

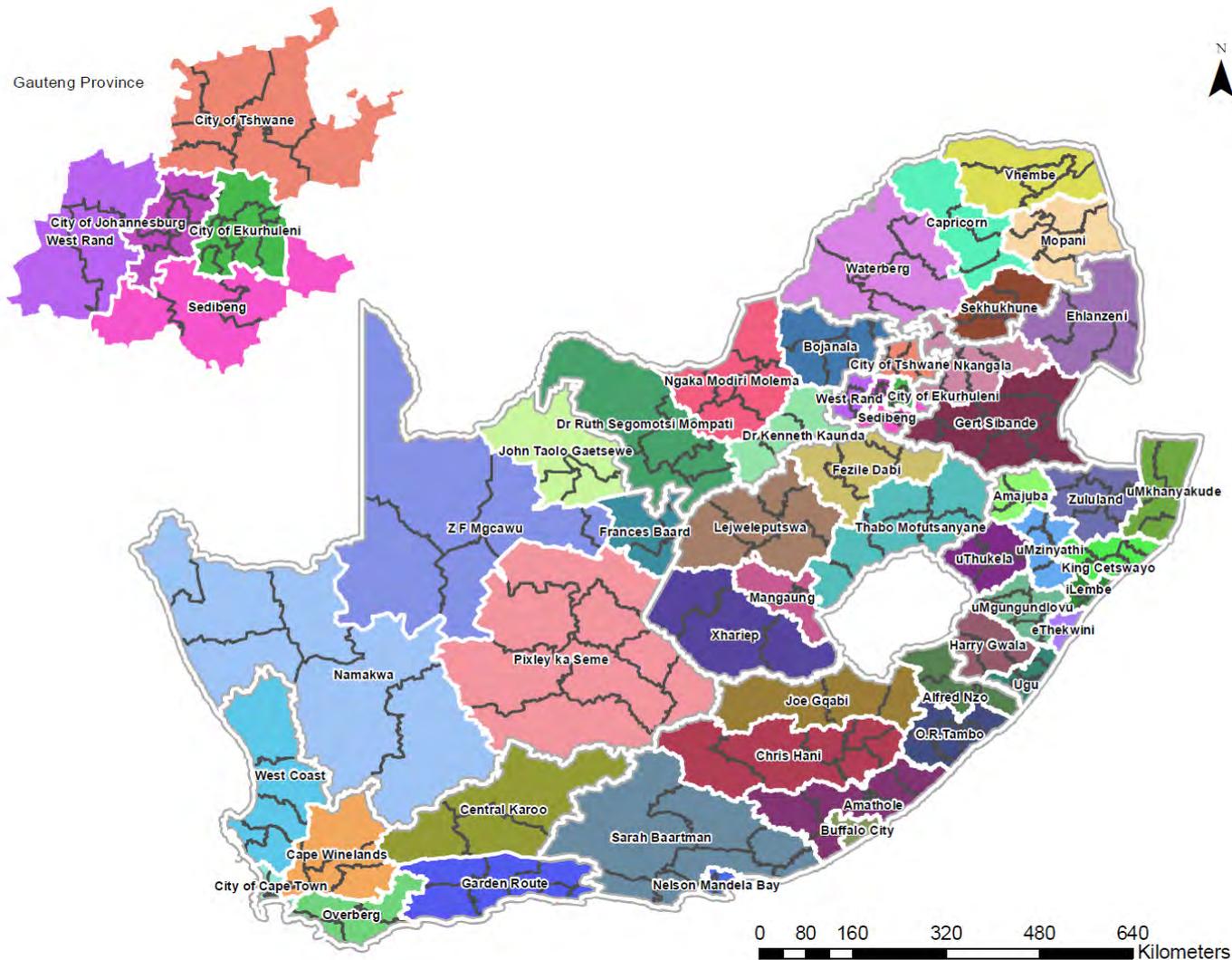
South Africa: the triple burden – HIV, tuberculosis and antimicrobial resistance



Andy Gray

Division of Pharmacology

Discipline of Pharmaceutical Sciences



2020 mid-year estimate:
 59 797 656

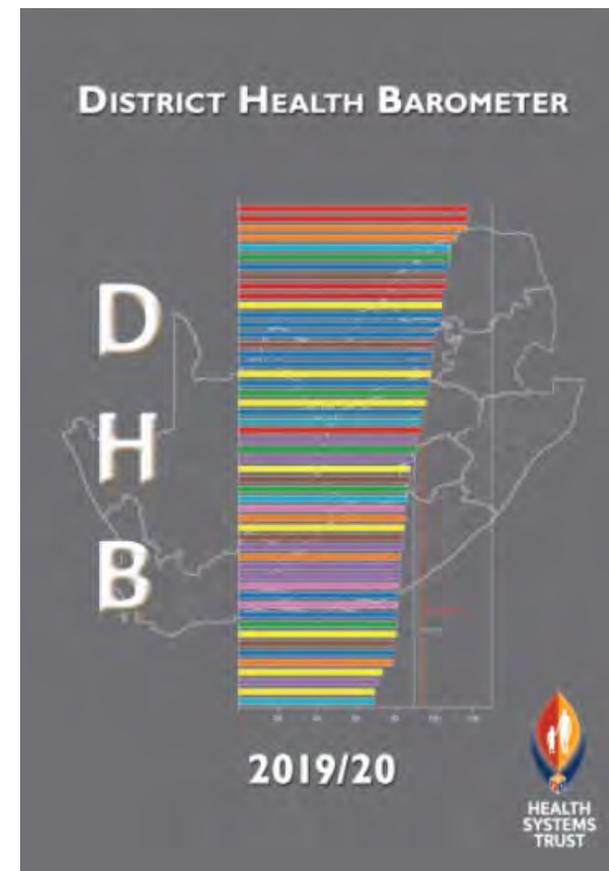
Gauteng is the most populous province (15 635 579), followed by KwaZulu-Natal (11 441 785)

Health services delivered by 9 provinces and 52 districts

AND

78 individual private sector insurers, via private sector

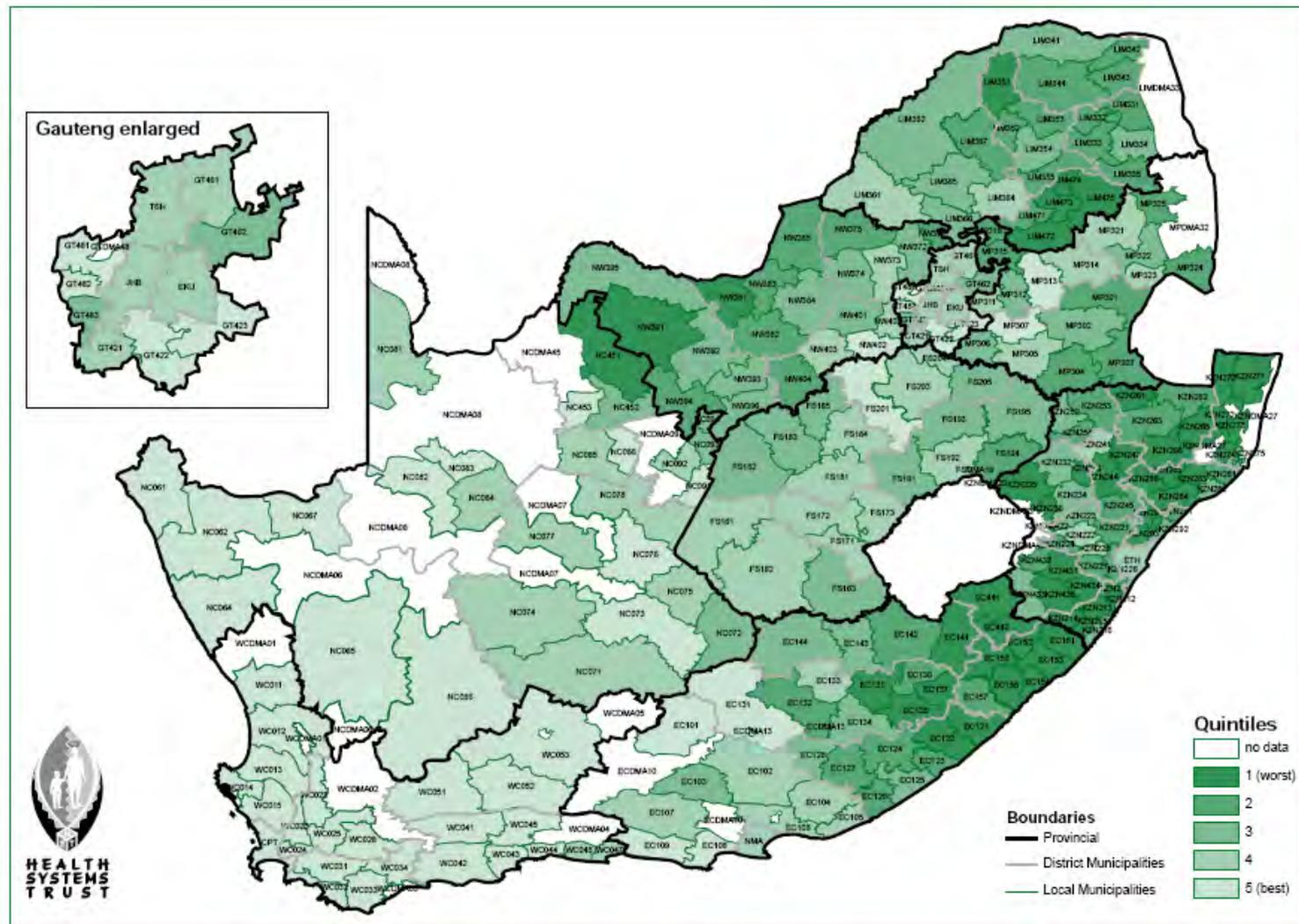
Two key resources



<https://www.hst.org.za/>

BUKO PharmaKampagne 40th April 2021

Persistent differences in levels of deprivation



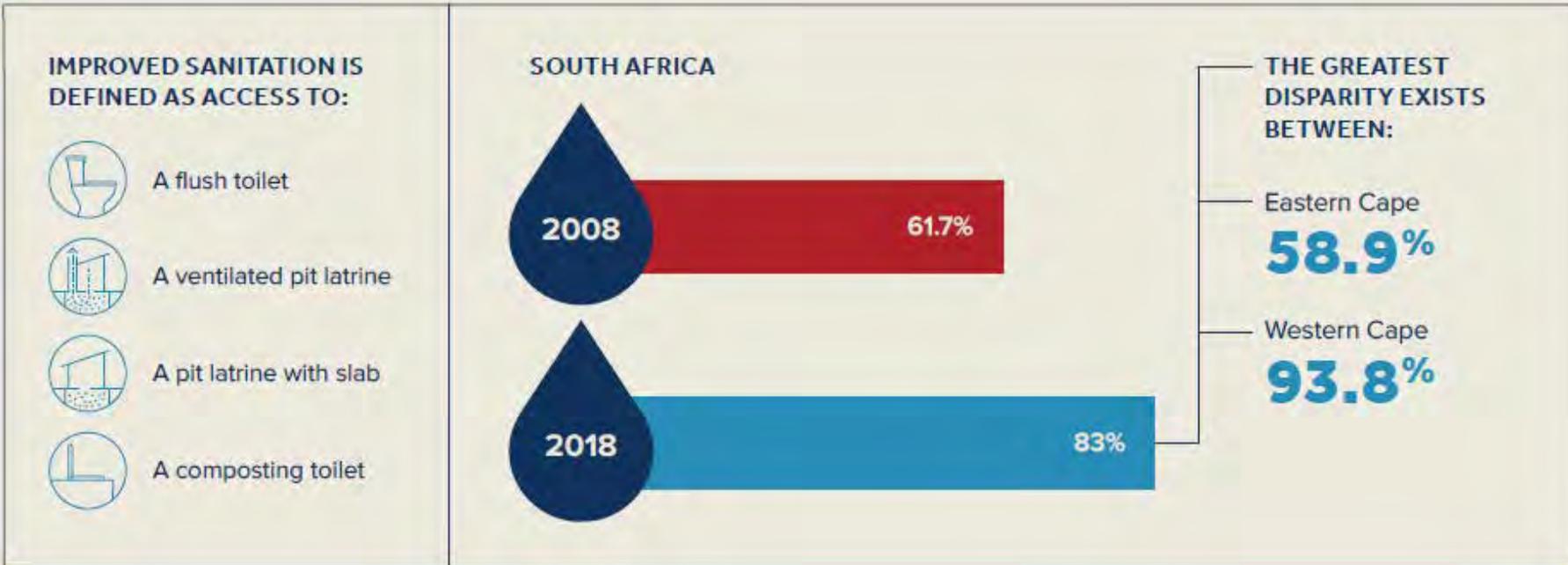
WATER AND SANITATION

UHC 8 % OF HOUSEHOLDS WITH ACCESS TO IMPROVED SANITATION

The assumption is that there is a positive correlation between access to improved sanitation and decreased risk of diarrhoeal disease.



PROGRESS HAS BEEN MADE BUT THERE ARE LARGE DISPARITIES BETWEEN PROVINCES



UHC 14

HEALTH WORKER DENSITY PER 100 000 (INDEX)

This index was calculated as the geometric mean of scaled scores for each cadre, with thresholds of 30 physicians, 100 nurses and midwives, and 5 pharmacists per 10 000 population.



THERE IS AN ABSOLUTE DEFICIT OF HEALTH WORKERS IN THE PUBLIC SECTOR

IN 2019, THERE WERE:



10.7

INDEX

MEDICAL PRACTITIONERS

32 medical practitioners per 100 000 population



14.5

INDEX

PROFESSIONAL NURSES

144.8 professional nurses per 100 000 population



23.1

INDEX

PHARMACISTS

11.6 pharmacists per 100 000 population

HEALTH WORKER DENSITY



UHC 6 ANTIRETROVIRAL EFFECTIVE COVERAGE (PLHIV ON ART AND VIRALLY SUPPRESSED)

HIV-related indicators recorded worldwide are linked to the concept of a cascade of care that is promoted by the joint UN programme, UNAIDS.



**THERE HAS BEEN STRIKING IMPROVEMENT
IN THE TREATMENT COVERAGE AND EFFECTIVE
COVERAGE OVER TIME**



NATIONAL CASCADE 2019:

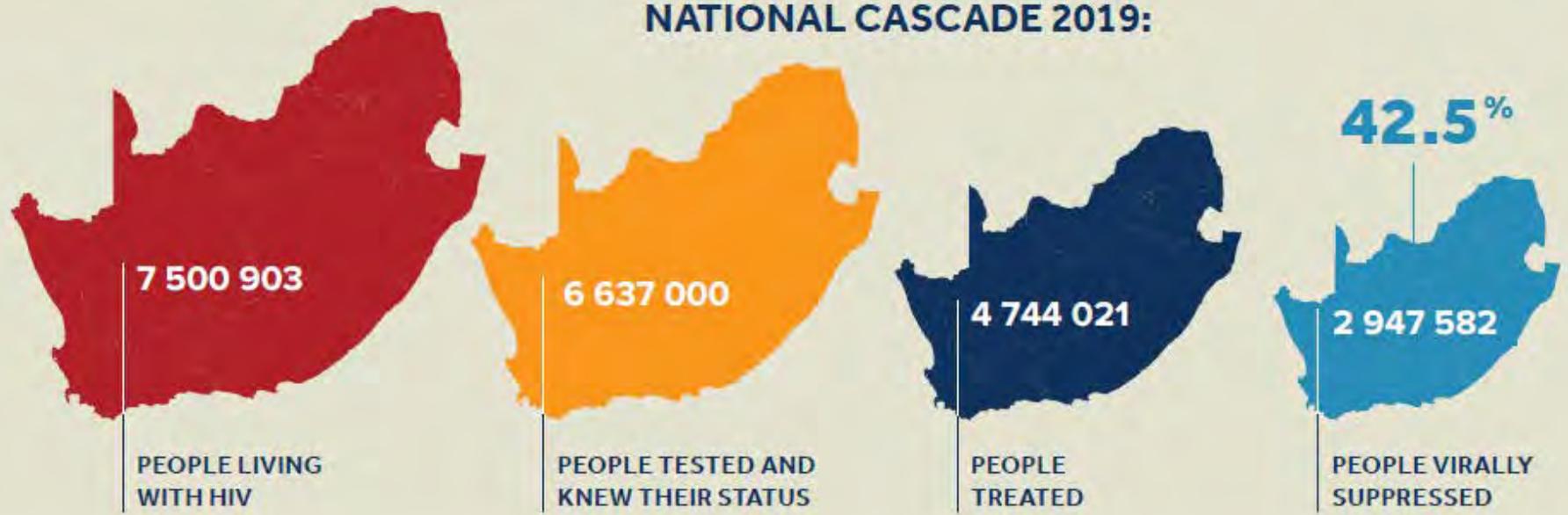


Figure 21: ART effective coverage by age group, DHIS, 2017-2020

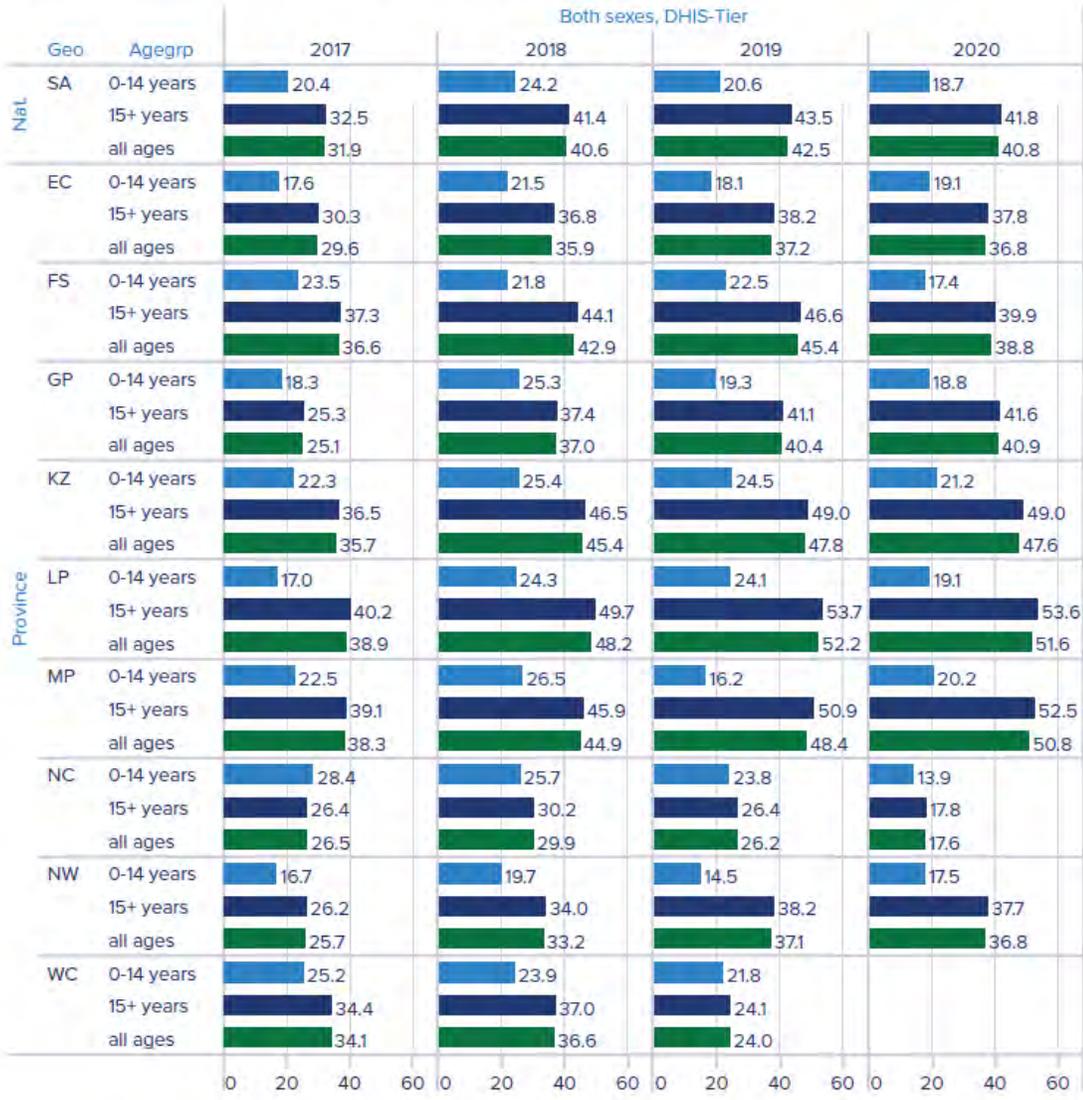
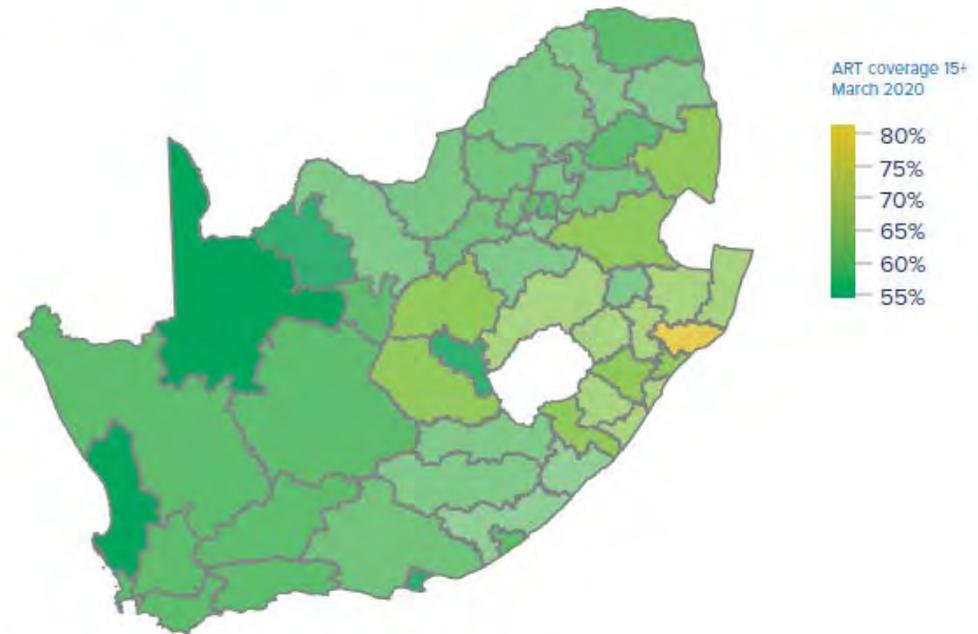


Figure 19: Naomi model ART coverage in adults (15+ years) by district, March 2020



Source: Naomi model, available from hivdata.org.za.



Case report: Emergence of dolutegravir resistance in a patient on second-line antiretroviral therapy



Authors:

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Introduction: The integrase strand transfer inhibitor dolutegravir (DTG) has a high genetic barrier to resistance. Only rare cases of resistance to DTG have been reported when it is used as a component of antiretroviral therapy regimens in treatment-experienced patients unless there was prior use of a first-generation integrase inhibitor.

Patient presentation: A 38-year-old woman diagnosed with tuberculosis was switched to a second-line antiretroviral regimen of zidovudine, lamivudine and dolutegravir 50 mg 12-hourly together with rifampicin-based TB treatment. Based on treatment history and a previous resistance test there was resistance to lamivudine but full susceptibility to zidovudine. The patient did not suppress her viral load on this regimen and later admitted to only taking dolutegravir 50 mg in the morning because of insomnia.

Management and outcome: A second resistance test was performed which showed intermediate level of resistance to dolutegravir. Her regimen was changed to tenofovir, emtricitabine and ritonavir-boosted atazanavir with rifabutin replacing rifampicin for the remainder of her TB treatment. She achieved viral suppression on this regimen.

Conclusion: To our knowledge this is the first case report from South Africa of emergent dolutegravir resistance in a treatment-experienced, integrase inhibitor-naïve patient. Factors that may have contributed to resistance emergence in this patient were that there was only one fully active nucleoside reverse transcriptase inhibitor in the regimen and lower exposure to dolutegravir because of the reduced dosing frequency while on rifampicin.

Keywords: HIV drug resistance; antiretroviral therapy; regimens; dolutegravir; rifampicin;

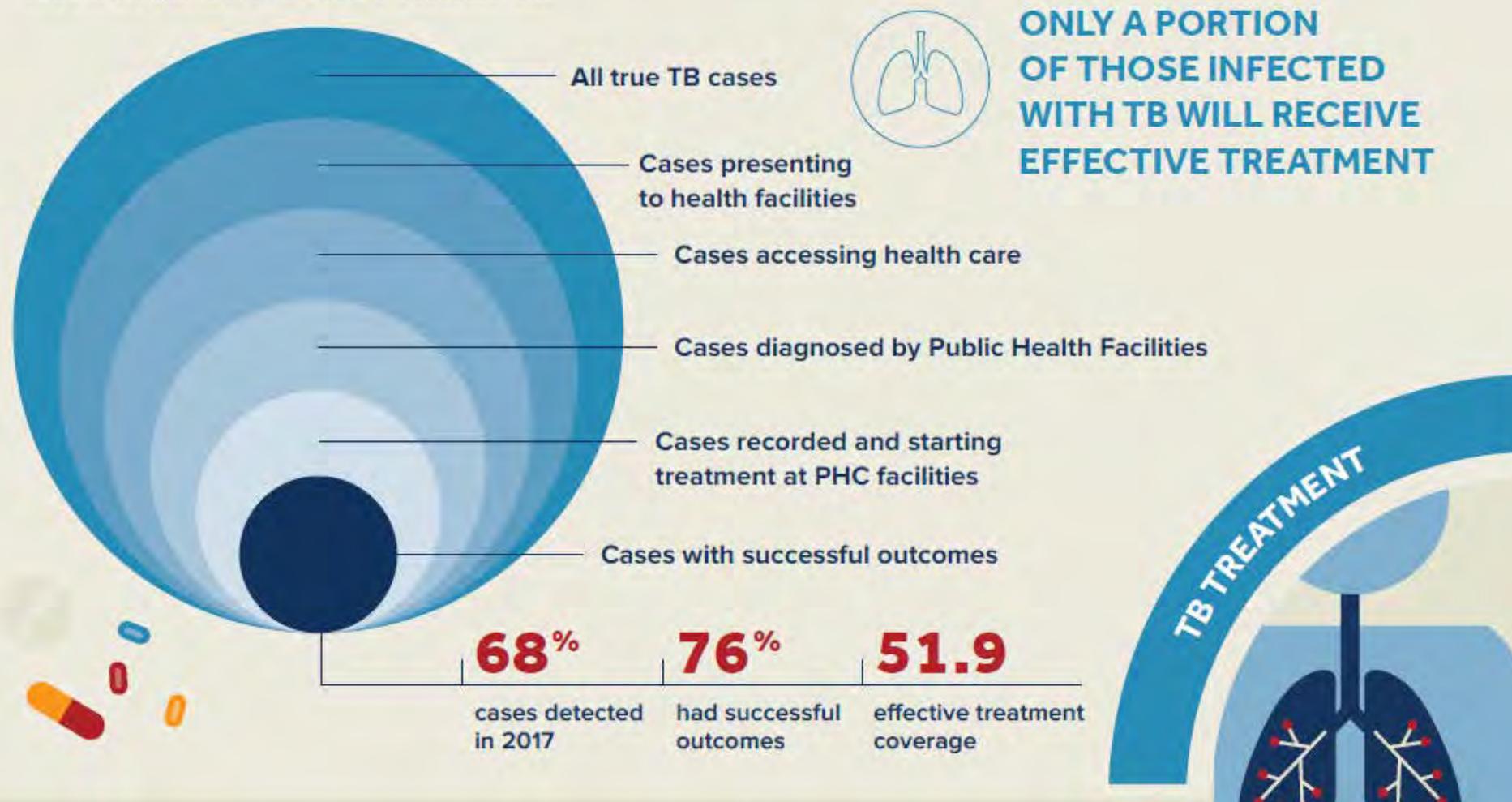
Southern African Journal of HIV Medicine

ISSN: (Online) 2078-6751, (Print) 1608-9693

UHC 5

TUBERCULOSIS EFFECTIVE TREATMENT COVERAGE

This indicator has been calculated using the globally reported national case detection rate and the drug-sensitive TB treatment success rate.

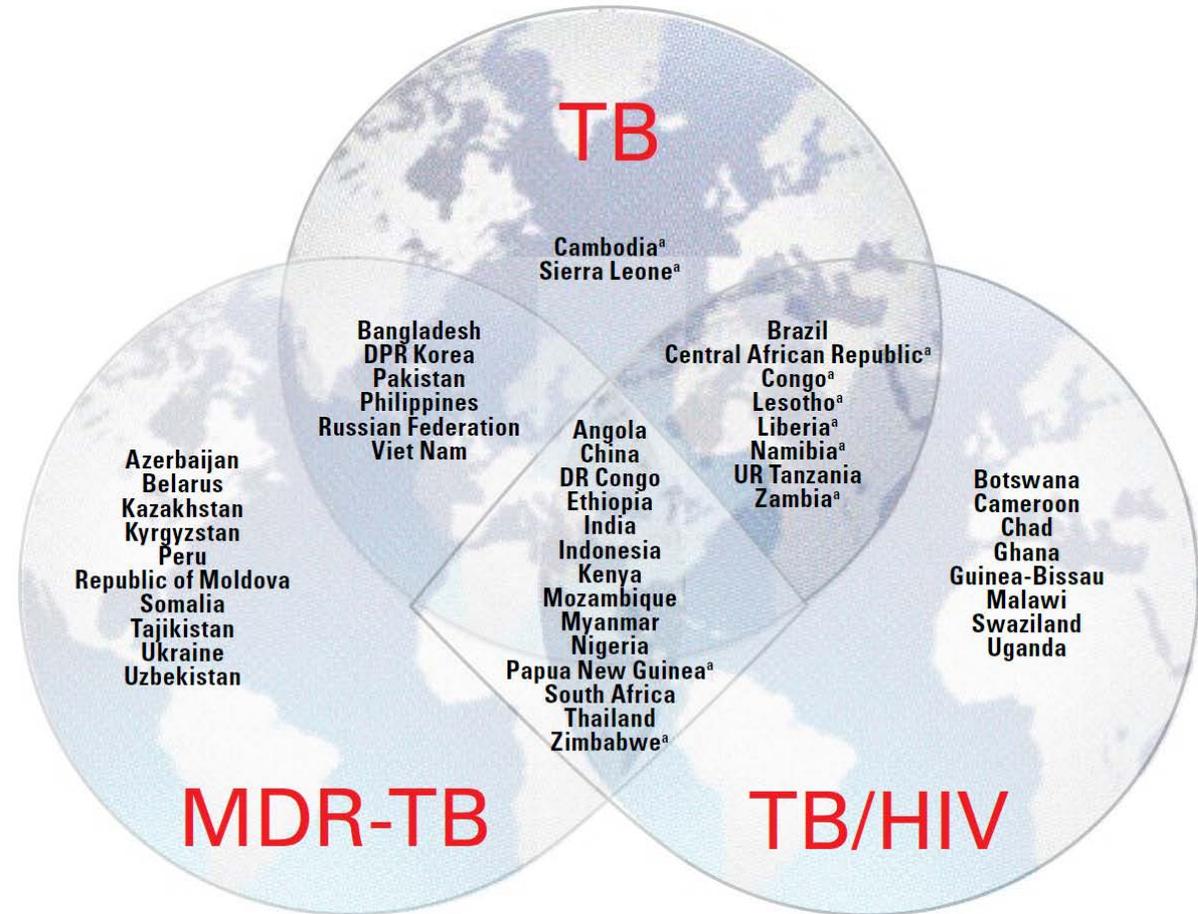


GLOBAL TUBERCULOSIS REPORT

2020



Countries in the three high-burden country lists for TB, TB/HIV and MDR-TB being used by WHO during the period 2016–2020, and their areas of overlap



International Spread of MDR TB from Tugela Ferry, South Africa

Graham S. Cooke, R. Kate Beaton,
Richard J. Lessells, Laurence John,
Simon Ashworth, Onn Min Kon,
O. Martin Williams, P. Supply, P. Moodley,
and Alexander S. Pym

We describe a death associated with multidrug-resistant tuberculosis and HIV infection outside Africa that can be linked to Tugela Ferry (KwaZulu-Natal, South Africa), the town most closely associated with the regional epidemic of drug-resistant tuberculosis. This case underscores the international relevance of this regional epidemic, particularly among health care workers.

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 17, No. 11, November 2011

Evolution of Extensively Drug-Resistant Tuberculosis over Four Decades: Whole Genome Sequencing and Dating Analysis of *Mycobacterium tuberculosis* Isolates from KwaZulu-Natal

Keira A. Cohen^{1,2}, Thomas Abeel^{3,4}, Abigail Manson McGuire³, Christopher A. Desjardins³, Vanisha Munsamy², Terrance P. Shea³, Bruce J. Walker³, Nonkqubela Bantubani⁵, Deepak V. Almeida^{2,6}, Lucia Alvarado³, Sinéad B. Chapman³, Nomonde R. Mvelase^{7,8}, Eamon Y. Duffy², Michael G. Fitzgerald³, Pamla Govender², Sharvari Gujja³, Susanna Hamilton³, Clinton Howarth³, Jeffrey D. Larimer³, Kashmeel Maharaj², Matthew D. Pearson³, Margaret E. Priest³, Qiandong Zeng³, Nesri Padayatchi⁹, Jacques Grosset^{2,6}, Sarah K. Young³, Jennifer Wortman³, Koleka P. Mlisana^{7,8}, Max R. O'Donnell^{9,10,11}, Bruce W. Birren³, William R. Bishai⁶, Alexander S. Pym^{2*}, Ashlee M. Earl^{3†*}

PLOS Medicine | DOI:10.1371/journal.pmed.1001880 September 29, 2015

“Our results suggest that drug-resistant strains circulating today reflect not only vulnerabilities of current TB control efforts but also those that date back 50 y.”

SA has encountered the resistant organisms of concern

SCIENTIFIC LETTER

NDM-1 has arrived: First report of a carbapenem resistance mechanism in South Africa

W Lowman, C Sriruttan, T Nana, N Bosman, A Duse, J Venturas, C Clay, J Coetzee

The New Delhi Metallo- β -lactamase (NDM) resistance mechanism in Enterobacteriaceae threatens to render serious Gram-negative infections untreatable. The NDM-1 enzyme hydrolyses all available penicillin, cephalosporin and carbapenem antibiotics, and is commonly accompanied by additional resistance mechanisms to multiple antibiotic classes. Initially identified as a significant

healthcare risk on the Indian sub-continent, it has rapidly become a global problem, posing significant diagnostic and management challenges. Here we report the first laboratory-confirmed case of NDM-1 in South Africa.

S Afr Med J 2011;101:873-875.

To the Editor: Resistance to β -lactam antibiotics in Enterobacteriaceae between bacteria, resulting in the emergence of resistance in other

CLINICAL ALERT

Emergence of plasmid-mediated colistin resistance (MCR-1) among *Escherichia coli* isolated from South African patients

J Coetzee, C Corcoran, E Prentice, M Moodley, M Mendelson, I Poirel, P Nordmann, A J Brink

Jennifer Coetzee, Craig Corcoran and Elizabeth Prentice are all specialists in the Departments of Clinical Microbiology and Molecular Sciences at the Ampath Reference Laboratory, Centurion, Pretoria, South Africa. Mischka Moodley is a clinical microbiologist at the Ampath National Laboratory Services, Cape Town, South Africa. Marc Mendelson is an infectious diseases specialist and Head of Infectious Diseases and HIV Medicine at the Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa. Laurent Poirel and Patricia Nordmann are microbiologists in the Emerging Antibiotic Resistance Unit, Department of Medical and Molecular Microbiology, Department of Medicine, Faculty of Science, University of Fribourg, Switzerland. Adrian Brink is a clinical microbiologist at Ampath National Laboratory Services, Milpark Hospital, Johannesburg.

Corresponding author: J Coetzee (coetzeej@ampath.co.za)

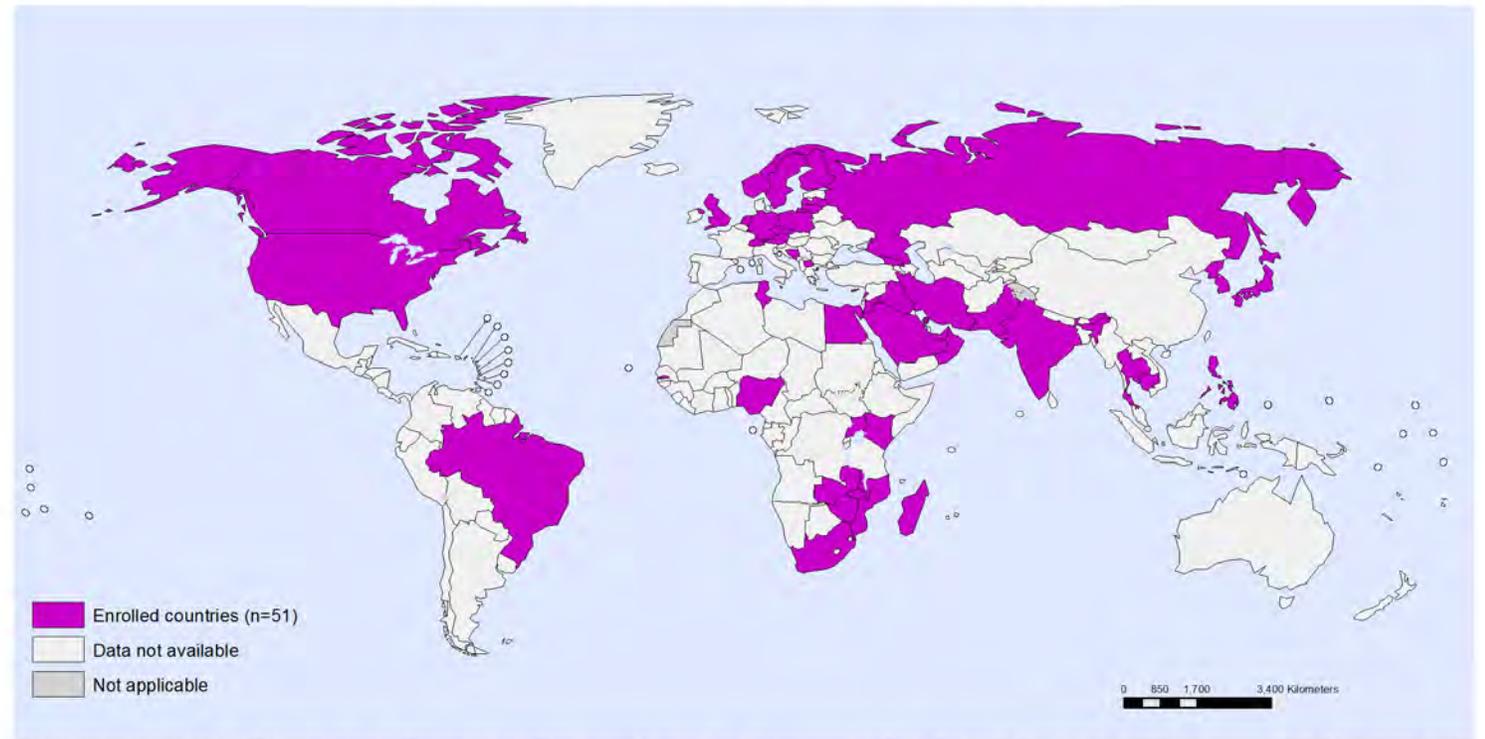
The polymyxin antibiotic colistin is an antibiotic of last resort for the treatment of extensively drug-resistant Gram-negative bacteria, including carbapenemase-producing Enterobacteriaceae. The *State of the World's Antibiotics* report in 2015 highlighted South Africa (SA)'s increasing incidence of these 'superbugs' (3.2% of *Klebsiella pneumoniae* reported from SA were carbapenemase producers), and in doing so, underscored SA's increasing reliance on colistin as a last line of defence. Colistin resistance effectively renders such increasingly common infections untreatable.

S Afr Med J 2016;106(5):449-450. DOI:10.7196/SAMJ.2016.v106i5.10710



2016-2017

GLASS country enrolment status, as of January 2018



The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Information Evidence and Research (IER)
World Health Organization



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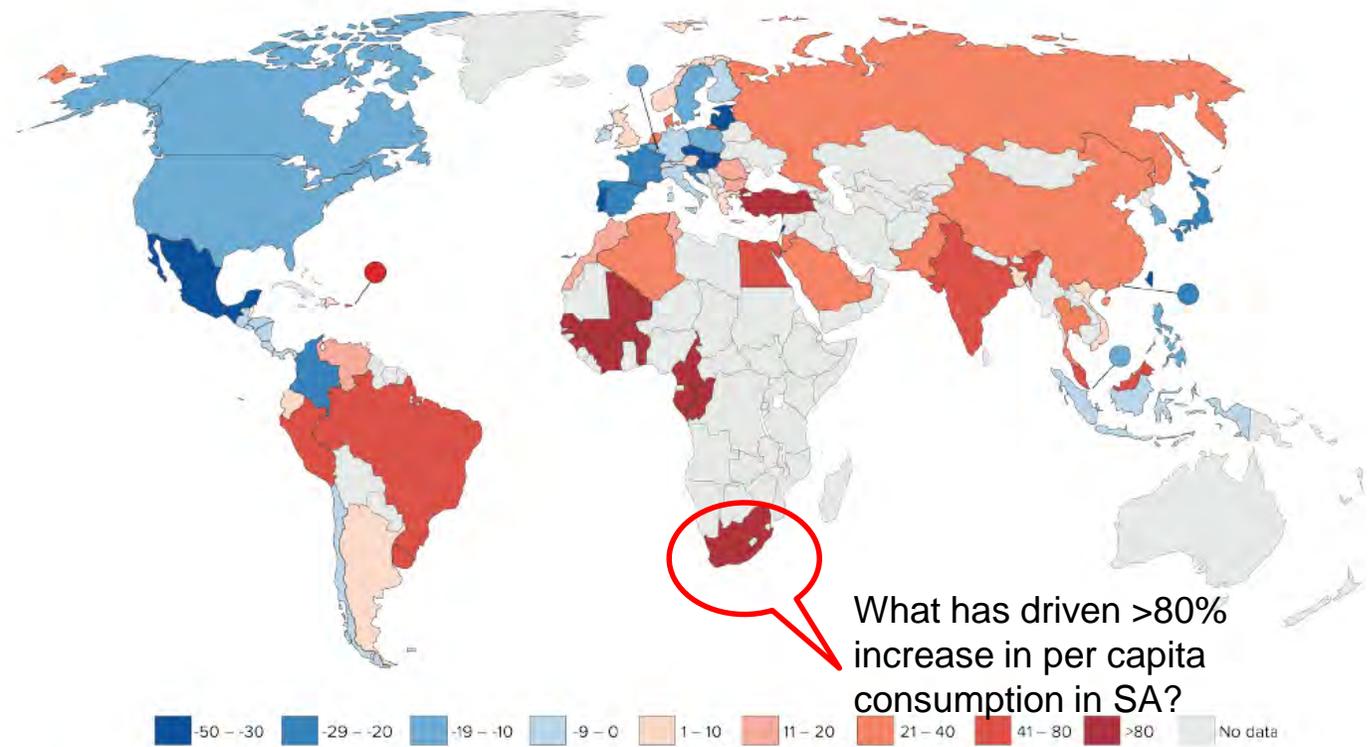
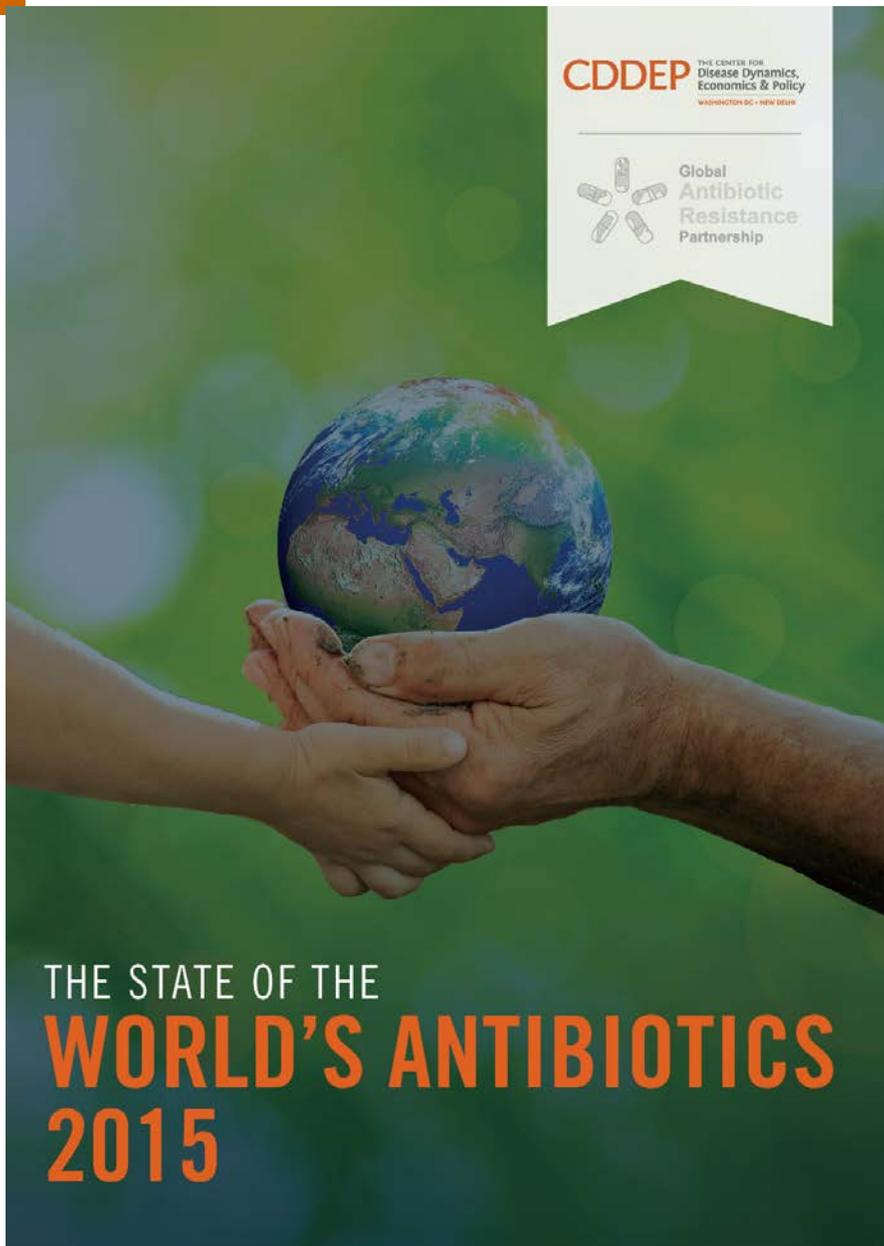


FIGURE 2-4: Percentage change in antibiotic consumption per capita 2000–2010*, by country

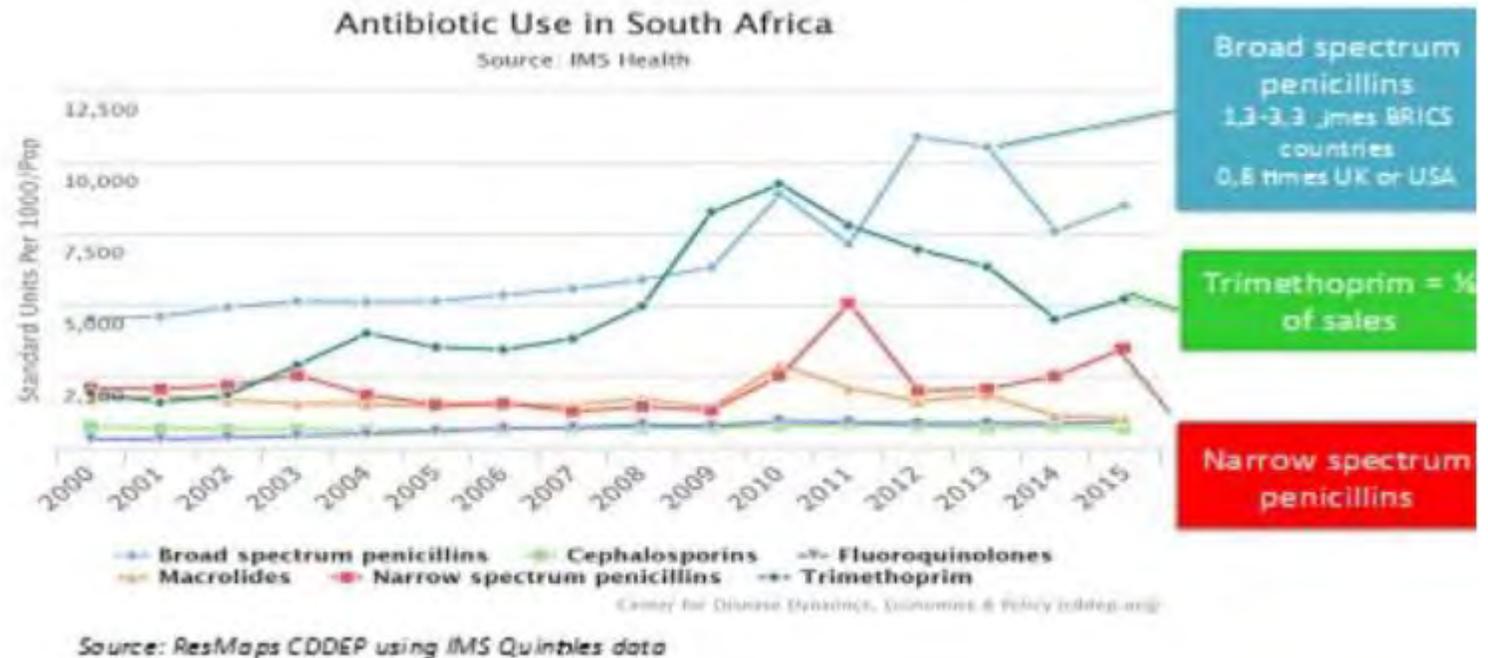
Source: Van Boeckel et al. 2015 (adapted; based on IMS MIDAS)

SURVEILLANCE FOR ANTIMICROBIAL RESISTANCE AND CONSUMPTION OF ANTIBIOTICS IN SOUTH AFRICA

NOVEMBER 2018

NATIONAL DEPARTMENT OF HEALTH

Note the problem with the units used – “standard units” = boxes of medicine





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Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid



Perspective

A situational analysis of current antimicrobial governance, regulation, and utilization in South Africa



Natalie Schellack^{a,*}, Deon Benjamin^b, Adrian Brink^{c,d}, Adriano Duse^e, Kim Faure^f, Debra Goff^g, Marc Mendelson^d, Johanna Meyer^a, Jacqui Miot^h, Olga Perovicⁱ, Troy Pople^j, Fatima Suleman^k, Moritz van Vuuren^l, Sabiha Essack^k

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^d Division of Infectious Diseases and HIV Medicine, Department of Medicine, Groote Schuur Hospital, University of Cape Town, Cape Town, South Africa

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ⁱ Centre for Opportunistic, Tropical and Hospital Infections, University of Witwatersrand, Johannesburg, South Africa

^j Aspen France, Marly-le-Roi, France

^k Antimicrobial Research Unit, College of Health Sciences, University of KwaZulu-Natal, Durban, South Africa

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ARTICLE INFO

Article history:

Received 20 July 2017

Received in revised form 1 September 2017

Accepted 1 September 2017

Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:

Antimicrobial governance

DOTS

Antibiotic consumption

Developing country

Antimicrobial exposure

ABSTRACT

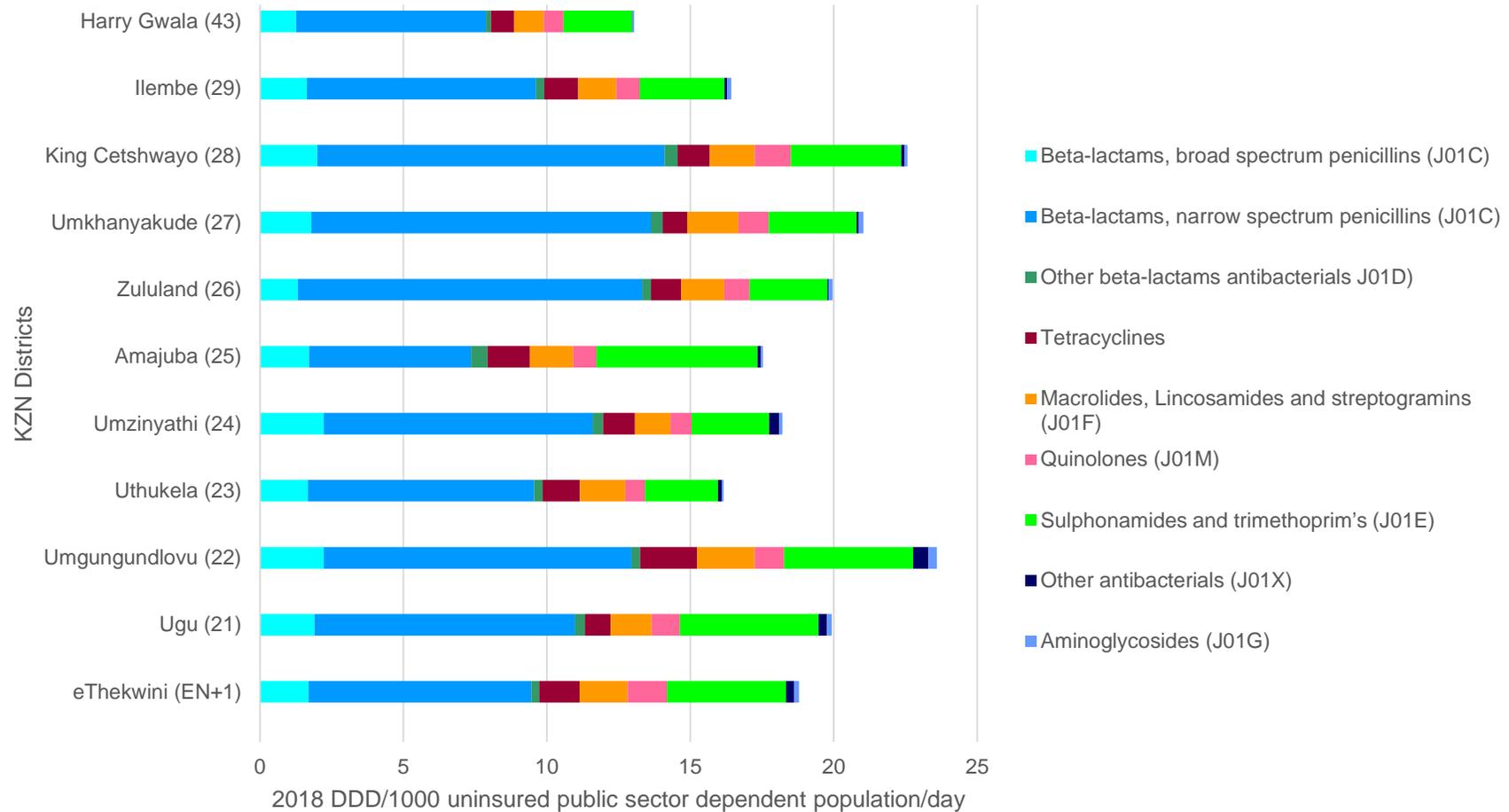
The Global Action Plan on antimicrobial resistance calls for the use of antimicrobial medicines in human and animal health to be optimized, in tandem with a strengthening of the knowledge and evidence base through surveillance and research. However, there is a paucity of consumption data for African countries such as South Africa. Determining antimicrobial consumption data in low-resource settings remains a challenge. This article describes alternative mechanisms of assessing antimicrobial consumption data, such as the use of Intercontinental Marketing Services (IMS) data and contract data arising from tenders (an open Request for Proposal, RFP), as opposed to the international norms of daily defined doses per 100 patient-days or per 1000 population. Despite their limitations, these serve as indicators of antimicrobial exposure at the population level and represent an alternative method for ascertaining antimicrobial consumption in human health. Furthermore, South Africa has the largest antiretroviral treatment programme globally and carries a high burden of tuberculosis. This prompted the inclusion of antiretroviral and anti-tuberculosis antibiotic consumption data. Knowledge of antimicrobial utilization is imperative for meaningful future interventions. Baseline antimicrobial utilization data could guide future research initiatives that could provide a better understanding of the different measures of antibiotic use and the level of antibiotic resistance.

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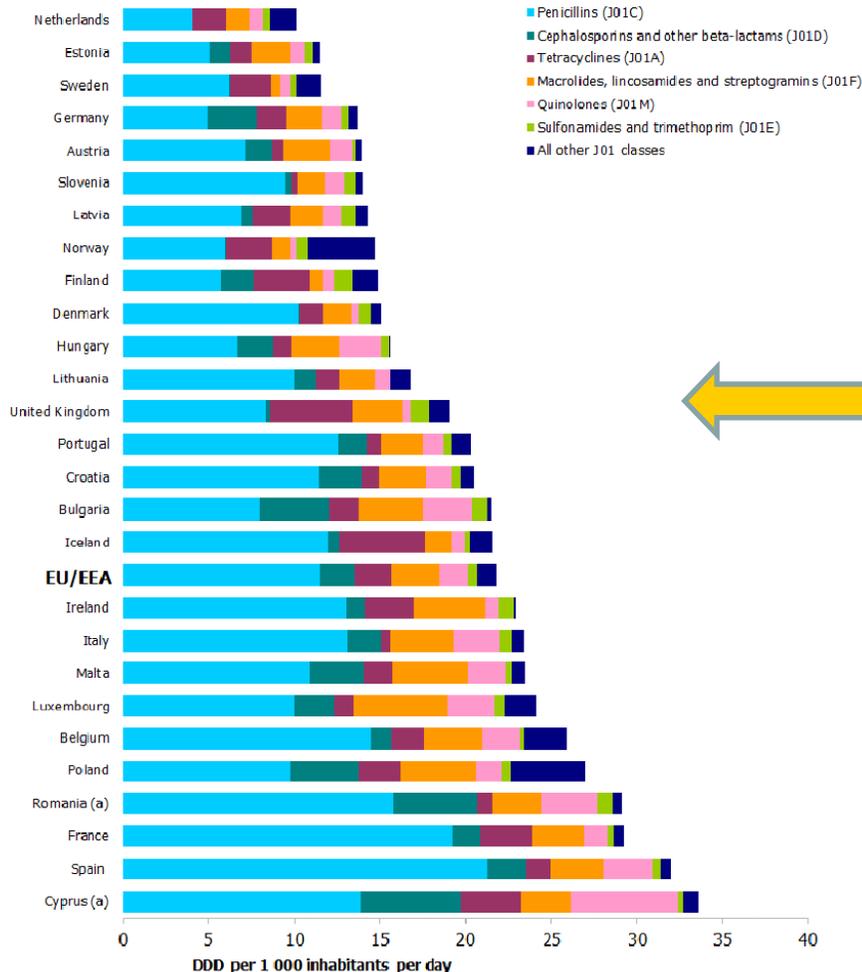
The DDD (the usual adult dose of an antimicrobial for treating one patient for one day) has been considered useful for measuring antimicrobial prescribing trends within a hospital, including the various denominators from hospital activities, i.e. beds, admissions, and discharges. **This type of surveillance data for antimicrobial usage is not routinely available in South Africa, although increasingly implemented as the AMR strategic framework is progressively rolled out.**

Consumption of Antibacterials for Systemic Use (ATC Group J01) per District in KwaZulu Natal, expressed as 2018 DDD/1000 uninsured public sector dependent population/day



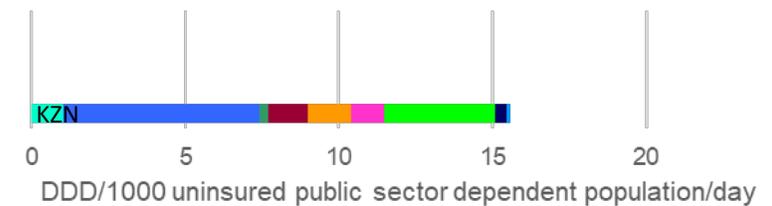
Comparison with European figures

Figure 3. Consumption of antibacterials for systemic use (ATC group J01) by country and ATC group level 3 in the community, EU/EEA countries, 2017, expressed as DDD per 1 000 inhabitants per day



Using the 2018 DDD, the overall KZN total (J01) utilisation was 18.5 DDD/1000 uninsured population/day; around the mid-point compared with 2017 data in Europe (comparable to that in the United Kingdom)

2019 Consumption of Antibacterials for Systemic Use (ATC Group J01) in KwaZulu Natal, expressed as DDD/1000 uninsured public sector dependent population/day



Antimicrobial stewardship across 47 South African hospitals: an implementation study



Adrian J Brink, Angeliki P Messina, Charles Feldman, Guy A Richards, Piet J Becker, Debra A Goff, Karri A Bauer, Dilip Nathwani, Dena van den Bergh, on behalf of the Netcare Antimicrobial Stewardship Study Alliance*

Summary

Background The available data on antimicrobial stewardship programmes in Africa are scarce. The aims of this study were to assess the implementation of an antimicrobial stewardship programme in a setting with limited infectious disease resources.

Methods We implemented a pharmacist-driven, prospective audit and feedback strategy for antimicrobial stewardship on the basis of a range of improvement science and behavioural principles across a diverse group of urban and rural private hospitals in South Africa. The study had a pre-implementation phase, during which a survey of baseline stewardship activities was done. Thereafter, a stepwise implementation phase was initiated directed towards auditing process measures to reduce consumption of antibiotics (prolonged duration, multiple antibiotics, and redundant antibiotic coverage), followed by a post-implementation phase once the model was embedded in each hospital. The effect on consumption was assessed with the WHO index of defined daily doses per 100 patient-days, and the primary outcome (change in antibiotic consumption between phases) was assessed with a linear mixed-effects regression model.

Findings We implemented and assessed the antimicrobial stewardship programme between Oct 1, 2009, and Sept 30, 2014. 116 662 patients receiving antibiotics at 47 hospitals during 104 weeks of standardised measurement and feedback, were reviewed, with 7934 interventions by pharmacists recorded for the five targeted measures, suggesting that almost one in 15 prescriptions required intervention. 3116 (39%) of 7934 pharmacist interventions were of an excessive duration. The antimicrobial stewardship programme led to a reduction in mean antibiotic defined daily doses per 100 patient-days from 101.38 (95% CI 93.05–109.72) in the pre-implementation phase to 83.04 (74.87–91.22) in the post-implementation phase ($p < 0.0001$).

Interpretation Health-care facilities with limited infectious diseases expertise can achieve substantial returns through pharmacist-led antimicrobial stewardship programmes and by focusing on basic interventions.

Funding None.

Lancet Infect Dis 2016;
16: 1017–25

Published Online
June 13, 2016
[http://dx.doi.org/10.1016/S1473-3099\(16\)30012-3](http://dx.doi.org/10.1016/S1473-3099(16)30012-3)

See [Comment](#) page 982

*Netcare Antimicrobial Stewardship Study Alliance members are given in the appendix

Ampath National Laboratory Services, Milpark Hospital, Johannesburg, South Africa (A J Brink MD); Department of Quality Leadership, Netcare Hospitals, Johannesburg, South Africa (A P Messina BPharm, D van den Bergh PhD); Faculty of Health Sciences, University of the Witwatersrand and Charlotte Maxeke Johannesburg Academic Hospital, Johannesburg, South Africa (Prof C Feldman DSc, Prof G A Richards PhD); Research Office, Faculty of Health Sciences, University of Pretoria, Pretoria, South Africa (Prof P J Becker PhD);

Undergraduate antibiotic stewardship training: Are we leaving our future prescribers ‘flapping in the wind’?

S Afr Med J 2017;107(5):357-358. DOI:10.7196/SAMJ.2017.v107i5.12496

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“A key strategy in facilitating appropriate antibiotic prescribing is the early introduction of the relevant knowledge, concepts and skills into undergraduate curricula.”

South African medical students' perceptions and knowledge about antibiotic resistance and appropriate prescribing: Are we providing adequate training to future prescribers?

S Wasserman,¹ MB ChB, MMed; S Potgieter,² MB ChB; E Shoul,³ MB ChB; D Constant,⁴ PhD, MPH; A Stewart,⁵ MPH;
M Mendelson,¹ MD, PhD; T H Boyles,¹ MD

¹ *Division of Infectious Diseases and HIV Medicine, Department of Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*

² *Division of Infectious Diseases, Department of Internal Medicine, Faculty of Health Sciences, University of the Free State, Bloemfontein, South Africa*

³ *Division of Infectious Diseases and HIV Medicine, Department of Medicine, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa*

⁴ *Women's Health Research Unit, School of Public Health and Family Medicine, Faculty of Health Sciences, University of Cape Town, South Africa*

⁵ *Clinical Research Centre, Faculty of Health Sciences, University of Cape Town, South Africa*

S Afr Med J 2017;107(5):405-410. DOI:10.7196/SAMJ.2017.v107i5.12370

Conclusion. There are low levels of confidence with regard to antibiotic prescribing among final-year medical students in SA, and most students would like more education in this area. Perceptions that ABR is less of a problem in their local setting may contribute to inappropriate prescribing behaviours. Differences exist between medical schools in knowledge about antibiotic use, with suboptimal scores across institutions. The introduction and use of antibiotic prescribing guidelines and greater contact with specialists in antibiotic prescribing may improve prescribing behaviours.



Final thoughts

- South Africa is far from alone in facing the impact of antimicrobial resistance BUT is at the same time a “high burden” country in terms of HIV and TB.
- Although much effort is being expended to track resistance in hospital isolates, less is being done about community isolates, and even less about tracking utilisation, and feeding back to prescribers.