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Gender patterns of tuberculosis testing and disease in South Africa

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SUMMARY

SETTING: In South Africa, tuberculosis (TB) has been the leading cause of death for over a decade. The TB incidence rate is the second highest in the world, and continues to rise.

OBJECTIVE: To examine gender patterns in South Africa's TB epidemic. This is one of the first studies to use National Health Laboratory Service (NHLS) data to evaluate the epidemic at the national level.

DESIGN: Observational study using NHLS retrospective data for every TB test performed in public health facilities between 2009 and 2011.

RESULTS: Despite an increase in the number of TB tests performed, the number of TB cases remained relatively constant. Although prevalence rates differ between health districts, we find a similar female-to-male ratio (0.70) in each district. The age profile for TB resembles that of human immunodeficiency virus (HIV), with peak TB prevalence in women occurring 7 years earlier than in men. The female-to-male ratio of TB cases and 3+ positive (severe) cases decreases rapidly between ages 25 and 35 years.

CONCLUSION: These age and gender patterns are driven by the HIV epidemic and risks associated with pregnancy and childbearing. Increasing the quality and quantity of active TB case finding at existing points of care would be a sustainable and cost-effective intervention for both treatment and prevention.

KEY WORDS: TB incidence; HIV/AIDS; TB-HIV; integration; maternal mortality

SOUTH AFRICA has the second highest tuberculosis (TB) incidence rate in the world.[1] The disease has been the leading cause of death for over a decade in South Africa, accounting for approximately 12% of all deaths due to natural causes.[2] Of the 22 World Health Organization (WHO) high-burden countries, South Africa and neighboring Mozambique are the only two where TB incidence continues to rise.[3]

The female-to-male TB incidence ratio of 0.83 in South Africa is one of the highest in the world compared to 0.71 in Africa overall, 0.50 in South-East Asia, and 0.43 in Europe.[4] In southern Africa, human immunodeficiency virus (HIV) comorbidity accounts for over 30% of TB cases, and is the primary driver of the feminization of the TB epidemic.[5] HIV infection increases the likelihood of reactivation of latent tuberculous infection (LTBI) and the pace of disease progression.[6] Of all demographic groups, young women face the highest risk of HIV.[7] The disproportionate vulnerability of female-headed households to poverty, sex-based violence and HIV puts women at further risk for TB.[8–10]

We use retrospective National Health Laboratory Service (NHLS) data to examine how gender patterns in South Africa's TB epidemic vary across space, over time, and throughout the lifecycle. A major strength of this data set is its large size and the high coverage of patients presumed to have TB in South Africa. This is one of the first studies to use NHLS data to evaluate the epidemic at the national level and draw conclusions that apply to the country as a whole.

METHODS

We extracted data from the NHLS database on every TB test performed on patients aged 16–64 years in public health facilities for the period January 2009–December 2011, which includes 16 292 741 test records from 5 623 157 unique patients in 9656 health facilities. The data include unique patient identifiers created by the NHLS as well as information on the date, type of test performed, test result, testing facility location and basic patient demographics. We use data only from the first 2 months the patient appeared in the database to limit the sample to one diagnostic episode per patient and exclude treatment monitoring tests. TB-positive cases are based on the presence of at least one positive result

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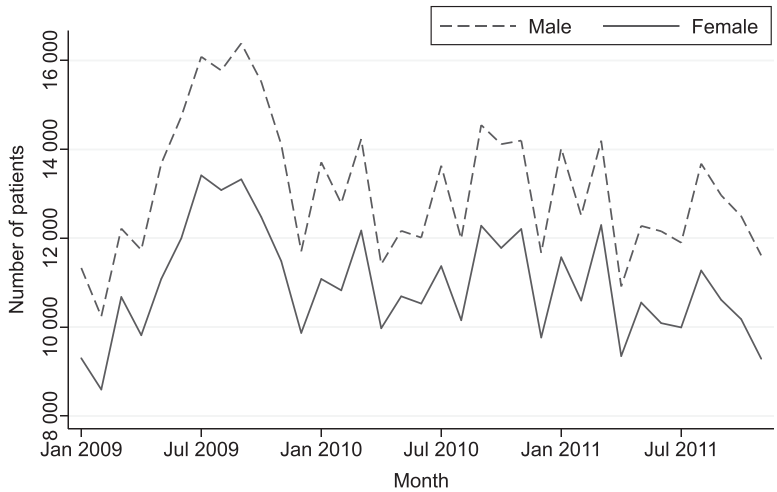

Figure 1 Number of TB cases by sex over time. TB = tuberculosis.

from smear microscopy, TB culture, polymerase chain reaction (PCR) test or the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA). For smear microscopy, we consider scanty positives of ⩾3 acid-fast bacilli (AFB) per 100 immersion fields as TB-positive based on the cut-off value used in practice. Severe TB is defined as 3+ positive (⩾100 AFB/10 immersion fields). We excluded 850 773 records (5.2% of the sample) that were missing either year of birth or sex. We also excluded KwaZulu-Natal from all analyses, as only a small fraction of tests performed in that province have been electronically captured. We examined patterns by province, the primary administrative and political unit in South Africa, and by health district, the single health authority responsible for primary health care under the decentralized political system.[11] There are 53 health districts in South Africa, with a median area of 15 307 km² and a median population of 750 000 residents.[12]

All analysis was performed using Stata 11 (Stata Corp, College Station, TX, USA). Smoothed curves were produced using locally weighted kernel regression. Ethics approval was obtained from the University of Michigan Institutional Review Board, Ann Arbor, MI, USA, and the University of Cape Town Faculty Ethics in Research Committee, Cape Town, South Africa.

RESULTS

The majority of the samples provided by patients with presumed TB consisted of sputum (93.7%); of these, 83.8% had at least one smear microscopy result, 28.6% had at least one culture result and 4.9% had at least one PCR-based test result. In the sample, 20.2% of the male patients and 13.6% of the female patients tested demonstrated evidence of TB.

The number of TB cases among patients tested in South Africa was relatively stable from 2009 to 2011,

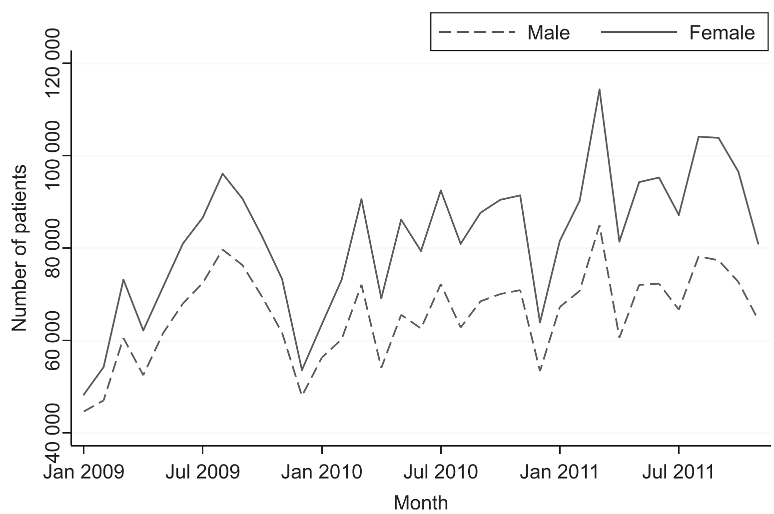

Figure 2 Number of patients with presumed TB by sex over time. TB = tuberculosis.

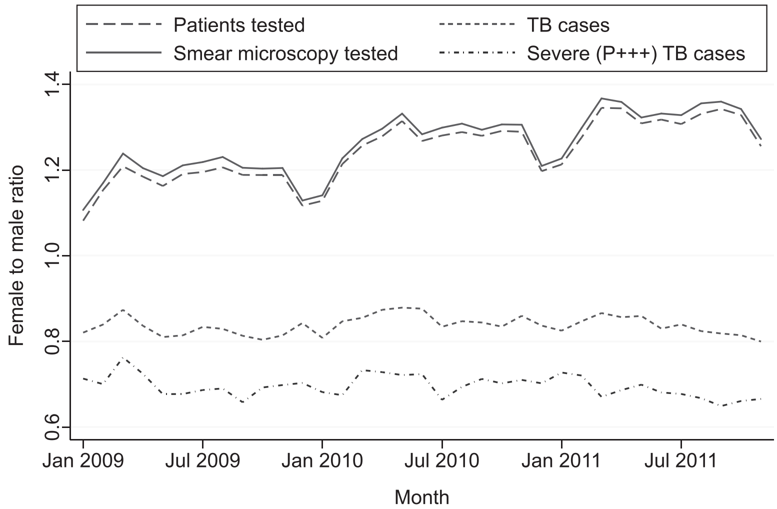

Figure 3 Female to male ratio of patients with presumed TB, patients who had at least one smear microscopy result (i.e., not culture, polymerase chain reaction, etc.), TB cases and 3+ positive (severe) TB cases over time. TB = tuberculosis.

apart from an increase in the winter of 2009 (Figure 1). There were approximately 13 000 male TB cases per month on average compared to 11 000 women; this sex gap remained consistent throughout the study period. The number of patients tested for TB rose over time from January 2010 onwards for both men and women (Figure 2). Despite the increase in the number of TB tests performed over the latter part of the study period, the number of TB-positive results remained relatively constant.

More female patients than male patients were tested for TB, and women accounted for an increasing proportion of patients with presumed TB over time (Figure 3). The female-to-male ratio of all patients tested for TB rose at a fairly constant rate over this period, from 1.20 in July 2009 to 1.31 in July 2011. The female-to-male ratio was fairly constant, at 0.84 for TB cases and 0.68 for 3+ positive (severe) TB cases, with a slight decrease in late 2011.

When we examine the data by health district and plot the district-level female TB rate (number of TB cases divided by the district female population) vs. the district-level male TB rate, we find a similar female-to-male ratio in each district (Figure 4). In 2011, the female TB rate was 70% of the male TB rate, and districts did not differ much from this overall ratio, regardless of the district-level TB rate ($R^2 = 0.95$). Even a flexible (semi-parametric) locally weighted regression line-of-fit that allows for non-linearities is virtually a straight line. This ratio increased from 68% in 2009 (not shown), reflecting an increasingly feminized epidemic.

The Table compares the population of patients with presumed TB and the population of TB cases with the general population by province. Column 3

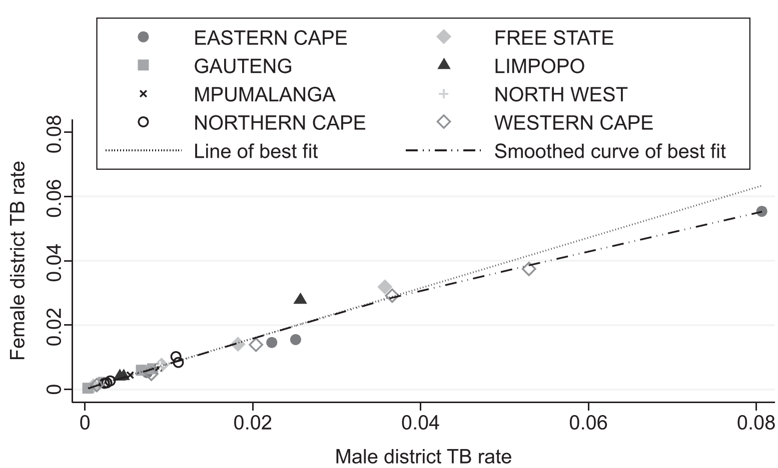

Figure 4 Female vs. male TB rate by health district with line and curve of best fit (KwaZulu-Natal excluded). TB = tuberculosis.

Table Provincial fraction of general population, patients with presumed TB and TB cases, proportion of female patients with presumed TB and TB cases (KwaZulu-Natal excluded from all calculations)

Province	Proportion of total population %	Proportion of patients with presumed TB %	Proportion of TB cases %	Proportion of females among patients with presumed TB %	Proportion of females among TB cases %
Eastern Cape	15.8	25.6	20.4	57.0	44.6
Free State	6.6	7.8	8.6	56.4	46.9
Gauteng	29.6	24.5	18.7	55.7	45.5
Limpopo	13.0	10.0	5.8	60.9	48.9
Mpumalanga	9.7	7.1	8.3	56.2	48.9
North West	8.5	7.9	8.7	55.6	46.3
Northern Cape	2.8	3.7	4.9	52.2	45.3
Western Cape	14.0	13.3	24.7	48.1	43.5

TB = tuberculosis.

shows that the greatest contribution to the national burden of TB cases comes from the Western Cape (24.7%), Eastern Cape (20.4%), and Gauteng (18.7%). Comparing columns 2 and 3 with column 1, it is clear that the Eastern Cape and Northern Cape account for a far greater fraction of patients with presumed TB and TB cases than the general population. The Western Cape accounts for a smaller fraction of patients with presumed TB than its general population, but a greater fraction of TB cases. The highest percentage of female patients with presumed TB comes from the eastern provinces, Eastern Cape and Limpopo, whereas the lowest comes from the western provinces of Northern Cape and Western Cape (column 4). The highest percentage of female TB cases comes from Limpopo and Mpumalanga Province (column 5). The Northern Cape and Western Cape have the lowest percentage of female patients, as does the Eastern Cape, despite its high percentage of female patients with presumed TB. (Appendix Table A* shows that these provincial patterns still hold if we disaggregate populations by sex).

The relatively constant sex ratio in TB rates over time obscures important differences in the sex gap throughout the lifecycle. For both sexes, a greater share of all TB cases occurs at a younger age (Figure 5). Peak TB prevalence in women occurs approximately 7 years earlier than in men, as is the case for HIV prevalence.[13–15] Among those aged <40 years, substantially more women than men are tested for TB; however, among those aged ⩾40 years, these rates are similar.

Figure 6 shows the female-to-male ratio of patients with presumed TB and of TB cases over the lifespan to examine differences between the curves in Figure 5. Among those aged <30 years, the female-to-male ratio of patients tested for TB and those with at least one smear microscopy test are identical; however, at older ages, women are slightly better represented among smear microscopy patients relative to all tests. The proportion of TB cases and 3+ positive (severe) cases who are female decreases rapidly between ages 25 and 35 years, and continues to fall slightly after the female-to-male ratio of patients with presumed TB has leveled off.

DISCUSSION

Between 2009 and 2011, the number of TB cases remained relatively constant for both men and women, while the number of patients with presumed TB rose for both sexes. This could be due to an increase in routine or follow-up TB testing, accompanied by increased funding for TB programs or the introduction of new testing technology. Funding for TB-HIV programs through the South African Department of Health and the President's Emergency Plan For AIDS Relief increased during the period of the study.[16,17] Xpert testing capabilities were piloted in March 2011 and rolled out later that year.[18] It could also be due to reduced TB rates among patients with presumed TB. There are generally higher female-to-male ratios of patients tested for TB and TB cases in the eastern than in the western provinces; however, the national female-to-male TB rate ratio of 0.70 holds when we disaggregate the data by health district. The age profile by sex for TB resembles the age profile for HIV, in that the highest rates for women occur at a younger age than for men. With increased age, the female-to-male ratio among TB cases declines at a faster rate than for patients with presumed TB (Figure 6). This can be partially attributed to mortality among those who are most at risk for TB. If women have poorer treatment and mortality outcomes and are under-represented in the sex ratios at older ages, then our analysis underestimates the female burden of TB. Given that TB is the leading cause of death in South Africa, the effect of mortality on our results is likely to be considerable.

The age-driven sex patterns observed in the data are likely explained by the HIV epidemic and risks

* The appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2015/00000019/00000001/art00019

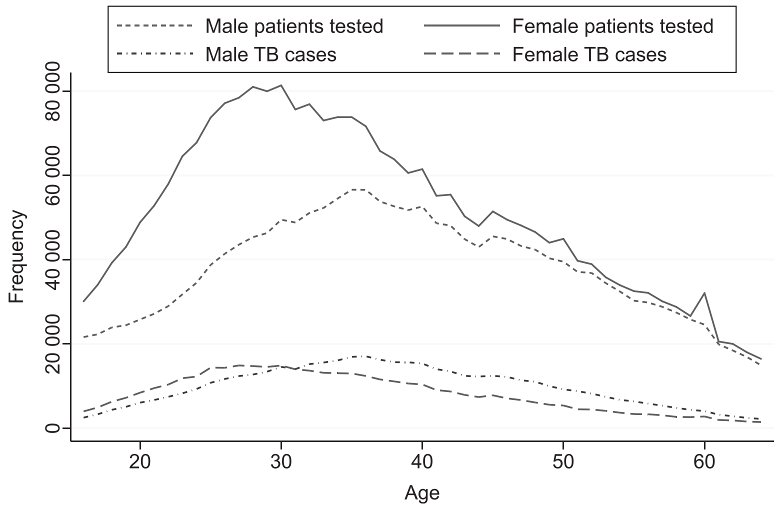

Figure 5 Age at initial TB test for patients with presumed TB and TB cases by sex. TB = tuberculosis.

associated with pregnancy and childbearing. The HIV epidemic has a sex-age profile similar to that of the TB age profile (Figure 5), due not only to the synergistic interactions between the diseases, but also to the myriad poverty-related risk factors that are common to both diseases.[9] Female HIV rates are almost twice as high as male rates in the 20–25 years age group, and peak 5–7 years earlier, dramatically increasing the risk of TB disease among young women.[6,14] HIV not only increases TB incidence among younger women, it also makes co-infection more difficult to diagnose due to the paucibacillary nature of HIV-associated TB.[19]

Even in low- and pre-HIV settings, the highest TB rates for women coincide with the prime childbearing years.[20] However, there is conflicting evidence on whether pregnancy causes tuberculous infection to progress to active disease.[21–24] The likelihood of reactivation of LTBI and the pace of disease progression may be influenced by the immune suppression and suppression reversal responses associated with pregnancy.[25] More research is needed on the mechanisms through which childbearing and child rearing lead to increased exposure and susceptibility to TB.

In South Africa, disparities in patient delay (access to health care) and provider delay (index of suspicion) between men and women are likely to be less important in explaining sex disparities than what has been documented in many Asian countries.[26,27] In the case of HIV, patient delays are shorter for women, as they have multiple interactions with the health care system for free maternal and child health care and are less encumbered by stigma.[27] More frequent use of

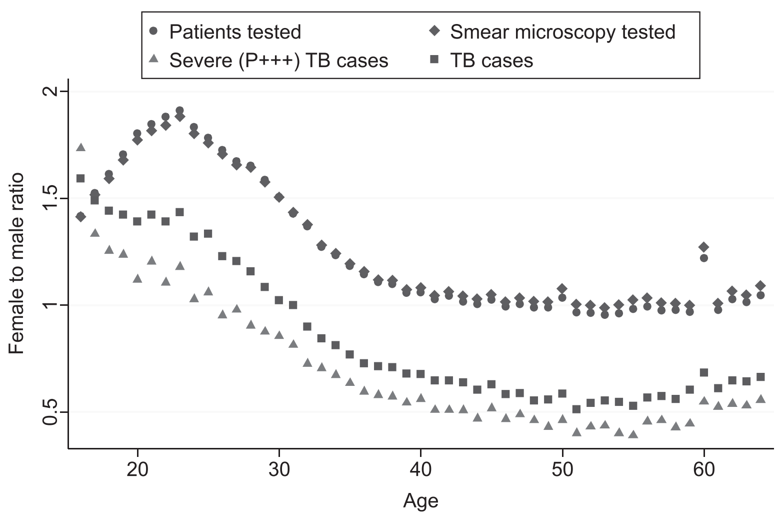

Figure 6 Female-to-male ratio of patients with presumed TB, patients who had at least one smear microscopy result, TB cases and 3+ positive (severe) TB cases throughout the lifecycle. TB = tuberculosis.

health care for any reason may lead to improved detection of TB cases if TB symptoms are evident during the provider visit.[20]

The data used in this study represent passive case finding of patients who were identified by a health care provider as having presumed TB when they encountered the health care system due to TB symptoms or other health concerns. Pregnant women and mothers of small children, who have more routine health appointments where they may be identified as having presumed TB, are likely to be over-represented in the data. False matches between records linked with a unique identification number are highly unlikely, as patient name is used in linking records. Although missed matches may occur, our results appear robust to this issue as the majority of patients only experience a single diagnostic episode. The majority of the test results for the province of KwaZulu-Natal are not available, as they have not been electronically captured; this province was thus excluded from the analysis, and approximately 5% of the sample has missing sex or age data. These limitations are outweighed by the large size and overall high quality of the test result data.

Our results point to two health policies that have the potential to address the high rates of TB among young women: increased TB screening during pre- and post-natal health care visits, and improved TB-HIV integration. The South African Department of Health has designated pregnant women as a ‘key population’ for HIV and TB prevention and recommended that all HIV-positive pregnant women be screened for TB.[28] Increased provision of WHO-recommended isoniazid preventive therapy for HIV-positive pregnant women would mitigate susceptibility effects during pregnancy.[29–31] Generally, women are only tested if they exhibit TB symptoms.[32,33] Strong leadership is required to address barriers to the integration of TB, antenatal, HIV, and prevention of mother to child transmission services, such as an inadequate supply of skilled workers, poor diagnostic tools, poor supervision, and under-resourced service delivery mechanisms.[34–37]

CONCLUSION

TB remains the leading cause of death in South Africa and a major non-obstetric cause of maternal mortality.[2,37] The illness and deaths of young women threaten the well being of households and families, increase the risk of transmission to children and undermine the South African government’s stated commitment to serving vulnerable populations.[38,39] Increasing the quality and quantity of active TB case finding at existing points of care would be a sustainable and cost-effective intervention for both treatment and prevention. The TB epidemic demands not only ‘urgent and sustained intervention’, but also targeted interventions that maximize limited public health resources to save the most lives possible.[14]

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Conflicts of interest: none declared.

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APPENDIX

Table A. Provincial fraction of general population, patients with presumed TB and TB cases disaggregated by sex (KwaZulu-Natal excluded from all calculations)

	Proportion of total population		Proportion of patients with suspected TB		Proportion of TB cases	
Province	Female %	Male %	Female %	Male %	Female %	Male %
Eastern Cape	16.4	15.2	26.3	24.7	20.0	20.7
Free State	6.7	6.6	7.9	7.6	8.8	8.3
Gauteng	28.6	30.5	24.6	24.4	18.7	18.7
Limpopo	13.8	12.2	11.0	8.8	6.2	5.4
Mpumalanga	9.7	9.7	7.2	7.0	9.0	7.8
North West	8.1	8.8	8.0	7.9	8.8	8.5
Northern Cape	2.7	2.8	3.5	4.0	4.8	4.9
Western Cape	14.0	14.1	11.6	15.6	23.6	25.6

TB = tuberculosis.

RESUME

CONTEXTE : En Afrique du Sud, la tuberculose (TB) a été la première cause de décès pendant plus d'une décennie. En matière d'incidence de la TB, l'Afrique du Sud est au deuxième rang dans le monde et l'incidence continue à augmenter.

OBJECTIF : Examiner les profils de l'épidémie de TB en Afrique du Sud en fonction du sexe. C'est l'une des premières études qui a utilisé les données des services du laboratoire national de santé (NHLS) afin d'évaluer l'épidémie au niveau national.

SCHÉMA : Etude d'observation utilisant les données rétrospectives du NHLS comportant tous les tests relatifs à la TB réalisés dans les structures de santé publique entre 2009 et 2011.

RÉSULTATS : Malgré l'augmentation du nombre de tests de TB réalisés, le nombre de cas de TB est resté relativement constant. Bien que la prévalence diffère d'un district de santé à un autre, nous avons trouvé un rapport femme/homme similaire, de 0,70, dans chaque district. Le profil d'âge de la TB ressemble à celui du virus de l'immunodéficience humaine (VIH), avec un pic de prévalence survenant chez les femmes 7 ans plus tôt que chez les hommes. Le rapport de cas de TB femmes/hommes et la proportion des cas très graves 3+ diminuent rapidement entre l'âge de 25 et de 35 ans.

CONCLUSION : Ces profils d'âge et de sexe sont liés à l'épidémie de VIH et aux risques associés à la grossesse et à l'accouchement. Augmenter la qualité et la quantité du dépistage actif des cas de TB dans les structures de soins existantes serait une intervention pérennisable et rentable à la fois en termes de traitement et de prévention.

RESUMEN

MARCO DE REFERENCIA: En Suráfrica, la tuberculosis (TB) ha sido la principal causa de muerte durante más de un decenio. La tasa de incidencia de TB del país ocupa el segundo lugar mundial y continúa aumentando.

OBJETIVO: Examinar la evolución de la epidemia de TB en función del sexo en Suráfrica. Este es uno de los primeros estudios que utiliza los datos del Laboratorio del Servicio Nacional de Salud (NHLS) con el fin de evaluar la epidemia a escala nacional.

MÉTODO: Se llevó a cabo un estudio de observación retrospectivo a partir de los datos del NHLS sobre todas las pruebas diagnósticas de TB realizadas en los establecimientos de salud pública entre el 2009 y el 2011.

RESULTADOS: Pese al aumento de la cantidad de pruebas diagnósticas de TB realizadas, el número de casos de TB permaneció relativamente constante. Si bien las tasas de prevalencia varían en los diferentes distritos de salud, se observó una proporción entre hombres y mujeres de 0,70 en todos los distritos. La distribución por edades de los casos de TB corresponde al perfil observado en los casos de infección por el virus de la inmunodeficiencia humana (VIH) y la prevalencia máxima de TB en las mujeres ocurre 7 años antes que en los hombres. El cociente entre mujeres y hombres de los casos de TB y de TB grave (baciloscopia 3+) disminuye rápidamente entre los 25 y los 35 años de edad.

CONCLUSIÓN: La distribución de los casos de TB en función del sexo y la edad se explica por la epidemia de infección por el VIH y los riesgos asociados con el embarazo y la maternidad. Una intervención que mejore la calidad e intensifique las actividades de búsqueda activa de casos en los centros de atención sanitaria existentes sería sostenible y rentable y mejoraría el tratamiento y la prevención de la TB.