

Contacts are broadly classified into four groups:

1. *Family contacts:* family members of the index case with whom the patient had interacted on a regular or periodic basis;
2. *Household contacts:* persons residing with the index case in a common living room (including shelters for the homeless), in an apartment, house, hostel, social welfare institution, or children's institution. The person must have spent one or several nights or long periods during the day with the index case;
3. *Occupational contacts:* persons working with the patient and staying in the same room up to 6-8 hours for at least one day;
4. *Risky interaction contacts:* persons who have had close verbal interactions with the index case in crowded places such as in the pub, on public transport (buses), at religious gatherings, during inpatient treatment, at the drug-taking point, and temporary detention centers.

These contacts are referred for TB investigations to TB facilities and are required to arrive within one month from the referral date. The index case receives a monetary incentive of 2 USD for each referred contact while each contact receives 3 USD as reimbursement for transportation costs. The contacts undergo a range of investigations according to National TB guidelines including clinical examination, X-ray examination (fluorography / radiography / computed tomography), and sputum examination (microscopy, GeneXpert MTB/RIF assay). Those diagnosed with TB are offered TB treatment. The treatment regimen is prescribed in accordance with the National TB Treatment Protocol which is consistent with the recent WHO TB treatment recommendations. The treatment is prescribed based on the identified Mycobacterium tuberculosis (MBT) sensitivity. The resistance profile of the revealed MBT in patients was determined using the GeneXpert, GenoType, VASTEC MGIT 960 systems. In case TB is excluded, the patient is followed up quarterly for repeat TB investigations for up to 12-months, and if appropriate, patients are administered isoniazid preventive therapy (IPT).

Study sites, study population and study period

The study sites included Kharkov, Rivne, Odessa, Zakarpattya, and Dnipropetrovsk regions of Ukraine with eight TB clinics. The study population included contacts of index TB patients originating from key population groups. The study period was from July 2018 to March 2020.

Data sources, variables, and statistical analysis

The sources of data were the SYREX database on key populations available at APH and TB patient cards and TB registers available in the TB clinics. Using a structured data collection form, we extracted data from these sources and analyzed them in EpiData (version 2.2.2.186 for analysis, EpiData Association, Odense, Denmark). Data variables included socio-demographic and clinical characteristics of index TB cases and contacts, type of key population group, nature of TB investigations, whether TB was diagnosed in contacts and if so, the category and type of TB, and finally, whether TB treatment was started. NNI to detect one TB case was derived by dividing the total number of contacts who were investigated by the total number of TB cases detected. To assess the difference in TB detection rates between OCF in key populations and the passive case finding strategy applied in the general population, we standardized the TB detection to 100,000 contacts and compared this rate with that in the general population. We also compared the detection rate with that reported nationally using active screening of all members of the household of an index TB case within the general population. Differences between groups were assessed using the Chi-square test with the level of significance set at $p \leq 0.05$.

Ethical considerations

Permission to use the data was obtained from the APH and the National TB Control program of Ukraine. Ethics approval was obtained from the Ukraine National Ethics Review Committee and the Union Ethics Advisory Group of the International Union against TB and Lung Disease, Paris, France. As we used secondary data, the issue of written informed consent did not apply.

Results

Index TB cases, referral of contacts, diagnosis of TB and linkage to care

There was a total of 726 index TB cases diagnosed in key populations and 6,998 close contacts were referred for TB investigations in health facilities. The mean number of contacts per index case was 9.6 (range: 5-12). Data on TB diagnosis was not available for 67 of these contacts. Of the remaining 6,931 where TB diagnostic information was available, 275 TB cases were detected including 183 drug-sensitive and 92 drug-resistant TB (Table 1). Using the OCF strategy, the NNI was 25 (for every 25 contacts investigated in key populations, one TB case was diagnosed).

There 99% (273) TB patients were linked to care and initiated TB treatment; 121 of the 275 TB patients were HIV-positive of whom 105 (87%) were also receiving antiretroviral treatment (ART).

Socio-demographic and clinical characteristics of index TB cases and contacts

The characteristics of the 726 index TB cases from key populations and the 275 TB cases diagnosed in contacts are presented in the Table 2. In both index TB cases and contacts, TB was most frequent among PWID followed by homeless groups. Among those with TB in contacts, 42 (15%) were family contacts, 103 (62%) were household contacts. 44 (16%) were involved with joint drinking of alcoholic beverages at community

Table 1. Tuberculosis (TB) detection, number needed to investigate to detect one TB case and linkage to treatment using an Optimized Case Finding strategy in key populations in Ukraine (July 2018 – March 2020).

Characteristics	n (%)
Index TB cases among key populations[a]	726
Contacts of index cases referred for TB investigation	6,931
Diagnosed with TB	275 (3.9)
NNI[b]	25
Started on TB treatment	273 (99)

[a] Key population groups include: People who inject drugs, partners of people who inject drugs, homeless, Roma people, sex workers and ex-prisoners; [b] Number Needed to Investigate (NNI) to detect one TB case; [c] Percentage calculated using number of diagnosed TB patients as denominator.

Table 2. Social-demographic and clinical characteristics of Index TB cases and TB contacts of an Optimized Case Finding Strategy in Ukraine (July 2018 – March 2020).

Characteristics	Index TB cases (N = 726) N (%)	Contacts diagnosed with TB (N = 275) N (%)	p-value
Gender			
Female	169 (23.3)	68 (24.7)	0.6
Male	557 (76.7)	207 (75.3)	
Age, years			
0-17	1 (0.1)	0	0.7
18-29	55 (7.6)	22 (8.0)	
30-49	486 (66.9)	176 (64.0)	
50+	184 (25.3)	77 (28.0)	
Population group			
Key populations			< 0.001
Homeless	246 (33.9)	88 (32)	
Ex-prisoners	42 (5.8)	6 (2.2)	
LGBT	9 (1.2)	0	
PWID	289 (39.8)	95 (34.5)	
Partners of PWID	12 (1.7)	4 (1.5)	
Roma population	31 (4.3)	1 (0.4)	
Sex-workers	4 (0.6)	1 (0.4)	
Internally displaced persons	0	1(0.4)	
Not from key populations	93 (12.8)	79 (28.7)	
TB diagnosis			
Bacteriological	378 (52.1)	172 (62.5)	< 0.001
Clinical	219 (30.2)	102 (37.1)	
Missing	129 (17.8)	1 (0.4)	
Drug resistance type			
Drug-sensitive	625 (86.1)	183 (66.5)	< 0.001
Drug-resistant	101 (13.9)	92 (33.5)	

LGBT: Lesbian, Transgender, Bisexual and Transvestite; PWID: People Who use Injectable Drugs.

sites and 66 (24%) at injecting drug user sites (shooting galleries). 28.7% of TB diagnosed in contacts of index cases were found outside key population groups that reside within the general population. There was a higher proportion of drug-resistant TB in contacts (34%) compared to index cases (14%).

Numbers needed to investigate to detect one TB case and TB detection rates

The TB case detection rate using OCF was 3,930/100,000 (Table 3). Compared to case detection using in households of index cases within the general population (1,090/100,000) [12], OCF was 3.6-fold more effective. Similarly, comparing OCF to passive case detection in the general population (60 /100,000) [12], OCF was 66 times more effective.

Discussion

This is the first study assessing the effectiveness of OCF for TB detection among key populations in the Eastern Europe and Central Asia region and beyond. The implemented OCF for TB strategy, which includes all contacts in both the family and social network of the TB index, has demonstrated an improved search for TB cases among vulnerable populations. It showed that low numbers of contacts needed to be investigated to detect TB, and the OCF strategy was 3.6 times more effective than active case finding in households and 66 times more effective than passive case finding in the general population. Importantly, 99% of all TB patients diagnosed through OCF were successfully linked to treatment.

This study provides an important way forward in reducing "missed TB cases" among key populations and a step towards achieving the STOP-TB target of ensuring that TB diagnostic and treatment services reach at least 90% of key populations [7,10]. The focus on key populations is in line with the motto of the Sustainable Development Goals – ensure equity and "leave none behind" [2,13].

The strengths of the study are that we included five geographic regions of Ukraine, and the findings are thus likely to reflect the operational reality on the ground. The study also included a large cohort of index TB cases and almost 7000 contacts, all of whom were investigated for TB. Since APH maintains a strong monitoring and evaluation team that ensures the quality of databases used for this study, we believe our data is robust. We also adhered to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for the reporting of observational studies in epidemiology [14].

The study limitations are that in one region of Ukraine (Zakarpatya), with mainly Roma people, we ran into operational difficulties in implementing the program which had to be consequently paused. This would have negatively influenced the number of TB cases diagnosed from this region. Furthermore, we do not know the primary source of infection – did TB contacts acquire TB from the index case or vice-versa? Finding answers to this question will require research involving gene typing to better understand the transmission dynamics of TB in key populations. Such studies would be pivotal to implement barrier measures to reduce TB acquisition and transmission in this high-risk group. Finally, it would have been useful to know the time taken between the identification of an index case and diagnosis of TB in contacts.

The study findings have several important implications for policy and practice. First, the APH successfully adapted the OCF approach for TB case finding in key populations from their prior experience in using this strategy for HIV detection in key populations [8,9]. The effectiveness of TB detection and linkage to care is commendable. As key populations are often left outside the realms of routine health systems, this experience highlights the important

Table 3. Increase in detection of tuberculosis (TB) through Optimized Case Finding (OCF) in key populations [a] compared to other TB screening strategies in the general population of Ukraine (July 2018 – March 2020).

Characteristics	n
Contacts of index cases referred for TB investigation through OCF	6,998
Diagnosed with TB	275
TB detection using OCF	
TB /100,000 contacts using OCF in key population s[b]	3,930
TB detection using active household screening	
TB /100,000 contacts using routine household contact screening [12]	1,090
Times in increase of detection using OCF strategy for TB case finding [c]	3.6
TB detection using passive case finding	
TB per 100,000 people in the general population [12]	60.1
Times in increase of detection using an OCF strategy for TB case finding [d]	66

[a] Key population groups include: People who inject drugs, partners of people who inject drugs, homeless, Roma people, sex workers and ex-prisoners; [b] 6,998/275×100,000; [c] 3,930 /1,090; [d] 3,930/60.1.

role NGOs can play in bringing on-board, vulnerable, and at-risk groups and thereby strengthening the health system. We advocate for further scale-up of this approach in Ukraine and beyond.

Second, key population groups are difficult to navigate through the health system as many of them are PWID who have co-infections including HIV, hepatitis C, and TB. Furthermore, they face the daily challenge of being stigmatized and shunned away by the general population. Despite these operational challenges, the fact that 99% of all diagnosed TB patients were placed on TB treatment and 87% who were HIV-positive were also placed on ART is commendable. It highlights the close collaboration established in linking up and integrating HIV and TB services in a holistic and patient-centered manner. The collaboration between programs is thus possible even in complex and difficult-to-reach populations. We encourage other programs struggling with the challenge of "how to deliver" to link up and share experiences so that this can be expanded further.

Third, an interesting finding was that 28.7% of TB diagnosed among contacts of index cases (from key populations) were found within the general population. Drug resistance was also considerably higher in contacts (34%) compared to index cases (14%). As we have no information on TB transmission dynamics, we are unable to localize the primary source of infection. Notwithstanding, this finding might indicate the existence of viable transmission links between key populations and the general population. Furthermore, higher levels of TB drug resistance in contacts residing within the general population heralds a real risk of transmission of drug-resistant TB from the general population to key populations. Awareness raising and robust operational research is needed to tackle these issues. How to expand OCF to include more at-risk sites within the social networks of key populations is also urgently needed.

Finally, this study was conducted through the Global SORT IT partnership and run close to the demand and supply of health services. It is an excellent example of how operational research conducted using "real life" program data can help demonstrate new and innovative models that can change the paradigm of "doing more of the same" to "doing things differently" [15,16]. Such evidence is key to achieving Universal Health Coverage [17].

In conclusion, in five regions of Ukraine, the introduction of Optimized Case Finding among key populations was found to be highly effective in detecting TB cases and linking them to care. Strategies which use recruitment in risk social networks can be considered for programs which work with key and vulnerable populations. We advocate for further support to continue this learning-by-doing approach to scale up such programs in Ukraine and beyond.

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Authors' Contributions

LM: Conception of the study; designing the protocol; data collection, analysis and interpretation; writing first draft of the paper; critically reviewing the paper and giving approval for the final version to be published. OD: designing the protocol; data analysis and interpretation; writing first draft of the paper; critically reviewing the paper and giving approval for the final version to be published. EG: designing the protocol; data collection; writing first draft of the paper; critically reviewing the paper and giving approval for the final version to be published. GA: designing the protocol; critically reviewing the paper and giving approval for the final version to be published. RZ: designing the protocol; data analysis and interpretation; writing first draft of the paper; critically reviewing the paper and giving approval for the final version to be published. ZI: designing the protocol; critically reviewing the paper and giving approval for the final version to be published.

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