Nationwide and regional incidence of microbiologically confirmed pulmonary tuberculosis in South Africa, 2004–12: a time series analysis

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Summary

Background South Africa has the highest incidence of tuberculosis in the world, largely resulting from a high population prevalence of HIV infection. We investigated the incidence of microbiologically confirmed pulmonary tuberculosis, and new cases of pulmonary tuberculosis registered for treatment, nationally and provincially in South Africa from 2004 to 2012, during which time there were changes in antiretroviral therapy (ART) coverage among individuals with HIV infection.

Methods We identified cases of microbiologically confirmed pulmonary tuberculosis from 2004 to 2012 from the National Health Laboratory Service Corporate Data Warehouse. New cases registered for treatment were identified from National Department of Health electronic registries. A time series analysis, using autoregressive models, was undertaken on incidence of microbiologically confirmed pulmonary disease nationally and provincially; this trend was also examined relative to ART coverage of adults with HIV infection.

Findings During the 9-year period, 3 523 371 cases of microbiologically confirmed pulmonary tuberculosis were recorded nationally. Annual incidence (per 100 000 population) increased from 650 (95% CI 648–652) in 2004 to 848 (845–850) in 2008, declining to 774 (771–776) by 2012 (9% decrease from 2008 to 2012). Incidence varied by age-group, sex, and province. There was an inverse association between incidence of microbiologically confirmed disease and ART coverage among HIV-infected individuals nationally and provincially. Trends in incidence of tuberculosis cases registered for treatment mirrored those of microbiologically confirmed cases nationally and provincially; however, incidence of microbiologically confirmed cases was consistently higher than cases registered for treatment nationally and in seven of nine provinces.

Interpretation Since its peak in 2008, the incidence of microbiologically confirmed pulmonary tuberculosis in South Africa had declined by 2012; this decline is associated with an increase in ART coverage. Future integration of registries for microbiologically confirmed cases and new cases registered for treatment would improve the assessment of the burden of pulmonary tuberculosis in South Africa.

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Introduction

South Africa has the highest annual incidence of tuberculosis per head, with WHO estimating 400 000 new cases in South Africa during 2012, the third highest absolute number of new cases worldwide.[1,2] Robust tuberculosis surveillance data are needed to assess the effect of new or improved interventions such as diagnostic assays, enhanced case-detection programmes, isoniazid preventive therapy (IPT), and expansion of antiretroviral therapy (ART) to individuals with HIV infection.[3,4]

Despite the high incidence of tuberculosis in South Africa, uncertainties remain about the accuracy of these estimates. A national evaluation of microbiologically confirmed pulmonary disease could be used to determine the veracity of incidence imputed from cases registered for tuberculosis treatment on the electronic TB databases (ETD) in South Africa. This analysis has not been previously undertaken, however, despite centralisation of tuberculosis microbiology testing in the public sector through the National Health Laboratory Service (NHLS). Longitudinal evaluation of the incidence of microbiologically confirmed pulmonary tuberculosis in South Africa, where the population prevalence of HIV infection is 18% and 70% of people with tuberculosis are HIV-infected, can also inform whether a temporal association exists between trends in incidence of microbiologically confirmed cases and increased access of HIV-infected individuals to ART.[3]

We undertook a time series analysis of new cases of microbiologically confirmed pulmonary tuberculosis and new cases of pulmonary tuberculosis registered for treatment in South Africa from 2004 to 2012, to identify trends in national and provincial incidence, in relation to the population prevalence of HIV and ART coverage in HIV-infected individuals.

Methods

Sources of data

In South Africa, there are three national sources of tuberculosis data: the NHLS Corporate Data

Warehouse (CDW); and the National Department of Health's Electronic TB Register (ETR) and Electronic Drug Resistance Register (EDR), together forming what is referred to as the ETD. The usefulness of CDW as a source of data for tuberculosis surveillance has been recognised.[5] CDW is managed by the NHLS, the sole laboratory service provider for all public health facilities in South Africa (which serve 84% of the population) and also serves private-sector patients with tuberculosis that are routinely managed through state health services.[6]

Data for all respiratory samples submitted to the NHLS for tuberculosis testing were identified from CDW and unique, patient-level data generated. The absence of unique patient identifiers required a series of record-linking processes to match multiple specimen

	2004	2005	2006	2007	2008	2009	2010	2011	2012
South Africa*									
Number	305 567	344 106	383 784	394 061	420 131	417 386	421 838	431 958	404 540
Incidence	650 (648–652)	722 (720–725)	795 (793–798)	806 (803–808)	848 (845–850)	831 (829–834)	829 (826–831)	837 (835–840)	774 (771–776)
Year-on-year change	..	11%	10%	1%	5%	–2%	0%	1%	–8%
South Africa (excluding KwaZulu-Natal)									
Number	238 932	265 111	294 313	295 783	318 058	307 826	300 727	298 135	282 629
Incidence	637 (635–640)	697 (695–700)	763 (761–766)	757 (754–759)	802 (800–805)	766 (763–768)	738 (735–740)	721 (719–724)	674 (672–677)
Year-on-year change	..	9%	9%	–1%	6%	–5%	–4%	–2%	–7%
Eastern Cape									
Number	45 573	50 383	59 568	62 022	74 398	71 183	70 871	73 020	72 101
Incidence	719 (712–725)	791 (784–798)	931 (923–938)	964 (957–972)	1152 (1143–1160)	1097 (1089–1105)	1087 (1079–1095)	1114 (1106–1122)	1095 (1087–1103)
Year-on-year change	..	10%	18%	4%	19%	–5%	–1%	3%	–2%
Free State									
Number	17 773	18 003	19 291	19 030	20 763	19 918	19 804	18 965	18 725
Incidence	652 (642–662)	660 (650–670)	707 (697–717)	697 (687–707)	759 (749–770)	728 (718–738)	723 (713–733)	691 (681–701)	681 (672–691)
Year-on-year change	..	1%	7%	–1%	9%	–4%	–1%	–4%	–1%
Gauteng									
Number	56 255	70 133	72 537	69 435	71 944	68 904	69 031	66 586	58 108
Incidence	536 (531–540)	654 (649–658)	662 (657–666)	620 (615–624)	629 (624–633)	589 (585–594)	578 (574–582)	546 (542–550)	466 (462–470)
Year-on-year change	..	22%	1%	–6%	1%	–6%	–2%	–6%	–15%
KwaZulu-Natal*									
Number	66 635	78 995	89 471	98 278	102 073	109 560	121 111	133 823	121 911
Incidence	700 (695–705)	822 (816–827)	921 (915–927)	1001 (995–1007)	1029 (1023–1035)	1093 (1087–1100)	1196 (1189–1202)	1307 (1300–1314)	1178 (1172–1185)
Year-on-year change	..	17%	12%	9%	3%	6%	9%	9%	–10%
Limpopo									
Number	9910	12 386	15 511	18 016	21 228	22 360	21 780	21 938	22 499
Incidence	200 (196–204)	247 (242–251)	305 (300–310)	350 (345–356)	408 (403–414)	425 (419–431)	409 (404–415)	407 (402–413)	413 (407–418)
Year-on-year change	..	24%	24%	15%	16%	4%	–4%	0%	1%
Mpumalanga									
Number	17 537	17 849	20 545	23 840	28 114	30 026	25 850	27 570	26 207
Incidence	479 (472–486)	481 (474–488)	546 (539–554)	625 (617–633)	727 (719–736)	766 (758–775)	651 (643–659)	685 (677–694)	643 (635–651)
Year-on-year change	..	0	14%	14%	16%	5%	–15%	5%	–6%
North West									
Number	16 571	24 614	27 435	25 434	26 376	24 741	24 248	21 731	21 181
Incidence	521 (513–529)	764 (754–773)	840 (830–850)	768 (759–778)	786 (777–796)	727 (718–736)	703 (694–712)	621 (613–630)	597 (589–605)
Year-on-year change	..	47%	10%	–9%	2%	–7%	–3%	–12%	–4%

(Table 1 continues on next page)

	2004	2005	2006	2007	2008	2009	2010	2011	2012
(Continued from previous page)									
Northern Cape									
Number	12 889	13 684	13 931	12 835	13 345	13 243	12 838	13 417	11 580
Incidence	1199 (1178–1219)	1261 (1240–1282)	1273 (1252–1294)	1162 (1142–1182)	1198 (1177–1218)	1178 (1158–1198)	1133 (1113–1152)	1174 (1154–1194)	1004 (986–1023)
Year-on-year change	..	5%	1%	−9%	3%	−2%	−4%	4%	−14%
Western Cape									
Number	62 424	58 059	65 495	65 171	61 890	57 451	56 305	54 908	52 228
Incidence	1236 (1226–1246)	1127 (1118–1136)	1246 (1237–1256)	1216 (1207–1225)	1132 (1123–1141)	1031 (1022–1039)	991 (983–999)	948 (940–956)	885 (877–892)
Year-on-year change	..	−9%	11%	−2%	−7%	−9%	−4%	−4%	−7%

Incidence is reported per 100 000 population with corresponding 95% CIs shown in parentheses. *Table includes incidence estimates imputed for KwaZulu-Natal province from 2004 up to 2010 (because data for the province during this period were incomplete).

***Table 1*: Number and incidence of microbiologically confirmed pulmonary tuberculosis cases from 2004 to 2012 in South Africa and in each of the nine provinces**

See Online for appendix

records to individual patients as detailed in the appendix.

We defined a case of microbiologically confirmed pulmonary tuberculosis as any case with at least one auramine smear-positive sample on microscopy, culture of *Mycobacterium tuberculosis*, or identification of *M tuberculosis* by Xpert MTB/Rif (Cepheid, Sunnyvale, CA, USA), from respiratory secretion samples (all ages) or from gastric washings in children. Details of types of *M tuberculosis* diagnostic assays used at NHLS between 2004 and 2012 are provided in the appendix.

Because individuals could have been tested for tuberculosis several times for the same episode of illness, including multiple samples sent for tuberculosis programme monitoring requirements, or visits to different health facilities, a conservative 24-month interval was applied to distinguish new cases from preceding episodes or cases currently under treatment and follow-up.

The ETR and EDR are maintained by the national Department of Health to register and track the progress of individuals initiated on treatment for susceptible and drug-resistant tuberculosis, respectively. Data for new cases of pulmonary tuberculosis recorded in the EDR for the same period were extracted and combined with the ETR data to derive data for new cases of tuberculosis registered for treatment. The appendix includes a description of the data processing for this dataset.

We used annual mid-year population estimates to calculate incidence of pulmonary tuberculosis by province, age, and sex.[7] These estimates are based on government census data gathered every 5 years, with imputation of denominator data for the interim years. HIV prevalence and ART coverage over the relevant years are based on the Actuarial Sciences of South Africa AIDS and demographic model (detailed in the appendix), which is the only available source of ART data covering the total period of our study and is similar to other sources of data.[8,9]

Statistical analysis

We investigated autoregressive and non-linear models to estimate trends in incidence of pulmonary tuberculosis, and selected the autoregressive models (up to 12th order) on the basis of fit. Each model was fitted to provincial and national data, excluding KwaZulu-Natal where data was only available for 2011 and 2012, because the laboratory system was largely paper-based in this province before 2011. We used data from the three provinces bordering KwaZulu-Natal, as well as available data for 2011 and 2012 for the province, to model incidence of microbiologically confirmed tuberculosis for KwaZulu-Natal for 2004 to 2010. The final models and details regarding model selection are provided in the appendix.

Annual incidence rates and the estimated structural portion of the model were plotted over time to assess the trends in tuberculosis at national, provincial, and age-group levels. To examine the association between ART and HIV infection with tuberculosis, model estimates for annual incidence of microbiologically confirmed pulmonary tuberculosis and HIV/ART rates are plotted against time.

We used descriptive statistics to cross-tabulate, characterise, and compare groups. All data management and descriptive statistics were undertaken with Stata MP version 13.0. We used SAS/STAT software version 9.3 for all trend analyses.

Role of the funding source

Employees of the funder of the study were involved in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 3 523 371 cases of microbiologically confirmed pulmonary tuberculosis during the 9-year

period, nationally. Annual incidence (per 100 000 population) increased from 650 (95% CI 648–652) in 2004, peaked at 848 (845–850) in 2008, and subsequently declined to 774 (771–776) by 2012 (9% decrease from 2008 to 2012; table 1, figure 1). There was a 10–11% year-on-year increase in incidence of microbiologically confirmed tuberculosis, nationally, from 2004 until 2006, and a further 5% increase from 2007 to 2008 (table 1). Thereafter, incidence declined with an 8% decrease between 2011 and 2012 (table 1). Excluding KwaZulu-Natal province, for which only imputed incidence data were available from 2004 to 2010, more consistent decreases in national incidence were noted, from a peak of 802 per 100 000 population in 2008, falling to 674 per 100 000 population by 2012 (table 1). During the period of this analysis, testing rates increased nationally and provincially in South Africa. Nationally (excluding KwaZulu-Natal province), the rate of testing for pulmonary tuberculosis (per 100 000 population) increased from 2926 in 2004, peaked at 6403 in 2011, and subsequently fell to 5616 by 2012 (appendix). Sensitivity analysis using a 12-month interval showed a less than 5% difference in incidence of microbiologically confirmed pulmonary tuberculosis (appendix); therefore, all data reported uses the 24-month interval.

The median age for cases of microbiologically confirmed pulmonary tuberculosis was 35 years (IQR 28–45): 33 years (26–42) in females and 38 years (30–46) in males. Throughout the 9 years, the highest to lowest rank order of age groups for incidence of microbiologically confirmed disease was 25–44 years, 45–64 years, 65 years or older, 15–24 years, and younger than 15 years in males, and 25–44 years, 15–24 years, 45–64 years, younger than 15 years, and 65 years or older in females (table 2). The age-group rank order of incidence of microbiologically confirmed disease was similar to the age-group rank order of HIV prevalence, which was 19–21%, 12–13%, 1–2%, 2–4%, and 2–3% in the corresponding age-groups for males and 23–28%, 12–15%, 4–9%, 2–3%, and <1% for females, respectively (table 2). Trends in incidence of microbiologically confirmed pulmonary tuberculosis were evident nationally and provincially and were similar across all age groups, increasing from 2004 to 2008, with declines seen until 2012 (figure 2). Overall, 54% of cases occurred in males. The incidence was greater among females than in males in the younger than 15 years and 15–24-year age groups, while being greater among males in older age-groups, especially in those aged 45–64 years (table 2). This trend was mirrored by a higher population prevalence of HIV infection in women than men in the 15–24-year age group; and vice versa in those aged 45–64 years.

To explore a possible explanation for the reported trend in microbiologically confirmed pulmonary tuberculosis, we examined the trend in HIV infection and ART coverage over the study period. Incidence of microbiologically confirmed cases peaked in 2008 and subsequently declined as the rate of HIV-infected individuals on ART increased (initially from 10–107 per 1000 between 2004 and 2008, followed by a sharper increase to 278 per 1000 by 2012; figure 1, table 3). The decline in incidence of microbiologically confirmed disease from 2008 onwards occurred despite a continuing increase in the number of individuals with HIV infection from 2008 to 2012 (table 3).

In examining the percentage change in slope of ART coverage (per 1000 population with HIV infection) between consecutive 2-year periods, the largest increases were between 2004–05 and 2005–06 (albeit from a low baseline) and subsequently between 2007–08 and 2008–09, which coincided with the national ART roll-out programme (appendix). The largest reductions in incidence of microbiologically confirmed pulmonary tuberculosis nationally occurred in 2009 (2%; about 4 years after the largest increases in percentage change in slope of ART coverage), and in 2012 (8%).

Annual incidence (per 100 000 population) of microbiologically confirmed pulmonary tuberculosis differed between the nine provinces, exceeding 1000 in Northern Cape (2004–12), Western Cape (2004–09), Eastern Cape (2008–12), and KwaZulu-Natal (2007–12; table 1, figure 1). Between 2004 and 2012, KwaZulu-Natal had the highest annual number of new cases, peaking at 133 823 in 2011. This number represented 31% of pulmonary tuberculosis cases in South Africa that year (table 1), from a province constituting 20% of the South African population.[7]

Western Cape was the first province in which incidence of microbiologically confirmed pulmonary tuberculosis started decreasing, with a 4–9% year-on-year decline from 2007 (1216 per 100 000 population) until 2012 (885 per 100 000 population; table 1, figure 2). Conversely, the incidence in the neighbouring Eastern Cape increased steadily by between 4% and 19% year-on-year from 2004 (719 per 100 000 population) until 2008 (1152 per 100 000 population), and remained relatively unchanged thereafter until 2012 (1095 per 100 000 population). In Gauteng, which constitutes 24% of the South African population, incidence of microbiologically confirmed disease was stable from 2005 to 2008 (620–662 per 100 000 population), and decreased by 2–6% year-on-year from 2008 to 2011, and by 15% between 2011 (546 per 100 000 population) and 2012 (466 per 100 000 population).[7]

Similar to the national trend, the decline in incidence of microbiologically confirmed pulmonary tuberculosis in provinces such as Gauteng, North West, Northern Cape, and Western Cape occurred despite an increase in the rate of people tested for the disease (appendix), and an increase in the total number of tests undertaken (appendix). Provincial trends in incidence of microbiologically confirmed disease coincided with ART programme expansion in the respective provinces, with earlier peaks in microbiologically confirmed tuberculosis in provinces with earlier increases in ART coverage (figure 1).

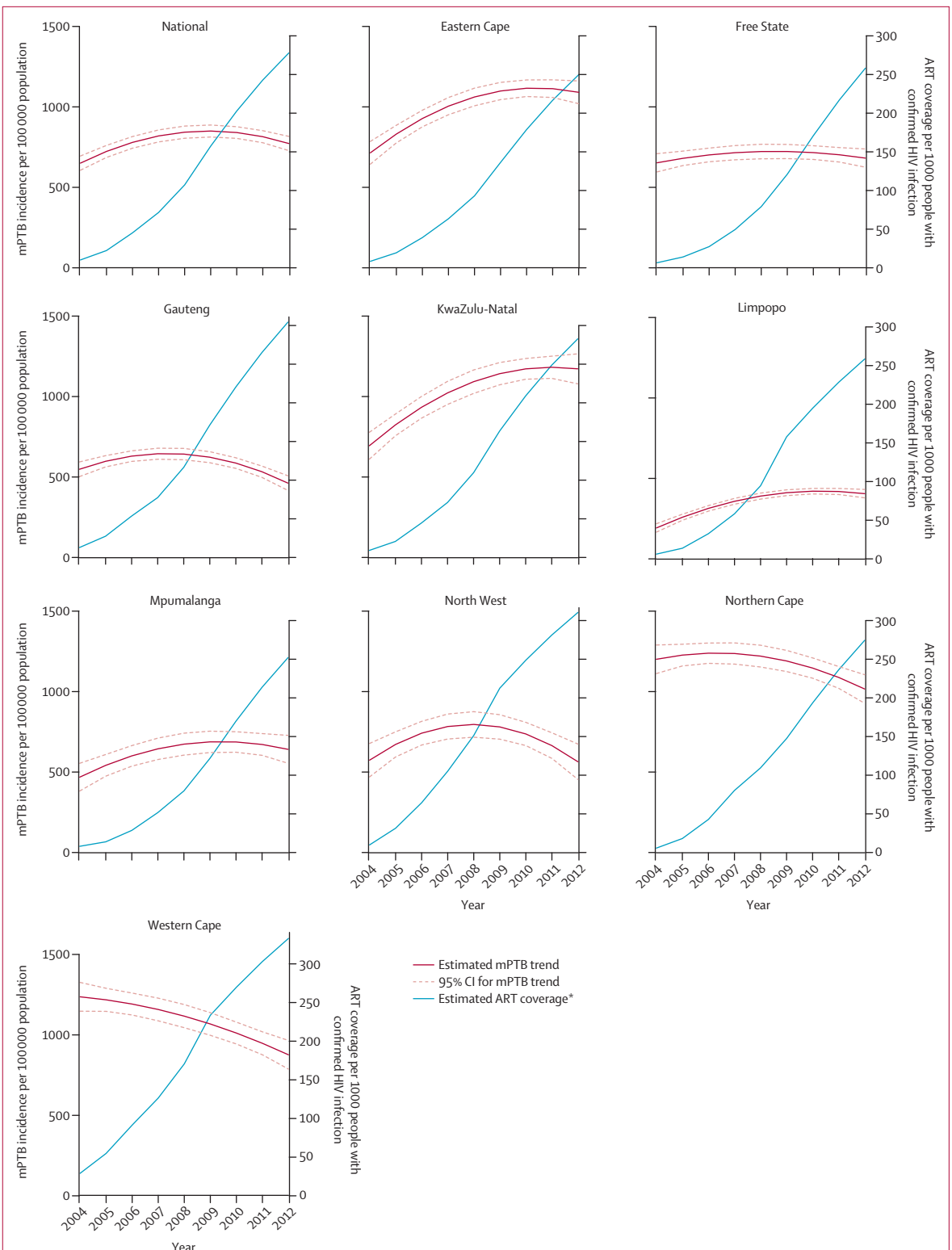

***Figure 1*: Incidence of microbiologically confirmed pulmonary tuberculosis (per 100 000 population) and ART coverage rates in people with HIV infection in South Africa, nationally and provincially, from 2004 to 2012**

*Based on data from the Actuarial Society of South Africa 2008 model.[8] ART=antiretroviral therapy. mPTB=microbiologically confirmed pulmonary tuberculosis.

	<15 years			15–24 years			25–44 years			45–64 years			≥65 years		
	HIV prevalence, n (%)	Number of people with mPTB	mPTB incidence	HIV prevalence, n (%)	Number of people with mPTB	mPTB incidence	HIV prevalence, n (%)	Number of people with mPTB	mPTB incidence	HIV prevalence, n (%)	Number of people with mPTB	mPTB incidence	HIV prevalence, n (%)	Number of people with mPTB	mPTB incidence
Male															
2004	156 426 (2%)	3130	40 (39–42)	171 569 (4%)	17 747	388 (382–394)	1 372 387 (21%)	91 868	1374 (1365–1383)	348 200 (12%)	37 568	1262 (1249–1275)	2958 (<1%)	3759	518 (501–534)
2005	171 241 (2%)	4025	52 (50–53)	163 511 (3%)	18 997	409 (403–415)	1 400 222 (21%)	95 886	1408 (1399–1417)	375 069 (12%)	40 166	1312 (1300–1325)	4204 (<1%)	4370	581 (564–598)
2006	185 028 (2%)	4001	51 (50–53)	152 244 (3%)	19 829	420 (414–426)	1 413 899 (21%)	104 320	1503 (1494–1512)	395 382 (12%)	44 507	1414 (1401–1427)	5687 (1%)	4879	628 (611–646)
2007	198 076 (3%)	4957	64 (62–65)	139 463 (3%)	19 526	408 (402–413)	1 419 245 (21%)	104 618	1477 (1468–1485)	410 896 (13%)	46 531	1438 (1425–1451)	7411 (1%)	5189	648 (630–665)
2008	207 724 (3%)	5513	71 (69–73)	125 302 (3%)	19 599	403 (397–409)	1 415 028 (20%)	109 868	1517 (1509–1526)	421 818 (13%)	49 381	1484 (1471–1497)	9354 (1%)	5646	684 (667–702)
2009	217 378 (3%)	5270	68 (66–70)	112 571 (2%)	20 042	406 (401–412)	1 411 973 (20%)	108 519	1465 (1457–1474)	432 648 (13%)	49 760	1456 (1443–1468)	11 664 (1%)	5670	667 (650–685)
2010	225 793 (3%)	5152	66 (65–68)	102 660 (2%)	19 373	387 (382–393)	1 413 503 (20%)	104 980	1386 (1378–1394)	444 998 (13%)	47 957	1367 (1355–1,379)	14 495 (2%)	5601	640 (623–656)
2011	232 508 (3%)	5107	66 (64–68)	95 686 (2%)	19 006	376 (371–382)	1 415 507 (19%)	102 625	1321 (1312–1329)	456 641 (13%)	47 276	1315 (1303–1327)	17 837 (2%)	5552	614 (597–630)
2012	237 326 (3%)	4718	61 (59–63)	92 922 (2%)	18 363	360 (355–366)	1 418 938 (19%)	100 205	1256 (1248–1264)	467 147 (13%)	45 302	1230 (1219–1241)	21 630 (2%)	5549	592 (576–607)
Female															
2004	155 688 (2%)	3899	51 (49–52)	737 113 (15%)	25 917	548 (541–554)	1 605 178 (23%)	64 288	902 (895–909)	134 161 (4%)	16 020	460 (453–467)	216 (<1%)	2484	193 (186–201)
2005	170 444 (2%)	5034	65 (64–67)	746 449 (15%)	28 611	601 (594–608)	1 687 618 (24%)	74 293	1029 (1021–1036)	162 894 (4%)	19 530	544 (537–552)	330 (<1%)	3088	232 (224–240)
2006	184 182 (2%)	5086	66 (64–68)	745 553 (15%)	30 030	626 (619–633)	1 758 506 (25%)	84 280	1151 (1143–1159)	193 048 (5%)	23 612	639 (631–647)	487 (<1%)	3705	268 (260–277)
2007	197 127 (3%)	5807	75 (73–77)	737 401 (15%)	30 027	621 (614–628)	1 827 920 (25%)	86 981	1171 (1163–1178)	225 319 (6%)	25 315	665 (657–674)	702 (<1%)	3942	276 (267–284)
2008	206 756 (3%)	6229	81 (79–83)	717 737 (15%)	30 727	631 (624–638)	1 889 013 (26%)	94 543	1252 (1244–1260)	257 804 (6%)	28 212	721 (713–730)	986 (<1%)	4463	302 (293–311)
2009	216 391 (3%)	6356	82 (80–84)	693 367 (14%)	30 540	623 (616–630)	1 952 020 (26%)	92 976	1210 (1203–1218)	291 822 (7%)	28 620	712 (704–721)	1376 (<1%)	4803	314 (305–323)
2010	224 794 (3%)	5991	78 (76–80)	666 964 (13%)	29 608	600 (593–607)	2 016 064 (27%)	91 943	1176 (1169–1184)	326 955 (8%)	28 538	693 (685–701)	1913 (<1%)	4953	313 (304–321)
2011	231 510 (3%)	5900	77 (75–79)	638 814 (13%)	28 065	563 (556–569)	2 079 147 (27%)	88 939	1120 (1113–1127)	362 174 (8%)	28 180	668 (661–676)	2643 (<1%)	4955	302 (293–310)
2012	236 316 (3%)	5268	68 (67–70)	614 650 (12%)	26 194	520 (514–526)	2 137 620 (28%)	80 903	1002 (995–1009)	396 514 (9%)	25 549	593 (585–600)	3604 (<1%)	4776	281 (273–289)

Incidence of mPTB per 100 000 population with 95% CIs in parentheses. mPTB=microbiologically confirmed pulmonary tuberculosis.

***Table 2*: Age-group specific incidence of microbiologically confirmed pulmonary tuberculosis by sex in South Africa from 2004 to 2012**

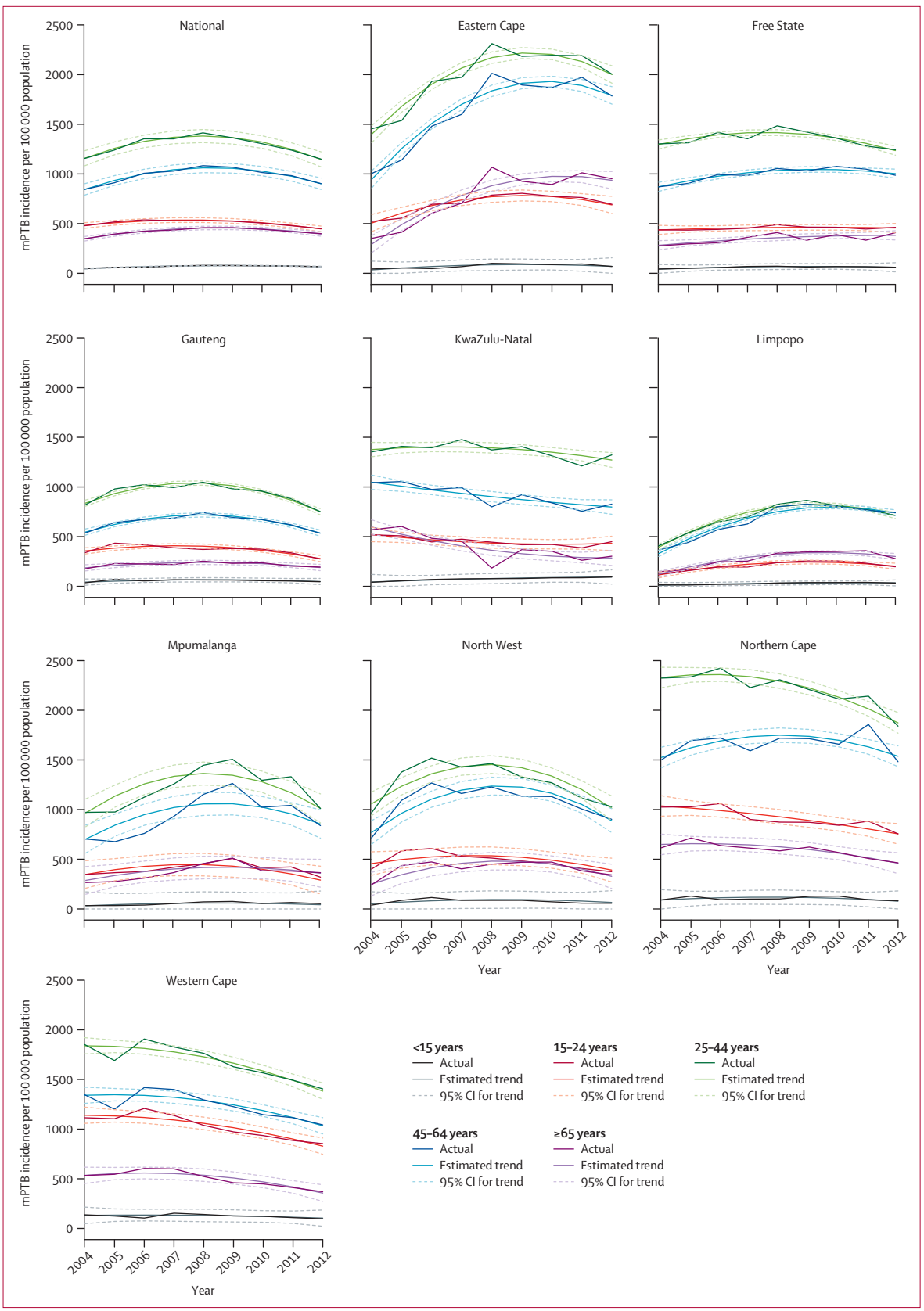

***Figure 2*: Incidence of microbiologically confirmed pulmonary tuberculosis (mPTB) in South Africa from 2004 to 2012, nationally and provincially, stratified by age group**

	2004	2005	2006	2007	2008	2009	2010	2011	2012
Number of people with HIV infection*	4 590 220	4 814 291	4 991 126	5 131 420	5 240 909	5 350 803	5 467 182	5 577 812	5 685 424
Number of people with HIV infection on ART*	46 723	107 515	225 926	367 272	561 783	842 002	1 108 417	1 354 709	1 580 117
Year-on-year increase in adults on ART	..	130%	110%	63%	53%	50%	32%	22%	17%
ART coverage (per 1000 people with HIV infection)*	10	22	45	72	107	157	203	243	278
Number of people with symptomatic AIDS*†	484 410	532 728	553 077	573 722	571 285	535 001	535 519	557 647	589 746
Year-on-year change in mPTB incidence	..	11%	10%	1%	5%	–2%	0%	1%	–8%

ART=antiretroviral therapy. mPTB=microbiologically confirmed pulmonary tuberculosis. *Sourced from provincial models of the Actuarial Society of South Africa (ASSA), 2008.[8] †Number of people who were symptomatic per ASSA model.

***Table 3*: Comparison of HIV prevalence, ART coverage, and annual percentage change in microbiologically confirmed pulmonary tuberculosis from 2004 to 2012 in South Africa**

Analysis of the ETD showed that the trends in incidence of new cases of pulmonary tuberculosis registered for treatment were similar to those for microbiologically confirmed disease, with both peaking in 2008–09, (appendix). Six of the nine provinces had peaks in incidence of registered cases between 2008 and 2009, whereas the incidence of registered cases peaked in the Western Cape in 2005 compared with 2006 for microbiologically confirmed cases. For Gauteng and Northern Cape, cases registered for treatment could not be identified because of missing or incomplete ETD data for several years in these provinces.

There were no statistically significant differences in incidence between microbiologically confirmed pulmonary tuberculosis and new cases registered for treatment in the North West and Free State provinces; however, the differences in incidence of microbiologically confirmed pulmonary tuberculosis and cases registered for treatment were consistently higher nationally and in seven of the nine provinces (appendix). The percentage difference in national incidence rates for microbiologically confirmed disease and cases registered for treatment ranged between 33% in 2006 and 11% in 2010, with a 16% difference seen in 2011—the only year with complete data from all provinces (appendix). The difference in incidence between microbiologically confirmed cases and cases registered for treatment in the Western Cape decreased between 2004 (37%) and 2012 (20%). For KwaZulu-Natal and Gauteng, the gap was more than 50% in 2005 and 2006; although the gap declined over time, it remained above 25% from 2011.

Discussion

Our study identified a 9% decline in incidence of microbiologically confirmed pulmonary tuberculosis in South Africa in 2012 compared with its peak in 2008. This decrease in incidence occurred despite a continuing increase in HIV prevalence among South African adults, as well as the use of more sensitive diagnostic assays and higher testing rates for tuberculosis since 2008. We recorded an increase in incidence of microbiologically confirmed pulmonary tuberculosis from 2004 to 2008, which coincided with an increase in prevalence of HIV/AIDS and limited use of ART; this was followed by a decrease in incidence from 2009 to 2012, which coincided with ART programme expansion in South Africa. The greatest decline in incidence of microbiologically confirmed pulmonary tuberculosis (19% between 2008 and 2012) was in the 25–44-year age group, which also consistently had the highest prevalence of HIV infection; these results are similar to those reported in a previous study in Cape Town.[10] These findings suggest that ART programme expansion is probably contributing to tuberculosis control in South Africa.

We noted that incidence rates of microbiologically confirmed disease in Eastern Cape and KwaZulu-Natal peaked later and did not show similar declines to the other provinces and seem to be stabilising. This pattern could be caused by higher rates of HIV and tuberculosis co-infection in these provinces, coupled with slower expansion of ART programmes. These provinces might need continuing surveillance of and further studies on the effect of newer diagnostics and increased ART coverage on the burden of tuberculosis, and possibly targeted interventions. KwaZulu-Natal and Eastern Cape constitute 32% of the South African population but accounted for 48% of all cases of microbiologically confirmed pulmonary tuberculosis in 2012.

To our knowledge, this study is the first to provide a nationwide report from South Africa of subnational population-based rates of microbiologically confirmed pulmonary tuberculosis (panel). Our incidence estimates, which excluded extrapulmonary cases (15–20% of immunocompetent adult tuberculosis cases),[13] were higher than those reported by the yearly WHO Global tuberculosis Reports, which include all forms of tuberculosis notifications from the ETD.[1] WHO reports are based on data submitted shortly after the close of a year and these figures are often later revised upwards as outstanding data are received and entered onto the ETD. The laboratory-based surveillance system is passive and despite using the most recent ETD data for comparing incidence rates, microbiologically confirmed pulmonary tuberculosis was higher than new cases of pulmonary tuberculosis

Panel: **Research in context**

Systematic review

We searched PubMed for original research that presented results for national and provincial incidence rates of tuberculosis in South Africa and its association with antiretroviral access published in English between Jan 1, 2003, and Dec 31, 2014. We combined search terms for tuberculosis/TB, incidence, and South Africa and looked for studies indicating temporal changes ("trends", "peak", "decline"), human immunodeficiency virus ("HIV", "AIDS"), and antiretroviral access ("ARV", "ART", and "coverage"). Including systematic reviews, we identified 135 studies with the terms "TB", "South Africa", and "incidence". Of these, 44 were in special populations, 31 were in limited geographical settings, 30 were on diagnostics and biomarkers, 17 were intervention studies, 11 were on extrapulmonary tuberculosis, eight were costing or modelling studies, three were immunological or vaccine research studies, and four were operations research studies. Only two studies were similar to our report, both of which were based on WHO and UNAIDS estimates but did not assess association with antiretroviral therapy (ART) coverage.[11,12]

Interpretation

To our knowledge, this is the first comprehensive time series analysis of incidence rates for microbiologically confirmed pulmonary tuberculosis in South Africa at a national and provincial level, with analysis of the association with HIV prevalence and ART coverage. We also highlight that current estimates of tuberculosis in South Africa, which are based on electronic TB registries, underestimate the incidence of tuberculosis, despite including non-microbiologically confirmed cases of tuberculosis and extrapulmonary tuberculosis cases. Although the decline in tuberculosis incidence since 2008 in South Africa was temporally associated with an expansion of the ART programme among people with HIV infection, further modelling work is needed to determine the interaction of ART coverage and the incidence of tuberculosis in South Africa.

registered for treatment. Discordance between ETD and laboratory data has been previously described at a regional level, and has been attributed to incomplete electronic records, loss to follow-up of diagnosed cases, failure to initiate cases of microbiologically confirmed disease on treatment, or death before accessing treatment.[14,15] Although we were unable to integrate data for microbiologically confirmed cases and new cases registered for treatment at a patient level, because of the absence of common unique identifiers, overall trends in incidence of microbiologically confirmed disease were similar to those for cases registered for treatment, with higher incidence of microbiologically confirmed disease seen nationally and in seven of the nine provinces.

The overall percentage difference between microbiologically confirmed pulmonary tuberculosis and new cases of the disease registered for treatment was lower nationally and in most provinces during the second half of the study period, coinciding with the decline in incidence of microbiologically confirmed disease. This finding suggests that challenges in health systems capacity might have contributed to a larger gap in earlier years, which has since improved with successes in reducing the burden of disease. In a study undertaken in five provinces in South Africa in 2009, the mean proportion of patients lost to follow-up was 25% and ranged between 21% and 34% for the sampled clinics in the respective provinces, which is similar to our findings.[16]

Temporal-spatial variations in the gap between incidence estimates for microbiologically confirmed pulmonary tuberculosis and new cases registered for treatment were noted, which could be caused by both patient and provider factors.[17,18] In 2012, this gap was more than 25% in five of the nine provinces, which is concerning because patients not linked to care could be the major source of persisting *M tuberculosis* transmission in the community. Several limitations were also noted for data for new cases registered for treatment, including some provinces lacking or only having limited data for some years. Furthermore, apart from removal of obvious duplicates, no further deduplication was feasible with the available data.

The higher incidence of microbiologically confirmed pulmonary tuberculosis cases compared with new cases of the disease registered for treatment is even more notable when considering that non-bacteriologically confirmed cases are included in the data for cases registered for treatment. Also, most of the microbiologically confirmed cases we report were diagnosed by smear, which has only 25–30% sensitivity for diagnosing pulmonary tuberculosis in adults with HIV infection. Hence, although the laboratory-based surveillance provided a higher estimate of incidence of pulmonary tuberculosis in South Africa than did registries of patients on treatment, this itself is probably an underestimate, especially in areas where culture-based testing is not routine, and in the era before the introduction of Xpert MTB/Rif.[19] Furthermore, incidence of pulmonary tuberculosis in individuals younger than 15 years, which represented 3% of all microbiologically confirmed cases in our study, is also likely to be an underestimate because of the low sensitivity of diagnostic assays in children, with cultures testing positive for *M tuberculosis* in only 10–40% of childhood tuberculosis cases.[20]

The temporal link between the increase in microbiologically confirmed pulmonary tuberculosis and increasing HIV prevalence seen here has been reported in other low-income countries with a high prevalence of HIV infection.[21] Similarly, temporal associations of declining tuberculosis rates after ART scale-up have been reported in a rural district of Malawi (33% reduction in 2 years) and in Cape Town (three-fold decline in tuberculosis incidence over 5 years).[22,23]

Important factors that affect laboratory-based tuberculosis surveillance data are diagnostic test availability and performance, as well as differential clinical application, both geographically and temporally. During the study period, there was a three-fold increase in testing rates since 2004, increased use of liquid-based culture from 2006 onwards, and the introduction of the Xpert MTB/Rif assay in 2011, which was expected to increase the number of tuberculosis cases diagnosed by 30–37%.[24] This period

also intensified case finding as part of the HIV–tuberculosis campaign during 2010. Despite these changes, which would have increased the sensitivity for diagnosing cases of microbiologically confirmed pulmonary tuberculosis in South Africa, incidence declined from 2008. This focus on greater case detection and use of more sensitive diagnostic assays in the latter part of our analysis period might yet change the trend in tuberculosis incidence in the coming years despite the sustained ART coverage.

Although there was variability in provincial incidence of microbiologically confirmed pulmonary tuberculosis, the overall trends over time were similar to those at the national level. These interprovincial differences, although likely to be multifactorial, could also be caused by differences in the population rate of testing for microbiologically confirmed disease, as indicated by the highest incidence reported from provinces with the highest rates of testing. This finding could suggest further underestimation of the incidence of microbiologically confirmed disease in some provinces caused by lower rates of testing. The peak in incidence of microbiologically confirmed tuberculosis also varied between provinces. The early decline in incidence recorded in Western Cape was probably related to it being the first province to have introduced an ART programme, coupled with a lower HIV prevalence than other provinces. Conversely, the slower decline noted in Eastern Cape, Northern Cape, and KwaZulu-Natal might have been caused by socioeconomic factors, as well as poorer access to health care in remote rural areas, which is characteristic of these provinces.[25]

Limitations of our study are the record-linking algorithm used to identify unique cases in the laboratory database, which could have under-linked or over-linked records. This would have led to a corresponding overestimation or underestimation in incidence. The incompleteness of data from KwaZulu-Natal for 2004 to 2010 required imputation of incidence of microbiologically confirmed pulmonary tuberculosis by use of data from geographically proximal provinces; nevertheless, the modelled trend in microbiologically confirmed disease was similar to the recorded trend in new cases registered for treatment. However, the imputed incidence of microbiologically disease in KwaZulu-Natal for this period is likely to be an underestimation for those years, as indicated by this province having the highest incidence during the period 2011–12.

We were unable to disaggregate incidence of microbiologically confirmed pulmonary tuberculosis by HIV status at a patient level because the HIV data used were only available at a population level; however, since most tuberculosis cases among South African adults (70%) are associated with underlying HIV infection, it is possible that the decline we recorded is mainly related to a decrease in pulmonary tuberculosis among people with HIV infection. IPT coverage in individuals with HIV infection could have also reduced the incidence of microbiologically confirmed tuberculosis; however, there is little published data on IPT coverage in South Africa. The effect of IPT has, however, been noted to be temporary in protecting against tuberculosis in settings such as ours, especially if only provided for 6 months, as was the recommendation during the period under analysis. Consequently, and in view of the poor application of the IPT policy, we consider it unlikely that IPT contributed much to the decline in annual incidence of pulmonary tuberculosis.[26] This postulation is further supported by the decline in pulmonary tuberculosis seen in the Western Cape that occurred in tandem with an increase in ART coverage at a time when IPT was unavailable in public health facilities (until 2011).[27]

Our direct measurement of a decline in incidence of microbiologically confirmed pulmonary tuberculosis of 9% since the peak in 2008 is predicted to continue based on recent modelling work suggesting that, with expanded ART eligibility criteria, cumulative incidence of tuberculosis could decline by a further 6–30% by 2033.[28] By takking advantage of the uniqueness of a single laboratory-service provider (NHLS) for over 80% of the population who use public health services, we showed an opportunity to provide robust data on cases of microbiologically confirmed pulmonary tuberculosis in South Africa, to assess the effect of programmatic interventions, and to provide a solution to monitoring progress towards the post-2015 tuberculosis targets.

Contributors

AN, SAM, CI, NAI, and AI were involved in the conception and design of the study. AN, CI, AI, NAI, SAM were involved in study implementation. AN and AI did the data analysis. AN, AI, NAI, CI, IA, DM, and SAM interpreted the data and provided important intellectual input. AN, SAM, CI, and NAI wrote the first draft.

Declaration of interests

SAM has received grants and personal fees from GlaxoSmithKline, Pfizer, and Sanofi Pasteur, and grants from Novartis. All other authors declare no competing interests.

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