Effective Antimicrobial StewaRdship StrategIES (ARIES): Cluster randomised trial of computerised decision support system and prospective review and feedback

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Key points:
Voluntary CDSS on broad-spectrum antibiotics with PRF did not result in differing clinical outcomes, antibiotic duration and length of stay.
However, in the setting of low antibiotic appropriateness, compulsory CDSS may be beneficial.

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Abstract

Background
Prospective review and feedback (PRF) of antibiotic prescriptions and compulsory computerised decision support system (CDSS) are two strategies of antimicrobial stewardship. There are limited studies investigating their combined effects. We hypothesised that the use of CDSS on demand (voluntary) would achieve similar patient outcomes compared with CDSS automatically triggered (compulsory) whenever broad-spectrum antibiotics are ordered.

Methods
A parallel-group, 1:1 block cluster randomised, cross-over study was conducted in 32 medical and surgical wards from March to August 2017. CDSS use for piperacillin-tazobactam or carbapenem in the intervention clusters was at the demand of the doctor while in the control clusters, CDSS use was compulsory. PRF was continued for both arms. Primary outcome was 30-day mortality.

Results
641 and 616 patients were randomised to voluntary and compulsory CDSS respectively. There were no differences in 30-day mortality (HR 0.87, 95% CI 0.67-1.12), re-infection and re-admission rates, antibiotic duration, length of stay and hospitalisation cost. The proportion of patients receiving PRF recommendations was not significantly lower in the voluntary CDSS arm (62 [10%] vs. 81 [13%], p=0.05). Appropriate indication of antibiotics was high in both arms [351/448 (78%) vs. 330/433 (74%), p=0.18]. However, in geriatric medicine patients where antibiotic appropriateness was less than 50%, prescription via compulsory CDSS resulted in a shorter length of stay and hospitalisation cost.

Conclusion
Voluntary CDSS on broad-spectrum antibiotics with PRF did not result in differing clinical outcomes, antibiotic duration and length of stay. However, in the setting of low antibiotic appropriateness, compulsory CDSS may be beneficial.
Introduction

Increasing antimicrobial resistance due to inappropriate antimicrobial use is a global concern and antimicrobial stewardship teams have become an integral part of the response to this issue.[1,2] Through prospective review of antibiotic prescriptions and feedback (PRF) to doctors, patients have improved clinical response, reduced adverse effects and mortality.[3-5] However, this strategy is labour-intensive and skilled healthcare workers are expensive and scarce resources.[6,7]

Antibiotic computerised decision support systems (CDSS) have been used to facilitate these processes to circumvent the lack of manpower. In observational studies, implementation of a CDSS correlated with an overall reduction in broad-spectrum antibiotic use, and increased susceptibility of *Pseudomonas aeruginosa* to imipenem and *Enterobacteriaceae* to gentamicin and ciprofloxacin.[8,9] CDSS also improved clinical outcomes in a randomized controlled trial.[10] While PRF and CDSS guidance are designed to be in accordance with the same institutional guidelines, there are differences in acceptance of recommendations between the two systems.[3,10-13] In previous studies, PRF recommendations had an acceptance rate of 60-70% while CDSS acceptance was only 40%. [3,4,13-14] Currently, there are limited studies comparing the combined effects of these two strategies.[2]

At Tan Tock Seng Hospital (TTSH) in Singapore, antimicrobial stewardship has focused on PRF by a team of infectious disease doctors and pharmacists. Since 2009, this team has reviewed piperacillin-tazobactam and carbapenem orders according to hospital antibiotic guidelines from day two of antibiotic prescription during office hours. In 2011 we implemented a CDSS which was triggered round-the-clock and at the point of antibiotic ordering of piperacillin-tazobactam and carbapenem in the electronic medical record. The compulsory CDSS provides guidance on antibiotic use and infection management based on hospital guidelines. Theoretically, compulsory CDSS may improve the timeliness of appropriate antibiotic and clinical outcomes such as mortality but doctors may find it cumbersome and intrusive, preferring on-demand CDSS use. [10] We hypothesised that together with prospective review and feedback, voluntary, on-demand use of CDSS in ordering antibiotics would achieve similar patient outcomes compared with compulsory, automatically triggered CDSS use at the point of antibiotic ordering.

We aimed to investigate in a real-world cluster randomised controlled trial, if compared with a compulsory CDSS, voluntary use of the CDSS when piperacillin-tazobactam and carbapenem were...
prescribed would achieve similar clinical outcomes, antibiotic prescribing and requirement for subsequent PRF in the individual patient.

**Methods**

**Study design and patients**

ARIES is a parallel-group, 1:1 block, real-world open labelled cluster randomised, cross-over study conducted in TTSH, a 1700-bed teaching hospital. Waiver for informed consent was approved by institutional review board (DSRB/F/2015/00671). The study was conducted in 32 medical and surgical wards over a 24-week period from March 2017 to August 2017. Intensive care unit (ICU), high dependency and step-down care wards were excluded as we had a specialised infectious disease team for ICU and high dependency patients. Piperacillin-tazobactam and carbapenems are rarely used in our step-down care wards. Patients in the clusters were enrolled at first prescription of piperacillin-tazobactam or a carbapenem. Each participant was only included once.

**Randomisation**

As modifications to the CDSS could only be done at the ward level, we clustered the patients by wards. This would also reduce contamination of intervention effects within wards which would be present in individual patient randomisation. Twenty-five wards had 30 (range 30-41) or more patients while 7 wards had fewer than 30 (range, 12-29) patients. Clusters were stratified into 2 blocks based on size and allocated to intervention or control group using a random number generator. Cross-over of the study arms occurred at week 12 without a washout period.

**Procedures**

To promote understanding and acceptance of CDSS guidance, an educational campaign was conducted. This began 24 weeks before initiation of the study and continued until completion (October 2016 to August 2017). The campaign comprised a monthly package of 3-minute videos with an accompanying short quiz. This was disseminated to all doctors via emails, hospital intranet and Facebook with weekly reminders and complimentary coffee cards to 2 doctors each month as an incentive for participation. The educational materials were developed following focus groups conducted in previous studies and a 1-day prospective evaluation of compulsory CDSS use in 81 patients. [12,14,16] The intervention group comprised of 15 clusters where piperacillin-tazobactam and carbapenem can be ordered by the voluntary use of CDSS (doctors are allowed to order without CDSS too) while the control group had 17 clusters with the compulsory use of CDSS when ordering both types of antibiotics. In both arms, PRF occurred on day 2 of prescription and was available only
During office hours. Patients’ electronic medical records at our hospital were reviewed prospectively for 6 months from the first prescription based on the periods specified in the primary and secondary outcomes. The CDSS provided antibiotic recommendations adjusted for renal function, and drug allergies were accounted depending on available clinical laboratory data and manually entered data such as the type of infection, severe penicillin allergy and dialysis status. It also provides alerts and clues that will help decide on diagnosis and management. Compulsory CDSS was triggered at the point of antibiotic ordering while voluntary CDSS was used on-demand at the point of antibiotic ordering. Review of CDSS guidance is necessary once activated for the antibiotic order to be completed but doctors are free to accept or reject its recommendations. Differences in terms of clinical workflows between CDSS and PRF are described in Supplementary Table 5.

**Outcomes**

To demonstrate the impact of education on acceptance of CDSS guidance, we monitored acceptance rate of CDSS recommendations for the first 12 weeks of the baseline period (April to October 2016, 24 weeks) and compared it to the first 12 weeks of the educational campaign (October 2016 to March 2017, 24 weeks). Data was collected for the first 1280 patients during each period.

The primary outcome was 30-day mortality from the date of the first piperacillin-tazobactam or carbapenem prescription. Secondary outcomes included number and types of recommendations from PRF, clinical response at day 7, 30-day re-infection rate, 30-day readmission rate, length of stay, diarrhoea during hospitalisation, 6-month incidence of multi-drug resistant organisms, duration of index piperacillin-tazobactam or carbapenem use (days of therapy), overall hospitalisation cost and appropriateness of antibiotic use according to institutional guidelines. Trained pharmacists assigned appropriateness independent of whether CDSS were used and they were not privy to the randomization process. Clinical response was defined as resolution of systemic inflammatory response syndrome. [17] Recommendations from CDSS and PRF were classified into de-escalation (switch to a narrower spectrum antibiotic), dose optimisation, antibiotic spectrum optimisation (increase in the spectrum of antibiotic therapy), infectious disease referral, additional investigation and setting antibiotic duration. Multidrug-resistant organisms were defined as methicillin-resistant *Staphylococcus aureus*, vancomycin-resistant enterococci, third-generation cephalosporin or carbapenem resistant *Enterobacterales* and multidrug-resistant *Acinetobacter baumannii* or *Pseudomonas aeruginosa* [18] and *Clostridiodes difficile*. Overall hospitalisation cost was determined from the final hospital bill size in Singapore dollars (1 Singapore dollar=1.3822 US dollar on 8 August 2019).
Statistical analysis

Sample size calculation accounted for intention-to-treat analysis and the following assumptions: 30% of patients in control arm may be transferred out to intervention arm; recommendations were accepted 50% of the time; mortality rate of the intervention group was 15%. [4] Simulation using 32 clusters indicated a total of 1280 patients (16 clusters and 640 patients in each study arm) would have a power of 80% to detect a 5% difference in mortality rates.[19] The uncertainty was set at 5% level of significance. Equal cluster sizes were assumed. As the primary outcome was binary, intra-cluster correlation was not needed to simulate power. Analysis for primary and secondary outcomes was carried out by intention-to-treat and per-protocol analysis. Univariate analysis using Chi-square test for categorical variables and Mann-Whitney test for continuous variables were performed. To report time to death, re-admission and re-infection, Kaplan-Meier estimators were calculated and plotted across time strata. Log-rank tests were performed to test for equality across interventions. Cox proportional hazards models were used to calculate the risk of various outcomes. Subgroup analysis of common departments and sources of infections was performed for 30-day mortality, re-admission, re-infection and length of stay to identify possible confounders. All tests were done at a 5% significance level. Sample size calculation was performed in R using the clusterPower package. All other analysis was performed using STATA 13. A data safety monitoring board was convened to review the interim results of the study before cross-over at week 12. The study was registered at ClinicalTrials.gov (NCT04011657).

Role of the funding source

The study was funded by the National Medical Research Council, Ministry of Health, Singapore (CNIG14MAY005). The funder of the study had no role in the 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 final responsibility for the decision to submit for publication.
Results
During the educational campaign, the number of patients who had at least one CDSS recommendation accepted was not significantly different during the baseline and educational phases (746/1213 [62%] vs. 796/1240 [64%], p = 0.11). There were more recommendations accepted during the educational phase (1300/3611 [36%] vs. 1571/3640 [43%], P<0.01). Acceptance of recommendations was significantly improved for: antibiotic spectrum optimisation (343/894 [38%] vs. 423/857 [49%], p<0.01), dose optimisation (361/430 [84%] vs. 442/482 [92%], p<0.01) and setting antibiotic duration (410/728 [56%] vs. 509/725 [70%], p<0.01). Acceptance of recommendations was not significantly different after the campaign for: de-escalation (19/347 [5%] vs. 27/362 [7%]), infectious disease referral (14/228 [6%] vs. 15/222 [7%]) and additional investigations (153/984 [16%] vs. 155/992 [16%]).

Intraclass correlation was low and insignificant, and the percentage of total variance accounted for by the wards for 30-day mortality was 0.7% (95% confidence interval [CI], 0.01% - 23%), 30-day readmission 2% (95%CI 0.2% - 16%) and 30-day reinfection 1% (95%CI, 0.2% - 12%) (Supplementary Figure 1). Therefore, we proceeded to analyse our data using the survival approach.

During the cluster randomised study from 28 March 2017 to 28 August 2017, a total of 4060 patients were prescribed piperacillin-tazobactam or carbapenems over the course of the study and screened for eligibility. One thousand two hundred and fifty-seven patients from 32 clusters were randomised to voluntary (n=641) and compulsory CDSS (n=616). Recruitment was stopped after 24 weeks. Baseline characteristics of patients in both study arms were similar. (Table 1) Most patients 92% (1161/1257) received the antibiotics for empirical therapy with piperacillin-tazobactam accounting for 86% (1076/1257). Most patients were under departments of General Medicine 29% (365/1257), Geriatric Medicine 18% (n=223/1257), Respiratory Medicine 9% (118/1257) and General Surgery 7% (84/1257). Respiratory, urinary tract, intra-abdominal and skin and soft tissue infections were common.

In the voluntary CDSS arm, 132 (21%) patients had their first course of piperacillin-tazobactam or carbapenems ordered using CDSS compared with 612 (99%) patients in the compulsory CDSS arm. A similar proportion of patients in both study arms were reviewed subsequently by the PRF team: voluntary CDSS (n=488, 70%) vs. compulsory CDSS (n=443, 72%) respectively. In the voluntary CDSS arm, 154 (24%) patients had broad-spectrum antibiotics started without CDSS or PRF review. The number and types of CDSS and PRF recommendations are summarised in Table 2. Overall, there
were fewer CDSS recommendations in the voluntary arm compared with the compulsory arm (425 vs. 1733) and about half of these were accepted (49% vs. 46%). Antibiotic spectrum optimisation, additional investigations and setting antibiotic duration were the most common recommendations. De-escalation was more often recommended in the compulsory arm but had lower acceptance than the voluntary arm. There were fewer PRF recommendations provided in the voluntary arm compared with the compulsory arm (74 vs. 99) and >75% of these were accepted. The most common recommendations were de-escalation, additional investigations and setting antibiotic duration. Among those with subsequent positive microbiology, patients with active empiric therapy were similar: voluntary CDSS (122/138 [88%]) vs. compulsory CDSS (107/129 [83%] (p=0.20).

Appropriateness of antibiotic use was similar between study arms in terms of indication, dose and duration. (Table 3) There were significantly fewer patients who received CDSS recommendations in the voluntary CDSS arm compared with the compulsory CDSS arm (132 [21%] vs. 612 [99%], p<0.01). There were fewer patients who received PRF recommendations in the voluntary CDSS arm compared with the compulsory arm, but it was not statistically significant (62 [10%] vs. 81 [13%], p=0.05). When either CDSS or PRF recommendations were provided, most patients (>90%) had at least one recommendation accepted. Per-protocol analysis showed similar trends. (Table 4)

There was similar 30-day mortality (hazard ratio [HR] 0.87, 95% CI 0.67-1.12), 30-day re-infection (HR 1.15, 95% CI 0.91 - 1.46) and 30-day re-admission rates (HR 0.99, 95% CI 0.74 - 1.33) between voluntary and compulsory CDSS. (Figure 2 and Table 3) There was no difference in clinical response at day 7 between voluntary and compulsory arms (106 [17%] vs. 99 [16%], p=0.22). Median length of hospital stay was similar (15 days [IQR 5-64] vs. 15 days [IQR 4-70], p=0.92). Incidence of diarrhoea during admission and 6-month acquisition of multidrug-resistant organisms were not significantly different. Median days of therapy of index antibiotic use were similar (4 days [IQR 3-5] vs. 4 days [IQR 3-5], p=0.47). Overall median hospitalisation cost was not significantly different between the voluntary and compulsory CDSS arms in ITT (SG$ 13 302 [IQR 3 221 – 67 110] vs. SG$13 307 [IQR 3 064- 64 666], p=0.91). (Table 3)

Subgroup analysis of the top 4 common departments namely General Medicine, Geriatric Medicine, Respiratory Medicine and General Surgery was performed. There was no difference in clinical outcomes, length of stay, hospitalisation cost and duration of index antibiotics between the study arms in patients of general medicine and respiratory medicine. (Supplementary Table 1) Subgroup analysis of common infections, namely respiratory, urinary tract, intra-abdominal and skin and soft
tissue infections did not identify any differences between the study arms. (Supplementary Table 2) Among Geriatric Medicine patients, the median length of stay was significantly higher (19 days [IQR 5-83] vs. 14 days [IQR 4-43], p= 0.03) in the voluntary CDSS arm corresponding to a significantly higher median overall hospitalisation cost ($13 945 [IQR 3 706- 57 133] vs. $10 444 [IQR 3 099 – 31 276], p= 0.02). There was no difference in patient characteristics between both arms except fewer patients in the voluntary CDSS arm received (29 [27%] vs. 114 [100%], p<0.01) and accepted (24 [22.0%] vs. 84 [74%], p<0.01) CDSS recommendations. (Supplementary Table 3) Among General Surgery patients, the median length of stay was not significantly higher in the voluntary CDSS arm (20 days [IQR 7—74] vs. 16 days [IQR 6-40], p=0.075); however the median overall hospitalisation cost was significantly higher in the voluntary CDSS arm compared with the compulsory CDSS arm ($35 303 [IQR 5 249-82 634] vs. $20 994 [IQR 4 333-61 243], p<0.01). Notably, appropriate indications of antibiotics were lower in both departments between voluntary and compulsory CDSS compared with the overall study (351 [78%] vs. 330 [75%]): Geriatric Medicine (52 [48%] vs. 57 [50%), p=0.50) and General Surgery (26 [68%] vs. 33 [72%], p=0.34). There were no significant differences in patient characteristics in both study arms other than more CDSS recommendations and acceptance in the compulsory CDSS arm. (Supplementary Tables 3 and 4)

Discussion

Piperacillin-tazobactam and carbapenems prescribed in the setting of voluntary CDSS use had similar clinical outcomes and appropriateness of use when compared with compulsory CDSS. It did not increase the need for PRF recommendations by the AMS team. However, compulsory CDSS was associated with significant reduction in hospital length of stay and hospitalisation cost for patients when antibiotic appropriateness was low. In the setting of high appropriate antibiotic use and PRF, it is likely that compulsory CDSS may not have clinical benefits and may inconvenience doctors in causing delay, distraction or irritation. A more sophisticated CDSS which uses artificial intelligence or machine learning to diagnose an infection rather than relying on doctors to enter their clinical diagnosis may be better. However, benefits may be magnified in settings with lower appropriateness of antibiotic use and when CDSS is implemented as a new system. [9] Notably voluntary CDSS with PRF did not lead to differences in appropriateness of antibiotic use, duration of index antibiotic use and clinical outcomes. A recent meta-analysis concluded that CDSS improved adequacy of antibiotic coverage (measured as compliance with guidelines) and marginally lowered mortality.[21] In addition, a separate report from our group conducted just after CDSS implementation between 2011 and 2012 reported
Our study was conducted several years after implementation of hospital antibiotic guidelines and PRF in 2009, and compulsory CDSS in March 2010. Doctors in the hospital had substantial experience with these interventions before the start of our study in March 2017. The high coverage of PRF may have addressed any possible difference between voluntary and compulsory CDSS use too. Further studies are needed to study the impact of mixed strategies of antibiotic stewardship in hospitalised patients.

Our study provided novel insights on the concurrent use of two common antimicrobial stewardship strategies of CDSS and PRF deployed in different ways. Piperacillin-tazobactam and carbapenems were mainly used for empiric therapy and most CDSS recommendations were to optimise antibiotic spectrum, suggest additional investigations and setting antibiotic duration. CDSS rarely provided de-escalation recommendations compared with PRF. PRF occurred on day 2 and subsequent days until the antibiotic was stopped. Additional clinical information or changes in patients’ condition could have driven these differences. Although fewer than 50% of CDSS recommendations were accepted in both compulsory and voluntary CDSS arms, it was interesting to note that >90% of patients in both arms had at least one recommendation accepted. A separate cohort study on our CDSS for piperacillin-tazobactam and carbapenem prescriptions found that almost 50% were ordered after office hours. Dose and antibiotic spectrum optimisation were the most often accepted CDSS recommendations, important factors to be correct early in the treatment of infection.

There are limited randomised studies on CDSS in AMS with mortality as a primary outcome and these focused on other surrogate outcome measures and did not report on the non-expert end-user workflow. We studied mortality as the primary outcome and our CDSS is integrated with clinical workflow as it is made available at the time of antibiotic prescription. It provides recommendations for investigations and referrals in addition to antibiotics. We studied the implementation hurdles of our CDSS, patients’ and physicians’ predictors and the psychosocial determinations of physicians’ acceptance of CDSS recommendations previously. We then designed an educational campaign aimed to optimise the non-expert end-user usage of our CDSS.

Our study did not evaluate the effect of CDSS on other antibiotics such as fluoroquinolones and third-generation cephalosporins. Between clusters, there may be contamination, possible Hawthorne effect and bias between the study arms due to doctors’ rotation, doctors managing patients in both study arms concurrently on different wards and patient transfers. We adopted a cross-over design to adjust for these effects. As CDSS as well as PRF were considered standard...
of care at our hospital and recommended by AMS guideline.[1] We were unable to introduce a washout period before cross-over or have a stand-alone CDSS or PRF study arm. Hence, we were not able to fully address effects of CDSS on mortality because of the concurrent use of PRF. COMPASS, a cluster randomised controlled trial focusing only on CDSS use is ongoing. However, the primary outcome is overall antibiotic use.[23] Further studies are needed to evaluate the effects of CDSS on AMS and mortality.

Conclusion
Voluntary CDSS for piperacillin-tazobactam and carbapenem prescriptions with PRF did not result in differing clinical outcomes, antibiotic duration and length of stay and PRF recommendations compared with compulsory CDSS and PRF. However, in geriatric medicine patients, where appropriateness of antibiotics was lower, compulsory CDSS with PRF resulted in lower length of stay and overall hospitalisation cost.
Contributors
TM Ng, DC Lye, B Young, J Wong, HL Tan and TW Lew contributed to the study design.
HL Tay, SH Tan, MY Yap, CB Teng, B Ang, DC Lye and TH Lee were part of the prospective review and feedback team.
ST Heng and J Wong did the statistical analysis.
ST Heng collected all the data.
TM Ng provided the first draft of the manuscript and all authors contributed to the final manuscript.

Declaration of interest
We declare no competing interests.

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Table 1. Baseline characteristics

| Characteristics          | Voluntary CDSS (n=641) | Compulsory CDSS (n=616) |
|--------------------------|------------------------|-------------------------|
| **Demographics**         |                        |                         |
| Age, years, median (IQR) | 74 (45-93)             | 76 (48-93)              |
| Male                     | 376 (59%)              | 333 (54%)               |
| Surgical discipline      | 103 (16%)              | 101 (16%)               |
| Charlson’s score, median (IQR) | 7 (2-13)     | 7 (2-13)                |
| APACHE II, median (IQR)  | 15 (6-28)              | 16 (6-29)               |
| Transferred to ICU       | 38 (6%)                | 47 (8%)                 |
| Transferred to step down care | 102 (16%)     | 104 (17%)               |
| Transferred out of randomized study arm | 59 (9%)   | 61 (10%)                |
| **Index antibiotic**     |                        |                         |
| Piperacillin-tazobactam  | 557 (87%)              | 519 (84%)               |
| Carbapenem               | 84 (13%)               | 97 (16%)                |
| Empiric therapy          | 600 (94%)              | 561 (91%)               |
| Targeted therapy         | 41 (6%)                | 55 (9%)                 |
| Positive microbiology    | 138 (22%)              | 129 (21%)               |
| Active empiric therapy   | 122/138 (88%)          | 107/129 (83%)           |
| **Source of infection**  |                        |                         |
| Respiratory              | 415 (65%)              | 420 (68%)               |
| Urinary                  | 109 (17%)              | 121 (20%)               |
| Intra-abdominal          | 38 (6%)                | 34 (6%)                 |
| Hepatobiliary            | 29 (5%)                | 23 (4%)                 |
| Bone and Joint           | 19 (3%)                | 8 (1%)                  |
| Skin and soft tissue     | 41 (6%)                | 44 (7%)                 |
| Vascular catheter        | 7 (1%)                 | 6 (1%)                  |
| Neutropenic sepsis       | 16 (3%)                | 11 (2%)                 |
| Unknown source           | 66 (10%)               | 55 (9%)                 |
| Others*                  | 14 (2%)                | 5 (1%)                  |

Data are n (%), unless otherwise stated. CDSS; Computerized decision support system, ICU: Intensive care unit.

*including neurological source, ear, nose and throat, infective endocarditis, eye, paraspinal abscess
Table 2. Type of recommendations and their acceptance (in percentages) provided for the use of broad-spectrum antibiotics guided by voluntary or compulsory computer decision support system (CDSS) and prospective review and feedback (PRF).

| Characteristics                      | Voluntary CDSS       | Compulsory CDSS      |
|--------------------------------------|----------------------|----------------------|
| Total CDSS recommendations           | 425 (49%)            | 1733 (46%)           |
| De-escalation                        | 15 (47%)             | 174 (9%)             |
| Dose optimization                    | 63 (98%)             | 199 (95%)            |
| Antibiotic spectrum optimization     | 111 (51%)            | 403 (48%)            |
| Infectious disease consult referral  | 24 (0%)              | 89 (5%)              |
| Additional investigations            | 117 (11%)            | 495 (17%)            |
| Setting antibiotic duration          | 95 (74%)             | 373 (83%)            |
| Total PRF recommendations            | 74 (76%)             | 99 (80%)             |
| De-escalation                        | 37 (76%)             | 42 (91%)             |
| Dose optimization                    | 1 (0%)               | 2 (50%)              |
| Antibiotic spectrum optimization     | 3 (100%)             | 5 (60%)              |
| Infectious disease consult referral  | 3 (33%)              | 3 (33%)              |
| Additional investigations            | 14 (64%)             | 18 (67%)             |
| Setting antibiotic duration          | 16 (94%)             | 29 (83%)             |

Data are for the intention-to-treat population
Table 3. Appropriateness of antibiotic use, acceptance of recommendations and outcomes of patients who received broad-spectrum antibiotics guided by voluntary or compulsory computer decision support system (CDSS) and prospective review and feedback (PRF) recommendations

| Characteristics                              | Voluntary CDSS (n=641) | Compulsory CDSS (n=616) | P     |
|----------------------------------------------|------------------------|-------------------------|-------|
| Reviewed by PRF                             | 448 (70%)              | 443 (72%)               | 0.43  |
| Appropriate indication under PRF reviews     | 351/448 (78%)          | 330/443 (75%)           | 0.18  |
| Appropriate dose                             | 625 (98%)              | 599 (97%)               | 0.77  |
| Appropriate duration                         | 587 (92%)              | 548 (89%)               | 0.12  |
| **Recommendations**                          |                        |                         |       |
| Received CDSS recommendations                | 132 (21%)              | 612 (99%)               | <0.01 |
| Accepted CDSS recommendations*               | 130 (20%)              | 556 (90%)               | <0.01 |
| Received PRF recommendations                 | 62 (10%)               | 81 (13%)                | 0.05  |
| Accepted PRF recommendations*                | 51 (8%)                | 71 (12%)                | 0.03  |
| **Outcomes**                                |                        |                         |       |
| 30-day mortality                            | 123 (19%)              | 102 (16%)               | 0.22  |
| 30-day re-infection rate                     | 132 (21%)              | 142 (23%)               | 0.29  |
| 30-day re-admission rate                     | 92 (14%)               | 87 (14%)                | 0.91  |
| Clinical response at day 7                   | 535 (83%)              | 517 (84%)               | 0.82  |
| Length of stay, days, median (IQR)           | 15 (5-64)              | 15 (4-70)               | 0.92  |
| 6-month multi-drug resistant organisms*      | 152 (24%)              | 171 (27%)               | 0.10  |
| Diarrhea this admission                      | 89 (14%)               | 86 (14%)                | 0.96  |
| Index antibiotic days of therapy, median (IQR)| 4 (3-5)                | 4 (3-5)                 | 0.47  |
| Index antibiotic days of therapy ≤3          | 295 (46%)              | 297 (48%)               | 0.45  |
| Gross hospitalization costs, median (IQR), SS| 13 301 (7184-24079)     | 13 308 (6743-24904)     | 0.96  |

*Patients were considered to have recommendations by CDSS or PRF accepted if at least one of the recommendations provided by the respective service was accepted. *Multi-drug resistant organisms were defined as methicillin-resistant *S. aureus*, Vancomycin-resistant *enterococi*, third-generation cephalosporin or carbapenem resistant *Enterobacterales* and multi-drug resistant *A. baumannii* or *P. aeruginosa* and *Clostridiodes difficile* diarrhea. Data are for the intention-to-treat population.
Table 4. Appropriateness of antibiotic use, acceptance of recommendations and outcomes of patients who received broad-spectrum antibiotics guided by voluntary or compulsory computer decision support system (CDSS) and prospective review and feedback (PRF) recommendations.

| Characteristics                                      | Voluntary CDSS (n=455) | Compulsory CDSS (n=416) | P     |
|------------------------------------------------------|------------------------|-------------------------|-------|
| **Reviewed by PRF**                                  |                        |                         | 0.80  |
| Appropriate indication under PRF reviews             | 259/324 (80%)          | 215/293 (73%)           | 0.05  |
| Appropriate dose                                      | 443 (97%)              | 402 (97%)               | 0.52  |
| Appropriate duration                                 | 424 (93%)              | 373 (90%)               | 0.06  |
| **Recommendations**                                  |                        |                         |       |
| Received CDSS recommendations                        | 91 (20%)               | 412 (99%)               | <0.01 |
| Received PRF recommendations                         | 41 (9%)                | 50 (12%)                | 0.15  |
| **Outcomes**                                         |                        |                         |       |
| 30-day mortality                                     | 85 (19%)               | 85 (20%)                | 0.52  |
| 30-day re-infection rate                             | 113 (25%)              | 106 (26%)               | 0.83  |
| 30-day re-admission rate                             | 85 (19%)               | 79 (19%)                | 0.91  |
| Clinical response at day 7                           | 383 (84%)              | 344 (83%)               | 0.56  |
| Length of stay, days, median (IQR)                   | 12 (4-41)              | 12 (4-35)               | 0.26  |
| 6-month multi-drug resistant organisms                | 91 (20%)               | 94 (23%)                | 0.35  |
| Diarrhea this admission                              | 59 (13%)               | 61 (15%)                | 0.47  |
| Index antibiotic days of therapy, median (IQR)       | 4 (3-5)                | 3 (3-5)                 | 0.23  |
| Index antibiotic days of therapy <=3                 | 213 (47%)              | 209 (50%)               | 0.31  |
| Gross hospitalization costs, median (IQR), S$        | 10520 (5826-18430)     | 9671 (5734-17576)       | 0.43  |

Data are for the per-protocol population
Figure 1. Trial profile. *5 Antibiotics not served, 4 Excluded due to inclusion for another trial, 1 Excluded due to age below 21 years old

Figure 2. Survival analysis of 30-day mortality in patients who received broad-spectrum antibiotics guided by voluntary or compulsory computer decision support system and prospective review and feedback recommendations. Data are for the intention-to-treat population
Figure 1

4060 Assessed for eligibility (n=4060)

2803 Excluded
1627 Not first episode of study antibiotics.
1009 Not in general ward
77 Excluded as recruitment target reached for control arm
53 Without use of CDSS entry due to system error in intervention arm
27 Only used renal dose module in intervention arm
10 Other*

1257 Randomized (n=1257)

641 randomized to Voluntary CDSS
354 reviewed by PRF only
39 CDSS query only
94 CDSS query and PRF review
154 Without CDSS query and PRF review

616 randomized to Compulsory CDSS
0 reviewed by PRF only
173 CDSS query only
443 CDSS query and PRF review
0 Without CDSS query and PRF review

641 included in intention to treat analysis

616 included in intention to treat analysis

455 included in per protocol analysis
46 excluded due to transfer to clusters randomized to intervention arm
33 excluded due to transfer to ICU/HD
86 excluded due to transfer to stepdown wards/outside of TTSH main building
21 excluded due to more than 1 of the above reasons

416 included in per protocol analysis
42 excluded due to transfer to clusters randomized to control arm
28 excluded due to transfer to ICU/HD
64 excluded due to transfer to stepdown wards/outside of TTSH main building
66 excluded due to more than 1 of the above reasons
Figure 2

Kaplan Meier Curves

HR: 0.87 (95% CI: 0.67 - 1.12)

Number at risk

|              | Voluntary CDSS | Compulsory CDSS |
|--------------|----------------|-----------------|
| Time to Death(days) |               |                 |
|               | 581            | 552             |
|               | 556            | 521             |

Compulsory CDSS
Voluntary CDSS