Original Article

Epidemiology of tuberculosis in Saudi Arabia following the implementation of end tuberculosis strategy

Analysis of the surveillance data 2015-2019

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ABSTRACT

الأهداف: تحليل تطور وبائيات السل في المملكة العربية السعودية خلال السنوات الخمس التالية لتنفيذ استراتيجية القضاء على السل.

المنهجية: أجرينا تحليل بأثر رجعي لبيانات المراقبة، التي أبلغ عنها البرنامج الوطني لمكافحة السل خلال الفترة 2015-2019م. أُجري حساب معدل الإصابة السنوي والنسبة المئوية للتغيرات السنوية ومقارنتهما بمعالم منظمة الصحة العالمية (WHO)، والتي تتوقع انخفاضًا سنويًا بنسبة 4-5%. بالإضافة إلى ذلك، أجري فحص مختلف المؤشرات الوبائية الأخرى لمرض السل.

النتائج: انخفض معدل الإصابة بالسل على المستوى الوطني من 10.55% لكل 100 ألف في عام 2015م إلى 8.76% لكل 100 ألف في عام 2019م، وبذلك يتماشى مع هدف منظمة الصحة العالمية لعام 2019م الذي يقدر بنسبة تتراوح بين 8.59 إلى 8.96% لكل 100 ألف. شكلت منطقة مكة المكرمة (40.3%) والرياض (24.6%) غالبية الحالات، أظهرت منطقة جازان باستمرار أعلى معدلات الإصابة طوال فترة الدراسة. تحولت السمات الديموغرافية نحو الفئة العمرية الأصغر سنا، والذكور، والهيمنة الأصلية. كان هناك انخفاض ثابت في المقاومة والحساسية المتوسطة لجميع أدوية الخط الأول المضادة للسل، المرتبطة بانخفاض كبير في كل من مقاومة الأدوية المتعددة (من 4.7 إلى 1.9%؛ قيمة الاحتمال $p<0.001$) ومقاومة الأدوية المتعددة (من 4.4 إلى 2.4%؛ $p=0.008$).

الخلاصة: إن أرقام الإصابة بالسل في المملكة العربية السعودية بين عامي 2015-2019م قد حققت معالم منظمة الصحة العالمية للقضاء على السل، مما تشير بالتقدم الناجح نحو هدف عام 2035.

Objectives: To analyze the evolution of tuberculosis (TB) epidemiology in Saudi Arabia in the 5 years following the implementation of the end-TB Strategy.

Methods: A retrospective analysis of surveillance data, reported by the national tuberculosis control program from 2015-2019, was carried out. The annual incidence and the percentage of yearly changes were calculated and compared to the World Health Organization (WHO) milestones, which anticipate a 4-5% annual decline. Additionally, various other epidemiological indicators of TB were examined.

Results: The national TB incidence declined from 10.55% per 100,000 in 2015 to 8.76% per 100,000 in 2019, aligning with the WHO's 2019 milestone estimated between 8.59-8.96% per 100,000. While Makkah Region (40.3%) and Riyadh (24.6%) accounted for the majority of cases, Jazan region consistently exhibited the highest incidence throughout the study period. Demographic features shifted towards a younger age category, male, and native dominance. There was a consistent decrease in resistance and intermediate sensitivity to all first-line anti-TB drugs, associated with a substantial decrease in both polydrug resistance (from 4.7-1.9%; $p<0.001$) and multidrug resistance (from 4.4-2.4%; $p=0.008$).

Conclusion: The figures of TB incidence TB in Saudi Arabia between 2015-2019 has met the WHO end-TB milestones, predicting successful progress toward the 2035 goal.

Keywords: tuberculosis, sentinel surveillance, epidemiology, drug resistance, Saudi Arabia

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Tuberculosis (TB) ranks as the primary infectious agent responsible for the highest number of human deaths.[1] Recent global estimates showed that approximately 6.4 million individuals have been infected with TB, and one-quarter of the world's population is a carrier of the causative agent, *Mycobacterium tuberculosis* (*M. tuberculosis*).[2,3] As of 2019, TB was responsible for up to 30.1 deaths per 100,000 and up to 91.9 years lost to disability (YLDs), varying by World Health Organization (WHO) region.[4]

The most common clinical presentation of TB is its pulmonary form, owing to its airway transmission. However, approximately 15% of *M. tuberculosis* infections are extrapulmonary without concurrent pulmonary symptoms, which poses diagnostic and therapeutic challenges.[5] Another challenging aspect of TB is the emerging drug-resistant TB strains, notably multidrug-resistant TB (MDR-TB), poses a significant challenge. In 2017, 558,000 new TB cases with rifampicin resistance were reported worldwide, with 82% developing MDR-TB. Delayed diagnosis, inadequate drug access, and patient noncompliance further contribute to treatment failures.[6]

In 2014, the WHO introduced the end-TB strategy with the objective of terminating the TB epidemic by 2035. This strategy encompasses 5-year milestones (2020, 2025, and 2030) and annual targets (a 4-5% reduction in TB incidence compared to the previous year). These goals are intended for national-level implementation.[7] Subsequently, the global TB incidence began a gradual decline at a rate of approximately 2% per year.[4]

In Saudi Arabia, TB surveillance and reporting commenced in 1970, with an incidence of 1298.5 cases per 100,000 population. Subsequently, there was a steady decline in TB incidence, reaching 135 per 100,000 in 1980 and 12 per 100,000 in 1997.[8] However, between 2000 and 2009, the TB incidence plateaued at approximately 15-16 cases per 100,000, while the crude number of incident cases rose from 3,284 to 3,964.[9]

The decline in TB incidence can be attributed to the implementation of vaccination programs and improved access to health services.[8] Furthermore, in response to WHO call, the Saudi government scaled up the already established national tuberculosis control program (NTCP) to align with the end-TB strategy's goals and milestones.[10] However, although classified as a "low-to-middle TB burden country", Saudi Arabia possesses specific features that could challenge the strategy's effectiveness. Notably the annual influx of millions of pilgrims and the increased population mobility contribute to heightened spread of TB.[8] In this context, the study was carried out to assess whether the adoption of the end-TB strategy facilitated a decrease in TB incidence over the ensuing 5 years (2015-2019) and whether the WHO milestones were achieved.

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Methods. We retrospectively collected and analyzed the national TB surveillance data reported by the NTCP from 2015-2019. All TB patients diagnosed and reported by the NTCP from 2015-2019 were included. The study received ethical approval by the Center of Excellence in Genomic Medicine Research bioethics committee at King Abdulaziz University, Jeddah, Saudi Arabia (Ref no.: 22-CEGMR-Bioeth-2022).

The NTCP health personnel routinely analyze TB data collected and sent by the TB program in the regions to generate monthly, quarterly, and annual statistical reports. In the present study, we captured data from annual statistical reports of 2015-2019 and consolidated it into a singular database. The data was then cleaned and coded. Collected data included: I) sociodemographic data of the patient, including age, gender, region, and nationality; II) clinical presentation including patient type (new, failure, relapse, and treatment post-failure), TB type (pulmonary, extrapulmonary, or both), presenting symptoms, history of TB, and comorbidities notably HIV/AIDS status and screening; and III) laboratory findings including anti-tuberculosis drug resistance, HIV serology, treatment regimen (first or second line), and more. Additionally, the patterns of drug resistance, including drug-susceptible, polydrug resistance (PDR; resistance to more than one first-line anti-TB drug, other than both isoniazid and rifampicin), multidrug resistance (MDR; resistance to at least both isoniazid and rifampicin), and extensive resistance (XDR; including MDR and resistance to any fluoroquinolone and at least one of the 3 second-line injectable drugs), were determined according to the WHO definitions.[11]

The initial database consisted of 15,696 observations from 2015-2019. Out of these, 7 were diagnosed in 2014, 27 in 2020, and 119 lacked a diagnosis date. Cases diagnosed in 2014 or 2020 were excluded, while the missing diagnosis dates for the 119 were imputed using the treatment start date, all of which fell between 2015-2019. Other missing data concerned 3 variables

and were imputed as follows: I) gender (4 observations were directly imputed by their names or jobs); II) nationality (15 observations, 11 of them were directly imputed based on job [exclusively Saudi or foreign job], and the 4 others were assigned randomly as Saudi or non-Saudi; III) age (18 observations were imputed using regression imputation, occupation and index case age as the predictors). Five imputations were run, and the rounded mean age was used.

Statistical analysis. Data were analyzed using the Statistical Package for the Social Sciences, version 21 (IBM Corp. Armonk, NY, USA). Descriptive statistics were used to present the categorical variables as frequencies and percentages and continuous variables as means ± standard deviations (SD). A Chi-squared test was used to analyze the association between two categorical variables. One-Way Analysis of Variance (ANOVA) was used to analyze the age variance across the years, completed with pairwise comparisons using Tukey's HSD test. A *p*-value of <0.05 was considered significant.

Results. A total of 15,662 cases were included. The yearly number of incident cases decreased gradually from 3,345 in 2015 to 3,003 in 2019, except for an increase in 2018. Adjusting to the country's population, the incidence risk decreased from 10.55 per 100,000 in 2015 to 8.76 per 100,000 in 2019. However, a surge in the incidence risk was observed in 2018, accounting for 9.97 per 100,000. All yearly incidence rates were lower than the corresponding WHO milestones, except the one of 2018. This indicates the successful achievement of the end-TB milestones for the studied period (Table 1).

Makkah Region, Saudi Arabia, contributed 40.3% of the total cases, followed by Riyadh (24.6%), Eastern Province (13.6%), and Jazan (9.0%), while the 9 other provinces accounted for 12.5% of the cases altogether (Table 2).

The highest incidence was observed in Jazan throughout the study period, decreasing from 20.44 per 100,000 in 2015 to 16.55 per 100,000 in 2019, followed by Makkah province (16.13 to 13.72 per 100,000) and Riyadh (from 10.88 to 7.47 per 100,000). In addition, we observed 2 patterns for the progression of the yearly incidence risk. The first pattern, observed in 7 provinces (Makkah, Riyadh, Jazan, Madinah, Al-Qassim, Hail, and Najran), showed an overall decreasing trend interspersed with an upsurge between 2017-2018. The second pattern, observed in the remaining 6 provinces (Eastern Province, Asir, Tabuk, Al-Jawf, Al-Baha, and Northern Borders), showed an initial decline followed by an increase between 2017-2019 (Table 3).

The mean age of the total participants was 40.12±17.58 years, which gradually decreased from 41.43 years in 2015 to 38.77 years in 2019, combined with a relative increase in the variance (One-Way ANOVA, $p<0.001$; Table 4). Post hoc analysis (Tukey's HSD test) showed statistically significant pairwise differences between 2015 and all following years ($p<0.05$). Gender distribution showed consistent male predominance, accounting for 69.5% of the total cases, with increase in male ratio reaching 2.53 in 2019 ($p=0.002$). Regarding patients' nationality, we observed a shift from predominant non-Saudi nationality in 2015 (54.4%) to Saudi national predominance in 2019 (54.3%, $p<0.001$; Table 4).

Of all cases, approximately two-thirds were pulmonary TB, approximately one-quarter were extrapulmonary, and less than 2.5% had both pulmonary and extrapulmonary manifestations, with no difference across the years ($p=0.880$). By excluding cases with unknown or pending HIV serology results, the prevalence of HIV coinfection remained stable (3.2-3.5%), with a decrease, however, to 2.5% in 2016 ($p=0.287$). Failures cases represented 0.6%, relapses cases represented 3.8%, and post-failure cases represented 1.9% of the total cases, with no significant difference

Table 1 - Yearly incidence of tuberculosis in Saudi Arabia from 2015-2019.

Year	Number of cases	Total population*	Incidence risk per 100,000	Change (%)†	Reference WHO milestones (4-5% annual decrease)
2015	3345	31,717,676	10.55 (10.19-10.90)	-	10.55
2016	2993	32,443,443	9.23 (8.89-9.56)	-12.5%	10.02-10.13
2017	2962	33,101,183	8.95 (8.63-9.27)	-3.0%	9.52-9.72
2018	3359	33,702,757	9.97 (9.63-10.30)	+11.4%	9.05-9.33
2019	3003	34,268,529	8.76 (8.45-9.08)	-12.1%	8.59-8.96

*Denominators used estimates provided by the World Bank data. †The change (%) is calculated as follows: 100 * (year's rate - previous year's rate) / previous year's rate. For example, the change rate in 2016=100 * (9.23-10.55) / 10.55= -12.5%, which corresponds to a 12.5% decrease in the incidence from 2015-2016. WHO: World Health Organization

Table 2 - Regional distribution of incident cases of tuberculosis in Saudi Arabia from 2015-2019.

Provinces	Total (N=15662)	2015 (n=3345)	2016 (n=2993)	2017 (n=2962)	2018 (n=3359)	2019 (n=3003)	*P*-values
Makkah	6317 (40.3)	1345 (40.2)	1201 (40.1)	1097 (37.0)	1435 (42.7)	1239 (41.3)	
Riyadh	3855 (24.6)	846 (25.3)	794 (26.5)	798 (26.9)	770 (22.9)	647 (21.5)	
Eastern Province	1545 (13.6)	270 (8.1)	258 (8.6)	279 (9.4)	329 (9.8)	409 (13.6)	
Asir	547 (3.9)	121 (3.6)	100 (3.3)	96 (3.2)	113 (3.4)	117 (3.9)	
Jazan	1604 (9.0)	306 (9.1)	292 (9.8)	351 (11.9)	384 (11.4)	271 (9.0)	
Madinah	705 (4.5)	176 (5.3)	130 (4.3)	128 (4.3)	135 (4.0)	136 (4.5)	
Al-Qassim	285 (1.8)	88 (2.6)	57 (1.9)	68 (2.3)	38 (1.1)	34 (1.1)	<0.001*
Tabuk	180 (1.1)	41 (1.2)	39 (1.3)	42 (1.4)	24 (0.7)	34 (1.1)	
Hail	91 (0.6)	23 (0.7)	21 (0.7)	16 (0.5)	17 (0.5)	14 (0.5)	
Najran	197 (1.3)	51 (1.5)	40 (1.3)	30 (1.0)	45 (1.3)	31 (1.0)	
Al Jawf	130 (0.8)	30 (0.9)	16 (0.5)	26 (0.9)	30 (0.9)	29 (0.9)	
Al-Baha	118 (0.8)	33 (1.0)	21 (0.7)	14 (0.5)	24 (0.7)	26 (0.9)	
Northern Borders	88 (0.6)	15 (0.4)	24 (0.8)	17 (0.6)	15 (0.4)	17 (0.6)	

Values are presented as numbers and precentages (%). The Chi-square test was used. *Statistically significant result

Table 3 - Incidence risk of tuberculosis in Saudi Provinces, per 100,000 of the population.

Provinces	2015	2016	2017	2018	2019
Makkah	16.13	14.40	12.79	16.30	13.72
Riyadh	10.88	9.91	9.69	9.12	7.47
Eastern Province*	5.80	5.39	5.68	6.54	7.94
Asir*	5.72	4.61	4.33	5.00	5.07
Jazan	20.44	19.02	22.36	23.95	16.55
Madinah	8.69	6.24	5.99	6.17	6.07
Al-Qassim	6.50	4.10	4.78	2.61	2.28
Tabuk*	4.71	4.37	4.61	2.58	3.58
Hail	3.44	3.06	2.28	2.37	1.91
Najran	9.18	7.02	5.15	7.55	5.09
Al Jawf*	6.18	3.21	5.10	5.76	5.45
Al-Baha*	7.24	4.50	2.93	4.99	5.23
Northern Borders*	4.27	6.67	4.63	4.00	4.44

Values are presented as precentages (%). *Provinces showing initial decrease in the incidence, followed by an increase. Incidence was calculated with respect of the number of populations in the respective year for each province. Values are number of cases per 100000 of population.

Table 4 - Yearly trends of demographic characteristics of incident tuberculosis cases in Saudi Arabia between 2015-2019.

Parameters	Total (N=15662)	2015 (n=3345)	2016 (n=2993)	2017 (n=2962)	2018 (n=3359)	2019 (n=3003)	*P*-values*
Age, mean±SD†	40.12±17.58	41.43±17.15	40.70±17.38	39.92±17.41	39.68±18.12	38.77±17.70	<0.001
Gender							
Male	10881 (69.5)	2309 (69.0)	2007 (67.1)	2049 (69.2)	2363 (70.3)	2153 (71.7)	0.002
Female	4781 (30.5)	1036 (31.0)	986 (32.9)	913 (30.8)	996 (29.7)	850 (28.3)	
Nationality							
Saudi	7765 (49.6)	1524 (45.6)	1447 (48.3)	1456 (49.2)	1708 (50.8)	1630 (54.3)	<0.001
Non-Saudi	7897 (50.4)	1821 (54.4)	1546 (51.7)	1506 (50.8)	1651 (49.2)	1373 (45.7)	

Values are presented as numbers and precentages (%). †Post hoc analysis (Tukey's HSD test): pairwise significant differences are 2015 vs. 2017 (p=0.005), 2015 vs. 2017 (p<0.001), 2015 vs. 2018 (p<0.001), 2015 vs. 2019 (p<0.001), and 2016 vs. 2019 (p<0.001). *Statistically significant difference between the years (p<0.05). OneWay ANOVA test was used for age and Chi-square test was used for gender and nationality. SD: standard deviation

across the years (p=0.076). Regarding treatment, 97.3% of patients received a first-line regimen, with a substantial decrease in second-line regimen prescribing over the years (p=0.004; Table 5).

The clinical presentation showed significant decrease in the prevalence of all common symptoms, such as cough (from 85.0 to 79.4%; p<0.001), sputum (from 74.4% to 70.5%; p<0.001), and fever (from 84.3% to 74.1%; p<0.001), as well as severe symptoms such as hemoptysis (from 25.5% to 17.9%; p<0.001). On the other hand, uncommon symptoms, such as digestive and neurological symptoms, increased from 6.1% in 2015 to 12.8% in 2019 (p<0.001).

There was a consistent decrease in resistance and intermediate sensitivity to isoniazid (p<0.001), ethambutol (p=0.002), and streptomycin (p<0.001). Resistance to pyrazinamide and rifampicin also decreased, with no statistical significance. Hence, the overall drug-susceptibility rate increased significantly from 88.1% in 2015 to 92.7% in 2019 (Chi-square, p<0.001). This was associated with a significant decrease in both PDR (from 4.7% to 1.9%; p<0.001) and MDR (from 4.4% to 2.4%; p=0.008). Of note, no case of XDR was observed (Table 6).

There were 206 children aged 5 or below; 66.6% were males, and 52.9% were Saudis. We observed rates of pulmonary (57.3%) and extrapulmonary TB (37.4%), and MDR (2.2%) without any difference across the years (p>0.05).

Discussion. The Saudi NTCP was scaled up to align with the global goal of a TB-free world by 2035.[7,10] Beginning in 2015, the goal was to reduce TB incidence by 4-5 % each year.[12] The present study analyzed the achievement of these goals in Saudi Arabia, besides other epidemiological features of TB, during the 5 years following the end-TB strategy implementation. The key observations are a gradual decrease of TB incidence from 10.55 to 8.76 per 100,000, meeting the end-TB strategy milestones; with the exception of 2018, where an upsurge was observed in all the provinces. A regional disparity was observed, with 87.5% of the cases concentrated in 4 regions and 40.3% in the Makkah region alone. A 2-phase pattern, showing initial decrease followed by increase, was observed in 6 provinces located in 3 geographical spots: Eastern Province, North (Tabuk, Al Jawf, and Northern Borders provinces), and Southwest (Asir and Al Baha). There was a notable shift in TB demography, moving towards a younger age category and increasing male and native-to-immigrant ratios. We observed a consistent proportion of HIV coinfection and a decreasing trend of TB resistance, associated with a significant decrease in second-line regimen prescribing.

Table 5 - Yearly trends of epidemiological characteristics of incident tuberculosis cases in Saudi Arabia between 2015-2019.

Parameters	Total (N=15662)	2015 (n=3345)	2016 (n=2993)	2017 (n=2962)	2018 (n=3359)	2019 (n=3003)	*P*-values
TB type							
Pulmonary	11465 (73.2)	2456 (73.4)	2172 (72.6)	2146 (72.5)	2489 (74.1)	2202 (73.3)	
Extrapulmonary	3868 (24.7)	817 (24.4)	756 (25.3)	752 (25.4)	799 (23.8)	744 (24.8)	
Both	329 (2.1)	72 (2.2)	65 (2.2)	64 (2.2)	71 (2.1)	57 (1.9)	0.880
AIDS	234 (2.4)	47 (2.1)	35 (1.9)	37 (2.2)	48 (2.4)	67 (3.6)	0.005*
HIV status							
Non-documented	4862 (31.0)	894 (26.7)	668 (22.3)	996 (33.6)	1315 (39.1)	989 (32.9)	
Pending	1218 (7.8)	202 (6.0)	110 (3.7)	354 (12.0)	462 (13.8)	90 (3.0)	
Unknown	3644 (23.3)	692 (20.7)	558 (18.6)	642 (21.7)	853 (25.4)	899 (29.9)	
Documented	2451 (69.0)	2451 (73.3)	2325 (77.7)	1966 (66.4)	2044 (60.9)	2014 (67.1)	
Negative†	10452 (96.8)	2365 (96.5)	2266 (97.5)	1904 (96.8)	1973 (96.5)	1944 (96.5)	
Positive†	348 (3.2)	86 (3.5)	59 (2.5)	62 (3.2)	71 (3.5)	70 (3.5)	0.287†
Patient's type							
New	14544 (92.9)	3094 (92.5)	2746 (91.7)	2747 (92.7)	3127 (93.1)	2830 (94.2)	
Failure	97 (0.6)	24 (0.7)	21(0.7)	19 (0.6)	20 (0.6)	13 (0.4)	
Relapse	595 (3.8)	124 (3.7)	139 (4.6)	120 (4.1)	121 (3.6)	91 (3.0)	
Post failure	291 (1.9)	73 (2.2)	65 (2.2)	45 (1.5)	59 (1.8)	49 (1.6)	
Other	135 (0.9)	30 (0.9)	22 (0.7)	31 (1.0)	32 (1.0)	20 (0.7)	0.076
Medication							
First line	14600 (97.3)	3104 (97.2)	2779 (96.6)	2841 (97.0)	3206 (97.8)	2670 (98.1)	
Second line	398 (2.7)	88 (2.8)	98 (3.4)	87 (3.0)	72 (2.2)	53 (1.9)	0.004*

Values are presented as numbers and precentages (%). †Percentages and statistical significance were calculated on patients with documented HIV serology. *Statistically significant difference between the years (p<0.05). Chi-square test was used. TB: Tuberculosis, AIDS: acquired immunodeficiency syndrome, HIV: human immunodeficiency virus

Table 6 - Resistance to first-line antituberculosis drugs.

Drugs	2015	2016	2017	2018	2019	*P*-values
Isoniazid						
Sensitive	89.5	87.2	91.3	90.5	93.6	
Intermediate	3.2	2.6	1.5	1.6	1.3	
Resistance	7.3	10.3	7.3	7.9	5.1	<0.001*
Pyrazinamide						
Sensitive	90.7	88.8	90.5	93.4	91.1	
Intermediate	3.4	2.6	2.2	2.1	2.3	
Resistance	6.0	8.6	7.3	4.5	6.6	0.055
Ethambutol						
Sensitive	94.1	93.5	96.1	96.5	97.2	
Intermediate	3.1	2.8	1.5	1.7	1.2	
Resistance	2.8	3.7	2.5	1.8	1.6	0.002*
Rifampicin						
Sensitive	94.1	92.4	93.9	93.8	96.2	
Intermediate	1.8	2.1	1.4	1.5	1.2	
Resistance	4.0	5.5	4.7	4.7	2.6	0.067
Streptomycin						
Sensitive	86.9	83.5	90.9	91.3	92.8	<0.001*
Intermediate	3.3	2.9	1.6	1.7	1.5	
Resistance	9.8	13.6	7.5	6.9	5.7	
Overall resistance patterns						
Drug-susceptible	88.1	85.8	89.6	89.7	92.7	<0.001*
Monoresistance‡	13.6	17.0	12.5	10.6	13.2	0.001*
PDR	4.7	5.7	4.0	2.2	1.9	<0.001*
MDR	4.4	5.7	4.0	4.4	2.4	0.008*
XDR§	-	-	-	-	-	

Values are presented as precentages (%). *Statistically significant difference between the years (p<0.05) and Chi-square test was used. §Data regarding second-line injectable drugs (capreomycin, kanamycin, and amikacin) were not available to establish XDR. ‡The calculation of monoresistance is not accurate, because all drugs were not tested for all the included patients; hence, the absence of result was assumed to be absence of resistance. PDR: polydrug resistance, MDR: multidrug resistance, XDR: extensive drug resistance

The observed decrease in TB incidence from 2015-2019 represents an average 4.05% yearly decline, aligning with the WHO milestones. This remarkable decrease results from a significant reduction in new cases combined with a simultaneous decline in demographic growth rate, projecting the attainment of the end-TB goal by 2035 in the Kingdom.

During the past decade, Middle Eastern and Gulf countries have also reported encouraging results concerning TB indicators.[13,14] For instance, in Oman, the incidence of TB declined by an average of 5.7% annually from 2011-2016.[13] Similarly, in Bahrain, studies showed a significant decline in TB incidence from 34 per 100,000 in 2007 to 11 per 100,000 in 2016, with annual declines reaching up to 26.7%, depending on the year.[14] Conversely, the incidence of TB in the United Arab Emirates increased relatively during the same period, 2015-2019, from 0.78 to 1 per 100,000.[12]

The present study highlighted the unequal distribution of TB across the Saudi regions, with some areas entailing a greater burden. Multiple local reports have highlighted similar regional disparities in TB burden, attributed to demographic factors, particularly the significant proportions of immigrants in major cities and the influx of pilgrims in Makkah and Al-Madinah Al-Munawarah.[8,15,16] However, inequalities observed in the present study cannot be fully explained by demographic factors, given the inconsistency between regional rankings of number of cases versus incidence risks. Regarding the number of cases, 87.5% were reported in 4 provinces, among which Makkah province accounted for 40.3%, followed by Riyadh, Jazan, and the Eastern Province. This was consistent with previous data between 2000 and 2009 showing Makkah (1035-1,738 cases), Riyadh (705-1,100), Eastern Province (315-397), and Jazan (171-225) as having the highest burden.[9] However, in terms of incidence risk, which is adjusted to the population size, Jazan showed the highest figures throughout the study period. Additionally, while Najran had one of the lowest cases, its incidence risk between 2015-2016 was

higher than that observed in the Eastern Province and Al-Madinah Al-Munawarah during the same period. Furthermore, we observed 2 distinct patterns in the annual changes of incidence risk. While highly endemic provinces showed a significant decline in the incidence, 6 provinces (all having relatively low baseline figures) showed an initial decline followed by a rise in incidence.

While the unique demographic characteristics of each region (such as population density and immigrant workforce influx) can account for these regional variations, other factors might also influence these trends. These other factors may be related to environmental or climatic parameters or differences in the level of implementation of the national program between the regions, with endemic areas having more stringent applications. This underscores the role of regional NTCP coordinators in setting specific targets and guidelines based on local challenges, building on the national policies.[17] Furthermore, we draw attention to the Eastern Province, the sole province displaying a steady rise in both crude cases and incidence risk. Local investigations are warranted to elucidate this unusual pattern and implement appropriate interventions.

From a demographic perspective, the most remarkable change is a shift towards the younger age group, with an increasing proportion of 0-29 age category and a decline in the 30-39 age bracket. This trend was combined with a rising male ratio and autochthonous cases surpassing immigrants by 2018. A closer examination of the data suggests that 2018 probably marked a pivotal point, with a peak in cases and incidence risk observed in nearly all regions.

Between 2015-2018, the impact of TB on young age groups in Saudi Arabia, in terms of mortality and disability adjusted life years (DALYs), was relatively comparable to that in North America and Western Europe, while being constantly and significantly lower than in Asian countries. However, as of 2018, a modest rise in YLDs associated with TB was noted among the younger demographics in Saudi Arabia, which concords with our findings.[4] This underscores the relevance of anticipating the potential threat of childhood TB by addressing emerging risk factors such as HIV epidemic or environmental exposure.[18] On the other hand, the rising ratio of native-to-immigrant cases could result from the country's ongoing reforms in foreign labor regulations, aligning with the national strategy to prioritize the Saudization of the workforce.[19]

Besides this demographic transition, we noted a change in the clinical presentation with an increasing occurrence of uncommon symptoms and rarefaction of more severe symptoms such as hemoptysis. The decline in severe symptoms may be explained by the enhanced diagnosis enabled by increasing awareness and health-seeking behavior among the general population and accessibility of health services. Furthermore, these figures were associated with a decreasing trend in HIV-coinfected patients (from 86 in 2015 to 70 in 2019), while their proportion remained constant due to the decreasing number of overall TB cases. Importantly, 31.1% of the total patients (22.3% to 39.1% depending on the year) lacked documented HIV serology, which may lead to an underestimation of HIV coinfection rates, potentially affecting the evaluation of its annual trends. The HIV infection and HIV-TB coinfection are rampant public health threats in the Saudi population. Regional and single-center reports established HIV infection as a significant risk factor for TB infection, notably in advanced stages of HIV, increasing morbidity and mortality of people living with HIV (PLHIV).[20-22] Successive case series from King Faisal Specialist Hospital and Research Centre, Riyadh, showed an increase in HIV coinfection prevalence among TB patients from 1.1% in 2002 to 16% in 2014.[21,23,24] These rates exceed those presented in this report, likely because they originate from a referral center that treats more complex cases. Nevertheless, both sources align in indicating an upward trend of HIV coinfection. This emerging trend may represent the most significant challenge in the coming decade, necessitating strategic implementation of rigorous measures to mitigate its rise and prevent progression into an exponential phase.

Another interesting observation was the decreasing trend in TB resistance to the major anti-TB drugs. Additionally, the prevalence of intermediate sensitivity decreased in all 5 anti-TB drugs, resulting in a significant decrease in PDR and MDR by approximately 50% between 2015-2019. Previous national data from 2014-2015 showed higher rates of resistance to isoniazid (10.2%), ethambutol (3.8%), rifampicin (5.9%), and streptomycin (11.0%).[25] Drug-resistant TB constitutes an emerging global issue that threatens patients' outcomes and healthcare systems and requires high levels of coordination, strategic planning, and good clinical practice.[26,27] Furthermore, patients with resistant or MDR strains have a greater risk of treatment failure and endure more extended treatment.[26,28,29] Thus, the enhanced national data on drug resistance suggests improved TB control and presents an opportunity to further augment the success of the national program.

On the other hand, this decline in drug resistance may explain the observed decrease in second-line anti-TB drugs prescribing. This further suggests improved management of drug-resistant cases and

effective prevention of secondary transmission.[26,30,31] Better compliance with prescribing guidelines prevents drug resistance, as inappropriate treatment increases the risk of developing drug resistance.[31,32] This highlights the bidirectional relationship between drug resistance and prescribing practice, stressing the importance of promoting good practice.

Study limitations. The current study's limitations are primarily associated with its reliance on the data and reporting system of the TB surveillance program. These limitations arise due to the inherent variations in assessment and reporting practices across different teams, regions, and over time. A specific concern is the substantial amount of missing data related to HIV coinfection status. To address these limitations and improve data quality, we recommend the implementation of more rigorous data management strategies aimed at standardizing these practices.

Given the changing face of the TB epidemic in the country, a multidisciplinary and visionary approach is essential to address the evolving challenges and to develop effective strategies for prevention and control. Future research directions and public health actions could include the following: I) youth-centric interventions to understand the factors contributing to the increasing prevalence of TB among younger age groups. This may involve investigating lifestyle factors, social determinants, and access to healthcare among younger populations. Developing targeted interventions and awareness campaigns for youth could be a critical step; II) in-depth analysis of the dynamics of autochthone (locally transmitted) TB cases, which can provide insights into the disease's spread within communities. Research should aim to identify the key drivers of autochthone transmission and evaluate the effectiveness of community-based prevention strategies; III) reinforcement of HIV-TB coinfection prevention and control, by improving screening, diagnosis, and treatment integration for individuals with both TB and HIV. Investigating the impact of HIV on TB transmission dynamics and the development of drug-resistant TB strains is also vital and should be urgently implemented to anticipate an escalation of the 2 epidemics; IV) tackling behavioral and environmental factors contributing to TB transmission and susceptibility, by exploring the role of urbanization, migration patterns, and other human factors. Additionally, investigating the impact of climate change on TB transmission dynamics may be pertinent; V) development of innovative strategies for TB prevention, such as community engagement and mobile health technologies, which rely on the proactive collaboration and awareness of the population. Additionally, the use of machine learning algorithms and artificial intelligence could contribute in improving diagnosis and enhancing epidemiological data analysis and modelling, besides other applications such as contact tracing and treatment adherence; and VI) enhancing surveillance systems to capture these changing trends, by implementing adaptive data collection, reporting, and analysis methods to provide timely and accurate insights into the evolving TB epidemic.

In conclusion, the incidence of TB in Saudi Arabia has significantly declined between 2015-2019, thereby meeting the WHO milestones and predicting the achievement of the end-TB goals by 2035. Another optimistic aspect is the significant decrease in drug resistance, notably MDR, reflecting an improved prevention, diagnosis, and treatment practice. Besides, the face of TB epidemic is changing, with a shift towards younger age groups, autochthone cases, and the insidious threat of HIV coinfection. These changes reflect a societal transition and other behavioral and environmental factors and forecast new challenges that require an urgent visionary strategy.

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