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High time to use rapid tests to detect multidrug resistance in sputum smear-negative tuberculosis in Belarus

V. Rusovich,[1] A. M. V. Kumar,[2] A. Skrahina, [3] H. Hurevich,[3] A. Astrauko,[3] P. de Colombani,[4] K. Tayler-Smith,[5] M. Dara,[4] R. Zachariah[5]

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Setting: Belarus (Eastern Europe) is facing an epidemic of multidrug-resistant tuberculosis (MDR-TB). In 2012, rapid molecular diagnostics were prioritised for sputum smear-positive pulmonary tuberculosis (PTB) patients to diagnose MDR-TB, while pulmonary sputum smear-negative pulmonary TB (SN-PTB) patients were investigated using conventional methods, often delaying the diagnosis of MDR-TB by 2–4 months.

Objective: To determine the proportion of MDR-TB among SN-PTB patients registered in 2012 and associated clinical and demographic factors.

Design: Retrospective cohort study using countrywide data from the national electronic TB register.

Results: Of the 5377 TB cases registered, 2960 (55%) were SN-PTB. Of the latter, 1639 (55%) were culture-positive, of whom 768 (47%) had MDR-TB: 33% (363/1084) were new and 73% (405/555) previously treated patients. Previous history of treatment, age, region, urban residence, human immunodeficiency virus (HIV) status and being a pensioner were independently associated with MDR-TB.

Conclusion: About half of culture-positive SN-PTB patients have MDR-TB and this rises to over 7/10 for retreatment cases. A national policy decision to extend rapid molecular diagnostics universally to all PTB patients, including SN-PTB, seems justified. Steps need to be taken to ensure implementation of this urgent priority, given the patient and public health implications of delayed diagnosis.

Eastern Europe is facing an epidemic of multidrug-resistant tuberculosis (MDR-TB).[1,2] Belarus is one of the 27 high MDR-TB burden countries designated by the World Health Organization (WHO). A countrywide survey conducted in 2011 in Belarus revealed a prevalence of MDR-TB of 32% among new and 76% among previously treated TB cases, the highest documented rates worldwide.[3,4] However, these levels were found among sputum smear-positive pulmonary TB (SP-PTB) patients. The levels of MDR-TB among smear-negative pulmonary TB (SN-PTB) patients are unknown, and this group accounts for 63% of all notified new pulmonary TB cases in Belarus.[1]

Countries in the WHO European region endorsed the 'Consolidated Action Plan, 2011–2015', with the aim of detecting 85% of estimated MDR-TB cases and successfully treating at least 75% of these by 2015.[5] Achieving these objectives will not be possible without appropriate management of MDR-TB among SN-PTB.

In Belarus, all TB patients have universal access to culture and drug susceptibility testing (CDST). In 2012, at the start of the countrywide roll-out of rapid molecular diagnostics (such as Xpert® MTB/RIF [Cepheid, Inc, Sunnyvale, CA, USA] and line probe assays), national policy prioritised their use for smear-positive TB patients, while SN-PTB patients were investigated using conventional methods, often delaying the diagnosis of MDR-TB by 2–4 months. While awaiting the results, SN-PTB patients were initiated on a first-line drug regimen, which was obviously inadequate if they harboured MDR-TB bacilli. With the increasing availability of rapid molecular diagnostics, the country is currently aiming at universal coverage of all presumptive TB cases with molecular testing. Despite the national policy, SN-PTB patients do not receive the same priority as smear-positive TB patients, as they are traditionally perceived to be less infectious and clinically less severe. Currently, there is no published information from Belarus or similar settings in Eastern Europe on the proportion of SN-PTB patients with MDR-TB. Such information provides the evidence required to decide on and justify the use of rapid molecular diagnostics for all SN-PTB patients.

In this countrywide audit in Belarus, we therefore aimed to assess the proportion of MDR-TB among SN-PTB patients registered in 2012 and the associated demographic and clinical factors.

METHODS

Study design

This was a retrospective cohort study using data routinely recorded in the national electronic TB register.

Setting

Belarus has a population of 9.5 million, with 72% living in urban areas. There are six administrative regions (Brest, Gomel, Grodno, Mogilev, Minsk and Vitebsk) and 121 districts. The Ministry of Health (MOH) oversees the implementation of TB control activities in the country. The Republican Scientific and Practical Centre for Pulmonology and Tuberculosis (RSPCPT) in Minsk is the central National Tuberculosis Programme (NTP) unit responsible for the development and implementation of TB policies. The Ministry of the Interior has a parallel health care system for managing TB patients in prisons, and reports to the NTP. Belarus follows the WHO-recommended Stop TB Strategy, and anti-tuberculosis control interventions

AFFILIATIONS
1 World Health Organization (WHO) Country Office, Minsk, Belarus
2 International Union Against Tuberculosis and Lung Disease, South-East Asia Regional Office, New Delhi, India
3 Republican Scientific and Practical Centre for Pulmonology and Tuberculosis, Minsk, Belarus
4 WHO Regional Office for Europe, Copenhagen, Denmark
5 Médecins Sans Frontières (MSF), Operational Centre Brussels, MSF-Luxembourg, Luxembourg

CORRESPONDENCE
Valiantsin Rusovich
World Health Organization
Country Office Belarus
28 Fabriciusa Street
Room 401
220007
Minsk, Belarus
Tel: (+375) 172 220 419
Fax: (+375) 172 262 165
e-mail: RUV@euro.who.int

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are delivered through a network of dedicated TB facilities and primary health care services.

In addition to the paper-based TB and MDR-TB registers, Belarus has implemented a national web-based individualised electronic register of all TB patients (including the penitentiary system) since 2009 and MDR-TB patients since 2011. The data for all TB and MDR-TB patients are entered via the web from six regional TB facilities — the regional monitoring and evaluation (M&E) units and the Republican TB Prison Hospital. These data are validated on main programme indicators by the central M&E unit located at the RSPCPT. Recording and reporting of case definitions and treatment outcomes follow WHO guidelines, and all patient-based information is captured in the national electronic TB register.

Diagnosis of smear-negative pulmonary tuberculosis patients

The case-finding strategy in Belarus involves an active and a passive strategy. The passive approach involves investigating individuals with presumptive TB who present to the health care facilities, while the active approach involves mass annual general population screening for TB with chest X-ray (fluorography). Coverage rates for the latter are more than 80% among the adult population.[4] Those with symptoms suggestive of TB or X-ray findings suggestive of TB are investigated further using sputum-smear microscopy with Ziehl-Neelsen staining and CDST on solid medium (egg-based Löwenstein-Jensen) or liquid medium (BACTEC™ MGIT 960 culture; BD Microbiology Systems, Sparks, MD).[6,7] For all strains resistant to rifampicin (RMP), second-line drug susceptibility testing is routinely performed. Patients with at least two sputum smears negative for acid-fast bacilli and clinical and radiological features suggestive of TB are diagnosed as SN-PTB by a panel of TB specialists at regional level and initiated on first-line treatment while awaiting the results of CDST.[8] If they are confirmed to have MDR-TB, first-line treatment is stopped, treatment outcome is declared as 'failure, primary MDR-TB' in the TB register and the patient is newly registered in the MDR-TB register. These patients are removed from the cohort of SN-PTB patients for cohort reporting of treatment outcomes, and are reported as part of the MDR-TB patient cohort. All detected MDR-TB patients have access to second-line anti-tuberculosis treatment as per national guidelines in line with WHO recommendations.[3,4,8] Treatment for MDR-TB is initiated by the board of TB specialists. All diagnostic and treatment services are provided free of charge.

Definition of multidrug-resistant tuberculosis

Patients with *Mycobacterium tuberculosis* showing in vitro resistance to at least isoniazid and RMP are considered to have MDR-TB. In addition, close contacts of MDR-TB patients diagnosed with TB are also considered as having MDR-TB, irrespective of the laboratory results.

Study population and study period

All SN-PTB patients (adults and children) diagnosed and registered in the national electronic TB register of Belarus from 1 January to 31 December 2012 were included in the study. The study was conducted between July 2013 and March 2014.

Data variables and data source

Variables relating to the study objectives were extracted from the national electronic database and included age, sex, previous treatment history, case-finding approach used for diagnosis, site of treatment (civilian versus penitentiary sector), HIV status, culture (positive or negative) and CDST results (MDR-TB or not), date of registration in TB register and date of diagnosis of MDR-TB.

Data analysis

Data were analysed using EpiData analysis software, version 2.2.2.182 (EpiData Association, Odense, Denmark) and STATA version 12.1 (Stata Corporation, College Station, TX, USA). Associations between demographic and clinical factors and MDR-TB were assessed using odds ratios (OR) and 95% confidence intervals (CI). The χ^2 test was used to compare proportions, and the level of significance was set at $P \leqslant 0.05$. Multivariate analysis using logistic regression was conducted to assess the factors independently associated with MDR-TB.

Ethics

Ethics approval was obtained from the ethics committees of the RSPCPT, Minsk, Belarus; Médecins Sans Frontières, Geneva, Switzerland; and the International Union Against Tuberculosis and Lung Disease, Paris, France.

RESULTS

Demographic and clinical characteristics of the study population

Of 5377 registered TB patients (after excluding transfer-in cases), 4868 (91%) had pulmonary TB; 2960 (55%) of these were SN-PTB: 2115 (70%) were males, the median age was 43 years (interquartile range [IQR] 33–53) and 1813 (61%) came from urban areas. About half of all patients were from the Gomel and Minsk regions, and Minsk city. Nearly half (1347, 46%) were unemployed. HIV status was reported in only 551 patients (19%) and 111/551 (20%) patients tested were HIV-positive. About 4% of the patients were treated in the penitentiary sector and 2338 (79%) were detected as part of an active case-finding approach.

Smear-negative pulmonary tuberculosis with multidrug resistance

Of 2960 SN-PTB patients, 1639 (55%) were culture-positive. Of the latter, 768 (47%) had MDR-TB: 33% (363/1084) among new and 73% (405/555) among previously treated patients. When all SN-PTB patients (including culture-negative) were used as the denominator, the proportion of MDR-TB was 27% — 16% of new patients and 63% of previously treated patients (Figure). The proportion of MDR-TB among culture-positive SN-PTB patients, stratified by demographic and clinical characteristics, is shown in Table 1. On multivariate analysis, previous history of treat-

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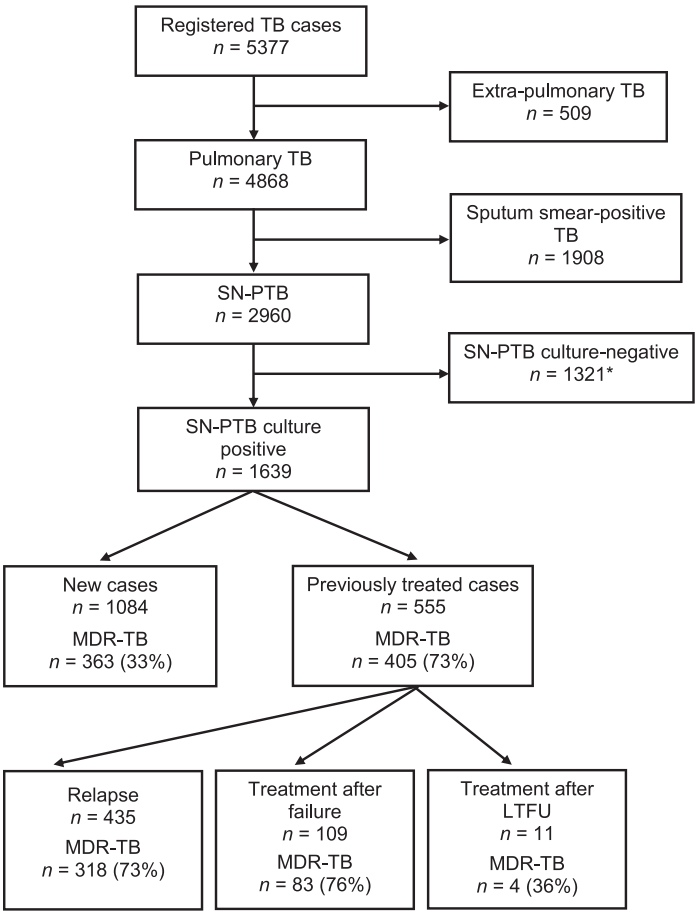

FIGURE Proportion of MDR-TB among smear-negative pulmonary tuberculosis patients in Belarus, 2012. *Of these, 17 patients were contacts of confirmed MDR-TB patients and were thus treated with MDR-TB regimens. TB = tuberculosis; SN-PTB = sputum smear-negative pulmonary tuberculosis; MDR-TB = multidrug-resistant tuberculosis; LTFU = loss to follow-up.

ment, age, region, residence, HIV status and being a pensioner were independently associated with MDR-TB. A similar analysis was carried out for new and previously treated cases separately (Table 2). There were no major changes in the directionality or magnitude of the associations, although some factors initially found to be statistically significant became insignificant due to smaller numbers.

Of 768 MDR-TB patients, information on treatment initiation was recorded for 660 (86%). Of these, 637 (97%) were started on treatment. As there were errors and inconsistencies in recording the date of TB registration, MDR-TB diagnosis and treatment initiation, we could not reliably assess the median delays between diagnosis and treatment initiation.

DISCUSSION

This is the first study from Belarus showing that nearly one third of new patients and three quarters of previously treated patients with culture-positive SN-PTB had MDR-TB. This confirms that the prevalence of MDR-TB among SN-PTB in the country is as high as that among SP-PTB patients.[3] While certain factors were associated with higher or lower likelihood of having MDR-TB, the prevalence remained consistently high, at around 40–50%, across the different regions and the various socio-demographic and clinical subgroups. Of concern is that all SN-PTB patients with MDR-TB were treated with first-line treatment regimens while awaiting the results of CDST by traditional methods. This might have involved delays of up to 3 months, given the turnaround time with conventional CDST methods. From a patient and public health perspective, this is tantamount to treatment with ineffective first-line drugs, with the concomitant potential risk of amplifying and spreading drug-resistant TB in the community.

There are a number of policy and practice implications. First, there is an urgent need to increase the availability and use of rapid molecular diagnostics for all TB patients from whom biological samples may be obtained. The way forward is for the health authorities to ensure access to rapid molecular diagnostic tests such as Xpert in all settings, either by purchasing new equipment or by arranging transport of samples. Two issues are of global concern with respect to the scale-up of rapid tests for diagnosing RMP resistance.[9] One relates to low positive predictive value (PPV) in areas of low MDR-TB prevalence, which is not applicable to Belarus, a country with high prevalence. Further, recent evidence indicates that the Xpert test is more specific than previously estimated, thus allaying fears of low PPV, even in areas of low MDR-TB prevalence.[10–13] The second relates to a lack of capacity of NTPs to cope with the increased demand for treatment as a result of the considerable increase in numbers of diagnosed cases. This is also not of concern, as the NTP in Belarus has sufficient capacity to treat all diagnosed MDR-TB patients.

The high proportion of MDR-TB found among SN-PTB patients articulates a call to the NTP to extend the use of molecular diagnostic tests to include all those with SN-PTB. From the patient's perspective, such action is likely to foster the institution of prompt diagnosis and early initiation on appropriate treatment, both of which should favourably impact treatment outcomes.

Considering the increasing availability of Xpert in the country, the relatively modest numbers of additional tests (~3000 annually in Belarus) that will need to be performed and the limited resource implications (~US$36 000, at US$12.00 per test), this recommendation seems feasible. This notwithstanding, if for any reason not all SN-PTB patients can be offered rapid diagnostic tests for MDR-TB right away, then the urgent priority would be to target the following SN-PTB risk groups: all previously treated patients (particularly relapse and treatment after failure cases), those aged <45 years, living in urban areas or living in Vitebsk or Grodno regions. This is, however, a much less preferred option.

Second, we found several factors associated with MDR-TB, the strongest being previous history of treatment. Previously treated patients had a nearly six times higher risk of MDR-TB than those with newly diagnosed TB, and this would seem logical as they have already been exposed to first-line anti-tuberculosis regimens in the past. Given that nearly three quarters of previously treated patients had MDR-TB, a logical option (while waiting for rapid diagnostics) would be to start second-line treatment empirically for patients with a high clinical probability of active MDR-TB, as per the WHO treatment guidelines.[14] Based on the results of the CDST, treatment may be modified accordingly. This may be lifesaving in certain seriously ill patients, including HIV-positive individuals.

Third, the study revealed gaps in the recording of a number of variables such as HIV status, drug resistance patterns, dates of TB and MDR-TB diagnosis and registrations. Notable was HIV status, with 81% not having their status recorded. Considering the previ-

TABLE 1 Prevalence of MDR-TB among all sputum smear-negative, culture-positive pulmonary TB patients in Belarus, 2012

Characteristic	Total *n*	MDR-TB at baseline *n* (%)	Crude OR (95%CI)	Adjusted OR (95%CI)
Total	1639	768 (47)		
Age, years*				
<45	854	434 (50)	1	1
⩾45	784	333 (42)	0.7 (0.6–0.9)†	0.7 (0.6–0.9)†
Sex				
Female	385	161 (42)	1	1
Male	1254	607 (48)	1.3 (1.0–1.6)†	1.1 (0.8–1.4)
Administrative region				
Brest region	180	73 (41)	1	1
Vitebsk region	157	79 (50)	1.5 (0.9–2.3)	2.1 (1.3–3.3)†
Gomel region	295	125 (42)	1.1 (0.7–1.6)	1.1 (0.7–1.7)
Grodno region	244	127 (52)	1.6 (1.1–2.3)†	1.9 (1.2–2.9)†
Minsk region	309	168 (54)	1.7 (1.2–2.5)	1.0 (0.6–1.7)
Minsk city	181	78 (43)	1.1 (0.7–1.7)†	0.9 (0.6–1.5)
Mogilev region	270	116 (43)	1.1 (0.8–1.6)	1.4 (0.9–2.1)
Other countries	3	2 (67)	2.9 (0.3–32.9)	4.2 (0.4–49.6)
Residence				
Urban	969	478 (49)	1	1
Rural	670	290 (43)	0.8 (0.6–0.9)†	0.7 (0.6–0.9)†
Occupation				
Employed	586	284 (48)	1	1
Pensioner	186	56 (30)	0.5 (0.3–0.7)†	0.6 (0.4–0.9)†
Unemployed	833	410 (49)	1.0 (0.8–1.3)	0.9 (0.7–1.2)
Student	34	18 (53)	1.2 (0.6–2.4)	1.2 (0.6–2.5)
HIV status				
Negative	282	166 (59)	1	1
Positive	64	36 (56)	0.9 (0.5–1.6)	0.7 (0.4–1.4)
Unknown	1293	566 (44)	0.5 (0.4–0.7†	0.4 (0.3–0.6)†
Civil vs. penitentiary				
Penitentiary	61	28 (46)	1	–
Civil sector	1578	740 (47)	1.0 (0.6–1.7)	
Case finding				
Active	1288	613 (48)	1	–
Passive	351	155 (44)	0.9 (0.7–1.1)	
Category				
New cases	1084	363 (33)	1	1
Previously treated	555	405 (73)	5.4 (4.2–6.7)†	5.9 (4.6–7.5)†

*Not recorded for one patient.
†Statistically significant ($P < 0.05$).
MDR-TB = multidrug-resistant tuberculosis; OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus.

ously documented strong associations of MDR-TB with HIV-positive patients[3,15] and unfavourable outcomes,[16,17,5] this missing information is of operational and clinical significance. The reasons for this shortcoming were not known, but the programme has already identified this gap and steps are being taken to increase the uptake of HIV testing and improve its recording in the TB registers.

There were several strengths to our study. First, this was a countrywide study which included all SN-PTB patients registered in 2012, and is thus representative of the situation in Belarus. Second, this is the first time globally that a study has reported on the prevalence of MDR-TB among SN-PTB patients. The study also met the requirements of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, including ethics.[18,19]

There were also some study limitations, mainly related to the operational nature of the study and reliance on data routinely recorded by the NTP. First, there were recording errors, including missing values and some inconsistencies across the variables, especially HIV and dates of TB and MDR-TB registrations. In this study, we could not assess the proportion of MDR-TB among extra-pulmonary TB patients, which could be a topic for future research. In addition, we could not analyse the drug resistance patterns, including that of second-line drugs. This information could have been valuable to the NTP for assessing whether or not the current first- and second-line treatment regimens are adequate in the context of an MDR-TB epidemic. From the programme perspective, this is an important finding, and additional efforts are needed to improve the quality of data collection, which includes staff training in the regions and enhancing supervision and data validation on key indicators at central NTP level. On the other hand, as rapid molecular diagnostic testing can detect any biological material, even dead bacilli, and the radiological evidence alone may not be indicative

TABLE 2 Risk factors for MDR-TB among sputum smear-negative, culture-positive pulmonary TB patients in Belarus, stratified by new and previously treated cases, 2012

Characteristic	New cases aOR (95%CI)	Previously treated cases aOR (95%CI)
Total	1084	555
Age, years*		
<45	1	1
⩾45	0.8 (0.6–1.0)	0.6 (0.4–0.9)†
Sex		
Female	1	1
Male	1.0 (0.8–1.5)	1.0 (0.6–1.9)
Administrative region		
Brest region	1	1
Vitebsk region	2.0 (1.1–3.5)†	2.0 (0.8–5.0)
Gomel region	0.9 (0.5–1.5)	1.5 (0.7–3.2)
Grodno region	1.7 (1.0–2.9)†	2.1 (1.0–4.7)†
Minsk region	0.8 (0.4–1.5)	1.4 (0.7–3.0)
Minsk city	0.9 (0.5–1.6)	0.9 (0.4–2.1)
Mogilev region	1.6 (0.9–2.6)	0.9 (0.4–2.0)
Other counties	3.6 (0.3–43.6)	–
Residence		
Urban	1	1
Rural	0.7 (0.5–0.9)†	0.7 (0.5–1.0)†
Occupation		
Employed	1	1
Pensioner	0.8 (0.5–1.3)	0.3 (0.1–0.6)†
Unemployed	1.0 (0.8–1.4)	0.7 (0.4–1.1)
Student	1.0 (0.4–2.3)	–
HIV status		
Negative	1	1
Positive	0.8 (0.4–1.6)	0.8 (0.1–4.2)
Unknown	0.4 (0.2–0.7)†	0.3 (0.2–0.7)†

*Not recorded for one patient.
†Statistically significant ($P < 0.05$).
MDR-TB = multi-drug resistant tuberculosis; aOR = adjusted odds ratio; CI = confidence interval.

of active TB, diagnosis of active MDR-TB among sputum smear-negative patients needs to be carefully balanced against clinical evidence.

In conclusion, this study showed that the prevalence of MDR-TB among culture-positive SN-PTB patients was as high as among SP-PTB patients in Belarus, and makes a strong case for a national policy decision to extend rapid diagnostics to all SN-PTB patients in the country. Anything short of that would mean sub-standard care with potentially serious patient and public health implications.

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Contexte : Le Belarus (Europe de l'Est) est confronté à une épidémie de tuberculose multirésistante (TB-MDR). En 2012, les patients atteints de tuberculose pulmonaire (TBP) à frottis positif ont bénéficié en priorité de diagnostics moléculaires pour confirmer une TB-MDR, tandis que les patients atteints de TBP à frottis négatif (SN-PTB) ont bénéficié de méthodes conventionnelles qui retardaient souvent le diagnostic de TB-MDR de 2 à 4 mois.

Objectif : Déterminer la proportion de TB-MDR parmi les patients SN-PTB enregistrés en 2012, ainsi que les facteurs cliniques et démographiques associés.

Schéma : Etude de cohorte rétrospective basée sur des données émanant de tout le pays grâce au registre électronique national de la TB.

Résultats : Sur 5377 cas de TB enregistrés, 2960 (55%) étaient des SN-PTB. Parmi ces derniers, 1639 (55%) avaient une culture positive, dont 768 (47%) avaient une TB-MDR : 33% (363/1084) nouveaux cas et 73% (405/555) patients déjà traités préalablement. La notion de traitement antérieur, l'âge, la région, la résidence en milieu urbain, le statut à l'égard du virus de l'immunodéficience humaine et le fait d'être retraité étaient indépendamment associés à la TB-MDR.

Conclusion : Près de la moitié des patients SN-PTB à culture positive ont une TB-MDR, et dans les cas de retraitement, on arrive à plus de sept patients sur dix. La décision politique nationale d'extension des diagnostics moléculaires rapides à tous les patients TBP, y compris les patients SN-PTB, semble donc justifiée. Il est nécessaire de prendre des mesures afin d'assurer la mise en œuvre de cette priorité urgente, en raison des implications d'un diagnostic retardé à la fois pour les patients et en termes de santé publique.

Marco de referencia: El país de Bielorrusia, en Europa oriental, afronta una epidemia de tuberculosis multidrogorresistente (TB-MDR). En el 2012, se privilegió la práctica de las pruebas moleculares rápidas con el fin de diagnosticar la TB-MDR en los pacientes con TB pulmonar (TBP) y baciloscopia positiva y los casos con baciloscopia negativa (SN-PTB) se investigaron mediante los métodos clásicos, lo cual solía retardar de dos a cuatro meses el diagnóstico de la TB-MDR.

Objetivo: Determinar en los pacientes SN-PTB registrados en el 2012, la proporción de casos TB-MDR y examinar los factores clínicos y demográficos que se asociaban con este diagnóstico.

Método: Un estudio retrospectivo de cohortes a partir de los datos del Registro Nacional Informatizado de Tuberculosis.

Resultados: De los 5377 casos de TB registrados, 2960 correspondían a SN-PTB (55%). De estos pacientes, 1639 presentaron un cultivo positivo (55%) y en 768 casos se diagnosticó TB-MDR (47%). De los pacientes con diagnóstico de TB-MDR, el 33% correspondió a casos nuevos (363/1084) y el 73% consistió en pacientes previamente tratados (405/555). Los factores que se asociaron de manera independiente con el diagnóstico de TB-MDR fueron el antecedente de tratamiento antituberculoso, la edad, el domicilio en zona urbana, la situación frente al virus de la inmunodeficiencia humana y el hecho de ser jubilado.

Conclusión: Cerca de la mitad de los pacientes con SN-PTB presentó TB-MDR. Esta proporción llegó a ser siete de cada 10 de los casos en retratamiento. Con base en estos resultados, está justificada una decisión política a escala nacional de ampliación del uso de las pruebas rápidas de diagnóstico molecular de manera universal a todos los pacientes con TBP, incluidos los pacientes con SN-PTB. Es necesario tomar medidas encaminadas a fomentar la ejecución de esta prioridad urgente, dadas las repercusiones que un diagnóstico tardío impone a los pacientes y al sistema de salud pública.

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