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Multimodal intervention to reduce acquisition of carbapenem-non-susceptible Gram-negative bacteria in intensive care units in the National Referral Hospital of Indonesia: An interrupted time series study

Yulia Rosa Saharman [a,b], Anis Karuniawati [a], Rudyanto Sedono [c], Dita Aditianingsih [c], Hongchao Qi [d,e], Henri A. Verbrugh [b], Juliëtte A. Severin [b,*]

[a] Department of Clinical Microbiology, Faculty of Medicine, Universitas Indonesia/Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
[b] Department of Medical Microbiology and Infectious Diseases, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands
[c] Critical Care Division, Department of Anesthesia and Intensive Care, Faculty of Medicine, - Universitas Indonesia/Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia
[d] Department of Biostatistics, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands
[e] Department of Epidemiology, Erasmus MC University Medical Center Rotterdam, Rotterdam, the Netherlands

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ABSTRACT

Purpose: To evaluate a low-cost multimodal intervention on the acquisition of carbapenem-non-susceptible *Acinetobacter baumannii, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* by patients in low-resource intensive care units.

Materials and methods: We performed a quasi-experimental study in a referral hospital in Jakarta, Indonesia: pre-intervention phase 1 (2013–2014), intervention phase 2 (2014–2015) and post-intervention phase 3 (2015–2016). The intervention was hand hygiene promotion and environmental cleaning and disinfection combined with patient disinfection and cohorting. The primary outcome was acquisition of resistant bacteria per 100 patient-days at risk, which was assessed by active microbiological surveillance and analysed with a multilevel Poisson segmented regression model.

Results: In phase 1 (387 patients), the acquisition rate was 4.3/100 days for carbapenem-non-susceptible *A. baumannii* versus 1.1/100 days for both *K. pneumoniae* and *P. aeruginosa*. There was a significant step change from phase 1 to phase 3 (361 patients) in the acquisition of carbapenem-non-susceptible strains, the incidence rate ratio (IRR) was 0.343 (99%CI: 0.164–0.717). This significant change was mainly due to reduced acquisitions of resistant *A. baumannii* (IRR 0.4, 99%CI: 0.181–1.061). Negative confounding was observed.

Conclusion: A multimodal intervention to prevent acquisition of resistant pathogens is feasible and may be effective in ICUs in lower-middle income countries.

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1. Introduction

Multidrug-resistant (MDR) microbial pathogens have emerged worldwide as major concerns both in and outside of the hospital environment. Carbapenem-non-susceptible Gram-negative bacilli of the species *Klebsiella pneumoniae, Acinetobacter baumannii-calcoaceticus* complex, and *Pseudomonas aeruginosa* are among the most dreaded emerging threats. These pathogens have been highlighted as critical pathogens by the World Health Organization (WHO) prioritization of pathogens to guide discovery of new antibiotics [1,2]. MDR pathogens pose tremendous challenges to healthcare systems, including challenges related to diagnosis, treatment, and containment of infections caused by them [3]. These challenges are amplified in the intensive care unit (ICU) environment, where pressures for the selection and emergence of resistance and risks of transmission of MDR pathogens are highest, and where the threat of potentially multiple drug resistance is a major driver of the prescription of empiric broad spectrum antimicrobial regimens [4]. Effective and targeted infection prevention and control (IPC) interventions, including contact precautions, environmental cleaning, and a hand hygiene improvement strategy are deemed essential to control the spread of carbapenem-non-susceptible Gram-negative bacilli in such settings. In general, multimodal interventions are more effective than a single mode of intervention [5,6]. However, in lower-middle income countries (LMICs), including Indonesia, such

* Corresponding author at: Department of Medical Microbiology and Infectious Diseases, Erasmus MC University Medical Center Rotterdam, Dr. Molewaterplein 40, 3015 GD Rotterdam, the Netherlands.
E-mail addresses: h.qi@erasmusmc.nl (H. Qi), h.a.verbrugh@erasmusmc.nl (H.A. Verbrugh), j.severin@erasmusmc.nl (J.A. Severin).

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multimodal interventions need not only to be effective but also inexpensive and relatively simple to apply. Such multimodal interventions have been little studied in these settings.

Therefore, we designed and evaluated the effectiveness of a low-cost multimodal infection control bundle at two ICUs in Jakarta, Indonesia, on the acquisition of carbapenem-non-susceptible *A. baumannii-calcoaceticus* complex, *K. pneumoniae,* and *P. aeruginosa*.

2. Methods

2.1. Study setting

We performed a study in two ICUs (adult ICU and Emergency Room (ER)-ICU) of the National Referral Hospital of Indonesia with 1200 beds, located in Jakarta. These ICUs were multibed open wards in which multidisciplinary teams provide patient care under the final supervision of intensivists (for physical layout see supplementary material). These ICUs together admitted approximately 1400 patients per year, both surgical and medical patients, and it also functioned as a post-anesthesia care unit after major surgery. There were ~50 healthcare workers (HCWs) providing care for patients in each unit, including three intensivists, anesthesiologist residents, nurses and other HCWs. Nurses did not rotate between the two ICUs, but the intensivists did. More details on patient-to-nurse ratios are described elsewhere [7,8]. These ratios remained stable during the course of this study. Cleaning of the ICU environment was outsourced and initially limited to mopping the floors twice daily with a detergent solution without systematically attending the doors, walls, wall fixtures, sinks, beds and instruments. Solutions containing quaternary ammonium salts where occasionally used for disinfection purposes.

2.2. Study design

The study used a quasi-experimental before-and-after design. All consecutive patients (≥18 years old) admitted to one of the two ICUs and hospitalized for more than 48 h were eligible for enrollment in this study. After a baseline phase, we introduced the interventions in a staggered fashion, as shown in Fig. 1. Thus, the study consisted of three phases: phase 1, a baseline observation phase (consisting of two separate periods between April 1st 2013 to July 9th 2014), followed by two intervention phases, phase 2 in which some infection prevention measures were introduced (July 10th 2014 – January 31st 2015) and phase 3 at the start of which additional infection prevention measures came into effect (February 2nd 2015 – January 8th 2016).

2.2.1. Phase 1: baseline

- In this exploratory phase of the study patients with multidrug-resistant bacteria were not isolated nor treated under contact precautions unless they carried MRSA. Only patients with MRSA were treated by HCWs wearing protective personal equipment (PPE; gowns, gloves and masks), they were not isolated in a separate room. Patients from which multidrug-resistant Gram-negative bacteria, including carbapenem-non-susceptible strains, had been cultured were not put in contact isolation. Only patients with sputum-positive tuberculosis were separated in an isolation room in the adult ICU (for location see Supplemental Fig. S1). Routinely, nurses and fellows wore ICU-dedicated scrub suits, but the doctors did not. PPE or partial PPE was only used when taking specimens from patients, when bathing patients, changing wound dressings, suctioning patients and other invasive procedures. Hand hygiene as defined by the WHO was already promoted in these ICUs, and compliance was monitored by the infection prevention link-nurse of the ICU on a weekly basis, and reported monthly to the Infection Prevention Committee of the hospital.
- Microbiological sampling. At the start of this study screening of patients for resistant bacteria was not routinely performed in the ICUs. In the framework of this study screening was initiated for all included patients on the day of admission, at the time of discharge from the ICU, and weekly if patients were admitted for 7 days or more. Two separate periods of such screening were performed in this phase (Fig. 1). Swabs were taken by well-trained nurses from throat and rectum or stools. Clinical samples were collected on indication from patients under aseptic precautions from the lower respiratory tract, blood, urine, tissues, or wounds. Environmental samples were taken once from various sites, and all HCWs of both ICUs were sampled once over the course of 1 month (September 2013, Fig. 1). All screening swabs and clinical samples were analysed according to a previously published protocol [7-9].
- Antibiotic use. Local guidelines on the use of antimicrobial agents were not available in these ICUs at that time. Therapies were mainly based on international guidelines, e.g. the Sanford Guide to Antimicrobial Therapy and professional guidelines like the VAP guideline of the ATS [10]. A multidisciplinary team consisting of an intensivist, a clinical microbiologist, a clinical pharmacist, a clinical pharmacologist, and an infectious diseases internist, fellows, and an intensive care nurse discussed every patient in the ICU on week days. The intensivists were primarily in charge of the ICU patients and prescribed antibiotics. However, other clinical specialists could suggest therapies, but all decisions and prescriptions were made by the intensivist.
- Environmental cleaning was done twice a day by personnel from an external cleaning service company, and cleaning was restricted to

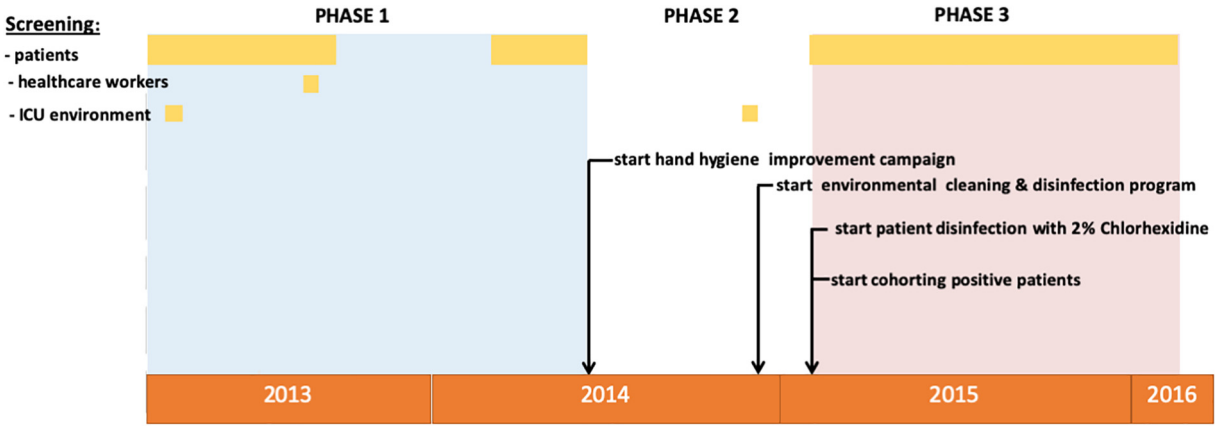

Fig. 1. Study timeline.

mopping the ICU floor and wiping the lower part of the walls only; they used a detergent containing solution. Importantly, the sinks (one per two beds) were not cleaned on a daily basis. In between consecutive patients, ICU beds and ancillary table tops were likewise cleaned using the detergent solution. Cleaning personnel was instructed by the hospital infection control team, and further supervised by the infection prevention link nurse of the ICU. Cleaning personnel needed to confirm their activities by entering their initials in checklists, which were kept by their supervising manager.

- Oral decontamination. Patients on the ICU were treated with an oral chlorhexidine gluconate 0.5% solution (Minosept®, Minorock) four times daily, this was done by intensive care trained nurses. These actions were routinely recorded in the patients' nursing notes.

2.2.2. Phase 2: first stage of the multimodal intervention

After phase 1, we started to introduce a multimodal bundle of IPC interventions that initially consisted of the following measures:

- A multifaceted hand hygiene improvement program was initiated. We based the hand hygiene programme on the WHO's Five Moments for Hand Hygiene guidelines and tools. The hand hygiene improvement program included education with pre- and post-questionnaires testing of knowledge and attitudes, performance feedback and reminders, interviews, and role models and was described in detail and published before [11].
- A single round of environmental cleaning and disinfection involving the whole environment of both ICUs was executed, using 1:100 sodium hypochlorite solution as disinfectant. This disinfectant solution was applied to walls, floors, doors, beds (mattresses and bed rails), sinks, overbed tables, infusion and suction pumps and stands, monitors and ventilators including connecting lines, and other counter tops and drawers. Importantly, the adjacent cleaning service rooms were included in this campaign. In addition, all curtains between beds were exchanged for clean ones.

During this intermediate phase of the study the microbiological screening of patients was temporarily interrupted, and no additional screening of HCWs was performed, but the environment was sampled once more just prior to the intensive cleaning campaign described above started (Fig. 1).

2.2.3. Phase 3: final stage of the multimodal intervention

In this phase 3, the following additional IPC measures were taken:

- Routine environmental disinfection was performed with 1:100 sodium hypochlorite solution that included the floors, beds, and immediate surrounding of the patients. This was done twice daily. In case of visible dirt, this was first removed with a brush and water, before the application of the sodium hypochlorite solution. The intensive procedure as described in phase 2 (see above) was repeated every 2 weeks in the adult ICU, but not in the ER-ICU due to lack of personnel and other managerial issues. The curtains between beds were refreshed every 1–2 months or immediately after visible soiling. The list for initializing the activities by the cleaning personnel was adapted to this changed protocol.
- All patients found positive for one or more carbapenem-non-susceptible *A. baumannii-calcoaceticus* complex, *K. pneumoniae,* or *P. aeruginosa* were cohorted in one dedicated corner of the ICU (see Supplemental Fig. S1). HCWs donned masks, gowns, and gloves when approaching and providing care for cohorted patients. The ICU was notified by the clinical microbiology service by phone once a resistant strain was identified, this was done on all days except Sunday. Compliance to the cohorting rule was checked during the daily multidisciplinary team meetings.
- Finally, in this phase, we introduced for all patients daily total body-washing with cloths soaked in a chlorhexidine gluconate 2% solution [12]. These cloths were prepared and pre-packaged individually in sealed plastic bags by the hospital pharmacy. The chlorhexidine gluconate 0.5% solution used for oral decontamination was replaced by a 2% chlorhexidine gluconate solution in this phase of the study because it was deemed more effective [13]. Bottles containing this solution were also prepared and provided by the hospital pharmacy (see Supplementary Fig. S2), and used per patient. The application of oral and total body wash with chlorhexidine was routinely noted in the patient files.

During this phase 3, the systematic screening of ICU patients as described for phase 1 was resumed (Fig. 1). This multimodal intervention was calculated to add approximately U$ 1.5 to the overall cost of treating one patient in the ICU (from admission until discharge).

2.3. Statistical analysis

The description of patients' baseline characteristics and the comparisons of the characteristics between phase 1 and phase 3 were analysed using Chi square or Fisher's Exact and Mann-Whitney tests in SPSS Version 24.0 (SPSS, Chicago, IL, USA). The primary outcome of interest in the study was weekly acquisition of carbapenem-non-susceptible *A. baumannii-calcoaceticus* complex, *K. pneumoniae,* and *P. aeruginosa* per 100 patient-days at risk. Patient-days at risk were number of days in the ICU from admission to discharge or to first positive culture of a carbapenem-non-susceptible strain of the indicated species, which ever came first. We assessed outcomes with a Poisson segmented regression analysis, the parameters of interest were step changes in the acquisition rate per 100 patient-days at risk and changes in trends of acquisition rates per 100 patient-days at risk from phase 1 to phase 3, the ICU number was also included in the model, the final model is shown below:

$$E(y_t) = \mu_t,$$

$$log\,\mu_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times phase_t + \beta_3 \times timeafterintervention,$$

where y_t represents the weekly acquisition per 100 patient-days at risk at week t, β_1 is the time trend in phase 1, β_2 is the step change of acquisition from phase 1 to phase 3, β_3 denotes the change in trend of acquisition rate per 100 patient-days at risk from phase 1 to phase 3. This statistical analysis was performed using R 3.6.1.(R foundation, R-project.org). The threshold for statistical significance was set at $p = 0.01$ and 99% confidence intervals (CI) were used to present the data [14].

3. Results

A total of 748 patients were enrolled during phase 1 (387 patients) and phase 3 (361 patients) of the study. The patients' characteristics, underlying diseases, length of stay, mortality and other risk factors of patients enrolled in phase 1 and phase 3 are summarized in Table 1. The comparison of patient characteristics in phase 1 versus phase 3 found patients enrolled in phase 3 to have a somewhat different spectrum of underlying diseases (especially more diabetes, less malignancies, and more with a medical indication for ICU care), they required more days of mechanical ventilation and, concomitantly, had more central venous catheter and urinary catheter days, they stayed longer in the ICU and had a higher mortality rate (Table 1). A higher fraction of the patients in phase 3 were prescribed carbapenem antibiotics as well, both prior to their ICU admission and during their ICU stay. Furthermore, shifts in hospital policies favoring short stay (<48 h) of postoperative surgical patients in the adult ICU resulted in relatively more patients, especially medical patients, to be enrolled in the ER-ICU in phase 3 of the study (Table 1). In phase 3, the daily oral application and body washes with the 2% chlorhexidine solution were well tolerated, as no lesions of the skin or the oral mucosa were reported by the attending personnel.

Table 1
Baseline characteristics and outcomes of patients enrolled by phase of the intervention study.

Characteristics	Phase 1	Phase 3
Number of patients enrolled	387	361
Age (years); median (IQR)	46 (33–58)	49 (34–69)
Gender		
Male (%)	200 (51.7)	193 (53.5)
Female (%)	187 (48.3)	168 (46.5)
ICU*		
Adult ICU	182 (47.0)	133 (36.8)
ER-ICU	205 (53.0)	228 (63.2)
Underlying diseases		
Cardiovascular (%)	23 (5.9)	30 (8.3)
Cerebrovascular (%)	28 (7.2)	23 (6.4)
Chronic kidney disease (%)	25 (6.5)	10 (2.8)
Diabetes mellitus (%)*	29 (7.5)	52 (14.4)
Malignancy (%)*	111 (28.7)	59 (16.3)
Indication for ICU admission*		
Medical (%)	129 (33.3)	166 (46.0)
Surgical (%)	258 (66.7)	195 (54.0)
Referral from*		
Other ward this hospital (%)	217 (56.1)	138 (38.2)
Other hospital (%)	70 (18.1)	57 (15.8)
Directly from Emergency Unit (%)	100 (25.8)	166 (46.0)
Antibiotic exposure (before admission to ICU)		
Any antibiotic (%)*	300 (77.5)	226 (62.6)
Carbapenem (%)	75 (19.4)	92 (25.5)
SIRS Score (%)		
Score < 2	32 (8.3)	44 (12.2)
Score ≥ 2	355 (91.7)	317 (87.8)
qSOFA Score (%)		
Score < 2	74 (19.1)	197 (54.6)
Score ≥ 2	313 (80.9)	164 (45.4)
Procedures (during ICU admission)		
Mechanical ventilation (%)	352 (91.0)	330 (91.4)
Mechanical ventilation duration*		
≥5 days (%)	168 (43.4)	207 (57.3)
<5 days (%)	219 (56.6)	154 (42.7)
Central venous catheter (%)	341 (88.1)	315 (87.3)
Central venous catheter duration*		
≥5 days (%)	205 (53.0)	237 (65.7)
<5 days (%)	182 (47.0)	124 (34.3)
Urinary catheter (%)	387 (100)	361 (100)
Urinary catheter		
≥5 days (%)	232 (59.9)	247 (68.4)
<5 days (%)	155 (40.1)	114 (31.6)
Antibiotic therapy (during ICU admission)		
Any antibiotic (%)	381 (98.4)	348 (96.4)
Carbapenem (%)*	188 (48.6)	224 (62.0)
Outcomes		
Length of stay (days); median (IQR)*	5 (3–9)	7 (4–13)
Death in ICU (%)*	110 (28.4)	137 (38.0)

Abbreviations: ER-ICU, Emergency Room Intensive Care Unit; ICU, Intensive Care Unit; IQR, Interquartile range; qSOFA, quick Sepsis-related Organ Failure Assessment; SIRS, Systemic Inflammatory Response Syndrome.
* $p < 0.01$ when comparing phase 1 versus phase 3.

We obtained at least two rectal swabs and two throat swabs from each patient. We analysed 4219 screening swabs in total and processed 287 clinical specimens. At admission to ICU, 110 patients were already colonized with carbapenem-non-susceptible *A. baumannii-calcoaceticus* complex, 53 were already colonized with carbapenem-non-susceptible *K. pneumoniae*, and 37 patients were colonized with carbapenem-non-susceptible *P. aeruginosa*. Thus, the large majority of enrolled patients were, at admission, still at risk of acquiring a carbapenem-non-susceptible strain of one or more of the three targeted bacterial species.

In phase 1 of the study 145 patients, representing 6831 days at risk, acquired a carbapenem-non-susceptible strain of one or more of the three targeted species, for an overall incidence of 2.1 (99%CI 1.7–2.6) acquisitions per 100 days at risk. The acquisition rates were similar for the adult ICU (2.0 [99%CI 1.5–2.7]) and the ER-ICU (2.2 [99%CI 1.6–3.0]) in this phase of the study. The acquisition rate was highest for resistant *A. baumannii-calcoaceticus* complex (4.3[3.2–5.6]), followed by resistant *K. pneumoniae* (1.3[0.8–2.0]) and resistant *P. aeruginosa* (1.3[0.8–2.0]). Environmental screening, performed in phase 1 and phase 2, yielded nine isolates of carbapenem-non-susceptible *A. baumannii-calcoaceticus* complex, four carbapenem-non-susceptible *K. pneumoniae*, and 15 carbapenem-non-susceptible *P. aeruginosa* (see Supplementary Table S1). We screened 167 healthcare workers once in phase 1 and found one to carry a carbapenem-non-susceptible *A. baumannii* in the throat. For genetic details on the mechanisms of carbapenem resistance among these strains we refer to our previous publications [7-9].

In phase 3 of the study 196 patients, representing 8543 days at risk, acquired a carbapenem-non-susceptible strain of one or more of the targeted species, for an overall incidence rate of 2.3 (99%CI 1.9–2.7) acquisitions per 100 days at risk. The overall acquisition rate fell in the adult ICU (1.6 [99%CI 1.2–2.3]), but rose in the ER-ICU (2.7 [99%CI 2.1–3.3]). Compared to phase 1, the acquisition rate of carbapenem-non-susceptible *A. baumannii-calcoaceticus* complex was lower in phase 3 (2.8[2.1–3.8]), as was the case for non-susceptible *P. aeruginosa* (1.1[0.7–1.7]), whereas the rate for non-susceptible *K. pneumoniae* was higher (3.1[2.7–4.1]). This latter increased rate of acquisition of carbapenem-non-susceptible *K. pneumoniae* in phase 3 was mainly due to a significant, three-fold increase in the acquisition of such strains in the ER-ICU whereas such acquisitions increased only 1.5-fold (not statistically significant) in the adult ICU (Supplementary Fig. S3).

Importantly, for all three species taken together there was a significant step change, from phase 1 to phase 3 in the rate of acquisition of carbapenem-non-susceptible strains, the incidence rate ratio (IRR) was 0.343 (99%CI: 0.164–0.717) for phase 3 compared to phase 1 (Table 2, Fig. 2, panel A). This significantly lower acquisition rate of carbapenem-non-susceptible strains of the three species in the first weeks of phase 3 was mainly caused by a significant downward step change in the acquisition of carbapenem-non-susceptible *A. baumannii-calcoaceticus* complex with some contribution by a lower acquisition rate of carbapenem-non-susceptible *K. pneumoniae* and *P. aeruginosa* (Table 2, Fig. 2). Otherwise, there was an upward trend observed in the rate of acquisition of resistant strains for each of the three species separately and for the three species taken together in phase 1, an upward trend which became less so or switched to a downward slope in phase 3 (Table 2, Fig. 2).

Table 2
Trends and step changes in the acquisition rate of carbapenem-non-susceptible strains of *A. baumannii-calcoaceticus* complex, *K. pneumoniae*, and *P. aeruginosa*.

	Overall	Carb_NS *A. baumannii*	Carb_NS *K. pneumoniae*	Carb_NS *P. aeruginosa*
Time trend in phase 1	1.014 (1.004–1.023; $p \le 0.001$)	1.008 (0.997–1.019; $p = 0.052$)	1.03 (1.009–1.051; $p \le 0.001$)	1.013 (0.988–1.039; $p = 0.189$)
Step change in phase 3	0.343 (0.164–0.717; $p \le 0.001$)	0.416 (0.171–1.011; $p = 0.011$)	0.283 (0.075–1.064; $p = 0.014$)	0.742 (0.117–4.721; $p = 0.677$)
Time trend change in phase 3	1.000 (0.984–1.016; $p = 0.976$)	0.992 (0.973–1.012; $p = 0.308$)	0.984 (0.957–1.012; $p = 0.147$)	0.982 (0.944–1.022; $p = 0.246$)
Time trend in phase 3	1.014 (1.001–1.027; $p = 0.007$)	1 (0.984–1.017; $p = 0.960$)	1.014 (0.995–1.033; $p = 0.065$)	0.995 (0.966–1.026; $p = 0.684$)

Abbreviation: Carb_NS, carbapenem-non-susceptible. Note: data are incidence rate ratio's with 99% confidence intervals in brackets as assessed by Poisson regression analysis (see Methods).

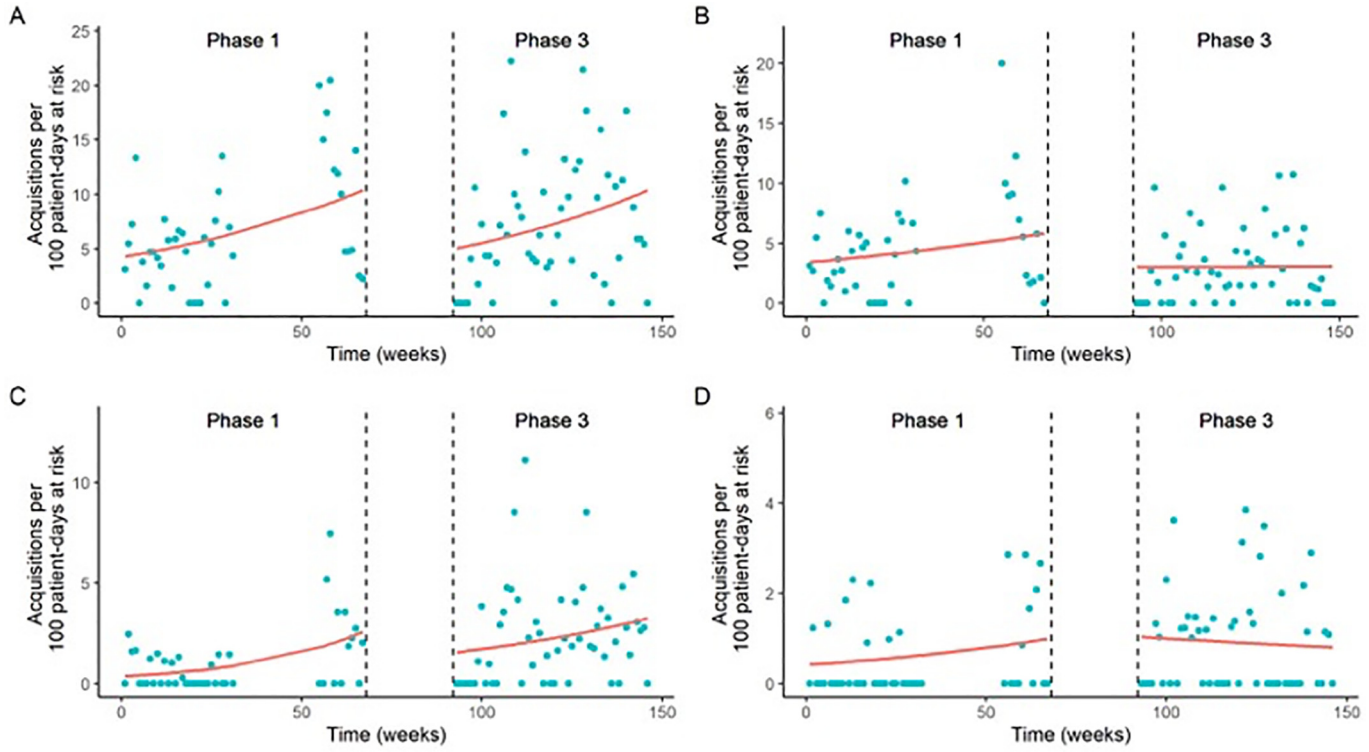

Fig. 2. Acquisition of carbapenem-non-susceptible bacteria per 100 patient-days at risk in both ICUs. Legend: For strains of all three species together (A), for carbapenem-non-susceptible *A. baumannii-calcoaceticus* complex (B), for carbapenem-non-susceptible strains of *K. pneumoniae* (C), and for carbapenem-non-susceptible strains of *P. aeruginosa* (D). The end of phase 1 and the start of phase 3 are marked with vertical dashed lines. Green dots represent weekly acquisition data. Pink lines are expected values from the Poisson segmented regression model. Note that during the middle part of phase 1 and between phase 2 and phase 3 patients were not screened and, therefore, no acquisition data were available for these periods. Also note that the range of Y-axis of each of the four panels (A-D) differs from the other three.

4. Discussion

This study showed that introducing a relatively simple and inexpensive bundle of infection prevention and control measures may rapidly reduce the risk of patients admitted to adult ICU in lower-middle income countries to acquire highly resistant strains of common nosocomial pathogens. Our report followed the guideline for describing intervention studies as published by Hoffmann et al. [15] (Supplementary file TIDieR checklist). The bundle consisted of improving hand hygiene practices, reducing contamination of the ICU environment, daily disinfection of patients' skin and oral mucosa, and cohorting of patients found to carry such strains. This multimodal intervention was associated with a reduced rate of acquisition of carbapenem-non-susceptible *A. baumannii-calcoaceticus* complex, the most prevalent species responsible for such acquisitions in our setting. The bundle was also associated with a marginally reduced acquisition of resistant strains of *P. aeruginosa*, and it affected the *K. pneumoniae* acquisition rate such, that it first was lower in phase 3 but quickly rose to an acquisition rate that was higher than in phase 1. The impact of the bundle may have been negatively confounded, since patients in the third phase of the study required more days on ventilators and with other devices, stayed longer in the ICU and more died during their ICU stay. In addition, a larger fraction of the patients in phase 3 had previously been exposed to or were prescribed carbapenems during their ICU stay. All and all this strongly suggests that patients in phase 3 were more at risk of acquiring carbapenem-non-susceptible strains than patients in phase 1. We did not attempt to perform a risk adjusted analysis of the effect of the intervention since such analysis was not planned à priori, is complicated (due to unknown relationships between parameters and outcome) and may lead to overestimation of the effect of the intervention.

At this time, we cannot offer a solid explanation why especially carbapenem-non-susceptible *A. baumannii-calcoaceticus* complex acquisitions were prevented by our multimodal intervention, *P. aeruginosa* acquisitions less so, and why, unexpectedly, the *K pneumoniae* acquisition rate even increased. Clearly, the rates of acquiring carbapenem-non-susceptible strains were initially much higher in case of *A. baumannii-calcoaceticus* complex than for *P. aeruginosa* or *K. pneumoniae*. Thus, there was less opportunity for strains of the latter two species to become significantly affected by the intervention. The main risk factors for acquisition of a carbapenem-resistant *P. aeruginosa* are the use of carbapenems and the application of medical devices [16]. These factors were not targeted in our bundle and both were higher in phase 3. At the genetic level, we, in another publication [17], noted that there was a significant shift from phase 1 to phase 3 in the genotype distribution of the strains circulating in the ICUs, which may have been induced by the intervention, possibly related to the varying susceptibility to sodium chlorite or chlorhexidine among *P. aeruginosa* strains [13]. Alternatively, the sources and transmission routes of *P. aeruginosa* may differ from those of *A. baumannii-calcoaceticus* complex in this setting and, therefore, *P. aeruginosa* may have been less affected by the intervention [18].

Similar factors may underly the observed increased rate of acquisition, after an initial decrease, of carbapenem-non-susceptible *K. pneumoniae* following the implementation of the intervention bundle [9,19]. Although *K. pneumoniae* can be found in soil and sewage samples this species is different from the predominantly environmental species *A. baumannii* and *P. aeruginosa*, *K. pneumoniae* is also a prevalent commensal in the human gut. Exposing patients to antibiotics may, thus, affect *K. pneumoniae* to a greater extent, posing greater risk for selecting antibiotic-resistant variants. The concomitant significant changes in patient mix, including more medical patients in phase 3, may have been a factor as well, favoring the acquisition of this particular species. Medical patients were significantly older than surgical patients, more had diabetes mellitus, a well-known risk factor for *K. pneumoniae* infection, and they were

more often exposed to carbapenems prior to and during their ICU stay. They also had more days on mechanical ventilation, had increased length of stay and a much higher mortality (48.1% versus 23.3% for surgical patients, Supplementary Table S2). Although the influx of carbapenem-non-susceptible strains of the three species into the ICU (by patients cultured positive on admission) occurred at comparable rates in phase 1 and phase 3 (22.7% versus 23.3% of patients carried them into the ICU in phase 1 and phase 3, respectively [data not shown]), the fraction of patients carrying non-susceptible *K. pneumoniae* into the ICU increased from 5.4% to 9.1% (data not shown), possibly contributing to the observed increase of acquisitions of these strains by patients enrolled in phase 3.

Finally, varying levels of compliance with the measures included in the intervention bundle may have been affected by dissimilar limitations in the staffing of the two ICUs [7,8], especially in the ER-ICU in phase 3 since the acquisition rate of carbapenem-non-susceptible *K. pneumoniae* rose three-fold in this ICU versus only 1.5-fold in the adult ICU. Note that the ER-ICU included more medical patients than the adult ICU, in phase 1 and, *à fortiori*, in phase 3 (Supplementary Table S3) [9]. The ER-ICU was also only partially compliant with the newly introduced environmental disinfection protocol.

Few studies in lower-middle income countries have previously implemented interventions to control the spread of MDR pathogens in hospitals, none from Indonesia, the second most populous LMIC following India. Only one other study, performed in Vietnam and published in 2013, aimed to reduce the rate of acquisition of MDR organisms in adult ICUs in LMIC by a multimodal intervention – improving hand hygiene, combined with antibiotic stewardship; they were partly successful and reduced the rate of acquisition of methicillin-resistant *Staphylococcus aureus* (MRSA), but not of species of Gram-negative bacilli [20]. Likewise, an earlier study from another lower-middle income country, the Philippines, but performed in a neonatal ICU, showed a multimodal intervention – hand hygiene, screening patients, renewed ventilator use protocol, antibiotic stewardship, contact precautions for positive patients, daily and monthly infection control checklists - to reduce MRSA colonization but not to affect the colonization of neonates by resistant Gram-negative bacilli [21] In contrast, in a quasi-experimental study Apisarnthanarak et al. in Thailand, an upper-middle income country in the same region of the world as Indonesia, applied a multimodal intervention – hand hygiene, screening and cohorting positive patients, and environmental disinfection with sodium hypochlorite – in three adult ICUs and found it to be effective in reducing the colonization and/or infection with drug-resistant strains of *A. baumannii* [22]; other species of drug resistant pathogens were not targeted in that study.

In our bundle, much emphasis was placed on reducing contamination of the ICU environment, since the ICU environment has been shown to provide niches for the three species of nosocomial pathogens targeted [16]. We now feel that assuring a clean ICU environment, including access to safe and clean water and water systems (sinks), is important and should be included in intervention bundles aimed to reduce the acquisition of MDR strains in ICUs. The bundle we designed was low cost and simple to apply. It was previously shown that hand hygiene compliance can be improved significantly in ICUs in other lower-middle income countries [23-26]. As with any measure, hand hygiene and environmental stewardship require a systematic approach and should be built into ICU protocols, effectively reinstating environmental cleanliness as a prime infection control issue [5]. Similarly, the crucial role of the environment of the ICU should be translated into and become part of the infection control efforts of the ICU, effectively regarding cleaning service personnel as important partners of the infection control team. Although introducing multifaceted hand hygiene programs have been shown to be efficacious in studies in lower-middle income countries, including Indonesia [11,28], observation of clinical practice has shown compliance to hand hygiene to fall back after hand hygiene improvement campaign has stopped [11,23]. Thus, a systematic permanent program to monitor and maintain hand hygiene compliance is needed.

We are aware of the potential side effects of chlorhexidine gluconate 2% as mentioned in a recent report by Plantinga et al. [29], but we did not observe and record such adverse events in our patient cohorts, possibly due the fact that such side effects are observed only after prolonged use of chlorhexidine (> 21 days), which is much longer than we applied chlorhexidine disinfectants in our patients [29].

The study has several limitations. First, it was a single centre study precluding extrapolation of our findings to other ICUs in Indonesia and other lower-middle income countries. However, much may be relevant and learned from our experience. Second, the quasi-experimental design has its limitations. In our case, potential negative confounding was introduced by significant differences in patient profiles between the two study phases, mostly due to uncontrollable managerial policy changes. Multicentre, cluster randomized studies provide a more robust design, and produce results that can be extrapolated [30], although these study designs would be much more expensive to implement and more difficult to manage in lower-middle income countries. We did not intervene with the use of antibiotics. Although it was part of the original study protocol, at the time of the study it was deemed not to be feasible because alternative regimens were not reimbursed under the national insurance programme or were not available in Indonesia. We acknowledge that including a restrictive antibiotic policy as part of an antibiotic stewardship program, would likely have increased the impact of the intervention. Finally, not all independent parts of the bundle were systematically checked for compliance after their introduction. For the hand hygiene improvement strategy, compliance was measured and shown to have improved much. However, proper compliance monitoring was stopped after a few months, and 1 year later compliance was measured again and found to have fallen back to pre-intervention levels [11]. For the chlorhexidine bathing and mouth wash and cohorting, this was executed well for each patient and recorded, but we did not analyse these records. The environmental cleaning efforts were likewise monitored by their supervisors using the checklists with the initials of the cleaning personnel, but these records were not kept for later analysis. Thus, the level of compliance with the intervention bundle may have fallen off soon after close monitoring them stopped. In a follow-up study, an auditing system should be used to monitor this. The contact precautions prescribed for cohorted patient management were sometimes difficult to implement, as in these cases the personal protective equipment had to be paid out of pocket by the patient, which was not always feasible. The added value of contact precautions in our bundle may, therefore, be questioned.

5. Conclusion

We conclude that a multimodal intervention aiming to prevent acquisition of resistant strains of important ICU pathogens is feasible and may be effective in ICUs in lower-middle income countries. Environmental cleaning should be an important part of the intervention and compliance with intervention measures should be closely and continuously monitored.

Ethics and regulatory considerations

- The Ethics Committee of the Faculty of Medicine, Universitas Indonesia, approved the research on 17th September 2012, No: 561/PT02.FK/ETIK/2012, No: 757/UN2·F1/ETIK/X/2014.
- A Material Transfer Agreement (MTA) was reviewed and approved by the Director of National Institute Research and Development, Ministry of Health (No: LB.02.01/I.9.4/8500/2013).
- Trial registration**:** The study was registered at Netherlands Trial Register http://www.trialregister.nl (No: 5541). Candidate number: 23527, NTR number: NTR5541, NL number: NL5425 (https://www.trialregister.nl/trial/5424), retrospectively registered: NTR: 22 December 2015.

Consent for participation

Informed consent was documented by the use of a written consent form approved by the Ethics Committee Faculty of Medicine Universitas Indonesia/Dr. Cipto Mangunkusumo General Hospital and signed and dated by the subjects/guardians and by the person who conducted the informed consent discussion and two witnesses. The signature confirmed the consent was based on information that had been understood.

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Competing interests

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All authors report no conflict of interest relevant to this article.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcrc.2021.04.016.

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