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A pharmacist-led prospective antibiotic stewardship intervention improves compliance to community-acquired pneumonia guidelines in 39 public and private hospitals across South Africa

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ABSTRACT

Introduction: Pharmacists in low-middle-income countries (LMIC) are few and lack antibiotic stewardship (AS) training. The ability was assessed of non-specialised pharmacists to implement stewardship interventions and improve adherence to the South African community-acquired pneumonia (CAP) guideline in public and private hospitals.

Methods: This was a multicentre, prospective cohort study of adult CAP patients hospitalised between July 2017 and July 2018. A CAP bundle was developed of seven process measures (diagnostic and AS) that pharmacists used to audit compliance and provide feedback. CAP bundle compliance rates and change in outcome measures [mortality, length of stay (LOS) and infection-related (IR)-LOS] during pre- and post-implementation periods were compared.

Results: In total, 2464 patients in 39 hospitals were included in the final analysis. Post-implementation, overall CAP bundle compliance improved from 47·8% to 53·6% (confidence interval [CI] 4·1-7·5, p<0·0001), diagnostic stewardship compliance improved from 49·1% to 54·6% (CI 3·3-7·7, p<0·0001) and compliance with AS process measures from 45·3% to 51·6% (CI 4·0-8·6, p<0·0001). Improved compliance with process measures was significant for five (2 diagnostic, 3 AS) of seven components: radiology, laboratory, antibiotic choice, duration and intravenous to oral switch. There was no difference in mortality between the two phases, [4·4%(55/1247) vs. 3·9%(47/1217); p=0·54], median LOS or IR LOS 6·0 vs. 6·0 days (p=0·20) and 5·0 vs. 5·0 days (p=0·40).

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antimicrobial stewardship
stewardship model
antibiotic stewardship scalability

Conclusion: Non-specialised pharmacists in public and private hospitals implemented stewardship interventions and improved compliance to SA CAP guidelines. The methodology of upskilling and a shared learning stewardship model may benefit LMIC countries.

1. Introduction

Community-acquired pneumonia (CAP) is a significant cause of global morbidity and mortality [1]. Antibiotic stewardship programs (ASPs) are recommended to ensure appropriate use of antibiotics, which are a cornerstone of therapy for CAP [2].

The South African Thoracic Society and the Federation of Infectious Diseases Societies of Southern Africa updated the CAP guideline in 2017 [3]. Adherence to CAP guidelines has the potential to limit selection of antibiotic resistance, decrease healthcare costs, and reduce patient mortality [3]. Documenting compliance with national CAP guidelines is an important component of ASPs as this can elucidate where interventions are necessary [4]. Sustainable and effective ASPs depend on teamwork to identify and implement interventions, and develop organisational infrastructure [5,6]. Previous studies of compliance with CAP guidelines in South Africa (SA) were single-site, retrospective studies in public-sector hospitals and no interventions were included [7-9].

In the South African context, particularly in the public sector, it is difficult to replicate resource-abundant stewardship models [10]. Utilising pharmacists as antibiotic stewards in low and middle income countries (LMICs) is challenging because pharmacists have no specialist infectious diseases or ASP training and are generally limited to dispensing roles [11-13].

However, previous successful pharmacist-led stewardship interventions highlight the role pharmacists can play as stewards [14–16]. In these multicentre studies, non-specialist private-sector pharmacists in SA were allocated one hour a day for stewardship interventions and used the breakthrough-series collaborative method for shared learning [14–16]. An important question is whether pharmacist-led stewardship interventions would work in the SA public sector, where 80% of the population receives healthcare, and which faces even more intense human resource and health system challenges. Additionally, there was an opportunity to explore whether a stewardship intervention could be co-ordinated across public- and private-sector hospitals.

The current study was initiated by the South African Antibiotic Stewardship Programme (SAASP), which provides leadership, advocacy for, and strengthening of, antibiotic stewardship across SA [17]. The primary objective of this study was to assess the utilization of non-specialised pharmacists in both public and private hospitals to implement community-acquired pneumonia (CAP) stewardship interventions.

2. Methods

2.1. Settings

This was a multicentre, pharmacist-led prospective study of a convenience sample of adult patients admitted to a public or private hospital for CAP between July 2017 and July 2018. No incentives were provided to encourage pharmacists to participate.

2.2. Ethics

Ethics approval was obtained from Sefako Makgatho University Research Ethics Committee (registration number SMUREC/H/262/2016). This approval was used to obtain approval from research governance structures at each participating public- and private-sector hospital. All study data were anonymised, with no unique identifiers recorded.

2.3. Community-acquired pneumonia antibiotic stewardship model

The SA CAP guideline was used to create a CAP bundle that pharmacists followed to audit compliance with defined diagnostic and antibiotic treatment criteria. The core process (n=7) and outcome (n=3) measures for pharmacist audit and feedback are summarised in Table 1. Implementation of the CAP stewardship model (Fig. 1) was based on the Breakthrough Series Collaborative [18] and Institute of Healthcare Improvement (IHI) Model [19], adapted as previously described [14–16].

A leadership team of seven experienced SA pharmacist stewards representing private and public sectors was formed to lead the study, including design of workshop content, facilitation of learning sessions, recruitment of pharmacists, and provision of support to participating pharmacists. The team was supported by four SA clinical and ASP advisors who were specialists in one each of the following disciplines; infectious diseases (ID), intensive care, pulmonology, and clinical microbiology, and in addition one ID pharmacist from the United States of America.

The content for training pharmacists in antibiotic stewardship skills for each phase of the study is summarised in Table 2. Each pharmacist attended three learning sessions. If sessions were missed, a study leader provided one-on-one training. After each learning session, a checklist of essential activities and deadlines was provided to each pharmacist.

Table 1
Process and outcomes measures for national pharmacist-led community-acquired pneumonia stewardship model.

	TYPE	PROCESS MEASURES	DEFINITION
1	Diagnostic measures	**Radiology** Was a chest X-ray performed? Did the report state presence of CAP?	Rate of compliance with correct diagnosis by confirmation of CAP in CXR report
2		**Admission criteria** Were admission criteria followed? - CURB 65>1[a] - Social circumstance - Age ≥65 years - Co-morbid disease[b] - Confusion	Rate of compliance with admission criteria
3		**Microbiology cultures** Were blood cultures[c] drawn prior to antibiotic administration? Were sputum cultures[b] taken prior to antibiotic administration?	Rate of compliance with blood cultures drawn prior to antibiotic administration Rate of compliance with sputum cultures drawn prior to antibiotic administration
4	Antibiotic measures	**Drug choice** Was the antibiotic agent chosen compliant with the CAP guideline?	Rate of compliance with the antibiotic selection of choice
5		**Drug dose** Was the prescribed dosage of the antibiotic agent consistent with the CAP guideline?	Rate of compliance with the antibiotic dosage selection
6		**Drug duration**[d] Was the antibiotic duration consistent with CAP guideline?	Rate of compliance with the recommended duration of antibiotic treatment
7		**IV to oral switch**[e] Was the antibiotic administration switched from IV to PO?	Rate of compliance with IVI to oral switch according to recommended criteria

[a] **CURB-65** stands for confusion, urea, respiratory rate, blood pressure, and **65** years of age or older. 1 point is allocated for each of: Confusion, Urea >7 mmol/L, Resp Rate ≥30 breaths/min, Low blood pressure (Systolic BP < 90 mmHg and/or diastolic BP ≤ 60 mmHg). Interpretation of CURB-65 score: 0-1: Probably suitable for home treatment; low risk of death; 2: Consider hospital supervised treatment; ≥3: Manage in hospital as severe pneumonia; high risk of death
[b] **Admission criteria.** Co-morbid diseases: presence of renal failure (defined as a CrCl of ≤30ml/min or Acute Kidney Injury 30-50ml/min); COPD; diabetes; heart failure.
[c] **Microbiology cultures.** Did not evaluate the appropriateness or quality of the specimen only if done or not.
[d] **Drug duration.** Duration 5-7 days.
[e] **IV to oral switch.** Criteria to switch included: temperature < 37.8° Celsius for 24 hours; antibiotic can be taken orally; patient is mentally normal.

	OUTCOME MEASURES	DEFINITION
1	**Length of stay**	Defined as time from admission to discharge or death for each patient diagnosed with CAP
2	**Infection related length of stay**	Defined as time from positive culture to antibiotics stopped or discharge from hospital. Alternatively, if culture negative (or no culture performed), defined as time from start of antibiotic to antibiotic stopped or discharge from hospital.
3	**Mortality rate**	The number of CAP related deaths /total number of patients diagnosed with CAP (%)

DEFINITION OF COMMUNITY ACQUIRED PNEUMONIA[28]
"Pneumonia is an acute infection of the lung parenchyma distal to the terminal bronchiole, most commonly bacterial in nature, and associated with clinical and/or radiological evidence of consolidation of part or parts of one or both lungs."

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3. Study Design

3.1. Phase 1: Call to action

This phase commenced in February 2016 at an SAASP meeting where the first call-to-action was made to engage pharmacists in the national SAASP Pharmacist CAP stewardship study. The level of interest expressed provided the impetus to establish the leadership structure, organise expert clinical and antibiotic stewardship advisors, develop a formal protocol and enrol pharmacists.

Pharmacists were required to commit to:

- obtaining approval from their pharmacy and hospital manager
- attending the three SAASP CAP study training sessions
- completing the field work required for the study after each session
- providing timely, accurate and complete data to their allocated leader
- building relationships with multidisciplinary team members to support the study

Although the 2007 SA CAP guidelines were not yet updated during the initial call to action in 2016, clinical advisors for this study were part of the SA CAP guideline Working Group and kept the study leaders informed of the publication date. Pharmacists were provided with the South African 2007 guideline during the call to action (February 2016) and the updated version was distributed electronically to all pharmacists enrolled in the study when it was published in June 2017. The criteria measured in the current study

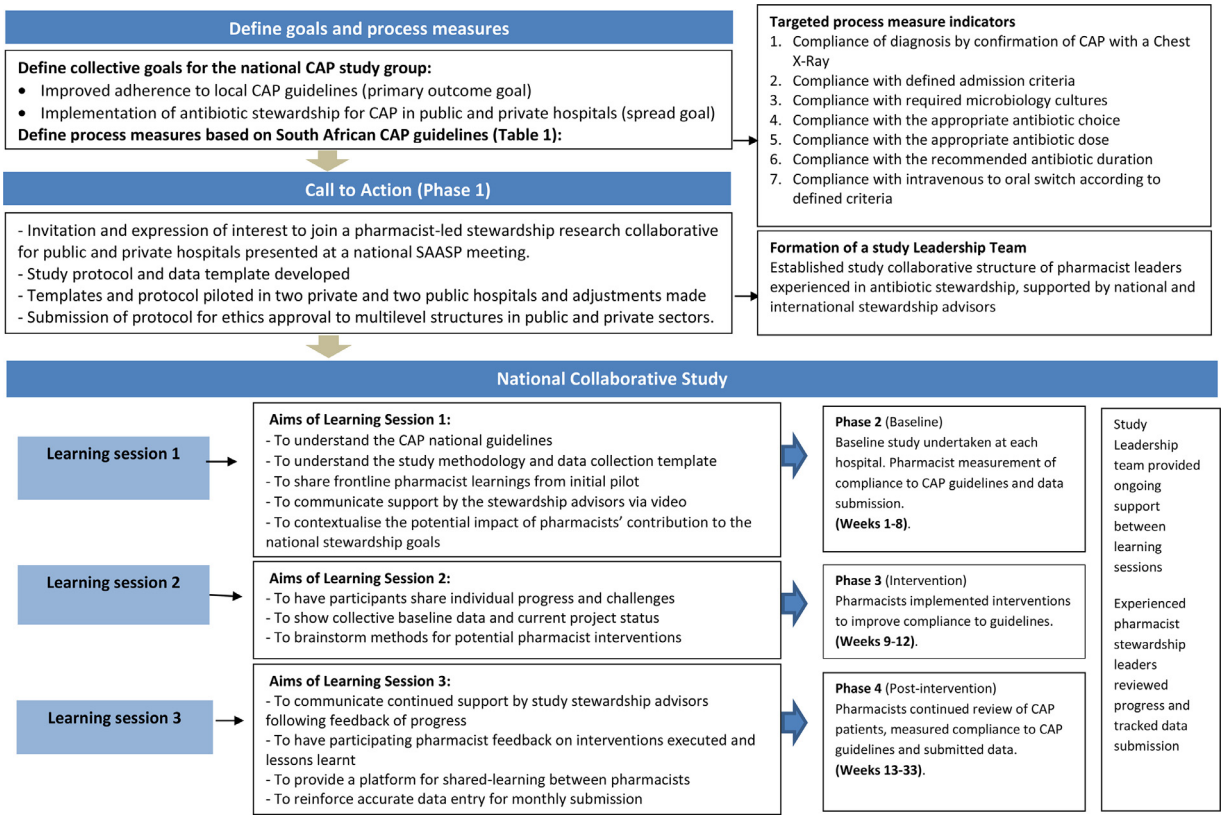

Fig. 1. South African Antibiotic Stewardship Programme (SAASP) Community Acquired Pneumonia (CAP) stewardship "Breakthrough Series Collaborative" Antimicrobial stewardship (AMS) model for national implementation and capacity building process (n=39 hospitals) adapted from Brink et al 2016[10]

were the same as the 2007 guideline, except for small changes regarding alternative antibiotic treatment.

3.2. Phase 2: Baseline compliance

Following the first learning session in late July 2017, eight weeks of baseline compliance data (Table 1) were collected on standardised daily sheets, then collated using a Microsoft Excel™ template and submitted to study leaders.

Pharmacists determined the most common wards to which CAP patients were admitted and identified these patients daily during normal working hours in the time allocated for the study. Patients with CAP were identified through a physician-determined admission diagnosis of CAP entered onto the patient charts. Pharmacists identified these cases by reviewing the charts and recruited CAP patients into the study in real-time during weekdays and retrospectively when the admission occurred over weekends or holidays.

3.3. Phase 3: Intervention

In the four-week period after learning session 2, pharmacists applied the ideas that had been generated to improve compliance and ways to give feedback to admitting physicians to facilitate implementation of interventions. Each pharmacist used their baseline data to identify gaps and intervened accordingly. During this phase, pharmacists engaged prospectively with multi-disciplinary team members and hospital leadership to drive improved compliance.

3.4. Phase 4: Post-intervention

Each participating pharmacist continued with prospective reviews of the cases, and with feedback and data collection for a further 21 weeks. The seven study leaders provided support either in person or by telephone and supervised regular follow-up of data.

3.5. Process and outcome measurement

Compliance to process measurements were calculated as percentages relative to the number of CAP patients enrolled, with the denominator the number of patients reviewed, and the numerator those who were compliant with each of the seven CAP process compliance measures. Process compliance data were further divided into diagnostic (n=3) and antibiotic stewardship (n=4) measures.

The three outcomes measures used for the study comprised in-hospital mortality, length of stay (LOS) and infection-related LOS (IR-LOS). However, 30-day readmission rates were not measured.

Although the starting date for each hospital was not the same, pharmacists collected eight weeks of baseline data. They then allowed four weeks for interventions and after that continued to monitor/measure for 21 weeks post-intervention. The weeks for each hospital were aligned (i.e. Week 1 at hospital 1 = Week 1 at Hospital 2 etc.) even though the dates may have been weeks apart.

3.6. Data analysis

To assess the pre- vs. post-implementation changes in compliance with the guideline, statistical analyses were conducted on pooled data and according to the pre-specified statistical plan. Sample size estimation was based on the key research question, viz. the detection of a 10% (absolute) improvement in any given compliance criterion from 50% to 60% from Phase 2 to Phase 4. Using the 5% significance level, and a power of 80%, a total minimum sample size of 808 (404 per Phase) was required.

Table 2
Learning session content for upskilling pharmacists and shared learning in pharmacist-led community-acquired pneumonia stewardship model.

CAP LEARNING SESSION 1	CAP LEARNING SESSION 2	CAP LEARNING SESSION 3
• Welcome and introduction of pharmacist participants, pharmacist leaders and clinical experts. • Video by SAASP co-chair on importance of the work in national antibiotic stewardship context. • Video with clinical experts on the South African CAP guidelines. • Question and answer (Q&A) session from updated SA guideline sent out prior to the session and videos. • An introduction to improvement methodology and the design of the study. • Step-by-step overview of the standardised data collection template. • Case study by 2 participating pharmacists on initial tests of the template – one each from private and public sector on how they worked through the process. • Q&A session on data collection and interpretation of criteria. • Getting started on enrolling support from members of the healthcare team at each hospital. • Role-play in small groups • Checklist of essential activities for next steps and timelines for the first 8 weeks.	• Welcome and check in by each participating pharmacist. ○ How many CAP patients? ○ One thing they felt proud of? ○ One main challenge they had? ○ One thing they were looking forward to going forward. • Quick recap of methodology and where we were • Overview of collective results to date (interim data) • Three case studies of hospitals in the field • Participating pharmacists' small group collective problem solving of challenges using challenges described in case studies • Feedback from small group process to larger group • Discussion on tackling interventions to improve compliance using individual hospital data and collective learning from the learning session. • Checklist of essential activities for next steps and timelines for next phase.	• Welcome and message from selected clinical experts on process to date • Overview of methodology to review journey to date and build understanding of how to use the methodology in a local context for other stewardship opportunities in the future. • Check in by participating pharmacist. ○ How many CAP patients in phase 2? ○ Sharing one thing each participant used to keep inspired and motivated to continue • Update of phase 1 data – demographics of participating pharmacists and baseline data on compliance to guidelines • Key issues to watch out for regarding data submission • Small group process where participating pharmacist shared their journey to date and as far as possible named key interventions and shared their impression of the impact and response by stakeholders including any challenges or highlights • Reflection on the group discussions: ○ What important questions came up for participants that they could take out of the conversation and into their forward journey? ○ What struck participants most? ○ What surprised participants? • Using individual data and commitment to the collective goals to decide the interventions • Checklist of essential activities for next steps and timelines for next phase.

ASP: Antibiotic Stewardship Programme; **CAP:** Community-acquired pneumonia; SA: South African; **SAASP:** South African Antibiotic Stewardship Program.

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Compliance scores (diagnostic, stewardship and overall) were determined by calculating mean compliance with the relevant criteria for each patient. Compliance with the seven measures and overall composite compliance over the eight-week baseline (Phase 2) was compared with the 21 weeks post-intervention (Phase 4). Data from patients reviewed during the implementation of interventions (Phase 3) was not included in the outcomes measurement.

For hospitals that participated in all phases of the study, where a patient had missing data it was removed from the denominator and numerator.

The following study variables were compared between phases: sex, ward, comorbidities, compliance with criteria, and mortality using the z-test for proportions. CURB-65 score was compared using the chi-squared test. Age and compliance scores were compared using the t-test for independent samples. Where the assumptions of this test were not met, the non-parametric Wilcoxon rank sum test was used. Change in outcome measures, including in-hospital mortality, LOS and IR-LOS, were performed using the z-test; however, the study was not powered to detect a difference.

The relationship between each compliance score and phase, after controlling for hospital sector, age, sex, ward, CURB-65 score and LOS, was determined using the General Linear Model (GLM) with compliance score as the dependent variable, and phase and the listed covariates as independent variables.

3.7. Role of funding source

The study was partly funded by a grant from Merck. The remaining costs were covered by volunteer contributions of time. The funders of the study had no role in study design, data collection, data analysis, data interpretation or 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.

4. Results

4.1. Participating pharmacists

A total of 63 pharmacists, 55 from private and 8 from public-sector hospitals, participated in the full study. Six pharmacists withdrew due to insufficient dedicated stewardship time resulting from staff shortages, two from the private sector and four from the public sector. The majority of the 69 original pharmacists

Table 3
Patient demographics for national pharmacist-led community-acquired pneumonia stewardship model: Comparison of Phase 2 and 4.

Variable	Category	Phase 2		Phase 4		Comparison of Phase 2 and 4			
		n	%	n	%	*P*-value	Difference Phase 4 and 2	95% CI for difference	
Total Patients		1247	100	1217	100				
Patients per sector	Private	1067	85·6	1026	84·3				
	Public	180	14·4	191	15·7	0·40	1·3	-1·6	4·1
Age (years)	18-64	696	55·8	709	58·3	0·22			
	65+	551	44·2	508	41·7		-2·4	-6·4	1·5
	Mean overall	1247	60·0	1217	58·3	0·027	-1·7	3·2	0·2
Sex	Female	762	61·1	705	57·9	0·11			
	Male	485	38·9	512	42·1		3·2	-0·7	7·1
Ward	General ward	1024	82·1	999	82·1	>0·99			
	ICU/High care	223	17·9	218	17·9		0·0	-3·0	3.1
CURB-65 score	0	392	31·4	391	32·1	0·36			
	1	357	28·6	376	30·9				
	2	322	25·8	272	22·4				
	3	138	11·1	139	11·4				
	4/5	38	3·0	39	3·2				

CI – confidence interval; CURB - confusion, urea, respiratory rate, blood pressure; ICU – intensive care unit.

had a bachelor's degree in pharmacy (65%; n=45) and 35% (n=24) had enrolled for, or completed, a master's degree. Most pharmacists (59%; n=41) had between 5 and 14 years of work experience. Thirty-nine percent of pharmacists had less than three years of antibiotic stewardship experience and 7% had none. The majority had no research experience, although 19 private-sector pharmacists had previous experience with the study methodology.

4.2. Hospital demographics

Forty-five hospitals, including 36 private and 9 public-sector hospitals, across eight of nine provinces in SA, initially enrolled in the study. Six of the 45 were subsequently excluded due to pharmacists withdrawing and data not being available for all phases. Overall, 39 hospitals (six public, 33 private) completed the study. Four hospitals had less than 100 beds, 20 hospitals had 100–249 beds, 12 had 250–499 beds, and three hospitals had 800–1652 beds. Eight hospitals were located outside of main urban cities.

4.3. Patient Demographics

A total of 3117 patients were reviewed between July 2017 and July 2018. Of these, 2464 were included in the final analysis. This included 1247 patients from Phase 2 (baseline) that were compared to 1217 patients from Phase 4 (post-intervention). Patients from the six hospitals where the pharmacists withdrew from the study were excluded (n=47). The 606 patients reviewed in Phase 3 (intervention phase) were also not analysed as this was the time in which pharmacists implemented interventions to improve compliance.

Patient demographics in Phases 2 and 4 are shown in Table 3. There was no significant difference in the public/private hospital type (P=0.40) between the two phases, nor in ward composition (ICU/high care vs. general ward) (P>0.99) and/or sex composition (P=0.11). The mean patient age in Phase 2 (60.0±1.1yrs) was significantly higher than in Phase 4 (58.3±1.1yrs) (P=0.027). There was no significant difference in distribution of CURB-65 scores. The difference in patient numbers in Phase 2 and Phase 4 was attributed to the seasonality of CAP with Phase 2 taking place in winter months.

4.4. Process measures

Comparing Phase 2 and Phase 4, compliance with diagnostic measures improved from 49.1% to 54.6% (P<0.0001), antibiotic stewardship measures from 45.3% to 51.6% (P<0.0001), and overall composite compliance from 47.8% to 53.6% (P<0.0001) (Table 4). There was a significant increase in compliance from Phase 2 to Phase 4 for the following individual measures: radiology, microbiology cultures, antibiotic choice, duration of therapy and intravenous (IV) to oral switch.

4.5. Outcomes measures

There was no significant difference between Phases 2 and 4 in overall in-hospital mortality (4.4% vs. 3.9%; P=0.54), total median LOS (6.0 vs. 6.0 days; P=0.20) or median IR-LOS (5.0 vs. 5.0 days; P=0.40).

4.6. Differences in private- and public-sector outcomes

Fig. 2 shows the public vs. private guideline compliance to the process and outcome measures. Mean overall compliance increased in both public (55.6% to 66.3%; P<0.0001) and private (46.5% to 51.2%; P<0.0001) sectors although the differences in the private sector were smaller. The greatest improvements were in the public-sector hospitals for compliance to laboratory guidelines (21.1% in Phase 2 vs. 38.2% in Phase 4) and antibiotic choice (51.7% in Phase 2 vs. 72.8% in Phase 4). This represents a 17.1% and 21.1% improvement (95% CI 8.0-26.2 and 11.5-30.8).

LOS and IR LOS were higher in the public sector in Phase 1 but equalised after the intervention phase with no change in the private sector. Public sector median LOS decreased significantly (from 8 to 6 days; P=0.0005) between Phase 2 and Phase 4. Mortality did not improve significantly in either sector as shown in Fig. 2.

Private-sector pharmacists reviewed a mean of 38 patients per pharmacist in Phases 2 and 4, whereas public-sector pharmacists reviewed a mean of 46 patients per pharmacist.

Diagnostic compliance score was significantly higher for older patients, in public hospitals, in ICU/high care wards, for CURB scores >0, and for longer LOS. The stewardship compliance score was significantly higher for females, in public hospitals, in general wards, for CURB-65 score of 3, and for shorter LOS. The overall compliance score was significantly higher for female patients, in public hospitals, and for CURB-65 scores >0. However, none of these factors detracted from the improvement in compliance score between Phases 2 and 4 (compared to unadjusted results).

Table 4
Compliance to CAP process measures between pre- (Phase 2) and post- (Phase 4) implementation.

Variable	Process measure	Phase 2 (n=1247)		Phase 4 (n=1217)					
		n	%	n	%	*P*-value	Δ %	95% CI for difference	
Diagnostic measures	Radiology	752	60·3	831	68·3	<0·0001*	8·0	4·2	11·8
	X-ray done (n=2463)	1138	91.3	1113	91.5	0.83	0.3	-1.9	2.5
	X-ray report stated CAP	765	61.3	835	68.6	0.0002	7.3	3.5	11.0
	Admission criteria	899	72·1	893	73·4	0·50	1·3	-2·2	4·8
	Microbiology cultures	185	14·8	269	22·1	<0·0001*	7·3	4·2	10·3
Overall mean compliance	to diagnostic measures (composite score)	1247	49·1	1217	54·6	<0·0001*	5·5	3·3	7·7
Antibiotic measures	Choice	686	55·0	773	63·5	<0·0001*	8·5	4·6	12·4
	Dose (n=1453/1459)[a]	628	91·5	725	94·2	0·065	2·6	-0·1	5·3
	Duration (n=2452)[a]	624	50·3	666	55·0	0·024*	4·6	0·7	8·6
	IV to oral switch (n=2450)[a]	202	16·3	237	19·7	0·031*	3·4	0·3	6·4
Overall mean compliance	to antibiotic measures (composite score)		45·3		51·6	<0·0001*	6·3	4·0	8·6
Overall mean CAP bundle compliance (composite score)	All		47·8		53·6	<0·0001*	5·8	4·1	7·5

* Denotes significant difference.
[a] - Different denominators reflects pharmacists' review of CAP patients on more than one antibiotic.

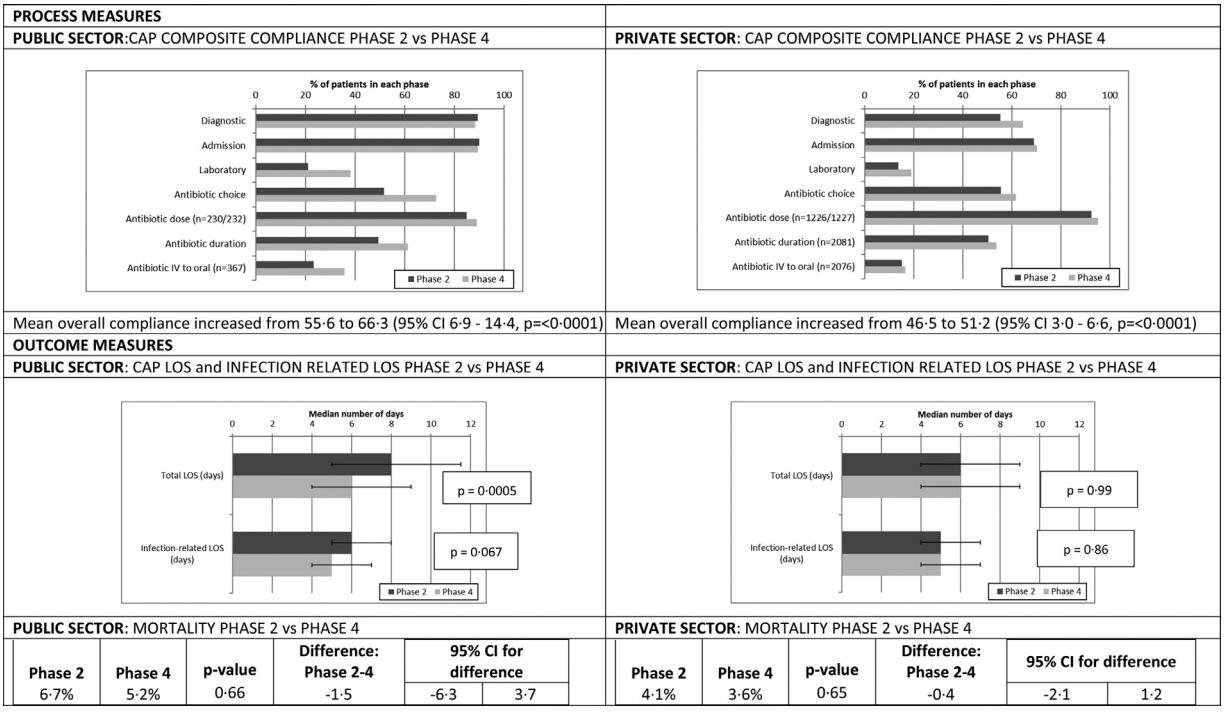

Fig. 2. Public and Private sector CAP compliance for process and outcome measures between pre- (Phase 2) and post- (Phase 4) intervention.

5. Discussion

This pharmacist-driven, antibiotic stewardship implementation study measuring compliance to a CAP guideline bundle in both public- and private-sector hospitals showed an overall improvement in both diagnostic and antibiotic measures.

The strength of this study is that it represents the first collaboration between public and private-sector hospitals in antibiotic stewardship and is, to the best of our knowledge, a novel multicentre study involving both sectors in an LMIC.

Private-sector pharmacists in SA have previously demonstrated success in stewardship interventions [14-16]. It was an important national goal to have representation from both public- and private-sector hospitals because 80% of health care delivery in SA is via the public sector.

Previous SA studies of CAP compliance were performed in single public-sector hospitals, used older versions of the SA CAP guideline (1996 [7] and 2007 [8,9]) and showed compliance as low as 8%. The current study showed modest improvement in guideline adherence over the 21 weeks and recognised opportunities for further improvement in compliance. Compliance data evaluating process measures are not routinely available in SA, although they are increasingly needed. Data on defined process and outcomes measures for CAP in these two hospital sectors enables identification and target of practice areas for improvement. Although the clinical significance of such improvement is unclear, the stewardship interventions by public- and private-sector pharmacists remain an important factor, particularly as previous SA CAP studies showed non-compliance was due to overtreatment with antibiotics rather than undertreatment. An Australian study using electronic medical records showed lower overall compliance to antibiotic guidelines for CAP in the public sector and recommend increased time for pharmacists to perform stewardship duties in the private sector, amongst other interventions [20]. A retrospective study in the United States using a Medicare database identified that improved duration of therapy in CAP patients offered an opportunity for na-

tional antibiotic stewardship efforts [21]. The current study was prospective with pharmacist-led interventions that resulted in improved compliance including duration.

The inclusion of diagnostic stewardship criteria was an important addition to conventional pharmacist interventions. Pharmacists recorded whether a chest X-ray was performed and, if so, whether the radiology report indicated the presence of CAP. As shown in Table 4, there was no difference in the percentage of X-rays requested but this was already above 90% in the first phase. After the interventions, there was a significant difference in X-ray reports that confirmed CAP in Phase 4. Pharmacists also measured compliance with guidelines for the performance of microbiological testing and used the test results to determine compliance with the choice of antibiotic and to recommend changes to treatment, as required. Compliance with both these process measures improved from Phase 2 to Phase 4 (see Table 4).

A study by the British Thoracic Society (BTS) [22] attributed poor CAP guideline compliance to insufficient timeframes for change, stating that up to two years is needed. Two further factors may have contributed to the lack of clinical benefit in the current study despite increased compliance with CAP guidelines. Firstly, in the BTS study, initial compliance was only 1%, whereas in the current study it was much higher at just under 50%. Secondly, the in-hospital mortality in both the public and private sector in the current study was low at 3.9- 4.4%, whereas the mortality of hospitalised CAP patients reported in the BTS study was 8.8-13.6%. Mortality in the current study was highest in patients with a CURB-65 score $\geq$3 in both phases of the study, which is consistent with other study findings [23,24].

In the current study, there was a low IV to oral switch pre- and post-intervention, particularly in the private sector. This needs further investigation, although it may have been impacted by perceptions regarding the criteria used by medical insurance companies for approval of admissions and level of care. Improvement in dose showed the least improvement but also had the highest compliance at baseline (91.5% to 94.2%).

Admission of patients with a CURB-65 score of zero or one did not improve from Phase 2 to Phase 4. The value of the scores, however, was not the only admission criterion used. For example, if the score was low but the patient had a comorbidity, or social circumstances that prevented home care, the admission would be considered appropriate. Furthermore, in HIV-positive patients, the presence of malnutrition and features of immunosuppression, such as oropharyngeal candidiasis may have swayed opinion to a more cautious approach. As a result, a significant number of patients who were classified in low CURB-65 categories, but had other criteria, were considered to have been admitted appropriately. Further work is needed to improve admission criteria for more appropriate use of health resources and level of treatment.

There were several challenges, including gaps in research experience and knowledge of systems improvement methodology among SA pharmacists. In this regard, the current model included implementation of a CAP bundle to improve compliance with guidelines, provided shared learning opportunities, and incorporated ongoing expert support to ensure every participating pharmacist had the tools necessary to succeed.

Such engagement with study leaders provided specific guidance regarding interventions and assisted with difficulties faced by pharmacists in the field. Pharmacists were taught how to calculate a CURB-65 score and to review diagnostic and antibiotic stewardship criteria to provide comprehensive interventions. The pharmacists were also instructed how to use hospital-specific data and information from the overall study, to provide feedback to their own stakeholders and team members and thus to create interdisciplinary awareness of the existing system and potential for improved patient care.

Professional boundaries and hierarchies have been found to be significant barriers to antibiotic stewardship, particularly in LMICs [25]. The current study reiterated the critical role of pharmacists trained in antibiotic stewardship as enablers of engagement between multidisciplinary health care providers. Tailoring systems and existing resources to support the key role of pharmacists in audit and feedback processes were successfully demonstrated.

The current study has several limitations. The focus was to test a real-world, multi-hospital, cross sector, disease-specific, antibiotic stewardship programme in SA using improved adherence to SA CAP guidelines. It was not powered to show a difference in mortality, LOS or IR-LOS.

The study did not audit time to administration of first antibiotic dose relative to time of admission [21] because of inadequate documentation; this may have impacted on any improvement in clinical outcomes. In addition, the study did not include collection of results of microbiological data or determine aetiology of the pneumonia.

Due to the prospective nature of the study there was limited time to implement interventions, as pharmacists were not dedicated researchers. However, in this real-world study of implementation of stewardship measures in an LMIC, there was a demonstrated improvement in process outcomes. There was a large difference in public and private representation as study leaders from the private sector had organisational leadership roles that enabled pharmacist recruitment. Public-sector study leaders were based in academic centres and had to work through the hospital and provincial structures for recruitment and were also hindered by delays in the provincial and individual hospital ethics approval timelines. It took 11 months for the protocol and ethics approval to be completed at each participating hospital, across the different provincial health departments and private hospital groups, a factor that needs urgent attention to facilitate other ASP interventions. More work is also required to increase participation of public-sector pharmacists in future studies.

Resource constraints in both the public and private sector were addressed by implementing the “allocated stewardship time” concept, which was verified by there being no significant difference in the average number of CAP patients reviewed per pharmacist in either sector.

A review of barriers to guideline implementation recommended that structured implementation tailored to specific settings and target groups could improve adherence [26]. Although the transfer of skills and behaviour changes was not formally investigated, the current study demonstrated that stewardship skills could be developed through a combination of educational input, shared learning, and testing in a real-world setting. Future studies to determine the barriers to guideline implementation in each sector and identify behavioural determinants for successful interventions could support pharmacists to lead further improvements in compliance.

The current study focused on the improvement in compliance to CAP guidelines; a more detailed review of the implementation methods, i.e. how and why it works, as advocated in the call for more in-depth studies of the implementation of interventions, would be valuable in future studies [27].

In conclusion, the unique success of the study was in demonstrating a successful pharmacist-led stewardship intervention in resource-constrained public-sector hospitals. In addition, the groundwork was set for disease-specific stewardship through a real-world prospective study that bridged different aspects of stewardship in a coordinated, large-scale intervention in both public- and private-sector hospitals. There is opportunity for frontline stewards across different settings, including LMICs, to collaborate in coordinated interventions and accelerate implementation of ASPs through upskilling existing resources and enabling interdisciplinary engagement across health systems.

Declarations

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Competing Interests: No

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Statement of Contributors

DvdB, AJB and MM conceived and designed the study. DvdB managed the project. DvdB, NS, AJB, DAG and APM did the scientific literature search. APM designed the data collection tools and study toolkit. MM, AJB, GAR, CF provided feedback on methods. NS, APM, AvJ, RC, EB, YdW and DvdB prepared the data. DvdB, NS, DAG, APM, and AJB did the analysis. All authors interpreted the data, wrote the report, approved the final version, and are accountable for all aspects of the work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijantimicag.2020.106189.

Research in context panel

Evidence before this study

Google Scholar and PubMed were searched for relevant studies published in English up to January 30, 2020, using the terms “community acquired pneumonia”, “CAP”, “guidelines”; “pharmacist or specialized pharmacists”, “public and private hospitals” AND “antibiotic or antimicrobial stewardship”, “diagnostic stewardship”; “LMICs”, “multicentre”, ”implementation”, “compliance”, “antibiotic stewardship training and skills”. Additional studies were identified from the authors’ personal reference lists and reference lists from articles that were retrieved. Studies were excluded if they did not describe antimicrobial stewardship (AMS) interventions in hospital in-patient settings or did not refer to pharmacists.

Surveys of implementation of antimicrobial stewardship programmes (ASPs) in hospitals frequently revealed considerable variation in scope and scale of programmes with most published studies being from ur0062an-academic settings in high resource countries. The latest Cochrane systematic review of interventions to improve antimicrobial prescribing included 221 studies, of which 183 (83%) were from Europe and North America and none were from Africa. There is a growing call for effective models to implement ASPs in low and middle-income countries (LMICs) and for support to enable interventions by front-line stewards in different hospital settings to be collated, evaluated and submitted for publication. The need to incorporate pharmacists as an essential member of ASPs in hospitals is acknowledged, yet progress in LMICs has been limited by a lack in pharmacist resources and training in infectious diseases (ID) and AMS.

Although the current search revealed some surveys of ASP across public- and private-sector hospitals, there were no interventional collaborative AMS studies across both sectors in LMICs. Thus, no literature is available globally on pharmacist-led, multicentre, collaborative, antibiotic stewardship initiatives across both public and private healthcare sectors in geographically disparate settings. Regarding community-acquired pneumonia (CAP), implementation of care bundles and guidelines were reported to have the potential to impact on process of care and clinical outcomes.

Added value of this study

This is the first national South African (SA) pharmacist-led multicentre collaborative AMS initiative across both public and private healthcare sectors. Although we previously demonstrated that our AMS model could be implemented across 47 SA hospitals using pharmacists without ID training, all the hospitals were private hospitals; therefore, it was imperative to have representation from both public and private hospitals because 80% of health care delivery in SA is via the public sector.

Disease-specific guidelines were used for the first time (in this case the SA CAP guidelines) and the same methodology and model for stewardship interventions was used to initiate an ASP across both sectors. An increase in overall CAP bundle compliance was demonstrated as well as improved diagnostic and antibiotic stewardship compliance with no difference between public- and private-sector hospitals. AMS skills were transferred to public-sector pharmacists who had not participated in AMS before in a setting where they face even more intense human resource and health system challenges than colleagues in the private sector. The ASP was also extended to include new private-sector hospitals with no previous stewardship experience.

Implications

To strengthen implementation and scalability of ASPs across public and private hospitals, health systems in LMICs may benefit from the methodology of shared learning and upskilling of non-specialised pharmacists in collaborative interventions, such as this focused disease-specific improvement initiative. Opportunities for frontline stewards across different settings to collaborate in coordinated interventions have the potential to accelerate implementation of ASPs through upskilling existing resources and enabling interdisciplinary engagement across health systems.

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