NATIONAL PUBLIC
HEALTH ORGANIZATION

Epidemiological surveillance of tuberculosis in Greece, 2021

Main points:

- Tuberculosis remains a transmissibledisease with severe morbidity and mortality on a global scale. Both in Greece and globally, the COVID-19 pandemicwas followed by an increase in advanced and severe forms of TB, as well in as highly transmissible disease.
- In recent decades TB incidence is declining in the Greek population. Greeceremains a low-incidence country, according to the World Health Organization's (WHO)definition (less than 10 cases per 100,000 populationper year).
- TB incidence rate is increasing among the foreign-bornoriginating from countries with high TB incidence.
- Active TB is a notifiable disease in Greece. Under-reporting remains a significant issue impacting the accuracy of the estimated burden of disease in the population. The effect of the COVID-19 pandemic on the public health system has exacerbated the problem of under-reporting.

Epidemiological surveillance of tuberculosis

Epidemiological surveillance of tuberculosis monitors new cases of active tuberculosis in the population. Demographic, clinical and laboratory data are collected such as age, sex, ethnicity, site of infection and drug susceptibility, as well as risk factors such as underlying diseases, exposure history etc.

Data analysis detects trends over time regarding the form and extent of the disease, risk factors for active disease and transmission and additional information, which can be used to optimize management and prevent further transmission in the setting of individual cases or clusters, as well as to guide public health strategies.

Moreover, the systematic notification of cases is essential for monitoring disease indicators set by the World Health Organization (WHO) and the European Centre for Disease Prevention and Control (ECDC) regarding the epidemiological surveillance of TB at European and global level.

Notification is mandatory for active TB cases in Greece. Latent tuberculosis (non-transmissible mycobacterial infection without active disease) is not currently being monitored.

Epidemiology of tuberculosis in Greece in 2021

Number of notified cases and incidence of tuberculosis

In 2021, 210 new cases of tuberculosis were reported in Greece. The notification rate is estimated at 1.98 per 100,000 population, lower than in 2020 (3.83 per 100,000).In 2019, before the outbreak of the COVID-19 pandemic, 460 cases had been notified, a notification rateof4.25 cases per 100,000 (Figure 1).

Due to the impact of the COVID-19 pandemic on the health system, the number of notified cases in 2021 is considered to underestimate the true burden of disease. The decrease in notified cases is primarily attributed to the limited capacity of the health system to diagnose and notify TB casesdue to the diversion of health resources towards the pandemic response.

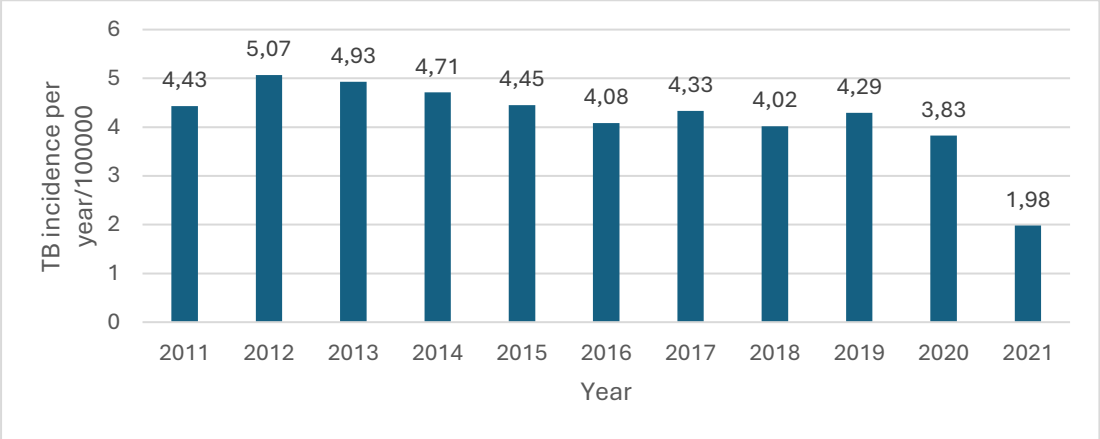


Figure 1: TB incidence per year/100000 population, 2011-2021

Most cases are notified inthe greater area of capital Athens, where most tertiary hospitals are located,including the national TB reference hospital, the General Hospital of Thoracic Diseases “Sotiria” (Figure 2).

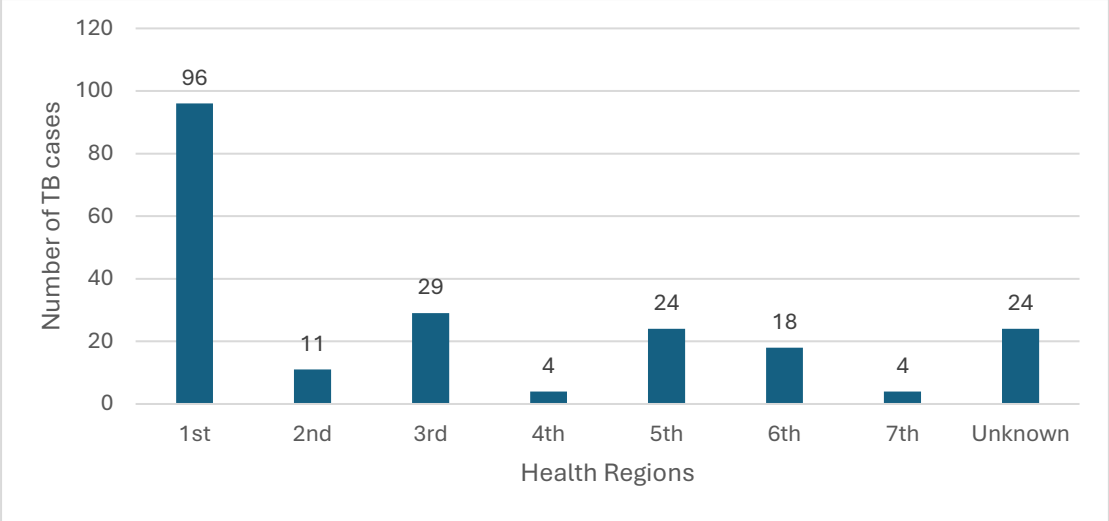
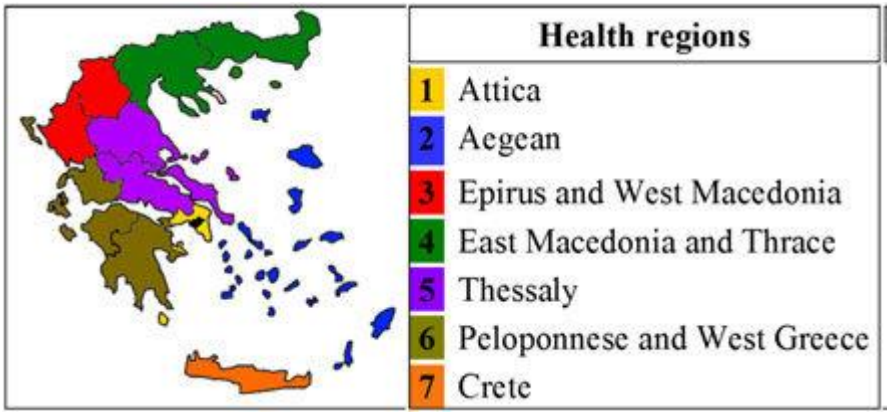


Figure 2: TB cases by Health Region, 2021



Demographic data

In 2021, 28.4% of cases were Greek, while 71.5% were foreign-born, namely refugees/migrants from countries with a high TB incidence. Over the last 10 years, TB is steadily declining in the Greek population, while there is an increasing trend among foreign-born cases. From 2018 onwards, the foreign-born account for most TB cases(Figures 3a, 3b).In 2021 most foreign-born cases originated from Central and South Asia (mostly Pakistan, Afghanistan, India, Bangladesh), accounting for 38% of foreign-born TB cases. Sub-Saharan Africa (Somalia, Congo, Cameroon) was the second most prevalent geographical area of origin with 26% of foreign-born cases.The third most prevalent **geographical area of origin** is Eastern Europe (Romania, Georgia, Albania, Bulgaria) accounting for 12 % of cases (Figure 4).

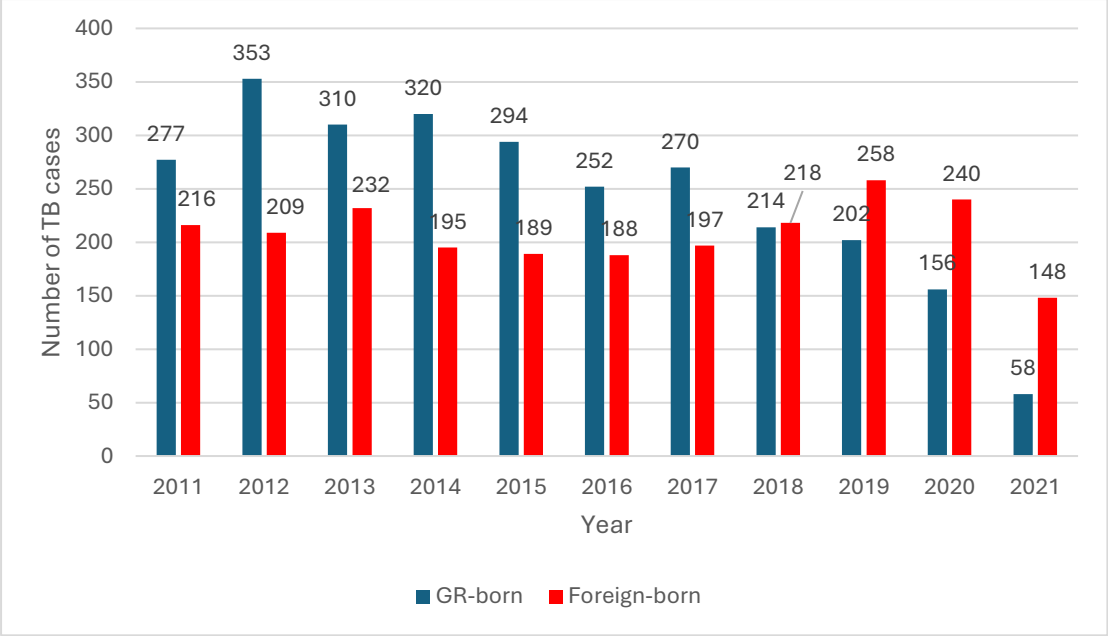


Figure 3a: TB cases by year and origin, 2011-2021

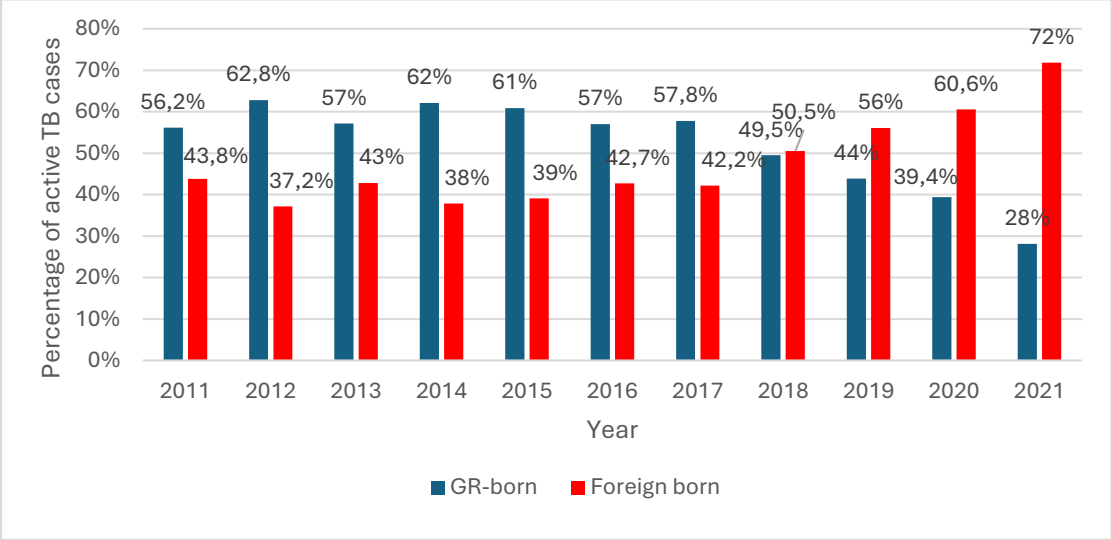


Figure 3b: Percentage of TB cases by year and origin, 2011-2021

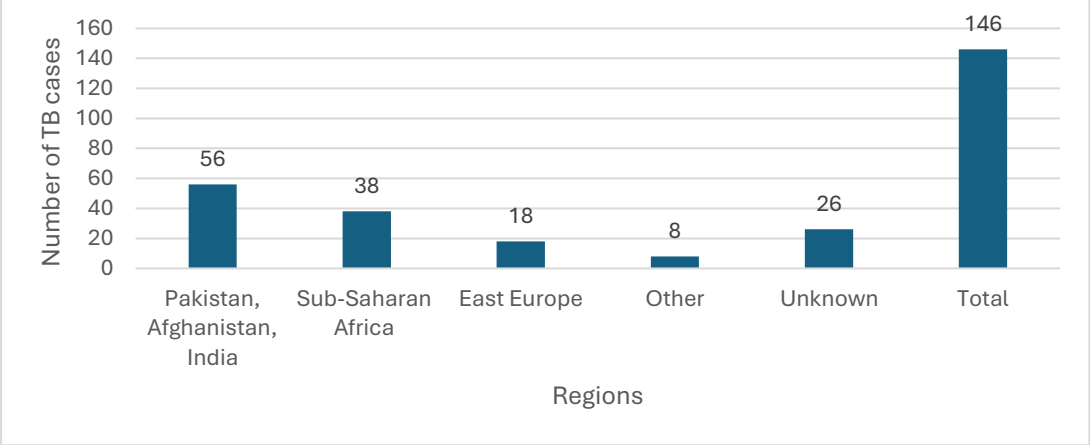


Figure 4: Foreign-born TB cases, 2021

Regarding the **age distribution**, people >65 years of age were the most represented Greek age group. In contrast, the age groups most affected among the foreign-born were 15-24 and 25-34 years of age (Figure 5).

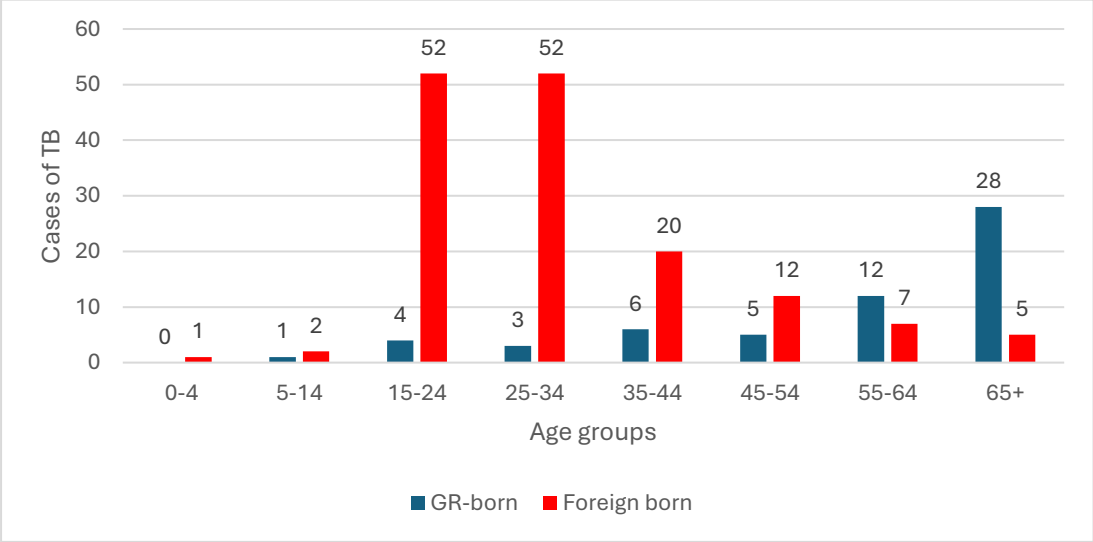


Figure 5: **TB cases by age group and origin, 2021**

Sex distribution was 157 males (74.76%) and 53 females (25.24%). Womenaccounted for 1/3 of Greek TB cases, while less than ¼ of foreign-born cases. It should be noted that men predominate in the refugee/immigrant population.

There were 15 notified cases in **minors** (3.3%). Four cases were in children under 14, all of whom had a known history of TBexposure within the family. The remaining 11 were adolescents (2 Greek, 9 foreign-born), of whom one had known exposure to an adult case in his family.

15.2% (32/210) of the notified cases were housed in **group living conditions**. Of these, 69% (22/32) lived in refugee/migrant facilities, 9% (3/32) in detention facilities (1 Greek, 2 foreign-born), 12.5% (4/32) in chronic care facilities(Table 1).

TYPE OF COMMUNAL LIVING	NUMBER OF CASES
Refugee/migrant facility: • Refugee/Migrant Acommodation Centres: 16 • Reception/Identification Centres: 3 • Pre-Departure Detention Centres: 3	22
Chronic Care Facility (Psychiatric Clinic, Elderly Care Unit)	4
Detention facility (prison)	3
Army unit	1
Monastery	1
ROMA camp	1
Total	**32**

Table 1: Number of TB cases living in groups, 2021

Clinical data

Pulmonary disease (potentially transmissibletype) represented the majority of notified TB cases in 2021 (Figure 6). Exclusively extrapulmonary TB (non-transmissible type of disease) was recorded in 11.6% of Greek and 18% of foreign-born cases (Figure 7). Lung cavitation, a feature associated with high transmissibility, was present in a significant proportion of pulmonary cases (Figure 8).

Regarding the **most severe forms** of TB, 3 **central nervous system** TB cases were reported: 2 young foreign-born tuberculous meningitis cases and one young Greek with TB brain abscess. There were 2 cases of **miliary** TB in elderly Greeks.

Most **extrapulmonary TB** pertained to tuberculous lymphadenitis (50) and tuberculous pleurisy (14). Skeletal TB (mainly vertebral) was reported in 10 cases, gastrointestinal TB in 2 cases, liver and kidney TB in 1 case respectively.

94.2% (198/210) of notified cases were new cases, while 9.19% (13/210) were **relapsed** cases.

Two **TB/HIV co-infection** cases were reported (one Greek and one foreign-born), but data were incomplete: HIV status was unknown for 75% (58/210) of cases.

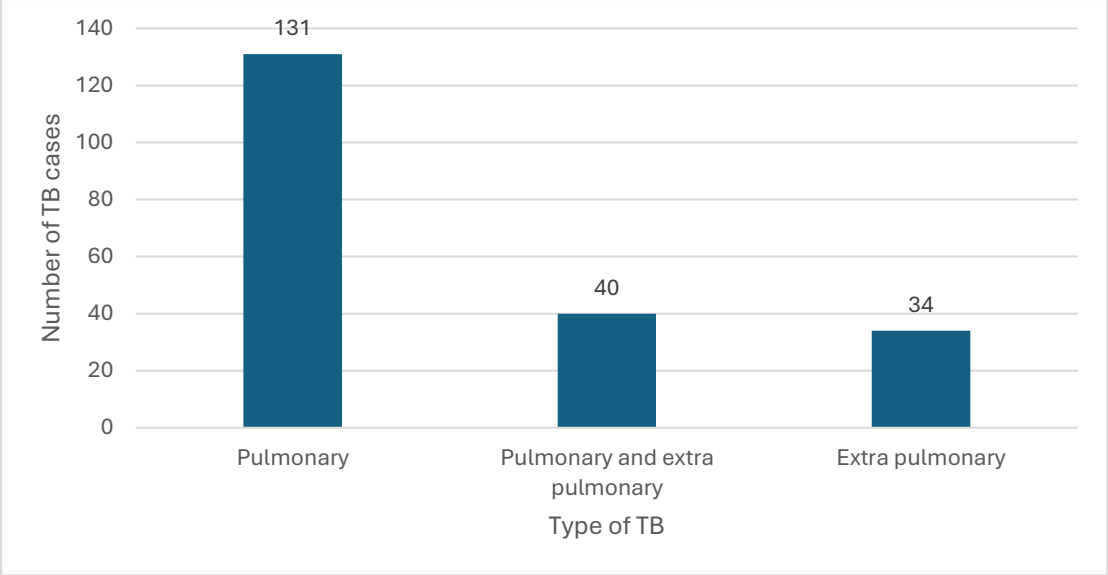


Figure 6: Type of TB, 2021

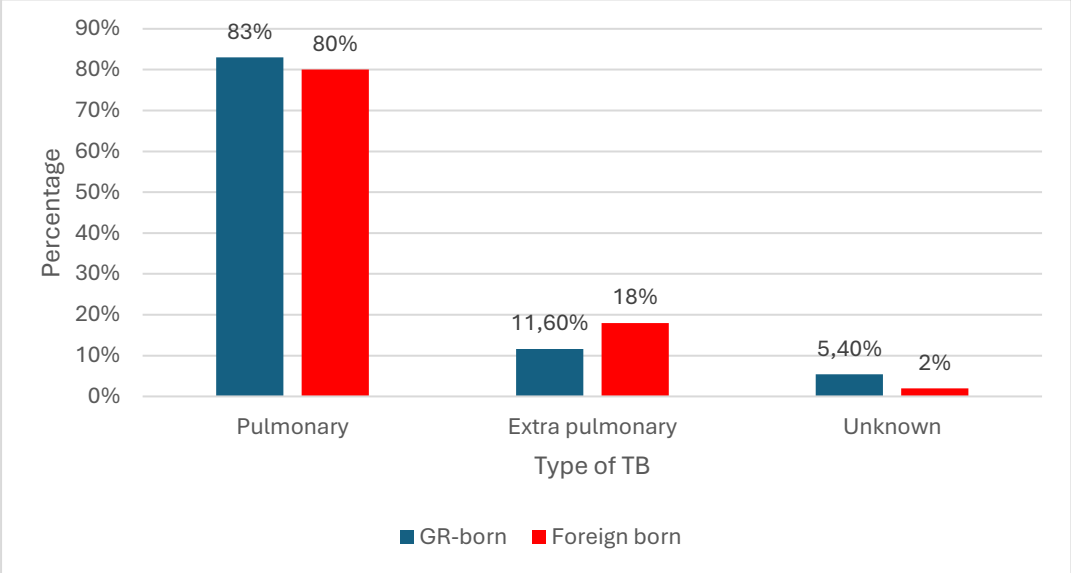


Figure 7: Pulmonary and exclusively extrapulmonary TB in Greeks and foreign-born, 2021

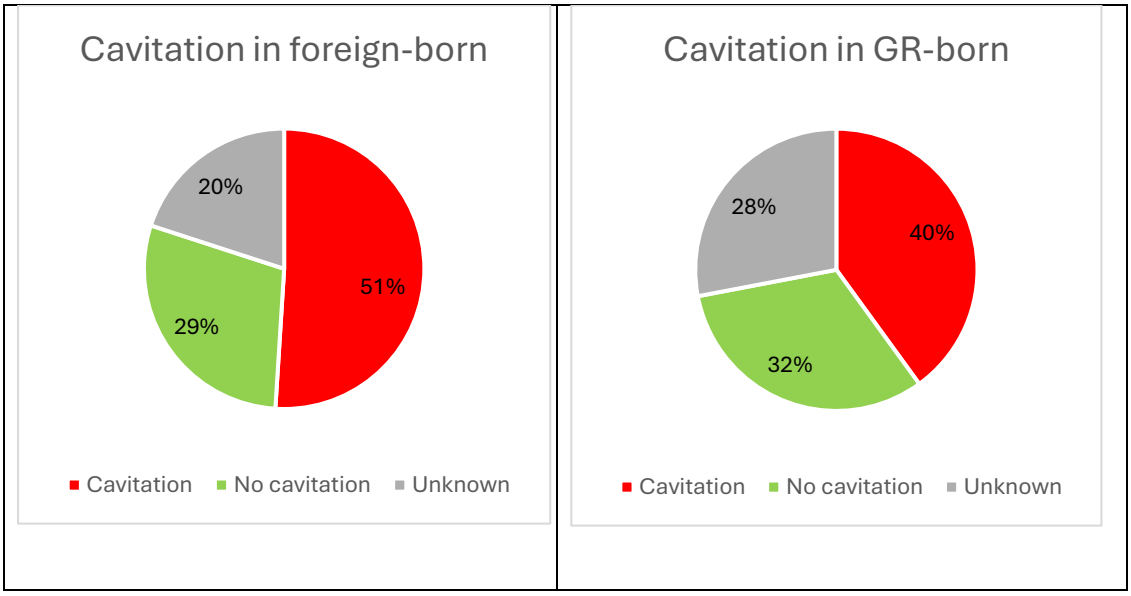


Figure 8: Cavitation in pulmonary disease, 2021

Laboratory data

Regarding bacteriological testing, 69% (146/210) of the total number of notified cases were laboratory confirmed by culture and/or molecular testing plus microscopy at the time of reporting, while 31% (65/210) were classified as probable/possible based on clinical and imaging findings.

In one case, the results confirming the TB diagnosis were obtained after the patient's death (**post-mortem** diagnosis).

Of the 171cases with pulmonary TB, 95 (55.56%) were reported to have a positive sputum microscopy, a finding associated with **high transmissibility**. The distribution of these cases is shown in Figure 9.

Molecular testing was done for 46% (97/210) of cases, of which 85.6% (83/97) were positive. **Culture** was done in 90.5% (190/210) of cases, of which 67.4% (128/190) were positive: 95% (122/128) were identified as *Mycobacterium tuberculosis* (Figure 10).

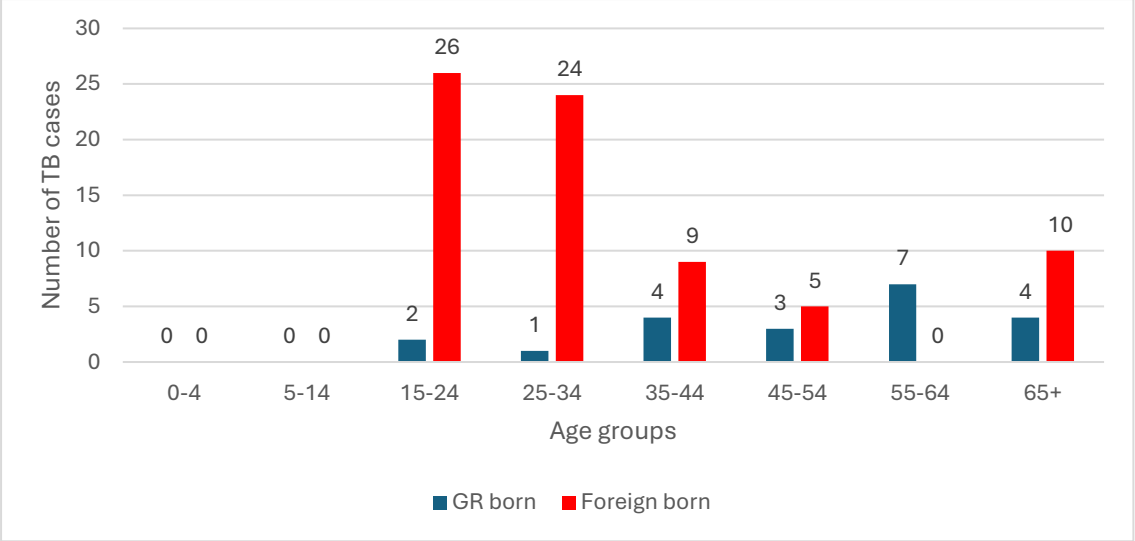


Figure 9: **Pulmonary cases with known positive microscopy, 2021**

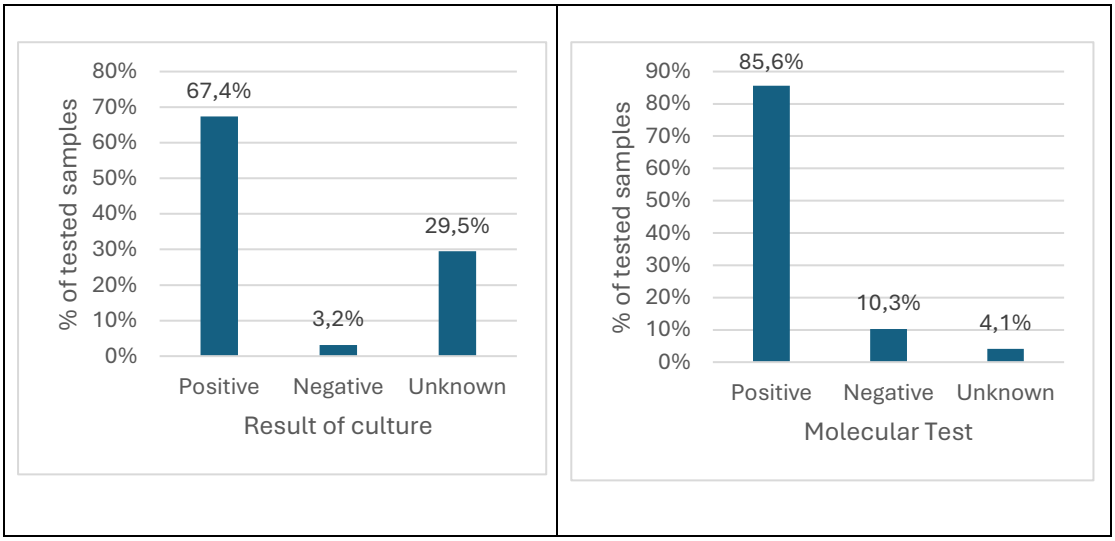


Figure 10: Laboratory confirmation of active Tb cases in 2021: result of mycobacterial cultures and molecular testing

Sensitivity to anti-tuberculosis drugs

Susceptibility results to the primary antituberculosis drugs were available for 66.4% (85/128) of notified cases with positive culture for *Mycobacterium tuberculosis*, i.e. 40.4% (85/210) of the total TB cases in 2021.

82.3% (70/85) were **sensitive** to all primary antituberculosis drugs: 83% of Greeks 82% of the foreign-born (Table 2).

11.7% (10/85) were resistant to one primary drug. Of note, isoniazid and rifampicin are the most critical drugs in TB treatment4.7% were **monoresistant to isoniazid**, while no monoresistance to rifampicin was observed (Figure 11).Combined resistance to isoniazid and rifampicin (**multidrug-resistant tuberculosis, MDR**) was present in 5.9% (5/84) of cases with known susceptibility results. All multi-drug resistance cases were foreign-born. In this population the MDR rate was 8.2% (Figure 12).

Type of resistance	**Number of strains with known result**	**Number (%) of resistant strains**	**Greekswith known susceptibility result (N=24)**	**Foreign-born with known susceptibility result (N=61)**
Isolated in isoniazid (**R-INH**)	84	4 (4,7%)	1 (4,2%)	3 (4,9%)
Isolated to rifampicin (**R-RIF**)	85	0	-	-
Isolated to streptomycin (**R-STR**)	81	2 (2,4%)	2 (8,4%)	0
Pyrazinamide isolate (**R-PZA**); probably M bovis strain	80	3 (3,8%)	1 (4,2%)	2 (3,3%)
Isolate of ethambutol (**R-ETH**)	81	1 (1,2%)	0	1 (1,6%)
Isoniazid and rifampicin (multi-drug resistance, **MDR**)	84	5 (5,9%)	0	5 (8,2%)
Extended (**preXDR**) & extremely extended (**XDR**)*	5 (MDR)**	0	-	-

Table 2: Sensitivity and resistance in notified cases with known sensitivity test

* PreXDR: Isoniazid, rifampicin AND fluoroquinolone **XDR**: Isoniazid, rifampicin, fluoroquinolone AND bedaquiline or linezolid

** In 5 out of 6 MDR strains further sensitivity testing to secondary anti-tuberculosis drugs was performed

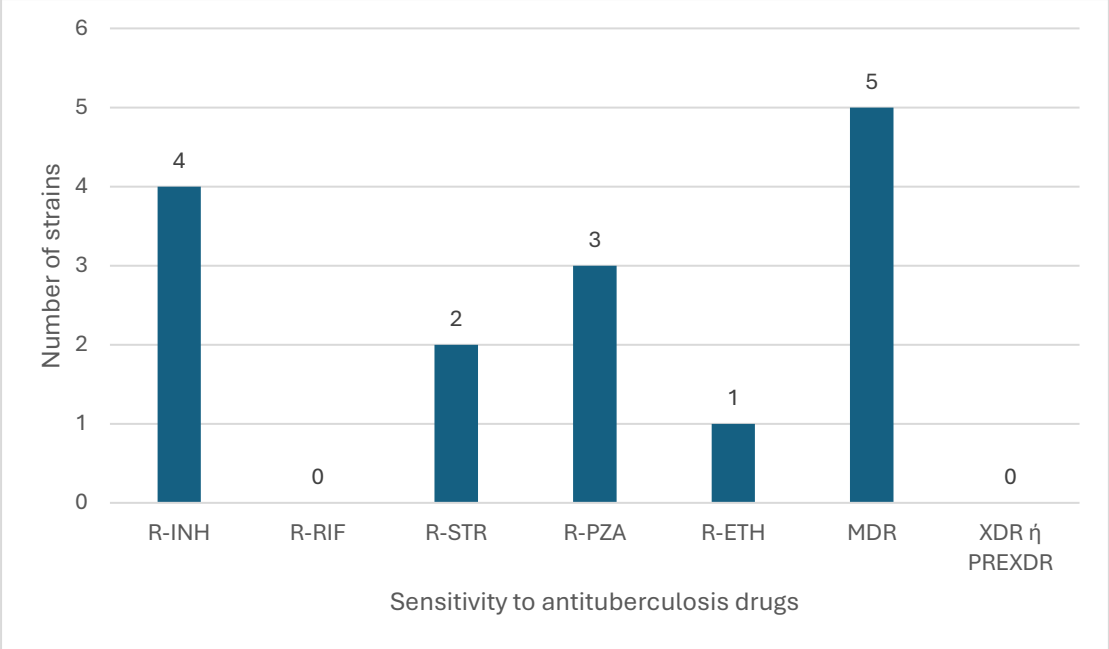


Figure 11: Number of resistant *M. tuberculosis*strains, 2021.

R-INH: Isolated isoniazid resistance,**R-RIF**: Isolated rifampicin resistance, **R-STR**: Isolated streptomycin resistance, **R-PZA**: Isolated pyrazinamide resistance, **R-ETH**: Isolated ethambutol resistance, **MDR**: Multi-drug resistance (Resistance to isoniazid AND rifampicin), **preXDR**: Extended (Resistance to isoniazid, rifampicin AND fluoroquinolone), **XDR**: Extended (Resistance to isoniazid, rifampicin, fluoroquinolone AND bedaquiline or linezolid).

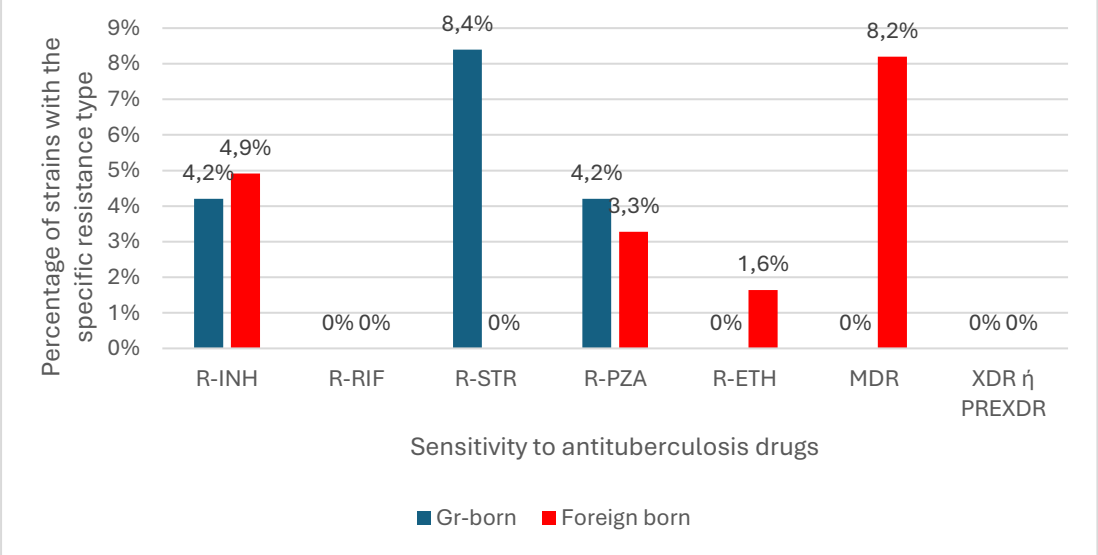


Figure 12: Percentage of resistant *M. tuberculosis*strains, 2021.

R-INH: Isolated isoniazid resistance, **R-RIF**: Isolated rifampicin resistance, **R-STR**: Isolated streptomycin resistance, **R-PZA**: Isolated pyrazinamide resistance, **R-ETH**: Isolated ethambutol resistance, **MDR**: Multi-drug resistance (Resistance to isoniazid AND rifampicin), **preXDR**: Extended (Resistance to isoniazid, rifampicin AND fluoroquinolone), **XDR**: Extended (Resistance to isoniazid, rifampicin, fluoroquinolone AND bedaquiline or linezolid).

Discussion

The COVID-19 pandemic had a significant impact on health care:pulmonary clinics were turned into COVID-19 clinics, physicians and infection control nurses were overloaded with emergency duties and ultimately access to TB services was severely impactedin many European countries. Therefore, the notified TB cases during the course of the COVID-19 pandemic are not considered to reflect the true burden of disease in the community.

While in previous decades TB in Greece mainly involved the Greek population, cases originating from countries with high TB incidence are steadily increasing recently. Two **epidemic curves** are unfolding in parallel: A downward curve pertains to the Greek mainly reflecting the activation of latent TB in older people. An upward curve, mainly involving primary infection, is noted in young refugees/migrants, with a higher absolute number of cases in those from central and southern Asia, and a higher incidence in those from Sub-Saharan Africa. Regardless of ethnic background, cases are observed in groups with social risk factors and/or precarious living conditions, such as intravenous drug users and prisoners.

Pulmonary TB was the most **prevalent type** of active disease, with or without additional extrapulmonary sites (most often lymph nodes), while purely extrapulmonary TB accounted for less than 1/6 of cases. Pulmonary TB confers a risk for transmission and is therefore particularly relevant from a public health perspective, whereas purely extrapulmonaryTB is non-transmissible.

Patients with positive sputum microscopy are considered **highly contagious**. The proportion of patients with pulmonary disease and positive microscopy increased in 2021 (55.56%) compared to the pre-pandemic rate (41% in 2019).

Pulmonary tuberculosis with lung **cavitation**is characterized by increased transmissibility, is therapeutically challengingand entailsan increased risk of relapse. Cavitation was observed in 51% of pulmonary TB foreign-born cases and in 40% of pulmonary Greek cases with known imaging results. The high proportion of cases with cavitation and positive sputum microscopy is an indirect indicator of delayed diagnosis, a phenomenon that has been exacerbated in Greece and in most countriesin the course of the pandemic.

Pediatric tuberculosis follows a downward trend. 20 years ago, 10% of TB cases were children <14 years of age, while less than 2% in 2021 (3.5% in 2019). In all notified cases <14 years of age, there was a known source of exposure in the immediate family environment, i.e. the source of infection of young children was within the family.

In 2021, 61% of notified cases had a positive result (67% of cases with culture performed). **Susceptibility** results to antituberculosis drugs were available for 40.4% of cases. Of the laboratory-confirmed TB cases with a positive culture, 11.6% were resistant to at least one primary anti-TB drug. Monoresistance to isoniazid was 4.7%, while no monoresistance to rifampicin was observed. Five multidrug-resistant TB cases were notified, all foreign-born.