OXFORD

JPHSR Journal of Pharmaceutical Health Services Research

Research Paper

National standard treatment guidelines: their impact on medicine use indicators in a resource-limited setting

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Abstract

Objectives Standard treatment guidelines improve patient care outcomes. Few studies assess the impact of standard treatment guidelines on population-level medicine use indicators in resource limited settings in sub-Saharan Africa, where the burden of disease is greatest. The objective of this study was to determine the immediate and long-term impact of the national standard treatment guidelines on medicine use indicators at the population-level in Namibia.

Methods An interrupted time-series modeling of the impact of national standard treatment guidelines implemented in Namibia in 2011, on population-level medicine use indicators. Antibiotic, generic and polypharmacy prescribing indicators were abstracted from the national Pharmaceutical Information System, over an eight-year period, 2007– 2015. This generated 15-quarterly time points. The impact was estimated by changes in trends of the indicators, immediately and after the intervention using R-software. The immediate impact was reflected by level change while long term impact was determined by trends/quarterly change after standard treatment guideline implementation.

Key findings Data points from 522 Pharmaceutical Information System reports from 38 health facilities were included. The eight-year period estimates were, 2.9 ± 0.1 medicines prescribed per outpatient, 48.1 ± 2.5% of prescriptions had an antibiotic and 74.0 ± 4.2% of medicines were prescribed by generic name. Of the 13 regions, 61.3% and 53.8% had a decline in the average medicines per prescription and prescriptions with antibiotics respectively, as well as 53.8% of the regions had an increase in prescribing of generic medicines immediately after implementation of the standard treatment guidelines. Thereafter, quarterly trends in the three indicators did not significantly improve after the intervention at national and in all regions, except for generic prescribing in Oshikoto region, 4.5% (95% CI: 2.6 – 6.3%, *P* < 0.001).

Conclusion Whilst national standard treatment guidelines immediately improved medicine use indicators, it is discouraging that the improvement over time was marginal across regions and was not sustained at the national level. Robust point of care interventions is needed for sustained and effective implementation of standard treatment guidelines.

Keywords: impact; medicine use indicators; Namibia; treatment guidelines

Introduction

Globally, the burden of irrational use of medicines is a considerable public health threat, leading to antimicrobial resistance and safety concerns.[1, 2] Deaths due to drug resistant infections are projected to reach 10 million per year by 2050, the majority among countries in sub-Saharan Africa.[3] The World Health Organization (WHO) estimates that 50% of medicines are used irrationally, particularly in resource-limited countries in sub-Saharan Africa.[4] This is a concern, given a high burden of diseases in sub-Saharan Africa against weak health systems.[5] In most resource-limited settings, Standard Treatment Guidelines (STGs) are valuable public health tools for promoting rational medicine use and access to essential medicines.[6–9] The implementation of the WHO essential medicines program across the sub-Saharan region since 1977, has scaled up the use of national STGs in public healthcare.[4] Consequently, Namibia implemented its first comprehensive STGs in 2011 in public health facilities.[10, 11] However, despite the wide implementation of STGs, medicine use remains sub-optimal in sub-Saharan Africa, mainly due to limited-resources for implementation.[3, 10, 12, 13] Sub-optimal medicine use indicators were estimated among 11 African countries, 3.1 medicines prescribed per outpatient (WHO target ≤ 2), 68.0% of medicines were prescribed by generic name (target = 100%), 46.8% of prescriptions had an antibiotic (WHO target ≤ 25%).[14] This is a concern, given that poor implementation of STGs is associated with inappropriate medicine use and health outcomes.[3, 13, 15, 16]

Limited studies have assessed the impact of national STGs on trends of the three medicine use indicators assessing antibiotic, generic and polypharmacy prescribing in sub-Saharan Africa over time.[13, 17] We hypothesize that the implementation of national STGs in Namibia in 2011 did not significantly improve medicine use indicators over time, given earlier limited compliance to STGs and non-alignment between STGs and medicine use indicators.[18]

Methods

Design and population

An interrupted time-series (ITS) analysis of the immediate and long-term impact of national STGs on three population-level medicine use indicators. Interrupted time-series analysis, a robust methodology for evaluating the impact of public health interventions such as STGs, was performed according to the framework suggested by Ramsay *et al.*[19] The primary outcome was change in the trend of three medicine use indicators (i.e. rate of antibiotic, generic and polypharmacy prescribing). The intervention was the implementation of STGs at public health facilities in Namibia in 2011. For the analysis, one-year lag period was included in the sensitivity analysis to allow for the effective implementation of the STGs and to detect the impact on medicine use indicators. The secondary outcome was the impact of time varying covariates such as STG training and patient load or coverage on the trends of medicine use indicators after implementation of STGs. The ITS analysis included fifteen (15) quarterly time points that constituted data on medicine use indicators aggregated in the national PIS database over an eight-year period, 2007 Q4 to 2014 Q4 by Pharmaceutical Services Division of the Ministry of Health and Social Services (MoHSS) of Namibia. The PIS quarters are defined according to the Government of Namibia's calendar where quarter 2 (Q2) is July to September and Quarter 4 (Q4) is January to March.

Intervention: nationwide implementation of STGs

The intervention/interruption was the implementation of a nationwide standard treatment guideline in public health facilities in Namibia from June/July 2011, represented by 2011 Q2 in this study. A one-year lag period was considered for effective implementation of the STGs. The pre-STG and the post-STG periods consisted of seven (2007 Q4 – 2011 Q4) and six (2012 Q2– 2014 Q4) quarterly time points respectively. The choice of the number and spacing of the time points was determined by the reporting period recommended by the MoHSS and WHO for PIS data.

The MoHSS of Namibia implemented its first-ever comprehensive national STGs[20] in all public health facilities from 2011 to promote rational prescribing and use of medicines. Prior to the implementation of nationwide STGs, Namibia used the Treatment Manual for Clinics and the Pocket Manual for Health Workers published in 1992 and 1996 respectively to guide prescribing and dispensing of medicines.[20] The Pharmaceutical services division of the MoHSS in partnership with a USAID-funded SIAPS project scaled up the design, access, training and support supervision to ensure effective implementation and use of STGs in all public hospitals. In addition, regional and health facility based Therapeutic Committees (TCs) supported the implementation of STGs within health facilities and regions. The implementation of STGs was supported by the PIS database to monitor medicine use and revision of the Namibia essential medicine list to enforce compliance to STGs. The nationwide implementation of STGs was supported by PIS training to ensure accurate collection of data on medicine use. A post-STG implementation assessment in 2012/2013 conducted by the MoHSS in public facilities in Namibia showed that STGs had been implemented and used by over 1500 health providers countrywide.[16]

Data collection procedure

Data on three medicine use indicators (i.e. polypharmacy, antibiotic and generic prescribing) were aggregated every MoHSS second (July to September) and fourth quarter (January to March) each year, giving a total of 15-time points that were included in the interrupted time series regression modelling using R-software. Health facilities collect and report PIS data using standardized forms. Subsequently, the Division of Pharmaceutical Services of the MoHSS consolidates data collected at each facility and region using an electronic database.

The data on three medicine use indicators and covariates were retrospectively abstracted from the national PIS database for public health facilities across 35 health districts and 13 regions of Namibia. In addition, PIS aggregates seven other PIS indicators pertaining to pharmaceutical service delivery in public healthcare, which were used as covariates. Two of these indicators pertain to the quality of health care, i.e. percentage of vital reference materials available at the pharmacy, one of which is the STGs; and percentage of therapeutics committee meetings held and minuted out of the number planned. The other covariates were percentage of pharmacists' posts filled; percentage of pharmacist's assistant posts filled; the average number of prescriptions received at the pharmacy/dispenser/day; percentage of medicines actually dispensed; annual expenditure per capita for pharmaceutical/clinical supplies and level of health facility i.e. hospital/health center.

Data management and analysis

The units of analysis were quarterly reports on three PIS medicine use indicators aggregated at public health facilities for the period 2007 Q4 - 2014 Q4. Prior to analysis, data were assessed for quality

(i.e. completeness, accuracy and consistence) and multiple imputations were performed to account for missing data.[21] The primary outcome was the immediate and long term impact of the implementation of national STGs on medicine use indicators. This was determined using ITS analyses for changes in three-medicine use indicators in terms of level (i.e. immediate change) and long term impact (i.e. trends/quarterly change) after STG implementation in 2011. The study hypothesized that effective implementation significantly improved the level and trend change in the three medicine use indicators. That is, a decline in the number of medicines per prescription and percentage of outpatient encounters with antibiotics decreased and percentage prescriptions of medicines with generic names increased. Changes in the observed level and trends were assessed before and after national implementation of the STGs in 2011 with a one-year lag period (2011 – 2012) considered for effective implementation of the STGs in Namibia.

The pre-STGs period covered 2007 Q4 to 2010 Q4, lag phase 2011 Q2 to 2011 Q4 and post-STG period 2012 Q2 to 2014 Q4. The impact of seasonality on trends of the medicine use indicators was assessed using the Durbin Watson test and autocorrelation was adjusted in the final model using the corARMA function and

validated using ANOVA of the two models. The final model was fitted using generalized least squares (GLS) by maximum likelihood. The impact of time varying covariates on trends of the three indicators was determined using ITS regression analyses. In addition, bivariate analyses were conducted to compare the medicine use indicators between the pre- and post- STGs implementation periods as well as by health facility level and region. The level of significance, alpha was set at 0.05 for a 95% confidence interval for all analyses.

Results

The 8-year review period included data for 38 public health facilities in all 35 districts and 13 regions of Namibia; 92% ($n = 35$) of the health facilities were hospitals versus three health centers (HC).

Period estimates of medicine use indicators

The eight-years period estimates of the three medicine use indicators were, 2.9 ± 0.1 medicines prescribed per outpatient, 48.1% ± 2.5 of prescriptions had an antibiotic and 74.0% ± 4.2 of medicines prescribed by generic name (Table 1). None of the 13 regions met

Table 1 Eight-year period mean estimates of medicine use indicators in Namibia

covariate	Medicine use indicators					
	HF11: Average number of medicines per prescription. Mean (±SD)	*P*-value	HF12: Percent of medicines prescribed by generic name. mean (±SD)	*P*-value	HF13: Percent of prescriptions with an antibiotic. Mean (±SD)	*P*-value
	Target ≤ 2.0;		Target = 100%;		Target ≤ 25.0%;	
	Threshold ≤ 2.5		Threshold ≥ 80.0%		Threshold ≤ 35.0%	
National rates	2.9 ± 0.1		74.0 ± 4.2		48.1 ± 2.5	
Facility level						
Health Centre	2.9 ± 0.2	0.000*	76.2 ± 12.9	0.012*	50.9 ± 9.0	0.001*
Hospital	2.9 ± 0.1		73.9 ± 4.2		48.0 ± 2.3	
Report period						
Quarter 2	2.8 ± 0.0	0.243	74.9 ± 4.3	0.465	49.3 ± 2.0	0.099
Quarter 4	2.9 ± 0.1		73.2 ± 4.5		47.1 ± 2.7	
Region						
Erongo	2.7 ± 0.2	0.000*	82.6 ± 5.7**	0.000*	48.7 ± 3.3	0.653
Hardap	3.2 ± 0.6		71.5 ± 8.1		44.5 ± 8.3	
Karas	2.5 ± 0.2**		74.0 ± 13.2		47.1 ± 16.5	
Kavango	2.8 ± 0.1		86.5 ± 10.2**		50.2 ± 7.7	
Khomas	3.3 ± 0.2		54.8 ± 5.7		45.0 ± 7.2	
Kunene	3.0 ± 0.2		71.0 ± 9.3		51.3 ± 7.0	
Ohangwena	3.1 ± 0.3		60.5 ± 9.9		54.8 ± 4.6	
Omaheke	3.1 ± 0.3		49.4 ± 15.7		47.8 ± 12.2	
Omusati	2.7 ± 0.3		74.1 ± 6.5		48.8 ± 7.8	
Oshana	2.6 ± 1.0		66.1 ± 15.6		34.5 ± 15.4**	
Oshikoto	2.7 ± 0.4		65.8 ± 9.1		54.8 ± 10.5	
Otjozondjupa	2.6 ± 0.2		84.6 ± 6.0**		41.5 ± 9.1	
Zambezi	3.2 ± 0.4		91.8 ± 5.6**		50.4 ± 11.8	
Regional trends						
Pre-STG trend						
Decreased (%)	7.7% (*n* = 1)	<0.050	7.7% (*n* = 1)	<0.050	7.7% (*n* = 1)	<0.050
Increased (%)	0.0%	< 0.050	23% (*n* = 3)	<0.050	7.7% (*n* = 1)	<0.050
No change (%)	92.3% (*n* = 12)	>0.050	69% (*n* = 9)	>0.050	84.6% (*n* = 11)	>0.050
Post-STG trend						
Decreased (%)	7.7% (*n* = 1)	<0.050	15.4% (*n* = 2)	<0.050	0.0%	<0.050
Increased (%)	15.4% (*n* = 2)	<0.050	7.7% (*n* = 1)	<0.050	30.8% (*n* = 4)	<0.050
No change (%)	76.9% (*n* = 10)	>0.050	76.9% (*n* = 10)	>0.050	69.2% (*n* = 9)	>0.050

*Statistically significant association (*P* < 0.05), **indicator within the PIS target/threshold.

the PIS targets but some regions achieved the threshold for the indicators (Table 1). Of the 13 regions, 1 (7.8% Karas region) met the PIS threshold for the average number of medicines per prescription, 4 (30.8%, Erongo, Kavango, Otjozondjupa and Zambezi) met the threshold for generic prescribing and 1 (7.8%, Oshana) met the threshold for antibiotic prescribing (Table 1). The eight-year estimates of the three medicine use indicators were significantly higher at hospitals versus health centers ($P < 0.05$) and varied across the 13 regions ($P < 0.05$) (Table 1).

Impact of implementation of STGs on medicine use indicators

Figure 1, Tables 2 and 3 show the regression model(s) that estimated the immediate impact/change in the three medicine use indicators after implementing the STG (β_2) and the quarterly trends in the post-STG period (β_3).

Impact of STGs on polypharmacy prescribing: average number of medicines

Before the STG-intervention, 53.8% ($n = 7/13$) regions (Erongo, Karas, Kavango, Omaheke, Omusati, Oshana and Otjozondjupa) had a declining trend in the average number of medicines prescribed

per outpatient (Table 2). After the implementation of the STGs, though not statistically significant ($P > 0.050$) it appears there was an immediate decline in the average number of medicines per prescription across most regions (61.5%, $n = 8/13$), public hospitals and health centers (Table 3). Thereafter, the quarterly trend in the average number of medicines appears to increase in most regions (53.8%, $n = 7/13$) and at the hospital and national levels. The improvement in quarterly trends was significant for one region, Zambezi ($P < 0.001$). The non-improvement in quarterly trends was significant for Omusati and Omaheke regions ($P < 0.001$), as well as the public hospitals (Table 3). After the implementation of the STGs, a national steady increase in the average number of medicines prescribed was observed on average 0.03 medicines/quarter though not significant ($P = 0.065$) (Table 3 and Figure 1A).

Impact of national STGs on antibiotic prescribing

Secondly, prior to the implementation of the STGs, 61.5% ($n = 8/13$) regions (Erongo, Hardap, Karas, Omaheke, Omusati, Oshana, Oshikoto and Otjozondjupa) showed a decreasing trend in the percentage of outpatient prescriptions with an antibiotic. Immediately after STG implementation, 53.8% ($n = 7/13$) regions (Erongo, Hardap, Kavango, Kunene, Ohangwena, Otjozondjupa and Zambezi) appeared to
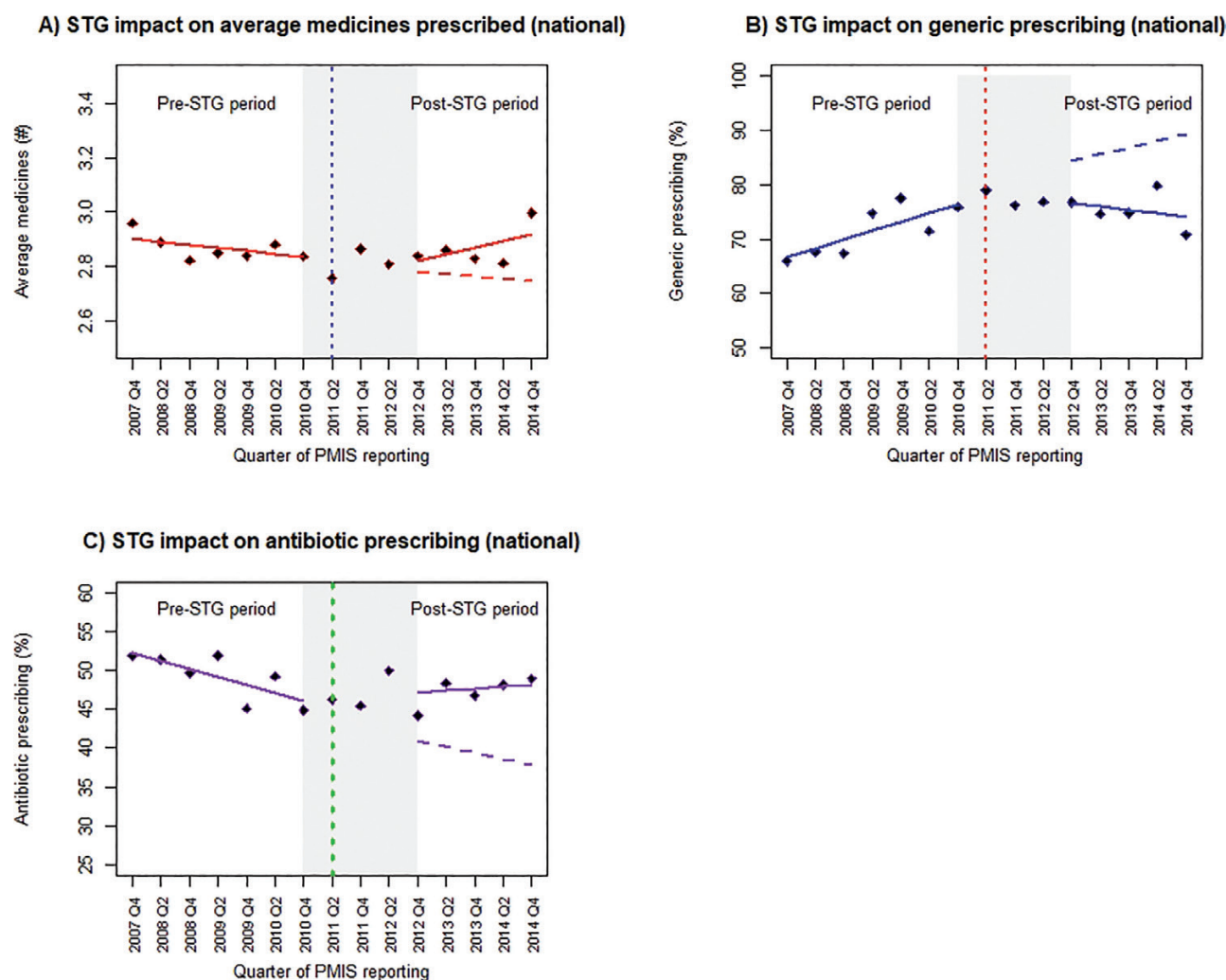

Figure 1 Impact of implementation of STGs on trends of medicine use indicators

Table 2 Immediate impact of national STGs on medicine use indicators

	Antibiotic prescribing		Polypharmacy prescribing		Generic prescribing	
	Post-intervention level change (β_2)		Post-intervention level change (β_2)		Post-intervention level change (β_2)	
	Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value
National (all facilities)	2.66 (0.02, 5.31)	0.076	−0.04 (−0.19, 0.11) [1]	0.6137	−1.83 (−10.2, 6.5)	0.676
National (Health centers)	1.45 (−15.0, 17.9)	0.866	−0.23 (−0.82, 0.36) [1]	0.4661	−26.83 (−53.2, −0.5)	0.074
National (Hospitals)	2.87 (0.03, 5.7)	0.076	−0.04 (−0.17, 0.10) [1]	0.6209	−0.35 (−8.6, 7.9)	0.934
Regions						
Erongo	−2.74 (−9.9, 4.4) [1]	0.469	−0.3 (−0.8, 0.3) [1]	0.385	8.23 (−8.6, 25.0) [1]	0.359
Hardap	−8.07 (− 20.2, 4.1) [1]	0.222	−0.09 (−1.42, 1.24) [1]	0.896	13.10 (−2.8, 29.0) [1]	0.138
Karas	38.94 (7.9, 70.0)	0.033*	0.2 (−0.3, 0.7)	0.394	0.02 (−14.9, 14.9) [1]	0.997
Kavango	−2.98 (−11.6, 5.6) [1]	0.512	0.03 (−0.42, 0.48)	0.896	−16.55 (−32.1, −1.0) [1]	0.063
Khomas	3.74 (−10.7, 18.2)	0.622	0.09 (−0.46, 0.64)	0.754	−9.20 (−23.8, 5.4)	0.245
Kunene	−4.83 (−17.3, 7.7) [1]	0.466	−0.16 (−0.63, 0.31) [1]	0.522	9.37 (−18.6, 37.3) [1]	0.525
Ohangwena	−10.30 (−18.7, −1.9) [1]	0.037*	−0.3 (−1.0, 0.5) [1]	0.513	−8.44 (−35.6, 18.7)	0.556
Omaheke	8.03 (− 5.8, 21.9)	0.281	−0.04 (− 0.55, 0.48) [1]	0.891	−23.56 (−65.0, 17.9)	0.291
Omusati	18.37 (1.4, 35.4)	0.060	−0.09 (−0.53, 0.35) [1]	0.694	−11.83 (−30.6, 6.9)	0.244
Oshana	13.05 (−16.5, 42.7)	0.407	−0.6 (−2.7, 1.5) [1]	0.603	1.70 (−18.5, 21.9) [1]	0.871
Oshikoto	7.07 (−16.9, 31.1)	0.576	−0.4 (−1.6, 0.7) [1]	0.481	31.87 (23.4, 40.4) [1]	0.000*
Otjozondjupa	−8.60 (−34.5, 17.3) [1]	0.529	0.2 (−0.4, 0.8)	0.564	1.84 (−16.9, 20.6) [1]	0.851
Zambezi	−18.51 (−37.1, 0.1) [1]	0.079	0.6 (−0.31, 1.42)	0.239	−11.1 (−26.6, 4.5)	0.192

Linear regression modelling; *(P < 0.05)-Statistically significant; CI: confidence interval. Durbin Watson statistic for average number of medicines = 2.04 (lag = 1, *P* = 0.242); Durbin Watson statistic for percent of medicines prescribed by generic name = 2.49 (lag = 1, *P* = 0.894); Durbin Watson statistic for percent of outpatient prescriptions with an antibiotic = 3.37 (lag = 1, *P* = 0.024). [1] Indicator improved.

decrease in antibiotic prescribing but this was only significant for the Ohangwena region (*P* = 0.037). Thereafter, the quarterly trend in antibiotic prescribing seemed to have increased in most regions (61.5%, *n* = 8/13), at the health center and hospital levels and nationally. The increases were significant in Erongo, Hardap, Kavango and Omaheke regions, health centers, hospitals and nationally (*P* < 0.050). The national percentage of outpatient prescriptions with an antibiotic was observed to increase significantly after STG implementation, on average by 1.28%/quarter (*P = 0.002*) (Table 3 and Figure 1C).

Impact of STGs on generic prescribing

Thirdly, prior to STG implementation, 76.9% (*n* = 10/13) of the regions (Erongo, Hardap, Karas, Kavango, Ohangwena, Omaheke, Omusati, Oshana, Otjozondjupa and Zambezi) had an increasing quarterly trend in the percentage of medicines prescribed by generic name in outpatient prescriptions. Immediately after STG implementation, 53.8% (*n* = 7/13) regions (Erongo, Hardap, Karas, Kunene, Oshana, Oshikoto and Otjozondjupa) showed an immediate increase in generic prescribing although this was significant only in the Oshikoto region (*P* < 0.001) Table 2. Thereafter, the quarterly trend in generic prescribing increased in 30.8% (*n* = 4/13) regions (Khomas, Omusati, Oshikoto and Zambezi) though significant only in Oshikoto (*P* < 0.001). The non-improvement in quarterly trends was significant for Kavango and Oshana regions; health centers and nationally (*P* < 0.050). A steady decrease in generic prescribing was observed nationally on average by 2.33% per quarter after STG implementation (Table 3 and Figure 1B).

Impact of time varying covariates on the model on the impact of STGs

A regression model of estimates of the impact of time varying covariates and level of health facility on the three medicine use indicators showed that both hospital and health centers significantly increased the average number of medicines prescribed, with hospitals increasing higher than health centers by 1.2 and 0.2 respectively (*P* < 0.050). The percentage of medicines prescribed by generic name increased by 5.01% with the increase in the percent of medicines actually dispensed and by 1.0% with prescriptions generated at the hospital level. The percentage of outpatient prescriptions with antibiotics increased by 0.3% with percent of pharmacist's assistant posts filled and by 0.9% with prescriptions from hospitals.

Discussion

The study aimed to determine the immediate and long-term impact of the implementation of national STGs in Namibia on three PIS medicine use indicators, i.e. polypharmacy, antibiotic and generic prescribing in public healthcare in Namibia.

Firstly, the study found that the implementation of comprehensive STGs in Namibia from 2011 did not improve the three medicine use indicators at the national level (Table 2). However, there was an immediate improvement in antibiotic prescribing in one (Ohangwena) region but this was not sustained. Trend improvements were observed in generic prescribing in one (Oshikoto) region. The average number of medicines per outpatient in one (Zambezi) region. This is a concern, given that STGs were implemented in 2011 to foster the rational use of medicines in public healthcare facilities in Namibia.[8, 10, 22, 23] One issue may be that prescribers occasionally followed the standard treatment guidelines, so that the baseline poor performance (of too many medicines, too frequent the prescription of antibiotics) was then added to some indicated medicines.

However, the findings concur with post-STG assessment done in 2013 that estimated generic prescribing at 81.0%, antibiotic prescribing at 43.9%[16] and sub-optimal compliance to STGs, i.e. 26.2% using strict criteria and 55.1% under loose criteria. The non-compliance to STGs existed in public health facilities despite the availability of at least an electronic and/or printed copy of the STGs in all health

Table 3 Long term impact of implementation of national STGs on medicine use indicators

	Antibiotic prescribing		Polypharmacy prescribing		Generic prescribing	
	Post-intervention trend change (β_3)		Post-intervention trend change (β_3)		Post-intervention trend change (β_3)	
	Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value	Estimate (95% CI)	*P*-value
National (all facilities)	1.28 (0.7, 1.9)	0.002*	0.03 (0.002, 0.07)	0.065	–2.22 (–4.1, –0.4)	0.040*
National (Health centers)	4.30 (0.6, 8.0)	0.047*	–0.10 (–0.23, 0.03)†	0.153	–8.61 (–14.4, –2.8)	0.016*
National (Hospitals)	1.07 (0.4, 1.7)	0.008*	0.04 (0.01, 0.07)	0.015*	–1.85 (–3.7, –0.03)	0.073
Regions						
Erongo	2.14 (0.5, 3.7)	0.025*	0.08 (–0.04, 0.20)	0.236	–1.41 (–5.1, 2.3)	0.472
Hardap	7.08 (4.3, 9.8)	0.000*	0.03 (–0.27, 0.33)	0.847	–2.24 (–45.8, 1.3)	0.241
Karas	–4.29 (–11.3, 2.7)†	0.257	0.07 (– 0.04, 0.18)	0.238	–3.74 (–7.0, –0.5)	0.050
Kavango	3.23 (1.3, 5.2)	0.008*	0.04 (– 0.06, 0.14)	0.407	–7.99 (–11.4, –4.5)	0.001*
Khomas	–2.33 (–5.6, 0.9)†	0.189	– 0.03 (– 0.15, 0.09)†	0.634	1.97 (–1.3, 5.2)†	0.259
Kunene	– 0.25 (– 3.1, 2.6)†	0.867	–0.11 (–0.21, –0.004)†	0.070	– 1.59 (– 7.8, 4.6)	0.625
Ohangwena	–1.52 (–3.4, 0.4)†	0.151	– 0.06 (–0.22, 0.11)†	0.508	–2.45 (–8.5, 3.6)	0.442
Omaheke	4.92 (1.8, 8.1)	0.011*	0.14 (0.03, 0.26)	0.032*	–9.24 (–18.4, –0.1)	0.076
Omusati	2.44 (–1.3, 6.2)	0.234	0.3 (0.2, 0.4)	0.000*	1.97 (–2.2, 6.1)†	0.372
Oshana	4.33 (–2.2, 10.9)	0.224	0.5 (0.01, 0.93)	0.074	–7.83 (–12.3, –3.4)	0.006*
Oshikoto	–2.38 (–7.7, 3.0)†	0.403	–0.1 (–0.4, 0.1)†	0.309	4.47 (2.6, 6.3)†	0.000*
Otjozondjupa	3.21 (–2.5, 8.9)	0.297	–0.05 (–0.19, 0.10)†	0.539	–2.27 (–6.4, 1.9)	0.309
Zambezi	1.71 (–2.5, 5.9)	0.447	–0.24 (–0.43, –0.05)†	0.034*	0.51 (–2.9, 3.9)†	0.778

*Linear regression modelling; *(P < 0.05)-Statistically significant; CI: confidence interval.* Durbin Watson statistic for average number of medicines = 2.04 (lag = 1, *P*= 0.242); Durbin Watson statistic for percent of medicines prescribed by generic name = 2.49 (lag = 1, *P* = 0.894); Durbin Watson statistic for percent of outpatient prescriptions with an antibiotic = 3.37 (lag = 1, P= 0.024). †*Indicator improved.*

facilities assessed and awareness/training having been conducted for health care workers.[16] Similarly, studies by Dogan *et al.*, Gasson *et al.* and Pereko *et al.* reported limited compliance to treatment guidelines by health workers;[24–26] and explains the limited or no impact of STGs on medicine use indicators. This necessitates implementation of point of care interventions and research to foster the implementation of up-to-date and usable forms of STGs in clinical care.

Secondly, the eight-year period estimates for the three-medicine use indicators were outside the national PIS/WHO targets. The study found a high number of medicines prescribed per outpatient (~3), above the WHO target of 2.0. Studies in other resource-limited settings in Ethiopia[27] and Pakistan[23] report lower rates of 2.2 and 2.3 medicines per prescription, but a study in Nigeria reports more medicine per prescription (5.8) compared to our study.[28] Moreover, the WHO estimated the burden of overprescribing among LMICs at 6.1 medicines per prescription and irrational prescribing of medicines at 50%.[11, 29] This is a major public health concern, given that unnecessary use of medicines depletes the limited-resources, leads to wastages, increases pill burden as well as untoward effects such as antimicrobial resistance in case of antibiotics.[22] Thirdly, in this study, the rate of antibiotic prescribing in public healthcare was almost double the WHO target (i.e. 48.1%, WHO ≤ 25%). Also, the study reported a significant increase in the quarterly trends of outpatient prescriptions with an antibiotic over the eight-years of review. Similar studies in LMICs report even higher rates of antibiotic use; 82.5% in Ethiopia, 66% in Sudan, 58.1% in Ethiopia, 39.6% in Pakistan and 52.4% in Pakistan.[23, 27, 31–34] Bagger *et al.* estimated the burden of unnecessary antibiotic prescribing in URTI at 45%, which are majorly viral in nature.[35] Similarly, antibiotic overuse remains high among developed countries such as the United States, Greece, France and Italy where the burden was estimated at over 25 defined daily dose (DDD) per 1000 inhabitants per day (DID).[36]

The high rate of antibiotic prescribing across LMICs and developed countries is a threat to global public health; given that the indiscriminate use of antibiotics is the main risk for the global epidemic, antimicrobial resistance and increases costs of health care.[30, 32] Studies in Namibia attribute the high rates of antibiotic use to limited implementation of antimicrobial stewardship interventions in public health facilities;[37] poor implementation and compliance to STGs,[16] non-alignment between STGs and essential medicines list for cotrimoxazole, amoxicillin and azithromycin.[15] Moreover, post-STG implementation assessment revealed that compliance of prescribers to treatment guidelines was limited.[16] This calls for the strengthening of antimicrobial stewardship in outpatient care in public health facilities. For instance, the United Arab Emirates reported lower rates of antibiotic prescribing estimated at 9.8%;[38] this can be achieved through the implementation of stringent inter-professional and multi-sectoral antimicrobial stewardship and awareness programs as recommended by WHO.[39–41]

Fourthly, for the eight-year review period, the rate of prescribing by generic names was low compared to the WHO and national targets (74.0% vs 100%). Furthermore, the rate of generic prescribing significantly declined by 2.2% every quarter for the eight-year review period (*P* = 0.040). Similar studies in Ethiopia[31] and WHO[29] in LMICs estimated generic prescribing in public healthcare at 97% and 69.8% respectively, and in Pakistan at 83.1%.[42] The WHO recommends the use of generic names of medicines in public healthcare to improve compliance with standard treatment guidelines and reduce healthcare expenditure.[43] The decline is generic prescribing after the implementation of the STGs is a concern and calls for review of the medicines in the STGs/essential medicines list to include generic names. In Namibia, the decline in the prescribing of generic medicines may be explained by the buy-out system employed at public health facilities; i.e. prescribers can request to buy a 'non-generic' medication for particular patients if not listed in STGs. Such processes are potential for manipulation from medicine sales/promotion activities reported in other studies. Or perhaps the implementation of STGs did not improve prescribers' practice in terms of generic prescribing and consequently this PIS indicator.

The study concludes that the implementation of the Namibia standard treatment guidelines in public healthcare did not improve national medicine use/indicators. There is a need to assess the barriers towards effective implementation of STGs. This may require interventions to strengthen the point of care compliance to STGs, alignment of STGs with essential medicines list and PIS indicators, use of electronic platforms to increase access to and utility of STGs and validate the current indicators. In addition, the MoHSS should evaluate current STGs-related strategies and interventions to foster compliance at points of care; such as review and update the STGs through a nationwide stakeholder engagement towards comprehensive, simplified and usable guidelines. Collaborative efforts between the MoHSS, donor-funded projects, academic institutions are needed to create awareness, build capacity through continued professional education of healthcare workers,[44] on STGs, regularly monitor compliance through annual medicine use assessments and pre-service training. More importantly, the MoHSS should utilise PIS information to provide targeted interventions for improving medicine use.

We acknowledge that this study has limitations. This was a population-based study and no patient level data were collected. Nevertheless, we believe that robust methods were used to assess a nationwide intervention and are the first study to model the impact of the implementation of a national STG in the sub-Saharan Africa region. The findings provide implications for strengthening the implementation of STGs and medicine use programs to improve outcomes.

Author Contributions

H.R.K., T.R. and H.M. participated in conceptualization and appraisal of the study through various stages. H.R.K. undertook data abstraction and compilation of the study dataset. H.R.K. and D.K. performed the interrupted time series (ITS) data analysis. H.R.K. wrote the manuscript. D.K., H.M. and T.R. appraised the manuscript through various stages of its development.

Conflicts of Interest

The authors have no conflict of interest to declare.

Data availability

The study used a Pharmaceutical Management Information System database of the Ministry of Health and Social Services of Namibia. Data for the period 2007–2015 was extracted as required for the study. The authors are not authorized to share the database, but permission may be obtained to access it.

Ethics statement

The Human Research Ethics Committee (HREC) of the University of Namibia (UNAM) and the Research and Ethics board of the MoHSS (26 February 2019) approved this study. The need for informed consent was waived as the study used secondary data and no human subjects were recruited in this study.

References

1. Marston HD, Dixon DM, Knisely JM *et al*. Antimicrobial resistance. *JAMA* 2016; 316: 1193–204.
2. Llor C, Bjerrum L. Antimicrobial resistance: risk associated with antibiotic overuse and initiatives to reduce the problem. *Ther Adv Drug Saf* 2014; 5: 229–41.
3. de Kraker MEA, Stewardson AJ, Harbarth S. Will 10 million people die a year due to antimicrobial resistance by 2050? *PLoS Med* 2016. http://doi.org/10.1371/journal.pmed.1002184
4. Laing R, Waning B, Gray A *et al*. 25 Years of the WHO essential medicines lists: progress and challenges. *Lancet* 2003. http://doi.org/10.1016/S0140-6736(03)13375-2
5. du Toit R, Faal HB, Etya'ale D *et al*. Evidence for integrating eye health into primary health care in Africa: a health systems strengthening approach. *BMC Health Serv Res* 2013; 13: 102.
6. Lancet (ed). The struggle for universal health coverage. *Lancet* 2012. http://doi.org/10.1016/S0140-6736(12)61485–8
7. Torres A, Ferrer M, Badia JR. Treatment guidelines and outcomes of hospital-acquired and ventilator-associated pneumonia. *Clin Infect Dis* 2010; 51: S48–53. http://doi.org/10.1086/653049
8. Higuchi M, Okumura J, Aoyama A *et al*. Application of standard treatment guidelines in rural community health centres, Timor-Leste. *Health Policy Plan* 2012; 27: 396–404.
9. Frenk J, De Ferranti D. Universal health coverage: good health, good economics. *Lancet* 2012. http://doi.org/10.1016/S0140-6736(12)61341–5
10. Pantoja T, Opiyo N, Lewin S *et al*. Implementation strategies for health systems in low-income countries: an overview of systematic reviews. *Cochrane Database Syst Rev* 2017; 9: CD011086.
11. WHO. Promoting rational use of medicines: core components. *WHO Policy Perspect Med* 2002. http://doi.org/10.5863/1551-6776-19.4.262
12. Docherty M, Shaw K, Goulding L *et al*. Evidence-based guideline implementation in low and middle income countries: lessons for mental health care. *Int J Ment Health Syst* 2017; 11: 8.
13. WHO. *Antimicrobial Resistance: Global Report on Surveillance*, 2014. http://doi.org/1.4.2014
14. Ofori-Asenso R, Brhlikova P, Pollock AM. Prescribing indicators at primary health care centers within the WHO African region: a systematic analysis (1995–2015). *BMC Public Health* 2016; 16. http://doi.org/10.1186/s12889-016-3428-8
15. Kibuule D, Mubita M, Naikaku E *et al*. An analysis of policies for cotrimoxazole, amoxicillin and azithromycin use in Namibia's public sector: findings and therapeutic implications. *Int J Clin Pract* 2017. http://doi.org/10.1111/ijcp.12918
16. Akpabio E, Sagwa E, Mazibuko G *et al*. Assessment of Compliance of Outpatient Prescribing with the Namibia Standard Treatment Guidelines in Public Sector Health Facilities, 2014. http://apps.who.int/medicinedocs/documents/s21715en/s21715en.pdf (30 May 2019, date last accessed).
17. Kafuko J, Bagenda D. *Impact of National Standard Treatment Guidelines on Rational Drug Use in Uganda Health Facilities*. Kampala: International Conferences on Improving Use of Medicines (ICIUM), 1994.
18. Kagoya HR, Rennie TW, Kibuule D *et al*. Alignment of standard treatment guidelines with medicine use indicators in a limited-resource setting: findings and implications. *J Pharm Heal Serv Res* 2020. http://doi.org/10.1111/jphs.12351
19. Ramsay CR, Matowe L, Grilli R *et al*. Interrupted time series designs in health technology assessment: lessons from two systematic reviews of behavior change strategies. *Int J Technol Assess Health Care* 2003; 19: 613–23.
20. Ministry of Health and Social Services (MoHSS). *Namibia Standard Treatment Guidelines. First Edition*. Windhoek, Namibia: Ministry of Health and Social Services, 2011
21. Kagoya HR, Kibuule D, Rennie TW *et al*. Optimizing data quality of pharmaceutical information systems in public health care in resource limited settings. *Res Social Adm Pharm* 2020; 16: 828–35.

22. Laing R, Hogerzeil H, Ross-Degnan D. Ten recommendations to improve use of medicines in developing countries. *Health Policy Plan* 2001; 16: 13–20.

23. Atif M, Azeem M, Sarwar MR *et al*. WHO/INRUD prescribing indicators and prescribing trends of antibiotics in the Accident and Emergency Department of Bahawal Victoria Hospital, Pakistan. *Springerplus*. 2016;5. http://doi.org/10.1186/s40064-016-3615-1

24. Dogan M, Mutlu LC, Yilmaz İ *et al*. Are treatment guides and rational drug use policies adequately exploited in combating respiratory system diseases? *J Infect Public Health* 2016; 9: 42–51.

25. Gasson J, Blockman M, Willems B. Antibiotic prescribing practice and adherence to guidelines in primary care in the Cape Town Metro District, South Africa. *S Afr Med J* 2018; 108: 304–10.

26. Pereko DD, Lubbe MS, Essack SY. Antibiotic use in Namibia: prescriber practices for common community infections. *South African Fam Pract* 2015. http://doi.org/10.1080/20786190.2015.1024021

27. Desalegn AA. Assessment of drug use pattern using WHO prescribing indicators at Hawassa University Teaching and Referral Hospital, south Ethiopia: a cross-sectional study. *BMC Health Serv Res* 2013; 13: 170.

28. Adisa R, Fakeye TO, Aindero VO. Evaluation of prescription pattern and patients' opinion on healthcare practices in selected primary healthcare facilities in Ibadan, South-Western Nigeria. *Afr Health Sci* 2015; 15: 1318–29.

29. WHO. Promoting rational use of medicines: core components Patient Care Indicators. *WHO Policy Perspect Med*, 2002. https://www.who.int/medicines/publications/policyperspectives/ppm05en.pdf (27 August 2020, date last accessed).

30. Holloway K. Promoting the rational use of antibiotics. *Reg Heal Forum* 2011; 15: 122–30.

31. Bilal AI, Osman ED, Mulugeta A. Assessment of medicines use pattern using World Health Organization's Prescribing, Patient Care and Health facility indicators in selected health facilities in eastern Ethiopia. *BMC Health Serv Res* 2016; 16: 144.

32. Cheraghali AM, Idries AM. Availability, affordability, and prescribing pattern of medicines in Sudan. *Pharm World Sci* 2009; 31: 209–15.

33. Atif M, Azeem M, Rehan Sarwar M *et al*. Evaluation of prescription errors and prescribing indicators in the private practices in Bahawalpur, Pakistan. *J Chin Med Assoc* 2018; 81: 444–9.

34. Summoro TS, Gidebo KD, Kanche ZZ *et al*. Evaluation of trends of drug-prescribing patterns based on WHO prescribing indicators at outpatient departments of four hospitals in southern Ethiopia. *Drug Des Devel Ther* 2015; 9: 4551–7.

35. Bagger K, Nielsen AB, Siersma V *et al*. Inappropriate antibiotic prescribing and demand for antibiotics in patients with upper respiratory tract infections is hardly different in female versus male patients as seen in primary care. *Eur J Gen Pract* 2015; 21: 118–23.

36. Goossens H, Ferech M, Coenen S *et al*. Comparison of outpatient systemic antibacterial use in 2004 in the United States and 27 European Countries. *Clin Infect Dis* 2007. http://doi.org/10.1086/512810

37. Brinkmann I, Kibuule D. Effectiveness of antibiotic stewardship programmes in primary health care settings in developing countries. *Res Soc Adm Pharm* 2020; 16: 1309–13.

38. Mahmood A, Elnour AA, Ali AAA *et al*. Evaluation of rational use of medicines (RUM) in four government hospitals in UAE. *Saudi Pharm J* 2016. http://doi.org/10.1016/j.jsps.2015.03.003

39. Hayat K, Rosenthal M, Gillani AH *et al*. Perspective of Pakistani physicians towards hospital antimicrobial stewardship programs: a multisite exploratory qualitative study. *Int J Environ Res Public Health* 2019. http://doi.org/10.3390/ijerph16091565

40. Massele A, Burger J, Katende-Kyenda NL *et al*. Outcome of the first Medicines Utilization Research in Africa group meeting to promote sustainable and rational medicine use in Africa. *Expert Rev Pharmacoecon Outcomes Res* 2015; 15: 885–8.

41. Godman B, Fadare J, Kibuule D *et al*. *Initiatives Across Countries to Reduce Antibiotic Utilisation and Resistance Patterns: Impact and Implications*, Cham, Switzerland: Springer, 2017. http://doi.org/10.1007/978-3-319-48683-3_24

42. Atif M, Azeem M, Sarwar MR *et al*. WHO/INRUD prescribing indicators and prescribing trends of antibiotics in the Accident and Emergency Department of Bahawal Victoria Hospital, Pakistan. *Springerplus* 2016. http://doi.org/10.1186/s40064-016-3615-1

43. Promoting rational use of medicines saves lives and money, WHO experts say. *Saudi Med J*. Arlington, VA: Management Sciences for Health, SIAPS Program, 2004. https://www.who.int/mediacentre/news/notes/2004/np9/en/ (27 August 2020, date last accessed).

44. Mabirizi D, Kibuule D, Adorka M *et al*. *Promoting the Rational Medicine Use of ARVs, Anti-TB and Other Medicines and Preventing the Development of Antimicrobial Resistance in Namibia : Workshop and Stakeholders Forum*, 2013.