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.

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*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); **Department of Pharmacy, The Ohio State University, Wexner Medical Center, Columbus, OH, USA** (Prof D A Goff PhD, K A Bauer PhD); **and Ninewells Hospital and Medical School, Dundee, Scotland, UK** (Prof D Nathwani MBChB)

Correspondence to: Dr Adrian J Brink, Ampath National Laboratory Services, Milpark Hospital, Parktown, 2193, Johannesburg, South Africa **brinka@ampath.co.za**

See Online for appendix

Introduction

In September, 2015, the Center for Disease Dynamics, Economics & Policy published a report into the state of the world's antibiotics,[1] citing evidence that the overall effectiveness of antibiotics has been decreasing globally and calling for strong antibiotic stewardship in its broadest sense—specifically the reduction of antibiotic overuse in human beings. A Cochrane meta-analysis[2] confirmed that interventions to reduce excessive prescription of antibiotics to inpatients can reduce antimicrobial resistance and improve microbiological and clinical outcomes. However, few studies provide data about the key interventional components and the effectiveness of antimicrobial stewardship programmes in resource-limited settings.[2,3] A global survey[4] of stewardship activities revealed that only 14% of respondents in Africa and 53% in Asia had any form of antimicrobial stewardship programme in place.[4]

Although many methods of improving prescribing practice have been studied, one of the core strategies is the use of prospective audits and feedback.[2,3,5,6] In this approach, investigators review current antimicrobial use and make recommendations with regard to appropriateness in terms of several predefined measurements, all of which can be implemented in health-care facilities irrespective of size.[2,3,6] The most obtainable targets in low-resource settings are unknown. However, limitation of duration of antibiotic use and use of multiple concurrent antibiotics, including redundant coverage, might represent such targets.[6–9]

In South Africa, the main barriers to implementation of antimicrobial stewardship programmes in almost all public and private hospitals have been inadequate infectious diseases expertise and resources; additionally, in large hospital networks, the geographical distribution of these institutions has also hindered implementation. The aim of this study was to assess the reduction of overall antibiotic consumption across a diverse group of 47 urban and rural hospitals in South Africa through the implementation of an antimicrobial stewardship strategy that uses existing resources.

Methods

Study design

In this study, an antimicrobial stewardship programme was implemented in 47 private hospitals operated by Netcare (Johannesburg, South Africa) in seven of the nine South African provinces. The study had three phases.

Research in context

Evidence before this study

We searched PubMed and Google Scholar for reports published in English between inception and Sept 1, 2015, using the terms "antibiotic or antimicrobial stewardship", "pharmacist or specialized pharmacists", "audit and feedback" AND "antibiotic or antimicrobial stewardship", "resource limited", "multicentre", "sustainability". We identified additional studies from the authors' personal reference lists and reference lists from articles that were retrieved, including two systematic reviews of 126 eligible interventions. We excluded studies that did not describe antibiotic stewardship interventions in inpatients, did not have complete key intervention and outcome components, involved surgical prophylaxis, or did not refer to pharmacists. A global survey of reports of antimicrobial stewardship programmes in hospitals in resource-limited circumstances revealed that data on efficacy is sparse and a systematic review published in 2014 revealed that few data were available on outcomes or on key interventional components. Notably, until 2013, no systematic evidence on sustainability or applicability on a wider scale was available. Additionally, the search revealed three other important facts for consideration regarding stewardship interventions. First, the impact of audit in conjunction with feedback to enable self-monitoring as a stewardship strategy—particularly when it includes both goals and action plans—is underestimated. This is supported by a Cochrane review. Second, of all the eligible antimicrobial stewardship programme studies included in the two systematic reviews referred to earlier, only Weinberg and colleagues reported the use of a quality improvement model, specifically an intervention to reduce infections in women undergoing caesarean section in Colombia. Finally, there is a need for alternative stewardship models that use available organisational infrastructure that is not necessarily dependent on or driven by clinical microbiology or infectious disease specialties.

Added value of this study

Our antimicrobial stewardship model, as shown by a sustained reduction (18·1%) in antibiotic consumption in the group as a whole, suggests that successful antimicrobial stewardship programmes can be implemented in a range of geographical and socioeconomic settings by health-care workers without infectious diseases training; that skills beyond infectious diseases are crucial in initiating and maintaining an antimicrobial stewardship programme; that by applying the so-called Pareto principle or Law of the Vital Few (derived from economic theory and implying that 80% of outcomes result from only 20% of potential causes) to antimicrobial stewardship programmes and thus focusing initially on a vital few interventions such as excessive antibiotic duration (>7 or >14 days) or prescription of antibiotics with overlapping or duplicate spectra, organisations can yield substantial returns with the least effort; and that an alternative model for stewardship, dependent on local context and resources, can become embedded within existing systems, a key goal that is often not achieved by many other programmes.

Implications

The implications of the present evidence for antimicrobial stewardship programmes in resource-constrained settings are that to accelerate change the incorporation of contemporary improvement methods and behaviour change principles into a model might represent a core paradigm in which to practise stewardship. In this scenario, we should not underestimate the role of the non-infectious diseases pharmacist in promoting interdisciplinary engagement in stewardship programmes in hospitals or across health systems.

The first phase was the pre-implementation phase, done before formal introduction of the antimicrobial stewardship programme model, followed by an implementation phase and a post-implementation phase.

The private hospitals had 9424 registered beds, which included 1601 intensive care and high-care beds. By contrast with the 64 pharmacists employed at the hospitals, the 4295 doctors are not their direct employees and are self-employed. The study covered a 5-year period between Oct 1, 2009, and Oct 1, 2014.

The model was approved by the executive management and ethical approval was obtained from Pharma-ethics, Johannesburg (registration number 150711996).

Antimicrobial stewardship model

The antimicrobial stewardship programme was implemented using an adaptation of the Institute for Healthcare Improvement Model[10] and the Breakthrough Series Collaborative[11] under the guidance of the Netcare quality improvement director (figure 1). Briefly, initial training sessions detailing the five process measures that would be audited by the pharmacists (panel 1) were provided through face-to-face regional learning sessions with doctors; hospital, pharmacy, and nursing managers; and clinical staff, including infection prevention practitioners from each of the hospitals (learning session 1). Thereafter, in accordance with the Breakthrough Series model, each pharmacist was required to do an implementation process in their hospital by auditing the five measures in inpatients on antibiotics, either in a stepwise manner or all at once.

Subsequently, learning cycles hosted by the quality improvement director and an antimicrobial stewardship programme project manager were held every 6–8 weeks initially, and then as needed once the model was entrenched, either via national teleconferencing with pharmacists and pharmacy managers or through face-to-face hospital (pending the need for on-site assistance) and regional workshops. In between these learning sessions,

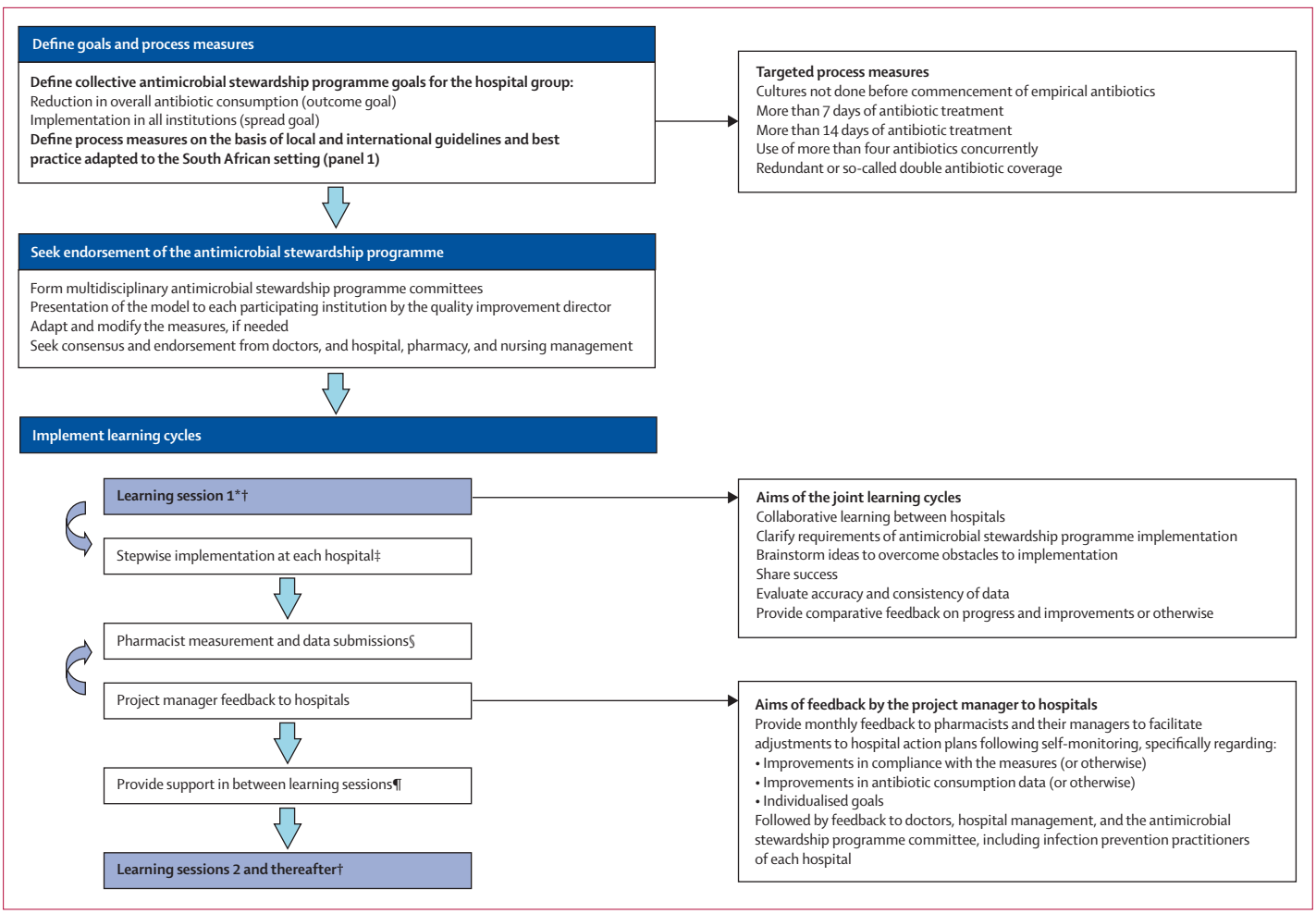

***Figure 1*: Netcare antimicrobial stewardship Breakthrough Series Collaborative model for group-wide implementation and monitoring process (47 hospitals)**
*Provide initial training for the five process measures through regional workshops. †Quality improvement director and project manager host shared learning sessions with participating institutions every 6–8 weeks initially and then as required, once the model is entrenched, either via national teleconferencing with pharmacists and pharmacy managers or via regional or hospital workshops (pending the need for on-site assistance). ‡Pharmacists audit the process measures either in a stepwise manner or by adopting all five at once; similarly implementation could occur in the hospital as a whole or initially in intensive care and high-care units, followed by wards pending time and resources. §Pharmacists record interventions on a standardised template every week and submit to a project manager every month. ¶Project manager provides intensive support via email, telephone consultations, regional workshops, and face-to-face site visits, if needed.

support was provided by the project manager. After obtaining permission from the front-line doctors, pharmacists recorded interventions weekly on standardised templates, which were submitted monthly via email to the project manager who in turn provided monthly feedback (improvements in compliance with the measures or otherwise), including antibiotic consumption data and individualised goals to the pharmacists and their managers of each institution. The pharmacists would then provide feedback on the progress of implementation and changes in antibiotic consumption to doctors, hospital management, and the antimicrobial stewardship programme committees, including infection prevention practitioners of each hospital. The quality improvement director and project manager obtained additional input from doctors during subsequent 12 monthly, face-to-face regional learning sessions.

Antimicrobial stewardship interventions

We chose the five process measures on the basis of a previous survey of private and public hospitals in South Africa, in which excessive antibiotic consumption was found to include prolonged duration, multiple concurrent antibiotics, and redundant coverage.[9] The quality improvement director and local experts defined the measures according to local and international guidelines and best practice adapted to the South Africa setting (panel 1).[9,12,13] For all interventions, pharmacists consulted the doctor before changes were made. This consultation was done verbally or by written or mobile phone messages. Only systemic (parenteral and oral) antibiotic use was audited. Exclusions from pharmacist audit included surgical prophylaxis; disorders requiring protracted antibiotics such as infective endocarditis, osteomyelitis, and septic arthritis; and treatment regimens in which multiple

Panel 1: Definition of the process measures*

Cultures not done before commencement of empirical antibiotics
Patients started on empirical antibiotics and no cultures done within 48 h before or on initiation of treatment.

More than 7 days of antibiotic treatment
Prolonged duration of treatment (continued for 8–14 days [inclusive])—ie, antibiotic treatment duration exceeded the length deemed appropriate for effective treatment of that particular infection according to local guidelines.

More than 14 days of antibiotic treatment
Prolonged duration of treatment (continued beyond 14 days)—ie, antibiotic treatment duration exceeded the length deemed appropriate for effective treatment of that particular infection according to local guidelines.

More than four antibiotics at the same time
The unintentional† overprescribing and concurrent systemic use of four or more antimicrobials in a given patient on the same calendar day for at least 2 consecutive days.

Concurrent double or redundant antibiotic coverage‡
The intentional§ concurrent administration of two or more antibiotics with overlapping or duplicate spectra in terms of Gram-negative, Gram-positive, and anaerobic cover, on the same calendar day for at least 2 consecutive days. Redundant coverage can be subdivided into three categories. First, redundant Gram-negative coverage: defined as the concurrent administration of two or more of any of the following drugs in or between groups: cephalosporins (cefuroxime, ceftriaxone, ceftazidime, cefotaxime, and cefepime), fluoroquinolones (ciprofloxacin and levofloxacin), β-lactam plus β-lactamase-inhibitor combinations (amoxicillin/clavulanate and piperacillin/tazobactam), aminoglycosides (amikacin, gentamycin, and tobramycin), carbapenems (meropenem, ertapenem, doripenem, and imipenem), and tigecycline. Second, redundant Gram-positive coverage: defined as the concurrent administration of two or more of any of the following drugs in or between groups: β-lactams (amoxicillin, amoxicillin-clavulanate, cefazolin, and cloxacillin), tigecycline, clindamycin, linezolid, and glycopeptides (vancomycin and teicoplanin). Third, redundant anaerobe coverage: defined as the concurrent administration of two or more of any of the following drugs in or between groups: metronidazole, β-lactam plus β-lactamase-inhibitor combinations (amoxicillin/clavulanate and piperacillin/tazobactam), carbapenems (meropenem, ertapenem, doripenem, and imipenem), moxifloxacin, clindamycin, cefoxitin, and tigecycline.

*For all process measures, doctors were consulted before any changes were effected. †We defined unintentional prescribing errors by doctors as inadvertent prescription of multiple antibiotics, incomplete knowledge of the patient's antimicrobial regimen (eg, multiple doctors' prescriptions for the same patient), or failure to discontinue previous treatments on initiation of a new antibiotic.[12] ‡In consultation with the doctor, ascertainment of the clinical indications for each episode was necessary to determine the appropriateness of the potentially redundant antibiotic combination. §We defined intentional prescribing errors by doctors as antibiotic combinations prescribed with intended overlap but which, according to local best practice and guidelines, are insufficiently proven or provide likely clinical benefit.[12]

antibiotics were used for prophylaxis or treatment of *Pneumocystis jirovecii*, mycobacteria, *Clostridium difficile*, or combination treatment for carbapenemase-producing Enterobacteriaceae, *Pseudomonas aeruginosa*, *Acinetobacter baumanii*, and *Staphylococcus aureus*.

Procedures

The pre-implementation phase involved a quantitative, non-uniform survey of stewardship activities, in which hospitals were requested to provide monthly details of stewardship activities, if any, to the quality improvement director who monitored such activities including individual hospital and overall group antibiotic consumption. During this period, the quality improvement director recruited pharmacists by means of a "call for champions" for those who wanted to develop stewardship skills. No incentives to participate were provided.

In the implementation phase, the model was introduced in a stepwise manner under executive group order and direction. The key components that were crucial to the implementation of the model are described earlier and summarised in panel 2. We chose an arbitrary conservative 10% reduction in overall group antibiotic consumption on the basis of high pre-implementation consumption and in view of that many hospitals were being introduced to an antimicrobial stewardship programme for the first time.

The post-implementation phase commenced with the completion of the implementation phase and an audit of all of the process measures in place in all units of each hospital. In this phase, monthly submission of data to the project manager for group-wide monitoring was made compulsory as part of the performance management assessments. Learning cycles every 6–8 weeks via teleconferences and on-site face-to-face meetings (pending need for support) were continued in this phase. Regular feedback and individualised process improvement and consumption goals were also continuously provided during this phase to facilitate adaptation of hospital action plans following self-monitoring. To stimulate further improvements, the project manager provided feedback to all hospitals on their compliance with the measures and the subsequent effect on antibiotic consumption by means of comparative tables (47 hospitals) and multiple graphs (47 hospitals).

We calculated hospital and group antibiotic consumption from hospital dispensing data using WHO's Anatomical Therapeutic Chemical index; the primary parameter was defined daily doses (DDDs) per 100 patient–days. Additionally, we analysed 104 weeks of

***Panel 2*: Key components of implementing the antimicrobial stewardship model**

- Formalise measurable goals for the hospital group (quality improvement director). The aim was to achieve at least a 10% reduction in antibiotic consumption and implement the antimicrobial stewardship programme in 33% or more of the institutions at 6 months, 66% of the institutions at 12 months, and 100% of the institutions (n=47) at 24 months.
- Form antimicrobial stewardship programme committees (consisting of hospital, pharmacy, and nursing managers; pharmacists; infection prevention practitioners; doctors; and, if available, clinical microbiologists) and consult with prescribers to ensure endorsement of the antimicrobial stewardship programme.
- Mandate so-called protected pharmacist stewardship time to do antibiotic audit rounds.
- Audit the five process measures (panel 1) either in a stepwise manner or all five at once.
- Develop and launch (through regional training workshops) a toolkit consisting of a standardised template using Microsoft Excel to facilitate uniform process measurement and data recording.
- Record the pharmacist's interventions every week for all inpatients on antibiotics either initially in the intensive care and high-care units and thereafter in selected wards or in all units at once.
- Submit data every month to an antimicrobial stewardship programme project manager via email.*
- Provide feedback to the pharmacists regarding progress of implementation, improvements (or otherwise) in the five measures, and antibiotic consumption delivered in both written (monthly emails) and verbal format during learning cycles.
- Concurrently, define and provide individualised hospital implementation progress, process improvement, and antibiotic consumption goals on the basis of historical trends.
- Regular (every 1–3 months) verbal and written feedback to doctors, hospital managers, and the antimicrobial stewardship programme committees, including infection prevention practitioners, of each hospital.
- Adapt action plans following hospital self-monitoring according to how many of the targeted interventions had been implemented, what improvements had taken place, and what the effect on individual hospital antibiotic consumption had been.
- Stimulate further improvement by providing feedback on the progress of the antimicrobial stewardship programme and its effects on compliance with the measures and antibiotic consumption via monthly emails to all hospitals in the form of comparative tables and graphs.†

*In the post-implementation phase, submission of monthly data to the project manager was compulsory. †Comparative graphs and tables were introduced in the post-implementation phase (n=47).

standardised data for the five measures, for each hospital. We calculated all percentages relative to the number of patients seen on pharmacy rounds. We calculated the percentage of patients using the number of patients in whom the targeted interventions had been implemented as the numerator and the number of patients on antibiotics as the denominator. The project manager measured improvements in the five process measures according to the run chart rules described by Langley and colleagues[10] and Perla and colleagues,[14] and feedback was provided as described previously (figure 1, panel 2).

Statistical analysis

For the primary analysis, we assessed change in antibiotic consumption between pre-implementation and post-implementation of the antimicrobial stewardship programme. We compared monthly DDD per 100 patient–days for the 16 months' pre-implementation phase with that for the 20 months' post-implementation phase. Data collection, within each of the 47 participating hospitals, was prospective and at fixed-time intervals. We used a linear mixed-effects regression model to assess the relation between the response variable (DDD per 100 patient–days) and the fixed-effects (pre-implementation and post-implementation), time, and their interaction. We specified hospitals as the random-effects component with an intercept and time as a covariate, using an independent covariance structure. We did testing at the 0·05 level of significance.

For the secondary analysis, we described the progression with implementation of the model and the improvement in antibiotic consumption during the 60 month study period in three phases (pre-implementation, implementation, and post-implementation of the antimicrobial stewardship programme). We fit a linear piecewise regression with nodes at 16·5 and 40·5 months to monthly DDD per 100 patient–days to quantify the rate of change in monthly antibiotic consumption during these three phases. We used a linear mixed-effects regression model to assess the relation between the response variable (monthly DDD per 100 patient days) and the fixed-effect time, reparameterised to the three phases. We specified hospitals as a random-effects component with an intercept, reparameterised times as covariates, and used an independent covariate structure.

We recorded standardised measurement of the five measures targeted for improvement, aggregated for the group of hospitals, for 104 weeks and graphically illustrated the data using local polynomial smoothing. We applied the default bandwidth, determined by Stata Release 13 statistical software, to each intervention (5·129 for no cultures done before empirical treatment;

5·749 for antibiotic treatment duration of more than 7 days; 4·531 for more than 14 days of antibiotic treatment; 5·126 for patients on four or more antibiotics; and 6·324 for concurrent redundant antibiotic cover).

Role of the funding source

There was no funding source for this study. The quality improvement director, the project manager, and all authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Figure 2 displays the mean monthly antibiotic consumption (DDDs per 100 patient–days) during the three phases of the stewardship model.

During the pre-implementation phase (Oct 1, 2009, to Jan 31, 2011), no stewardship activities were practised in 41 (87%) of the 47 hospitals. In six of the hospitals (13%), stewardship consisted of one or more of the following: occasional multidisciplinary rounds (n=4) or irregular didactic lectures (n=5), or both, and prospective audit and feedback rounds (n=2) including inconsistent use of antibiotic prescription charts (n=2). None of the hospitals had local antibiotic policies or guidelines. Hospital managers were not involved, antimicrobial stewardship programme committees did not exist, and reporting and feedback of data were haphazard. Measurement of antibiotic data showed stagnant or increasing consumption (figure 2). The overall mean consumption of antibiotics was 101·38 DDD per 100 patient–days (95% CI 93·05–109·72).

During the implementation phase (Feb 1, 2011, to Jan 31, 2013), we revised goals to increase implementation and to reduce individual hospital consumption throughout 31 learning cycles. By September, 2011, 17 (36%) of the 47 hospitals had implemented the model and by February, 2012, 32 (68%) were doing the targeted stewardship interventions. A staggered approach to implementation of the five interventions took place and by September, 2012, 40 of the hospitals (85%) were auditing all five.

By the post-implementation phase (Feb 1, 2013, to Sept 30, 2014), the model had been embedded in pharmacist practice, with daily auditing of the five targets for improvement, becoming the routine standard of care for inpatients receiving antibiotics. 22 learning cycles were held and benchmarking, by means of comparative tables and multiple graphs describing the success

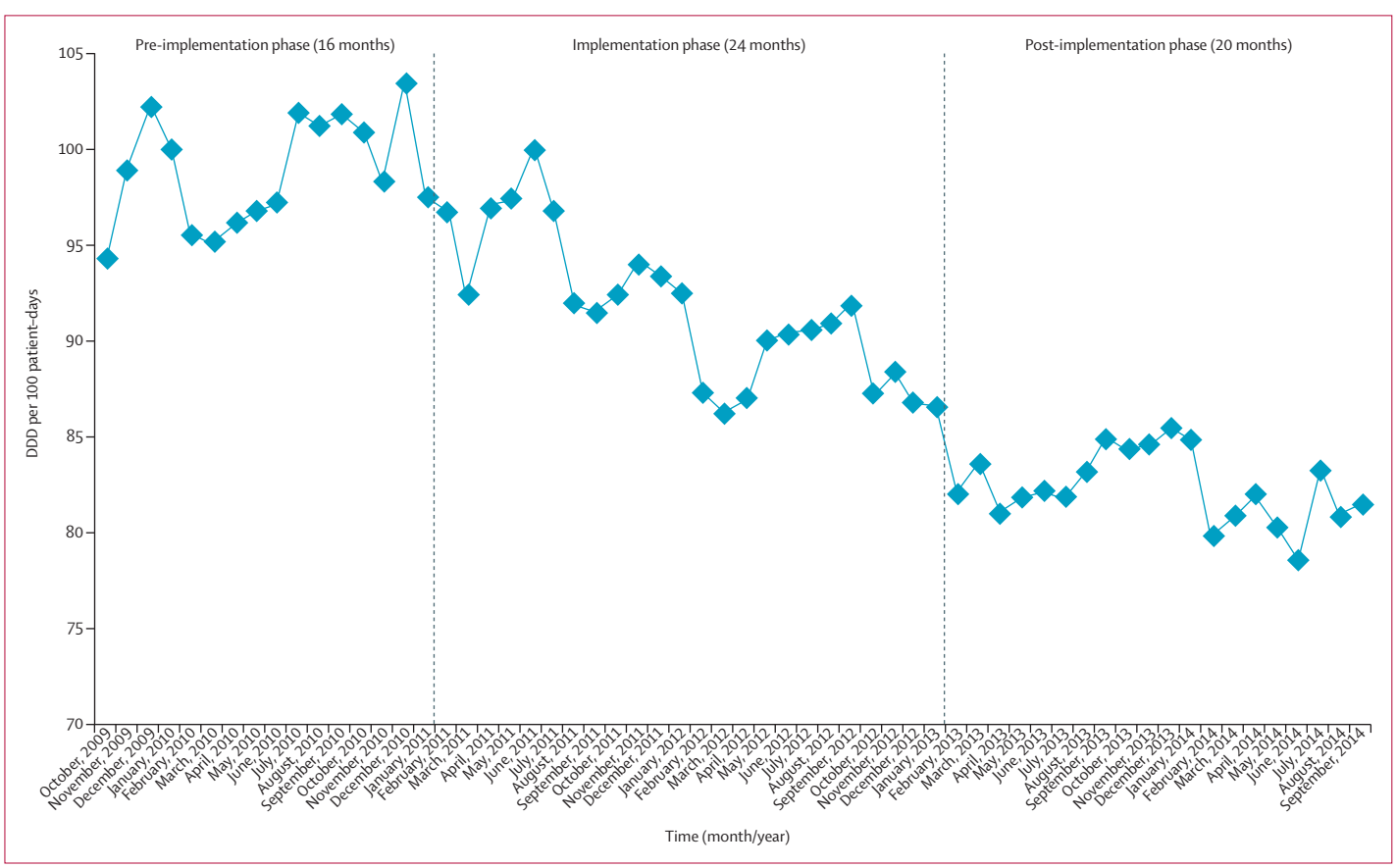

Figure 2: **Longitudinal cohort survey of mean antibiotic consumption for three phases of the Netcare antimicrobial stewardship model**
The entire study took place between Oct 10, 2009, and Sept 30, 2014, in 47 hospitals. Mean antibiotic consumption is measured in defined daily doses (DDDs) per 100 patient days.

	Pharmacist interventions (N=7934)
Cultures not done before commencement of empirical antibiotics	2971 (37%)
More than 7 days of antibiotic treatment*	2615 (33%)
More than 14 days of antibiotic treatment*	501 (6%)
More than four antibiotics at the same time	739 (9%)
Concurrent double or redundant antibiotic coverage	1108 (14%)

*Collectively prolonged duration represented the majority of pharmacist interventions (3116 [39%] of 7934).

***Table*: Proportion of patients needing pharmacist interventions for each of the five targeted areas of improvement**

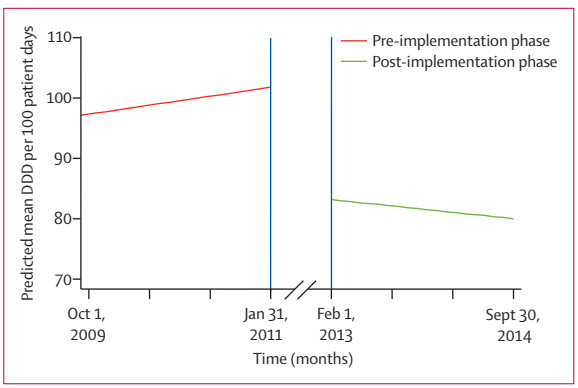

***Figure 3*: Predicted mean antibiotic consumption for the pre-implementation and post-implementation phases**
Mean antibiotic consumption is measured in defined daily doses (DDDs) per 100 patient–days. More detail is available in the appendix.

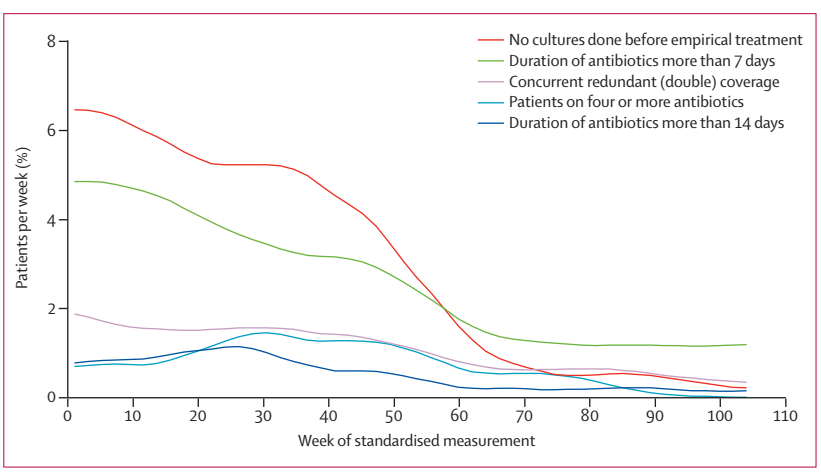

***Figure 4*: Local polynomial smoothed curves for the five parameters targeted for improvement (weeks 1–104)**
More detail is available in the appendix.

or otherwise of each hospital or region, led to competitiveness, particularly among pharmacists and doctors. Mean consumption during this phase was 83·04 DDD per 100 patient–days (95% CI 74·87–91·22).

During 104 weeks of standardised measurement, 116 662 patients on antibiotics were reviewed with 7934 interventions recorded for the five targeted variables, suggesting that one in 14·7 prescriptions required an intervention. As depicted in the table, the greatest improvement was seen in the duration of treatment.

In the primary analysis, the linear mixed-effect regression model detected a significant (p<0·0001) reduction of 18·34 (95% CI 15·92–20·76) in mean DDD per 100 patient–days after implementation of the antimicrobial stewardship programme. The interaction between the fixed effects and time was also significant (p=0·004), as shown by the different slopes in figure 3.

By contrast with the implementation phase, in which the rapid reduction in monthly antibiotic consumption was significant (β_2 –0·559; p<0·0001), the rate of change during the pre-implementation phase was not significant (β_1 0·064; p=0·622), and during the post-implementation phase the change in DDD per 100 patient–days per month was slower (β_3 –0·203; p=0·054; appendix). Figure 4 shows the polynomial smoothed plots for the five main areas targeted for improvement. Limited pharmacist intervention was necessary or required after 60–72 weeks and this was sustained until the end of the study (figures 2 and 4).

Discussion

This multicentre antimicrobial stewardship initiative, led by non-specialised pharmacists, reduced antimicrobial prescribing across a large network of urban and rural hospitals in an infectious diseases resource-limited setting. The significant overall reduction in antibiotic DDD per 100 patient–days (of 18·1%, 95% CI 15·71–20·4) confirmed that antimicrobial stewardship is possible despite most hospitals never having practised stewardship before, the wide geographical distribution, the large number of hospitals involved, and the necessity to coordinate the interventions throughout all the hospitals simultaneously.

Very few data are available for the implementation of antimicrobial stewardship programmes on the African continent.[4] A study[15] from an academic teaching hospital in South Africa introduced an antibiotic prescription chart and a weekly stewardship ward round that led to a 19·6% reduction in consumption. This programme required intensive infectious diseases resource input and is not representative of present infectious diseases resourcing in South African hospitals. An alternative model, in which doctors, pharmacists, and nurses without specialised training in infectious diseases, and other health-care providers such as infection prevention practitioners, lead and support the delivery of stewardship activity is perhaps more relevant. This view is exemplified by the effect of another pharmacist-driven process improvement intervention in the same hospitals, which resulted in a significant change in the timing of administration ("hang-time") of intravenous antimicrobials in more than 32 000 patients.[16] The increasing role of pharmacist-led antimicrobial stewardship activities has also been

substantiated by implementation in English hospitals.[17] The creation of such alternative models for stewardship that can be embedded within existing systems is dependent on local context and resources and is key to success across diverse settings.[18]

Our study findings support the creation of alternative models to decrease antibiotic overprescribing as a possible approach in South African hospitals. Although some people might question the applicability of our findings to the public sector where most of the population in South Africa receive health care, we would contend that, despite insufficient infectious diseases expertise, this model could be valuable in view of the similar documented overprescribing practices.[9] Successful implementation of the model would require commitment from organisational leadership and tailoring of systems and resources to support the key role of pharmacists in the monitoring, implementation, and feedback process. The crucial role of the development and use of a range of behavioural and improvement science skills beyond those of infectious diseases and microbiology[16,19,20] cannot be underestimated if sustainable success is to be achieved. Our study findings suggests that this antimicrobial stewardship model not only had an effect during the implementation phase but also a sustained benefit once the process was embedded within the existing system.

The study has several limitations. First, we did not record patient outcomes as a means of defining the success of the model. Although the optimum measure of the success of an antimicrobial stewardship programme includes the assessment of both process and outcome, comparison of DDDs of one hospital or region with another was an important stimulus to quality improvement, particularly among doctors and pharmacists, for whom comparisons had the potential to trigger change. Second, we did not have knowledge of the patient location, such as whether they were in an intensive care unit or not, and therefore we could not determine in which environment the model had the biggest effect. However, our aim was merely to implement the antimicrobial stewardship programme model in all participating hospitals. Nonetheless, data about patient location are now being recorded in the study hospitals where the antimicrobial stewardship programme is ongoing. Third, the low-hanging fruit concept used in this study represented only the most basic interventions, but their implementation could nevertheless make a difference.[7]

One of these interventions was to ensure that cultures were taken before initiation of empirical antibiotics, a practice that is poorly performed in South Africa and elsewhere.[9,21] Although not a target in the present study, increased compliance with this intervention facilitates de-escalation and reassessment of treatment.[13,22] In a survey[9] in South African ICUs, antibiotic duration was inappropriate in 53·2% of patients in the public sector and 81·7% of patients in the private sector. As such, excessive duration unsurprisingly represented most (39%) of our pharmacist interventions. In support of the choice of this intervention, several studies have shown that a shorter duration of antibiotic treatment is equivalent to the traditional longer durations.[13] We made the decision to restrict the number of concurrently administered antimicrobials mainly because previous treatments are not necessarily discontinued on initiation of a new antibiotic.

Unnecessary combinations of antibiotics with overlapping spectra also represent a form of overprescribing. Redundant antibiotic combinations, used mainly for Gram-positive and anaerobic organisms, constitute a substantial proportion of antimicrobial regimens.[12] The reasons for this overprescribing are unclear although a potential explanation is that many prescribers provide broad coverage "to get it right the first time" without the requisite knowledge of the overlapping spectra of activity. In our experience, redundant combinations are an easy target for stewardship because they are fairly straightforward to identify without time-intensive audits.

Future research should investigate the behavioural determinants that influence local antibiotic prescribing practices and whether compliance with antimicrobial stewardship programme measures would be enhanced by including the prescribing doctors in the design of more complex pharmacist-driven interventions. This inclusion might be of particular importance in settings where doctors are not employed by the hospitals. Additionally, as shown recently in a systematic review,[23] sparse information is available on the financial impact and cost-effectiveness of stewardship interventions in different resource settings—potentially a promising topic for research.

In conclusion, although the implementation of a successful antimicrobial stewardship programme is a challenge in any health-care setting, non-academic and rural hospitals present unique challenges. We believe stewardship should be approached by means of a stepwise implementation of process improvement initiatives and principles targeted to institutional needs. By focusing on the so-called vital few (interventions),[24] health-care facilities with limited resources and infectious diseases and microbiology expertise can have a substantial effect on antibiotic use with less effort, while embedding antimicrobial stewardship practices within existing resource structures and systems. This focus on key interventions ensures sustainability and provides a platform for targeting more complex stewardship interventions in the future.

Contributors

DvdB conceived and designed the study. AJB, DAG, and DN did the scientific literature search. DvdB and APM prepared the data. AJB, APM, DN, and DvdB did the analysis. PJB did the statistical analysis. All authors interpreted the data, wrote the report, and approved the final version.

Declaration of interests
We declare no competing interests.

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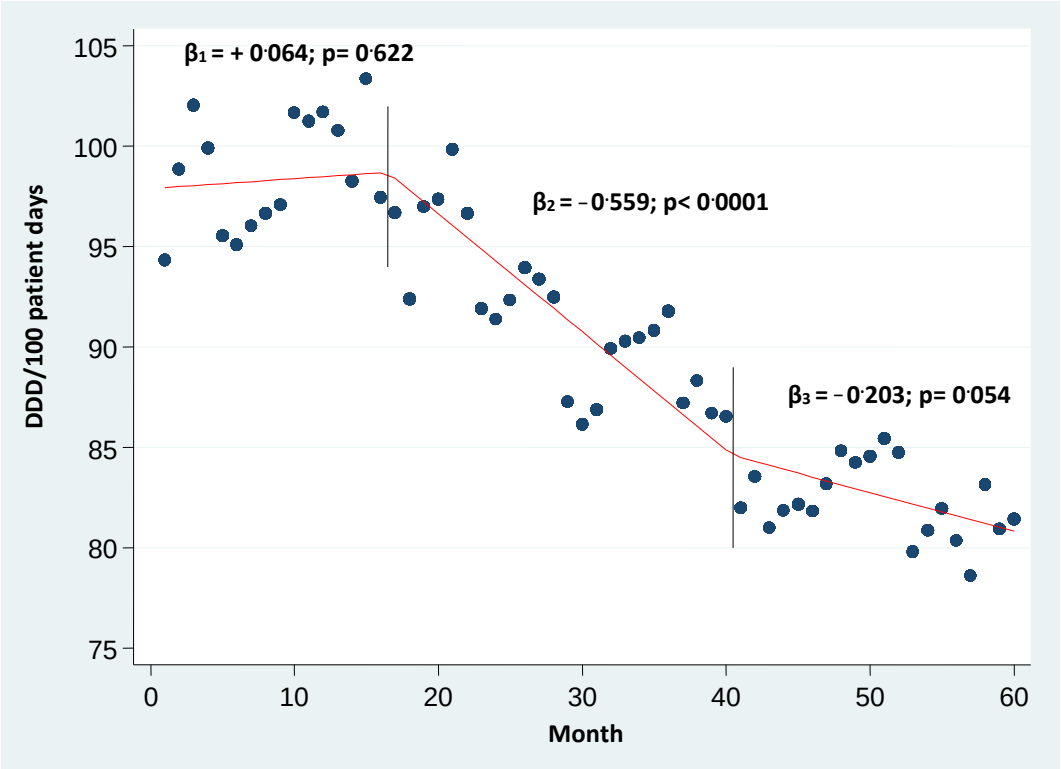
Supplementary webappendix

This webappendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

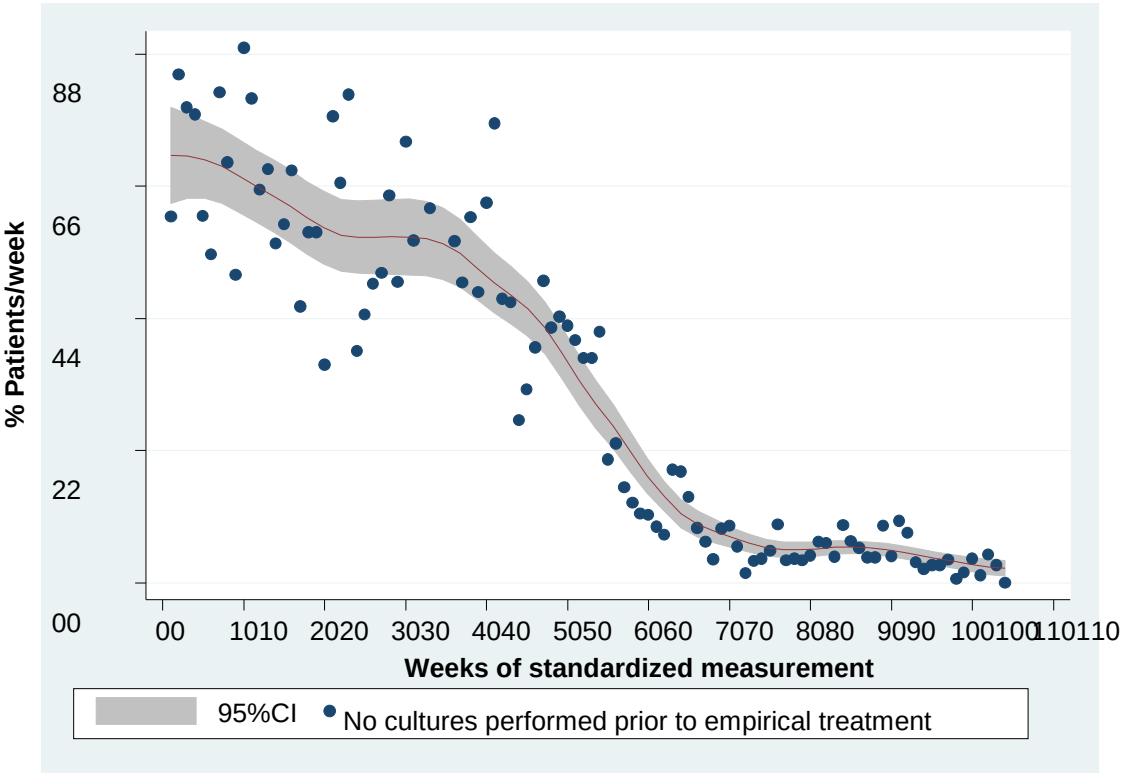
Supplement to: Brink AJ, Messina AP, Feldman C, et al, on behalf of the Netcare Antimicrobial Stewardship Study Alliance. Antimicrobial stewardship across 47 South African hospitals: an implementation study. *Lancet Infect Dis* 2016; published online June 13. http://dx.doi.org/10.1016/S1473-3099(16)30012-3.

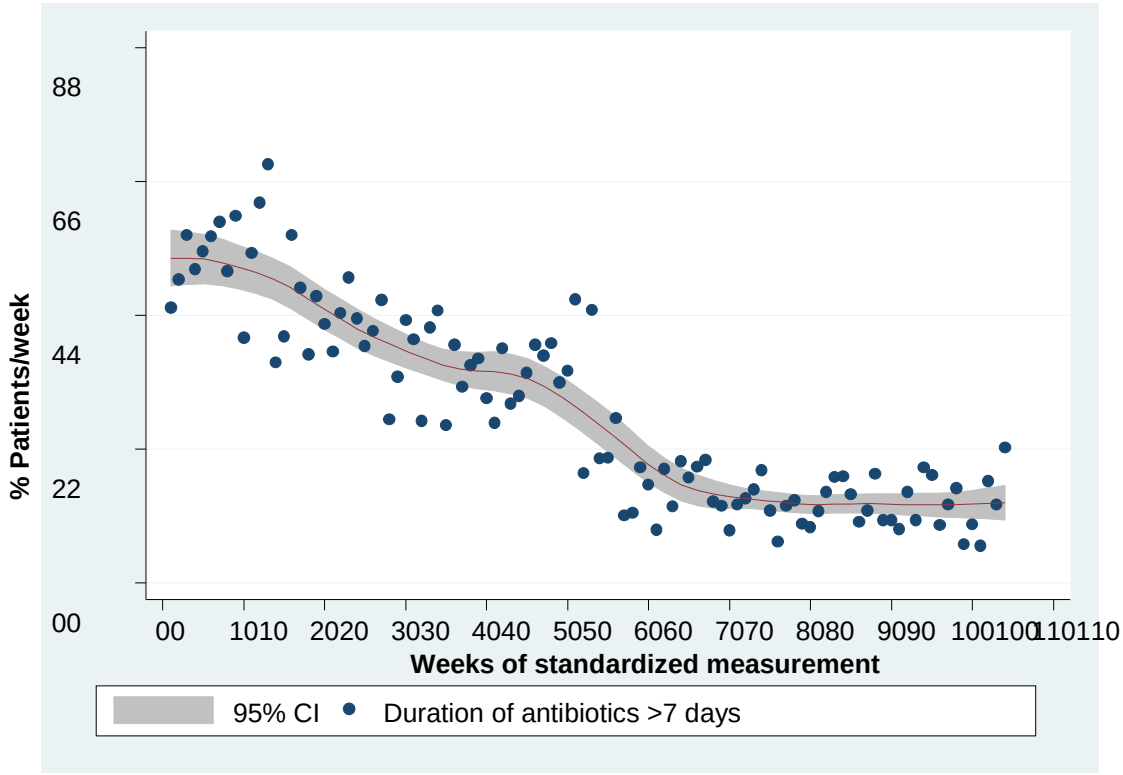
Figure 5: Piecewise linear regression of monthly antibiotic DDDs/100 patient days over 60 months

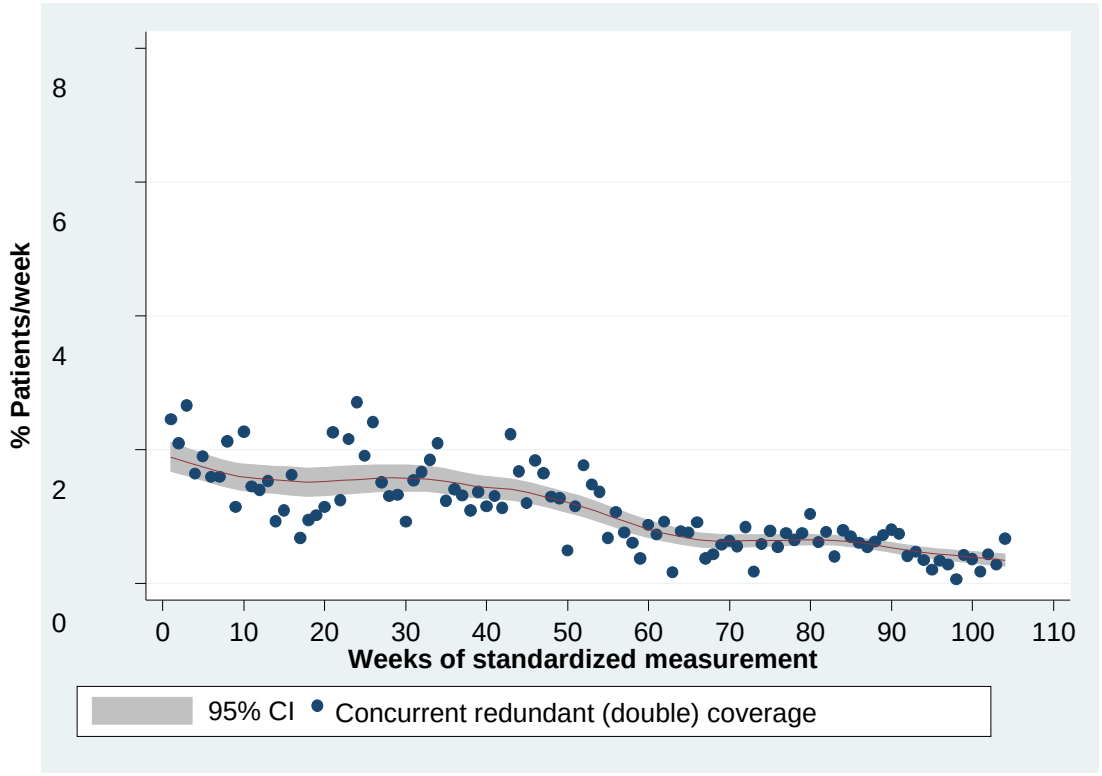


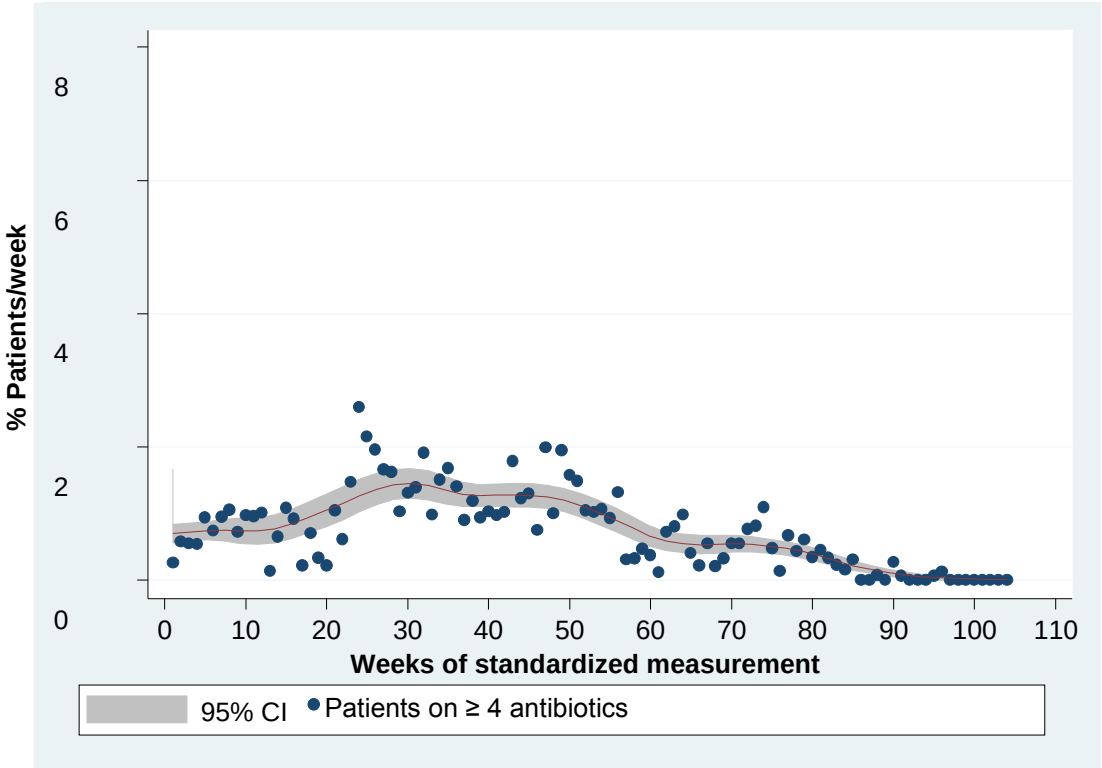
DDD: Defined daily doses
β1, β2, β3: Rate of change in monthly antibiotic consumption in pre-implementation, implementation and post-implementation phases
The scatter displays monthly mean DDDs, whilst the piecewise linear regression line was obtained using the full dataset

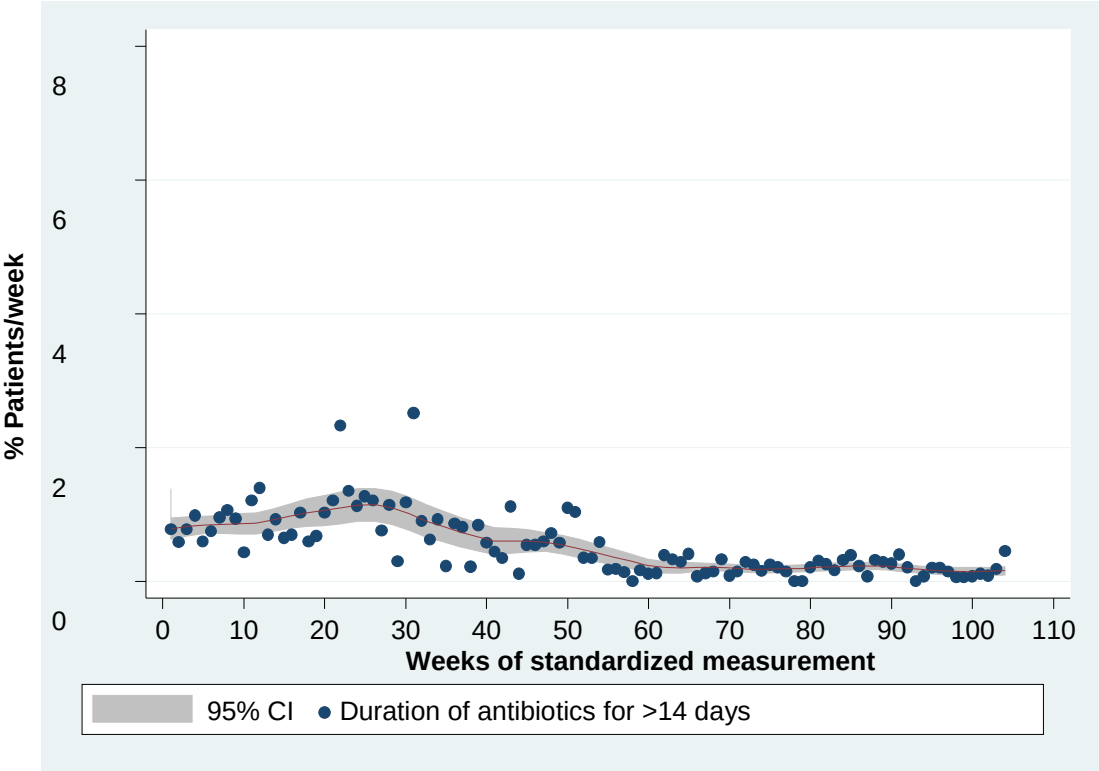
***Figure 6*: Individual graphs displaying data points and 95% CI of local polynomial smoothed curves for the five process measures targeted for improvement**






% Patients/week
0
2
4
6
8
0
10
20
30
40
50
60
70
80
90
100
110
Weeks of standardized measurement
95% CI
Concurrent redundant (double) coverage


% Patients/week
0
2
4
6
8
0
10
20
30
40
50
60
70
80
90
100
110
Weeks of standardized measurement
95% CI
Patients on ≥ 4 antibiotics



CI: Confidence interval

Netcare Antimicrobial Stewardship Study Alliance (NASSA)

Antimicrobial Stewardship Working Group Leadership
(A Messina, D van den Bergh, I Jenkinson, K Swart, L Devenish, L Vieira, N Singh, T Bester, V Gokool- Sewram).

Clinical Microbiologists
(A. Esterhuysen, AK. Peer, B. Jordan, B. Prinsloo, C. Bamford, C. Corcoran, C. Moore, C. Soldin, C.Govind, E. Hoosien, E. Silberbauer, F. Botha, GJJ. Moolman, HCJ. van Rensburg, I. Zietsman, J. Coetzee, J. Du Bruyn, J. Smit, J. Trussler, J. van Greune, JD. Deetlefs, K. Moodley, L. Marcus, L. Nutt, M. Botha, M. Mennen, M. Moodley, M. Myburg, M. Passman, M. van Rensburg, N. Janse van Rensburg, PA. Ekermans, R. Bohmer, R. Gandy, R. Writes, RF Botha, S. Budavari, S. Khan, S. Martin, S. Miller, S Sithole, T. Marshall, T. Moeletsi, T. Vanmali, W. Lowman, X. Poswa).

Hospital ASP Committees

Netcare Akasia hospital (A. Marais*, A Nadarajah, BJ Mphahlele*, C Coetzee, CT Kuzwayo*, G Lukhele, GJM Wolmarans*, H Tladi*, J Pretorius, M Mchenga* M Tshabalala); **Netcare Alberlito hospital** (A Maharaj, A Naidoo*, I Lander*, J Voerman*, L Lekha*, M Abraham, S Maharaj, S Nayager, U Maharaj); **Netcare Bell street hospital** (A Moosa**,** A Lombard, B Welgemoed, C Samb, M Motsoane); **Netcare Blaauwberg hospital** (A Coetzee, A Kistan*,C O'Brien, D Truter, K Barnard*, N Barnes, S Ninham, T Kotze*, W Chaaban*); **Netcare Bougainville hospital** (C Coetzee, L Joubert, N van den Heever, R de Kok, T Palane); **Netcare Christiaan Barnard hospital** (A Wilbers, C Tilney, E Gaertner*, E Steyn*, G Kantor*, J O'Brien*, M Leadsom, M Raff*, N Schlapoberskry*, O Thanning*, M Griesel, P Budnik*, R van Dyk*, S Lison*, V Cilliers); **Netcare Clinton hospital** (D. Demopolous*, E Abrahams, E Human, M Myburgh, S Mhlongo, S Persotam); **Netcare Cuyler hospital** (A van den Bergh*, C Beckley, E Musoke*, F Sirkhotte, K Schutte, R van Wyk, W Kurten); **Netcare Femina hospital** (C Erasmus, C. Schuman*, G Jones, J Breedt, J de Wit*, I Mulder*, L Hamilton, L van Tonder, M Kriel, N Bagwan*, V Naidoo*); **Netcare Ferncrest hospital** (A Schoembee, C Stassen, M van der Walt, N Jumna, L Lethuli); **Netcare Garden City hospital** (A Seedat*, D Mokwele*, J Sandows, L Singh*, M Kharodia, N Moshesh*, P du Toit*, R Naidoo*, S Mckaw, V Booysen, Z Birkenstock); **Netcare Greenacres hospital** (A Bothma, B Stamps, C Naested, G Heuff, L Stone, M Kambale*, M Langehoven*, S Cullis); **Netcare Jakaranda hospital** (L Jacobs, L Kirsten*, L Roets, M Laubscher, P Botha, W van den Bergh); **Netcare Kingsway hospital** (A Demetriou, B Lehnerdt, M

Abdool-Gaffar*, M Amod, S Thompson, Z Randeree); **Kokstad private hospital** (B Craig, H Groeneveld*, K Smith, M Craig, M Ngubo, P Fynn); **Netcare Kroon hospital** (B van Graan*, C Brink*, E Parkin, J Rood*, M Claasen, M Grobler, S le Roux, T Hugo); **Netcare Krugersdorp hospital** (A Moosa, A Saaiman, C de Hoog*, C Samb, C Wehrstedt, G Brand*, H Vermooten*, L Maimani, M Motsoane); **Netcare Kuils River hospital** (C Bezuidenhoudt, C Stephanus, D Plekker*, J de Wet*, L Jannetjies , M Gal, N Daniels, S van Wyk); **Netcare Linksfield hospital** (C Els*, D Verweerd, E Cutler, E Bock, I Hunt*, J Sochen*, M Erasmus, M Hockman*, S Kolman); **Netcare Linmed hospital** (A Abrahams, A Berry, C Dubert*, D de Bruin*, DL Bruce*, I Joubert*, I van Rensburg, M du Plessis*, M van der Merwe, P Marais*, Q Koen*, SG Smit*, S Jacobs, S Sheik*); **Netcare Margate hospital** (A Flowerday, C Potgieter, J Gopiechand, L Mortlock, R Ferreira); **Netcare Milpark hospital** (A Gillis, C Bodika-Caninda, H Geertsema, H Pahad*, J Moloisi, K Boffard*, M Sussman*, P Williams*, R Saloojee, R van der Watt, S Hoosain, S Sallie, W Smith); **Netcare Montana hospital** (AG Burger*, Adele Colyn, A van der Westhuizen, D Slabbert, J Koning*, L Hardy*, L Johnson-Loots*, R Bosman, R Dhilraj, RE Zeelie*); **Netcare Moot hospital** (C Wessels*, E Read, JA Myburgh*, M Nkala, M. Vermeulen, P Botha, T Bezuidenhout, T Venter); **Netcare Mulbarton hospital** (A Pienaar, A Wessels, D Somwe*, M Khoza, N Koen, N Nkosi, T Chacko*); **Netcare N1 City hospital** (A Potgieter*, A van Wyk, J Jacobs*, K van der Walt, L Blom, M Kielblock, M vd Walt, R Brown, , Z Els*); **Netcare N17 hospital** (A Joubert, A Schutte, A Stone, A Zambakides*, JJ vd Merwe*, P Naicker, U Mahomed); **Netcare Olivedale hospital** (A Savvidou*, B Welman, F Skosana*, G Bartman, G Fotheringham*, K Smith, L Fourie, M Weideman); **Netcare Parklands hospital** (A Kalpee*, F Salie, HI Rajput*, K Naidoo, L Sitharam, M van Staden, RN Nadar*, S Khoosal); **Netcare Parklane hospital** (C Venter, D Legari, G Mngola, M Janse v Rensburg, N Stoykova*, R Butler); **Pelenomi Private hospital** (A Modise, E Hugo, K Mvila, S Masalla, W Japtha, Y Williamson,); **Port Alfred hospital** (A Rex, F Sirkotte, J Houston, M Stiglingh, V Mutle); **Netcare Pretoria East hospital** (B Rood, C Beukes, C Kaalsen, D Kruger, E Pavkovich, J Morare, T Dinwoodie, W Sieling*, Y Hurwitz); **Netcare Rand hospital** (A Angwin, A Carrim*, C Mabuza, C Venter, G Mngola, JCL Mbuyamba*, P Ngewu); **Netcare Rehabilitation hospital** (A Bester, E du Preez, M van Vuuren, S Chothia, V Wilson*); **Netcare Rosebank hospital** (A Kala, A Kreusch*, B Levy*, D Chetty, G Cox*, G Lorge*, G Smith, L Bossert, L Francis, V Chathury*); **Settlers hospital** (A Rex, F Sirkotte, M Norden, V Mutle); **Netcare St. Anne's hospital** (A Ballim, A Norman, B Cullis*, L Joubert, N Naidoo, S Singh); **Netcare St. Augustine's hospital** (A Dorning*, B Collins, B Kara, D Chunnilall, F Moola, I Abdulla*, J Pieterse, K Naidoo, L Kalideen*, S Akoojee*, Y Moosa*); **Netcare Sunninghill hospital** (A Bornman, B Hewitt, D Campbell*, H Ebrahim, K Mey, L Fingleson*, N Conrad, P Louw); **Netcare Sunward Park hospital** (A Petrova*, B Kleyn, C Scheepers, D Subrayen, FN Schutte*, F van der Westhuisen*, H Joubert, J du Plessis, JHS Beetge*, PS Fourie*, S Naidu, V Diab*); **Netcare The Bay hospital** (H Venter, J Samjowan, P Mahadeo, P van de Walt*, R Visagie, T Adams); **UCT Private Academic hospital** (A Barendse, C Smith, L Shield, M Miller*, T Ferger); **Netcare Umhlanga hospital** (K Chetty*, K Viljoen, M van Heerden, , N Banwari, P Moodley, S Rohit, S Uys); **Netcare Union hospital** (A Kok*, A Stavrides*, A Verwey, B Botha*, D Barnes*, E Abrahams, E van der Merwe, H Swart, J Goosen*, L Barros, M Scop*, N vd Westhuizen, P Dlakane*, T Moledi*); **Netcare Unitas hospital** (A Esterhuizen, B van Niekerk, D du Plessis, EJ Joseph*, G Herselman, H van Lill, I Rossouw, JHJ van Rensburg*, JLW de Jager*, L Bosenberg*, MA van Dyk*, NA Lourens*, R Jordaan, S van Vuuren); **Netcare Universitas hospital** (A Booyens , E Janse van Rensburg, H Coetzer*, H Jacobs*, L Botha, M van der Merwe, SP Grobler*, TJ Ramanamane); **Netcare Vaalpark hospital** (C Whelan, E van Zyl, K Jansen van Vuuren, L Scheepers, N Koen); **Netcare Waterfall City hospital** (B Mahala*, MA Nabbie, N Ndlovu, S Khoza, S Singh, R Kuhne)

* Doctors