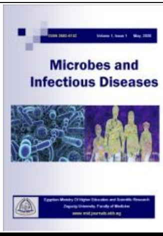

Microbes and Infectious Diseases 2020; 1 (3): 153-167

Microbes and Infectious Diseases

Journal homepage: https://mid.journals.ekb.eg/

Systematic review and meta-analysis

Hospital antibiotic stewardship interventions in low- and middle- income countries: A systematic review and meta-analysis

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ARTICLE INFO

Article history:
Received 3 April 2020
Received in revised form 4 May 2020
Accepted 9 May 2020

Keywords:
Antibiotic use
Educational strategies
Antibiotic stewardship
Antibiotic resistance
Infection control

ABSTRACT

Background: In low-and middle-income countries (LMICs), infectious diseases burden and increased rates of antimicrobial use, make the implementation of antimicrobial stewardship (AS) an indispensable choice. The study aimed to demonstrate the characteristics of AS interventions and to assess their impact on antibiotic, economic and clinical outcomes among hospitalized patients in LMICs. **Methods:** Data from studies reporting the efficacy of hospital AS interventions and their impact on antibiotic, economic and/or clinical outcomes across LMICs were collected and interpreted. The data from the same outcomes were pooled and analysed using a random-effects meta-analysis model. **Results:** The antimicrobial consumption showed a 14.8% reduction (95% CI: 3.02 to 1.82, I^2: 94.8%, $p<0.001$). No evidence of small-study effect across studies was detected (Egger's regression: 3.2, *p-value* 2-tailed: 0.12). The antimicrobial consumption was decreased by 1.1% (95% CI: 1.34 to 0.54, I^2: 97.3%, $p<0.001$). The implementation of AS has led to decrease in antimicrobial cost of 2.4% (95% CI: 1.47 to 1.27, I^2: 92.6%, $p<0.001$). The mean hospital length of stay (LoS) was reduced by 19.1% (95% CI: 5.99 to 0.61, I^2: 97.7%, $p<0.001$). **Conclusion:** All the investigated interventions succeeded to positively affect the targeted outcomes. Education was not underscored as an AS intervention, with complete absence of behavioural elements. Antimicrobial exposure/use/consumption is the most commonly used outcome indicator. For economic and LoS concerned studies, more data is needed to provide a stronger business case to encourage investing in AS. Limited data on AS interventions in LMICs entails urgent attention.

Introduction

The global continuous surge in drug resistant infections has been associated with the increasing use of antimicrobials worldwide, which impends to return back to the pre-antibiotic era **[1]**. The scenario is more dramatic in low- and middle-income countries (LMICs) where a higher burden of infectious diseases has been reported **[2]**. Adding to the limited resources and poor infrastructure of healthcare facilities, Antibiotic stewardship (AS) programs data from LMICs is scarce and fragmented **[3]**.

Antibiotic stewardship has been developed as a comprehensible set of interventions and actions. It is intended to achieve a more prudent use for antimicrobials and to ensure improving the quality of

DOI: 10.21608/MID.2020.27164.1004
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patients care **[4]**. The AS interventions could be either structural (such as the introduction of new diagnostic tests to guide antibiotic treatment), persuasive (expert audit with feedback to prescribers), enabling (such as developing guidelines or educational courses on antibiotic use) or restrictive (such as applying the use of a restricted antibiotic list) **[5]**. From a practical point of view, different interventions are frequently combined in intervention bundles in healthcare facilities **[6]**.

Although AS is challenging. It becomes more problematic with limited resources and absent formal programs, a situation that applies to LMICs **[7]**. Published reports displayed the positive impact of AS in high income countries. Being a matter of context, it is unclear whether those results also apply to LMICs **[6]**. **Cox et al.** recommended developing specific guidance for setting up AS in LMICs **[7]**. The current report aims to demonstrate the characteristics of AS interventions and to assess their impact on antibiotic, economic and clinical outcomes among hospitalized patients in LMICs.

Materials and methods

This systematic review and meta-analysis were conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines **[8]**. The World bank classification was used to specify studies from low- and middle-income countries **[9]**.

Search strategy

A systematic electronic search of PubMed, Web of Science and Google Scholar databases was performed for relevant studies from July 2004 to June 2019. All published studies conducted in LMICs and reporting the efficacy of hospital AS interventions and their impact were included in this analysis. The search terms were combinations of the following: ‘antibiotic OR antimicrobial’, ‘stewardship OR policy AND intervention’, ‘impact OR outcomes’, ‘hospital OR inpatient’, and ‘low- and middle-income countries’. The literature search was limited to studies published in English language. The lists of references of retrieved studies and relevant review articles and meta-analysis were reviewed for eligibility for inclusion. Moreover, a manual search by country name was set.

The eligibility of enrolled studies was assessed by both authors. In case of disagreement, consensus was sought after reading the full text articles. The selected data was further discussed with a panel of experts to identify the inclusion and exclusion criteria for enrolled studies.

Inclusion and exclusion criteria

Studies that did not contain a hospital AS intervention, measure any key outcomes, or that were conducted in countries other than LMICs were excluded. AS-based studies targeting antiviral, antifungal or anti-mycobacterial agents were excluded. All inclusion and exclusion criteria were established prior to the review.

The term AS intervention applies to any intervention aiming to improve appropriate prescribing of antibiotics **[6]**.

Data extraction and quality assessment

Information collected from each study included the title, year of publication, authors, country, study design, description of intervention, and the description of AS outcomes.

For systematic review analysis, the main outcomes of interest were antimicrobial, economic and clinical outcomes. Antimicrobial outcomes included antibiotic use/exposure/consumption. Key economic outcomes were antibiotic/hospital costs. Length of stay (LoS) was the main clinical outcomes of interest.

For data meta-analysis, we selected three main outcomes that were most frequently reported in the literature. The first outcome was the change in antimicrobial consumption in terms of the percentages of patients treated with antibiotics, and the measured defined daily doses (DDD) per 1000 patient days before and after the intervention among hospitalized patients. The second outcome was the calculated inpatients’ costs (including the costs for hospital stay, medication, and antibiotics calculated by U.S. Dollars). The third outcome was the change in the average duration of hospital stay calculated in days.

The quality of eligible studies was assessed using the Newcastle Ottawa scale **[10]**. Studies with ≥ 5 stars were considered of adequate quality for extraction of relevant information.

Data meta-analysis

The data from studies that reported the same outcomes were pooled and analyzed using a random-effects meta-analysis model, and pooled estimates were described as a forest plot with Odd’s Ratios (ORs) and a 95% confidence interval (CI). The *P* value of each study was extracted from the studies or calculated when crude data were available. The percentage change and *P* value for each study were used to calculate the 95% CI and standard error **[11]**.

The heterogeneity across studies was assessed using I^2 statistic. The I^2 index values of <25%, 25-50%, and 50-75% were interpreted as low, medium, and high heterogeneity, respectively. For I^2 values of > 75%, a large between-study heterogeneity considering diversity of variants between studies is anticipated, and a meta-regression model was used to evaluate predictors and covariates between studies **[12]**.

Publication bias was examined using a funnel plot, and the funnel plot asymmetry was further tested using Egger's regression method, which yields a statistically significant *p-value*. The statistical analysis was performed using Comprehensive Meta-Analysis program, version 3 **[13]** and *p-values<0.05* were considered statistically significant.

Results

The enrolled studies were selected as shown in **figure (1)**. A total of initial 6163 citations were retrieved. Search in the list of references of retrieved studies and relevant researches added 48 studies. The duplicates were removed. We started the screening process for 6183 records. Due to the few number of eligible studies, authors performed another manual search by country name. A total of 20 studies **[14-33]** were included for systematic review data analysis, of which, 17 studies were included in data meta-analysis **[14-18, 20-22, 24-32]**.

Systematic review

The twenty enrolled studies reported different interventions from various geographic regions: China, Iran, Kenya, Egypt, Lebanon, India, Serbia, Indonesia, Brazil, Turkey, Thailand and South Africa. All intervention types were represented: structural, enabling, persuasive and intervention bundle **(Table 1)**.

Fifteen studies report antibiotic exposure/use/consumption as an outcome **[14, 15, 17, 18, 20-27, 30, 31, 33]**. **Table 2** presents a significant decrease in antibiotic prescriptions and use, restricted antibiotic exposure and antibiotic therapy upon admission. A significant increase in the percentages of appropriate therapy assessed prescriptions is reported in one single study **[11]**.

Eight studies investigated the economic impact of AS interventions **(Table 3) [16, 20, 24, 25, 28, 29, 31, 32]**, including: antibiotic cost (8 studies) **[16, 20, 24, 25, 28, 29, 31, 32]**, hospital cost (3 studies) **[24, 29, 31]**, antibiotic and consumable cost (one study) **[16]**, AS savings (one study) **[31]** and restricted/non restricted antibiotic cost (one study) **[31]**.

Five studies reported the Los as an outcome measure **(Table 4) [15, 18, 24, 25, 29]**. All of them showed a significant decrease in the length of hospital stay.

Meta-analysis

A total of 17 studies were included. The meta-analysis of the AS impact on overall antibiotic consumption included 10 studies **[14, 17, 20-22, 25-27, 29, 30]**. The pooled percentage change of antimicrobial consumption after AS implementation was14.8% reduction (95% CI: 3.02 to 1.82, I^2: 94.8%, *p<0.001*). The high level of heterogeneity detected between studies (I^2: 94.8%) was assessed using the funnel plot test **(Figure 2)**. Interestingly, no evidence of small-study effect across studies was detected (Egger's regression: 3.2, *p-value* (2-tailed): 0.12) **(Figure 3)**. A meta-regression model was used to assess predictors between studies heterogeneity, co-variates including publish year, sample size and type of study design. The variables of publish year and sample size did not show association with the heterogeneity (*p: 0.65* and *0.13*, respectively). However, the type of study design remained associated with the heterogeneity between studies (*P=0.02*). The change in antimicrobial consumption after the implementation of AS in hospitals in terms of calculated (DDD/1000-patient-days was evaluated in 5 studies **[18, 26, 29, 31, 32]**. The pooled effect size was 1.1% decrease in the total DDDs across studies (95% CI: 1.34 to 0.54, I^2: 97.3%, *p = <0.001*) **(Figure 4)**.

The implementation of AS has led to decrease in antimicrobial cost of 2.4% in 6 studies (95% CI: 1.47 to 1.27, I^2: 92.6%, *p < 0.001*, **Figure 5**) [16, 20, 24, 28, 31, 32]. The mean hospital LoS was reduced by 19.1% based on 5 studies (95% CI: 5.99 to 0.61, I^2: 97.7%, *p <0.001*, **Figure 6) [15, 18, 24, 25, 29]**.

Figure 1. PRISMA Flow Diagram for studies selection process.

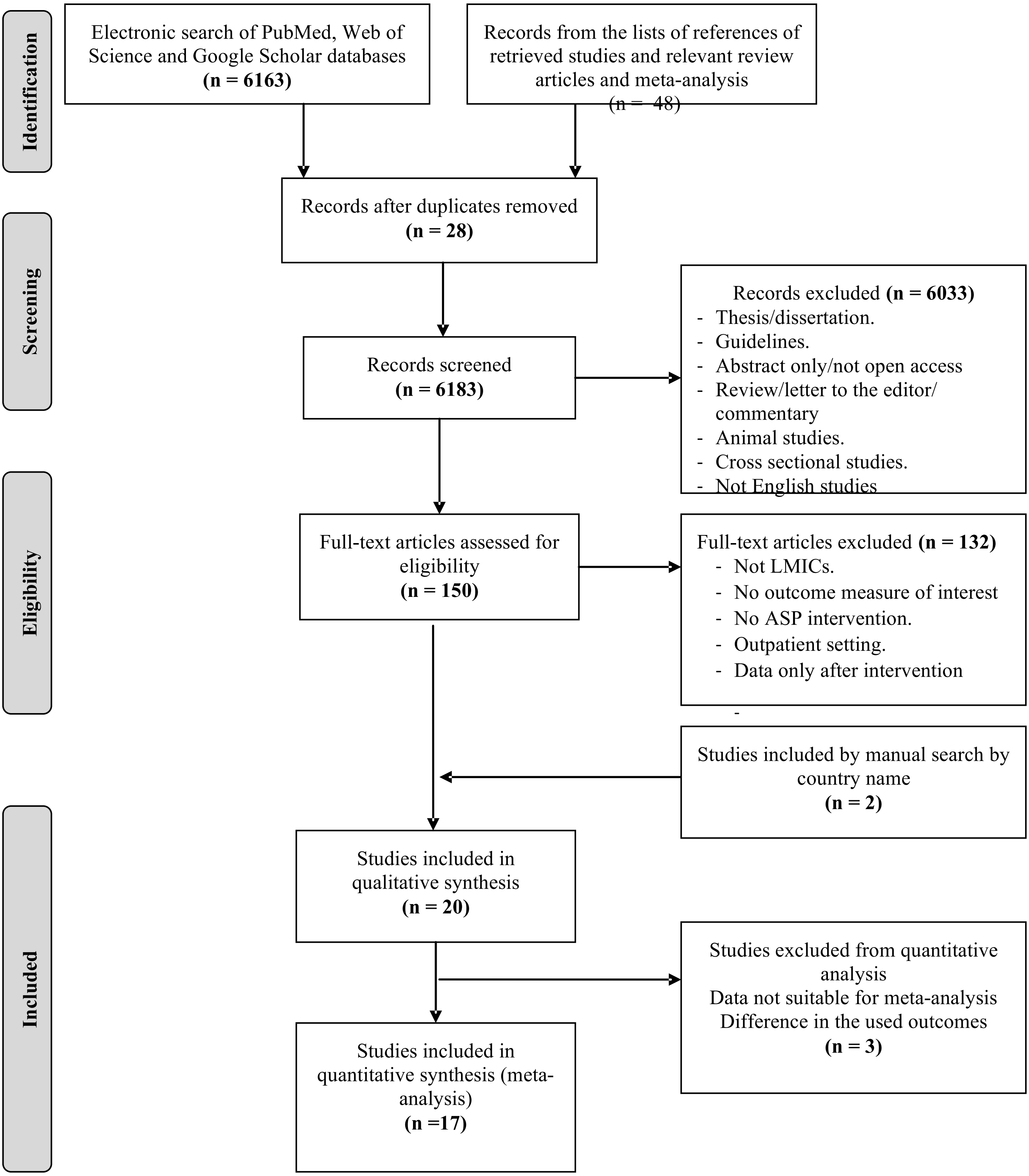


Table 1. Characters of the Studies included in systematic review and meta-analysis

	Authors	Year of publication	Country	Study design	Study duration weeks	Study settings	Type of intervention	Details of intervention
1-	Tang et al., [14]	2013	China	randomized controlled trial	76	emergency department	structural	PCT guided antibiotic therapy in the study group. In the control group, antibiotic therapy guided by the physician decision.
2-	Najafi et al., [15]	2015	Iran	single-blind randomized study	12	ICU in a single hospital	structural	PCT guided antibiotic therapy in the study group. In the control group, antibiotic therapy guided by the physician decision.
3-	Aiken et al., [16]	2013	Kenya	An interrupted time series.	17	a 300-bed Governmen t Hospital	bundle	Guidelines on surgical antibiotic prophylaxis; clinician education; patient education posters; audit and feedback to prescribers
4-	Long et al., [17]	2014	china	randomized controlled trial	36	one hospital	structural	PCT guided antibiotic therapy in the study group. In the control group, antibiotic therapy guided by the physician decision.
5-	Saied et al., [18]	2015	Egypt	intervention study	12	5 tertiary acute care surgical hospitals	bundle	ASP: leadership- audit and feedback-education
6-	Ibrahim and Bazzi., [19]	2017	Lebanon	intervention study	36	a private teaching hospital	structural	Physicians told the rationale behind using antibiotics by filling an antibiotic assessment form
7-	Gong et al., [20]	2016	china	uncontrolled, observational	9	1012-bed tertiary pediatric hospital	bundle	Antibiotic guidelines and prescribing restrictions; audit and feedback to prescribers by pharmacists and infection control physicians; financial penalties according to number of noncompliant prescriptions
8-	long et al., [21]	2011	china	a randomized controlled trial	47	800-bed university-affiliated hospital	structural	PCT guided antibiotic therapy in the study group. In the control group, antibiotic therapy guided by the physician decision.
9-	ding et al., [22]	2013	china	randomized controlled trial	36	a 3000- bed tertiary care hospital	structural	PCT guided antibiotic therapy in the study group. In the control group, antibiotic therapy guided by the physician decision.
10-	Chandy et al., [23]	2014	India	Interrupted time series	120	tertiary care teaching hospital	enabling	Implementation and dissemination of antibiotic prescribing guidelines

PCT; procalcitonin, ASP; antibiotic stewardship.

	Authors	Year of publication	Country	Study design	Study duration weeks	Study settings	Type of intervention	Details of intervention
11-	Bao et al., [24]	2015	China	intervention study	48	65 public general hospitals	bundle	Implementation of a nationally imposed multifaceted ASP
12-	Maravić-Stojković et al., [25]	2011	Serbia	A prospective, randomized controlled trial		one academic tertiary care hospital	structural	Antibiotic initiation guided by serum procalcitonin level versus routine care (based on clinical signs, C-reactive protein levels and leukocyte count)
13-	Hadi et al., [26]	2008	Indonesia	a prospective intervention	12	five wards of the internal medicine department	enabling	Antibiotic guidelines; education for prescribers
14-	Özkaya et al., [27]	2009	Turkey	cross sectional single blinded trial	5	emergency department in urban children's teaching hospital	structural	Antibiotic initiation guided by influenza rapid test versus no laboratory investigation
15-	Magedanz et al., [28]	2012	Brazil	quasi experimental	72	250 bed cardiology hospital	bundle	Restriction of certain antibiotics; audit and feedback to prescribers by (i) infectious diseases specialist and (ii) pharmacist
16-	Shen et al., [28]	2011	China	prospective controlled study	10	two independent respiratory wards of a tertiary teaching hospital	persuasive	Audit and feedback to prescribers by clinical pharmacist
17-	Apisarnthanarak et al., [29]	2006	Thailand	Intervention study	24	a 350-bed tertiary care university hospital	bundle	Education, introduction of an antibiogram, use of antibiotic prescription forms and prescribing controls
18-	Ng et al., [30]	2007	China	Intervention study	24	an 1800-bed acute service hospital	bundle	Policy and guideline formulation, education and feedback
19-	Boyles et al., [31]	2013	South Africa	Intervention study	24	2 general medical wards comprising 32 beds each	bundle	An antibiotic prescription chart and weekly antibiotic stewardship ward round were introduced.
20-	Huo et al., [32]	2014	China	intervention	18	ICU at a tertiary hospital in China.	bundle	Antimicrobial stewardship strategies: formulary restriction, preauthorization, perioperative quinolone restriction, and control of total antibiotic consumption

Table 2. Interventions' impact on antimicrobial exposure/use/consumption.

	Authors	**Outcome measures**
1-	Tang et al., 2013	Antibiotics usage in the PCT group (461%) was lower than that in the control group (748%)
2-	Najafi et al., 2015	Total antibiotic exposure days in the intervention group were 128 vs 320 in the control group
3-	Long et al., 2014	Antibiotics usage in the PCT group (47.9 %) was lower than that in the control group (87.8%)
4-	Saied et al., 2015	Drugs use for surgical prophylaxis decreased from 843 DOT/1000 patient-days in the pre-intervention period to 335 DOT/1000 patient-days in the post-intervention period
5-	Gong et al., 2016	The proportion of antibiotic prescriptions reduction = 19.8% for inpatients
6-	Long et al., 2011	In the PCT guidance group, compared with patients treated according to current guidelines: • Prescription of antibiotics on admission (84.4% vs 97.5%). • Total antibiotic exposure (RR 0.55, 95% CI: 0.51–0.60). • Duration of antibiotic treatment (median 5 days vs 7 days).
7-	Ding et al., 2013	- All Patients in control group were exposed to antibiotics treatment vs 69.4% in the intervention group. - Duration of antibiotic treatment in control group was 14.5±5.2 days vs 8.7±6.6 in intervention group.
8-	Maravić-Stojković et al., 2011	18.6% of patients in procalcitonin group received antibiotics vs 46.6% in routine care group.
9-	Chandy et al., 2014	Overall antibiotic use increased at a monthly rate of 0.95 (SE = 0.18), 0.21 (SE = 0.08) and 0.31 (SE = 0.06) for Segments 1, 2 and 3, stabilized in Segment 4 (0.05; SE = 0.10) and declined in Segment 5 (20.37; SE = 0.11).
10-	Bao et al., 2016	- The average antibiotic prescribing rates declined by 2.27% - The average prescribing rate was reduced significantly from 62.9% during the preparation period to 35.3% during the assessment period in the inpatient settings. - Significant decreases in the duration of peri-operative antibiotic treatment (3.97 vs. 0.96 day) during the assessment period compared with the preparation period.
11-	Hadi et al., 2008	- Antibiotic therapy upon admission included (88% vs 71%) in the pre and post intervention phases. - Appropriate therapy, assessed prescriptions were (16% vs 25%) in the pre and post intervention phases. - Antibiotic treatment was not correctly stopped after 72 in all cases in both phases.
12-	Özkaya et al., 2009	Patients in intervention were less likely to be prescribed antibiotics when compared to those in control group: 32% vs 100%, respectively.
13-	Apisarnthanarak et al, 2006	There was a 24% reduction in the rate of antibiotic prescription (640 vs. 400 prescriptions/ 1000 admissions. The incidence of inappropriate antibiotic use was significantly reduced (42% vs. 20%). A sustained reduction in antibiotic use was observed.
14-	Ng et al., 2007	Restricted antibiotics were prescribed in 19.6% of admissions, which decreased to 12.3% after intervention
15-	Huo et al., 2014	- After implementation of ASP, the initial selection of no antibiotic or single antibiotic increased significantly (5.0% vs 2.3%, 78.9% vs 20.5%). The initial selection of two antibiotics were significantly lower (16.1% vs 74.1%). - In the 'before' period, between the infectious and the non-infectious group, there was no significant difference in initial selection concerning whether to use and how many varieties used. - In the 'after' period, the initial selection between the two groups was significantly different with a higher proportion of no antibiotic and single antibiotic use (5.5% vs 2.3% and 81.3% vs 65.9%, respectively) and a lower proportion of two antibiotic use (13.2% vs 31.8%) in the non-infectious group .

PCT; procalcitonin, DOT; Days of therapy, ASP; antibiotic stewardship.

Table 3. Interventions' impact on inpatients' cost.

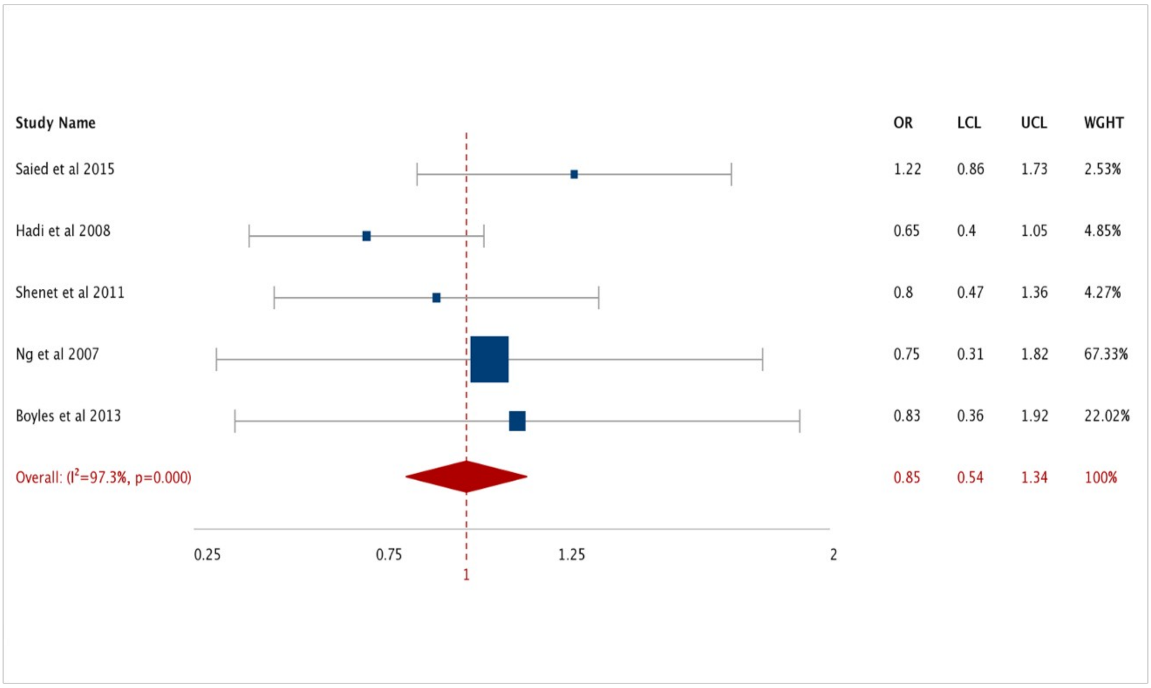
	Authors	**Outcome measures**
1-	Aiken et al., 2013	A net reduction in the costs for intravenous antibiotics and associated consumables of approximately $2.50/operation (from $ 6.2 to $ 3.6 /operation).
2-	Gong et al., 2016	A reduction of 16.3% of total antibiotic expenditure after intervention; β = −4.933, *p = 0.001*
3-	Bao et al., 2015	A significant decreases in the average costs on hospital stay ($1396.2 vs. $1382.2; *p = 0.041*), medication ($606.7 vs. $541.8; p < 0.001), antibiotics ($203.7 vs. $95.4; a reduction of 53%; *p < 0.001*), and on the very-restricted antibiotics ($51.3 vs. $6.9; a reduction of 87%; *p < 0.001*) for hospitalized patients during the assessment period compared with the preparation period.
4-	Magedanz et al., 2012	A significant reduction of 69% in hospital antibiotics costs. The mean monthly antibiotic cost, during the first stage, was US$ 30,727.56 (American dollars), US$ 18,034.89 in the second period, and US$ 9,623.73 in the last period of the study (*P < 0.001*).
5-	Maravić-Stojković et al., 2011	The mean cost of antibiotics per patient in procalcitonin group was €193.3±636.6 vs. €372.1±841.1 (*p=0.206*) in the standard group, while the mean cost per hospital day was €8.0±18.4 vs. €17.8±36.3 (*p=0.028*).
6-	Shen et al., 2011	The total costs of hospitalization in the intervention group were significant lower compared to the control group ($1442.3 ± 684.9 vs. $1729.6 ± 773.7, *p<0.001*), as well as the cost of antibiotics ($832.0 ± 373.0 vs. $943.9 ± 412.0, *p = 0.01*)
7-	Ng et al., 2007	After implementation of the ASP: - The monthly cost of restricted antibiotics was significantly reduced by 52.0% (*p,0.001*) and by 46.4% (from; *p,0.001*), respectively. - The cost of non-restricted antibiotics increased by 6.1% (*p=0.052*) and 11.9% (*p=0.003*), respectively. - The total savings of the ASP was US$ 309 745 per year. - The average hospital bed cost per patient-day was US$387.5 per year.
8-	Boyles et al., 2013	The total cost of antibiotics during the control period was R1 068 325 compared to R694 705 during the intervention period representing a cost saving of R373 620 with a cost reduction of 35% of the pharmacy's antibiotic budget.

ASP; antibiotic stewardship

Table 4. Interventions' impact on length of hospital stay (days)

	Authors	Outcome measures
1-	Najafi et al., 2015	Median and range decreased from 22 (6-65) to 20 (8-44) in the control and intervention groups respectively.
2-	Saied et al., 2015	Mean± SD and range decreased from 4.3± 5.0 (1-38) to 5.1± 5.6 (1-31) after intervention.
3-	Bao et al., 2015	The average duration of hospital stay decreased by 0.16 day (se = 0.03; *p < 0.001*) per month during the intervention period. A significant decreases in the duration of hospital stay (6.41 vs. 5.27 day; *p < 0.001*).
4-	Maravić-Stojković et al., 2011	Mean± SD and range decreased from 12.93±10.73 to 12.08±11.28 after intervention. RR:1.01; 95% CI, 0.98-1.03
5-	Shen et al., 2011	Mean± SD decreased 15.8 ± 6.0 from in the control group to 14.2 ± 6.2 in the intervention group. *P= 0.03*

Figure 2. Forset plot of the pooled percentage of studies for the impact of ASPs on the antimicrobial consumption.



OR: Odds Ratio, LCL: Lower confidence level, UCL: Upper confidence level

Figure 3. Funnel plot of 10 studies included in the meta-analysis.

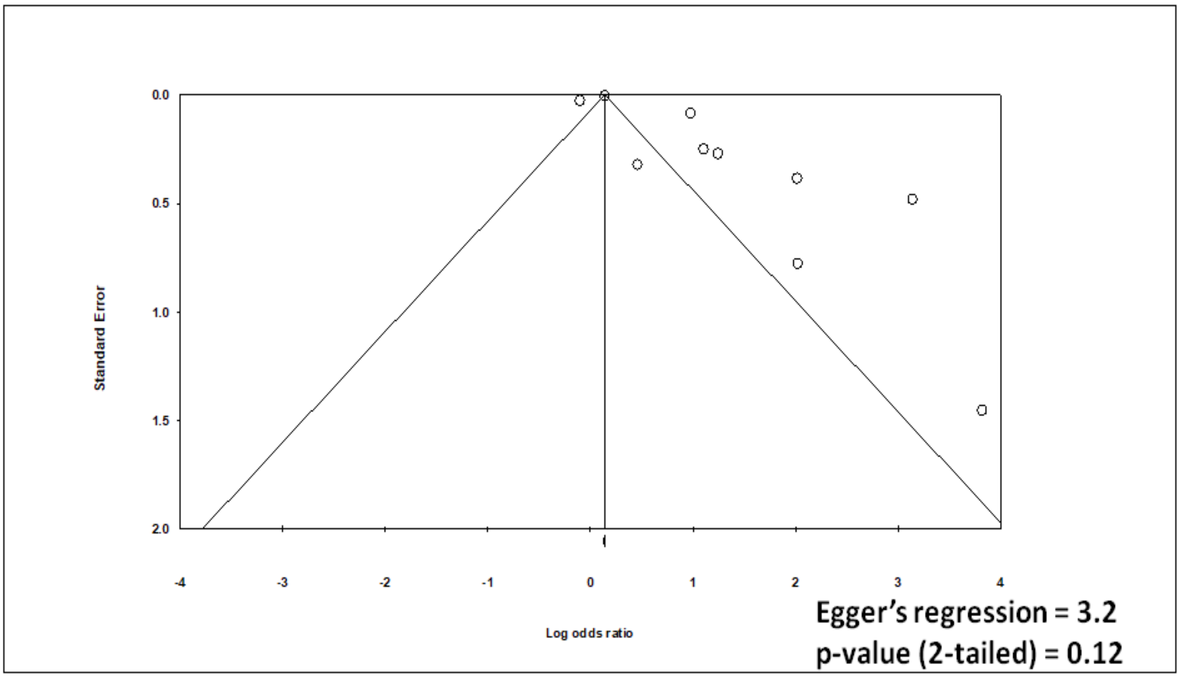
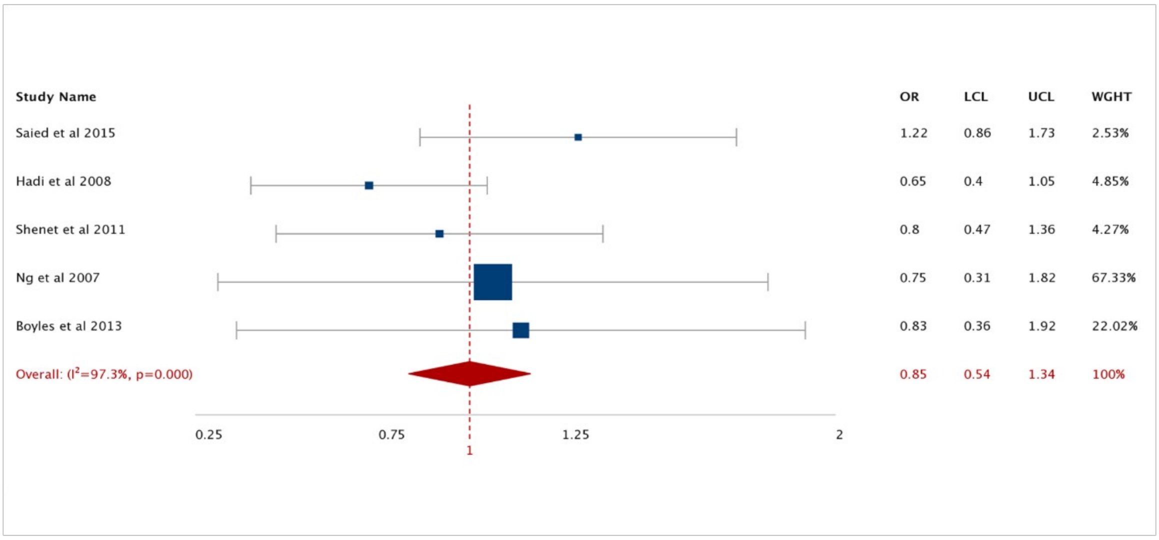
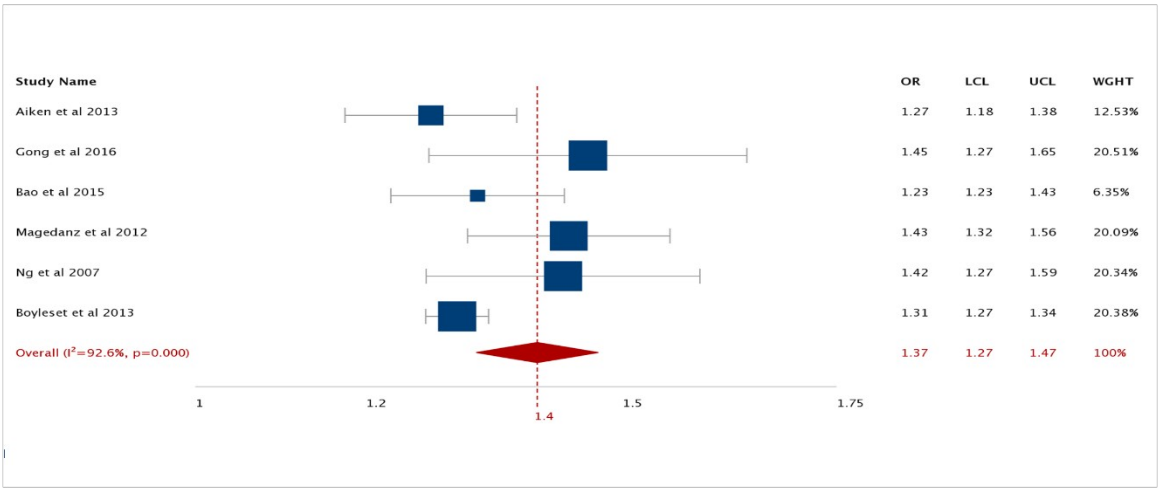


Figure 4. Forset plot of the pooled change in the total DDDs across studies after ASPs implementation.



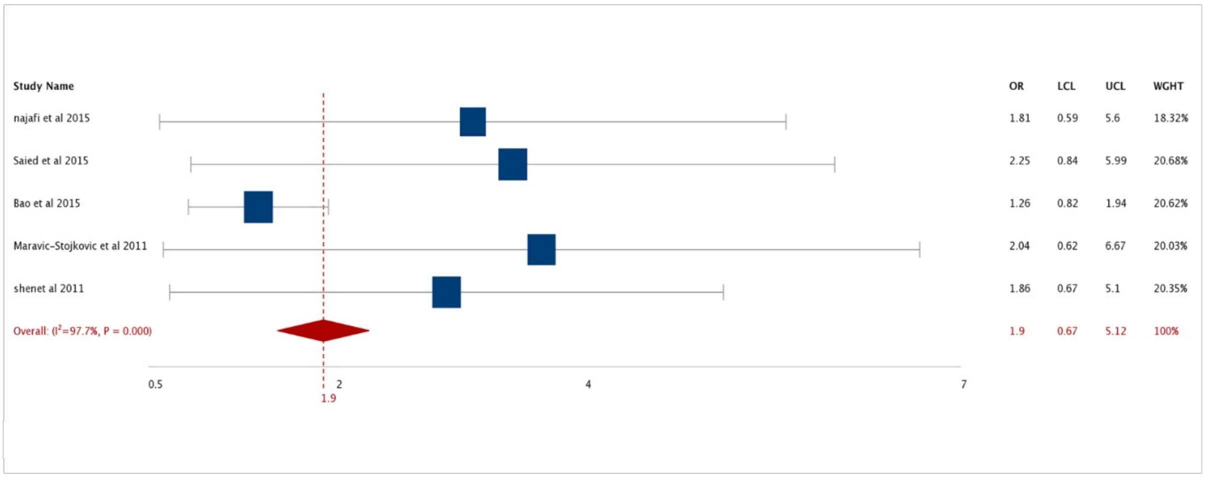
OR: Odds Ratio, LCL: Lower confidence level, UCL: Upper confidence level

Figure 5. Forset plot of the pooled change in the total cost across studies after ASPs implementation.



OR: Odds Ratio, LCL: Lower confidence level, UCL: Upper confidence level

Figure 6. Forset plot of the pooled change in the mean hospital length of stay across studies after ASPs implementation.



OR: Odds Ratio, LCL: Lower confidence level, UCL: Upper confidence level

Discussion

Poor quality of methods is a consistent theme among antibiotic stewardship studies in countries of all income levels. There is a real need to address this defect to strengthen the evidence-based practice for AS implementation **[5, 34]**. To the best of our knowledge, this report is the first to provide both quantitative and qualitative analysis of the effect of antimicrobial stewardship interventions in LMICs.

In a resource-limited setting, it is not the rule that multifaceted interventions are more effective than single-component interventions **[35]**. Hence, flexibility is accepted in designing antimicrobial stewardship strategies that adequately reflect local needs and resources **[36]**. Out of the twenty enrolled studies, ten studies used a single-component intervention; procalcitonin (PCT) guided therapy in six studies. The results of the current study support the concept that PCT guidance reduces antibiotic exposure. However, to evaluate the cost-efficiency of PCT-based strategy, different cost aspects should be further studied **[17]**.

At the individual facility level, a growing number of AS initiatives in LMICs have brought theory into practice **[7]**. Thus, it was not surprising to see such a wide range of stewardship interventions applied in the included studies. Education, as an effective strategy, was applied in only five studies. This was disagreeing with previous reports from higher income countries **[6, 36]**. Although a large number of cross-sectional studies investigated knowledge, skills and practice gaps in different aspects of antibiotic stewardship program in low resources settings **[7]**, yet the study of education role in intervention studies is still missed **[6]**. It goes without saying that education is essential to generate sustainable improvement in antibiotic prescribing. Nevertheless, it still represents a great challenge in many LMICs **[7]**. Notably, behaviour change was completely missed as an intervention target, this highlights the need to shed some light on this very important and effective strategy.

On the other hand, although it is an intense and resource heavy intervention **[37]**, audit and feedback strategy was applied in six studies from five different countries. This may reflect the awareness of researchers of the benefit of such type in spite of the anticipated limitations for application.

Some 'low-hanging fruit' activities were reported **[16, 20, 28, 38]**. The term entails selecting the most obtainable targets rather than confronting more complicated management issues. The selection considers the limited resources, the availability of (evidence-based) interventions and their possible impact **[38]**. Reported examples include perspective optimization of surgical antibiotic prophylaxis **[16]**, antibiotic restriction **[20, 28]** and the introduction of dedicated antibiotic justification forms **[19]**.

The critical importance of implementing studies to reduce antibiotic consumption in LMICs is still underscored **[39]**. In this report, recorded results suggest a significant reduction in antimicrobial consumption by 14.8% when pooling across all types of interventions. **Karanicka et al.,** reported a 20% decrease in antibiotic use in 26 studies from different resources settings **[40]**.

One of the main factors involved in the process of proper treatment selection and completion is the cost. It is a critical factor that has an evident impact in LMICs. The implementation of AS has led to decrease in antibiotic cost of 2.4% in six studies **[16, 20, 24, 28, 31, 32]**. A similar finding could be noticed in previous systematic reviews studied interventions from LMICs **[6]** and other settings [36, 40]. Many indirect expenses are expected to proportionally decrease the cost, e.g., the decrease in the hospital stay cost **[41, 42]**.

A 3.7% decrease in LoS was reported by the current report [**15, 18, 24, 25, 29]**. An impressive decrease of 15% in LoS was reported earlier **[40]**. Several factors can affect hospital LoS, e.g., admission diagnosis, institutional features, social status **[42]**, and certain hospital-acquired infections **[43]**. The exact cause leading to decrease LoS is beyond the scope of this analysis. Additional studies are needed for further exploration.

This study has some limitations. First: lack of adequate numbers of studies investigating the AS interventions in LMICs, poor quality studies and absence of agreed upon outcome measures. Second: many countries were not represented. This makes it difficult to reach common recommendations to be generalized. Third: the high level of heterogeneity detected between studies in this report due to the wide variations in study designs, antibiotic stewardship interventions, outcomes, and co-implemented infection control measures among different studies. However, being the first report in LMICs settings to investigate the effect of stewardship interventions, it would be of a benefit to highlight the importance of sustained implementation of AS.

In conclusion: No universal intervention or outcome measures were shared in common between the studies.

All the investigated interventions succeeded to positively affect the targeted outcomes, this support the prospect of being context specific. Nearly half of the studies used a single-component intervention. Education was not underscored in most enrolled studies, with complete absence of behavioural aspects. Easily applicable feasible outcome measures that can be set for LMICs should be highlighted. The largest number of studies used antimicrobial exposure/use/consumption as an outcome indicator. For economic and LoS concerned studies, more data is needed to provide a stronger business case to encourage investing in AS. Limited data on AS interventions in lower- and middle-income countries entails urgent attention.

Conflict of interest: None declared

Authorship: Both authors had read and approved the final version of the manuscript.

Financial disclosure: None declared

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