treatment). Thus, although the results of the Honeypot study[1] show the efficacy of mupirocin versus Medihoney, the important question of whether patients with a healthy catheter exit site for peritoneal dialysis should receive prophylactic treatment remains to be addressed. In our view, and according to the principle of primum non nocere (first do no harm), the key to preservation of exit-site integrity is optimal catheter fixation and avoidance of unnecessary manipulations. We realise, however, that this approach of let nature do the work is difficult to assess in a randomised controlled trial and probably not endorsed in modern medicine.

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Antimicrobial resistance in intensive care units

More than two-thirds of cases of ICU-acquired bacteraemia are caused by multidrug-resistant or extensively drug-resistant bacteria.[1] Although the prevalence of meticillin-resistant *Staphylococcus aureus* is decreasing, glycopeptide-resistant enterococci, extended-spectrum β-lactamase-producing Enterobacteriaceae, and Gram-negative bacteria resistant to carbapenems have become a cause for concern.[2] The effectiveness of universal strategies based on hand hygiene and decolonisation or active surveillance culture and contact precautions for the control of multidrug-resistant bacteria in ICUs is unclear.

Active surveillance with contact precautions for carriers was effective for controlling meticillin-resistant *S aureus* in one study[3] but not in another,[4] despite use of similar interventions. However, the negative study had several flaws,[4] whereas the other was quasi-experimental, with other interventions possibly accounting for the effect.[3] Universal decolonisation with chlorhexidine body-washing—with[5] or without[6] nasal mupirocin—can decrease acquisition of meticillin-resistant *S aureus* and glycopeptide-resistant enterococci, with some reduction in infections. These studies raised more questions than they answered, did not address the spread of resistant Gram-negative bacteria, and collected, at best, incomplete data for compliance with hand hygiene and contact precautions.

In *The Lancet Infectious Diseases*, Lennie Derde and colleagues[7] report a sophisticated and ambitious study, with epidemiological and statistical analysis of 13 European ICUs, involving almost 9000 patients and more than 40 000 hand-hygiene opportunities. The researchers aimed to answer two major questions. Should we use a universal approach—ie, improving hand hygiene and chlorhexidine body-washing or a strategy of active surveillance with contact precautions for carriers? And which bacteria will be affected?


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The acquisition rate of extended-spectrum β lactamase-producing Enterobacteriaceae (n=1966) was much higher than that of vancomycin-resistant enterococci (n=346) or meticillin-resistant *S aureus* (n=508). The universal strategy was effective for controlling meticillin-resistant *S aureus* with no additional efficacy from active surveillance with contact precautions. But no reduction occurred with any type of intervention for highly resistant Enterobacteriaceae (mostly extended-spectrum β lactamase-producing Enterobacteriaceae) despite an impressive hand-hygiene compliance of 77%.

How can we explain the failure to control extended-spectrum β lactamase-producing Enterobacteriaceae? First, 77% compliance might not be high enough in view of the high prevalence of extended-spectrum β lactamase-producing Enterobacteriaceae at admission, the high colonisation pressure, and the ease of cross-transmission. However, higher compliance would be very difficult to achieve, perhaps impossible, in routine clinical practice.

Second, some factors that drive the spread of extended-spectrum β lactamase-producing Enterobacteriaceae were not taken into account, such as other routes of transmission and the role of antimicrobial selective pressure. Indeed, mathematical modelling suggested differences in the predominant routes of acquisition of different multidrug-resistant bacteria, with highly resistant Enterobacteriaceae possibly originating from an endogenous source, whereas meticillin-resistant *S aureus* is predominantly acquired through cross-transmission.[8] Finally, different epidemiological features at each centre could be a result of levels of compliance with the prevention programme, in addition to compliance with hand hygiene.

The combined effect of improving hand hygiene and chlorhexidine body-washing helped to control meticillin-resistant *S aureus*, but which part of the intervention was effective is unclear. Other studies suggest that universal chlorhexidine body-washing can control transmission of meticillin-resistant *S aureus* and glycopeptide-resistant enterococci.[6,9,10] Anecdotally, chlorhexidine body-washing was not effective for control of highly resistant Enterobacteriaceae.

Active surveillance by culture with contact precautions for carriers of meticillin-resistant *S aureus* identified either by conventional or rapid PCR screening had no incremental effect on acquisition. The cost-benefit balance of isolating ICU patients is still controversial,[11,12] and this result raises many methodological questions that need to be answered before contact isolation is abandoned. Active surveillance with contact precautions was added in the third phase of the study, but was done in several ICUs during the first two phases. Moreover, compliance with contact isolation was not assessed. Because only 18% of rooms were single, contact isolation precaution might have been difficult to implement immediately. All rooms in new ICUs should be single rooms.[13] Finally, the lack of contribution of active surveillance with contact precautions might be partly explained by the high hand-hygiene compliance.

In conclusion, this pragmatic study provides important evidence for systematically including hand-hygiene strategies in any programme to control multidrug-resistant bacteria. The absence of an effect on antibiotic-resistant Gram-negative bacteria is worrisome. Strategies to prevent overgrowth of endogenous flora—such as selective digestive decontamination—should be investigated[14] although results of preliminary studies are unclear.[15] Methods to reduce antibiotic selection pressure should also be explored.

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The HIV care cascade through time

HIV care and treatment can prevent morbidity, mortality, and virus transmission. Optimum care for individuals and communities of people living with HIV involves identification of infected individuals, linkage to initial HIV care, long-term retention in care, and treatment adherence—the so-called cascade of care.[1] However, in many settings, the scope of the cascade is such that few patients actually achieve undetectable viral loads, the end goal of engagement in care. Understanding how to measure and intervene to improve engagement in HIV care is a subject of intense debate.

In *The Lancet Infectious Diseases*, Bohdan Nosyk and colleagues[2] from the STOP HIV/AIDS Study Group chart the longitudinal changes in the cascade of HIV care in British Columbia, Canada, from 1996 to 2011. Their study is the first longitudinal examination of the HIV care cascade. The investigators assessed the numbers and proportions of individuals in eight distinct stages of the cascade: HIV infected, diagnosed, linked to HIV care, retained in care, antiretroviral treatment indicated, receiving antiretroviral treatment, adherent to antiretroviral treatment, and virologically suppressed.

The study's strengths derive from the extensive use of comprehensive linked databases from national and provincial health programmes, and population-based registries from the BC Centre of Excellence in HIV/AIDS (Vancouver, BC, Canada)—the sole provincial agency providing HIV diagnostic testing and distribution of all antiretroviral drugs. Additional information was derived from provincial hospital, pharmacy, and vital statistics databases. The analysis shows that overall engagement in care and use of antiretroviral treatment improved between 1996 and 2011, but that substantial numbers of individuals are still lost from each step of the cascade. In 2011, an estimated 29% of HIV-infected individuals remained undiagnosed, an additional 4–10% were not linked to HIV care, and another 20% were not retained in care. Overall, viral suppression increased from 1% to 35% of the HIV-infected population over the study period.

Nosyk and colleagues' study shows us the value of looking longitudinally at the use of HIV care. Although changing standards for when to begin antiretroviral treatment limit the ability to analyse trends in viral suppression over time, increasing numbers of individuals are achieving this important benchmark. However, only a minority of HIV-infected individuals in British Columbia are virologically suppressed, and this finding is surprising and disappointing. As the investigators suggest, emigration from the province might account for some losses to follow-up; in a recent US study,[3] about 15% of individuals emigrated from the state in which they were diagnosed during 3–5 years of follow-up. Other potential losses of data in British Columbia, such as receiving care through participation in clinical trials, seem to have had little effect on estimates of viral suppression.

The implications of persistent gaps in cascade steps before administration of antiretroviral treatment and viral suppression are particularly worrying. Compared with research from the USA,[1,4] the investigators in British Columbia report fairly similar proportions of HIV underdiagnosis, linkage to care, and retention in care.

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Interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in intensive care units: an interrupted time series study and cluster randomised trial

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Summary

Background **Intensive care units (ICUs) are high-risk areas for transmission of antimicrobial-resistant bacteria, but no controlled study has tested the effect of rapid screening and isolation of carriers on transmission in settings with best-standard precautions. We assessed interventions to reduce colonisation and transmission of antimicrobial-resistant bacteria in European ICUs.**

Methods **We did this study in three phases at 13 ICUs. After a 6 month baseline period (phase 1), we did an interrupted time series study of universal chlorhexidine body-washing combined with hand hygiene improvement for 6 months (phase 2), followed by a 12–15 month cluster randomised trial (phase 3). ICUs were randomly assigned by computer generated randomisation schedule to either conventional screening (chromogenic screening for meticillin-resistant *Staphylococcus aureus* [MRSA] and vancomycin-resistant enterococci [VRE]) or rapid screening (PCR testing for MRSA and VRE and chromogenic screening for highly resistant Enterobacteriaceae [HRE]); with contact precautions for identified carriers. The primary outcome was acquisition of resistant bacteria per 100 patient-days at risk, for which we calculated step changes and changes in trends after the introduction of each intervention. We assessed acquisition by microbiological surveillance and analysed it with a multilevel Poisson segmented regression model. We compared screening groups with a likelihood ratio test that combined step changes and changes to trend. This study is registered with ClinicalTrials.gov, number NCT00976638.**

Findings **Seven ICUs were assigned to rapid screening and six to conventional screening. Mean hand hygiene compliance improved from 52% in phase 1 to 69% in phase 2, and 77% in phase 3. Median proportions of patients receiving chlorhexidine body-washing increased from 0% to 100% at the start of phase 2. For trends in acquisition of antimicrobial-resistant bacteria, weekly incidence rate ratio (IRR) was 0·976 (0·954–0·999) for phase 2 and 1·015 (0·998–1·032) for phase 3. For step changes, weekly IRR was 0·955 (0·676–1·348) for phase 2 and 0·634 (0·349–1·153) for phase 3. The decrease in trend in phase 2 was largely caused by changes in acquisition of MRSA (weekly IRR 0·925, 95% CI 0·890–0·962). Acquisition was lower in the conventional screening group than in the rapid screening group, but did not differ significantly (p=0·06).**

Interpretation **Improved hand hygiene plus unit-wide chlorhexidine body-washing reduced acquisition of antimicrobial-resistant bacteria, particularly MRSA. In the context of a sustained high level of compliance to hand hygiene and chlorhexidine bathings, screening and isolation of carriers do not reduce acquisition rates of multidrug-resistant bacteria, whether or not screening is done with rapid testing or conventional testing.**

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Introduction

Antimicrobial-resistant bacteria have become more widespread worldwide. Intensive care units (ICUs) are especially affected by three major groups of highly resistant pathogens—meticillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), and highly resistant (ie, resistant to third-generation or fourth-generation cephalosporins) Enterobacteriaceae (HRE). Controlling the spread of these organisms is a major public health challenge and often involves labour-intensive, protracted efforts. Several control measures have been advocated[1] including improved adherence to standard precautions,[2] chlorhexidine body-washing,[3–9] introduction of contact precautions for known carriers of antimicrobial-resistant bacteria and putting carriers in single-patient rooms,[10,11] and rapid detection of carriers at admission to ICU combined with isolation of carriers. However, evidence for these interventions is mainly based on small, quasi-experimental studies. Universal screening of patients at ICU admission for antimicrobial-resistant bacteria followed by contact precautions—a costly and labour-intensive intervention—remains the most controversial, with conflicting results precluding evidence-based recommendations.[12]

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See Online for appendix

No controlled study has tested the effect of rapid screening and isolation of carriers on colonisation with antimicrobial-resistant bacteria in settings that already have best standard precautions in place. We assessed the effect of different infection control strategies on acquisition of antimicrobial-resistant bacteria in ICUs.

Methods

Study design and participants

We assessed 13 European ICUs between May, 2008, and April, 2011, in three phases. Implementation of costly and labour-intensive interventions—eg, screening and isolation—is probably futile in the absence of good basic hygiene. Therefore, after a 6 month baseline period (phase 1), we introduced a hygiene improvement programme at all ICUs in an interrupted time-series phase (phase 2) before beginning a cluster randomised, controlled phase (phase 3). In phase 2, we tested the effect of optimised hand hygiene plus unit-wide implementation of chlorhexidine body-washing on acquisition of antimicrobial-resistant bacteria. In phase 3, we tested the additional effect of screening followed by contact precautions for identified carriers, using either PCR for MRSA and VRE together with chromogenic screening for HRE (rapid screening), or chromogenic-based screening for MRSA and VRE only (conventional screening).

Interrupted time series are useful if a randomised controlled trial is not feasible.[13,14] We planned to use a stepped-wedge design for phase 2 but this proved impractical because of logistical and financial constraints. However, we did enrol ICUs consecutively to account for seasonal effects.

We aimed to include ICUs with a moderate to high proportion of resistant bacteria. Adult ICUs with at least eight beds were eligible, provided that—of the ICU-acquired bacteraemias recorded in 2006 or 2007—MRSA accounted for more than 10% of *S aureus* bacteraemias, VRE accounted for more than 5% of enterococcal bacteraemias, or extended-spectrum β-lactamase resistance accounted for more than 10% of Enterobacteriaceae bacteraemias.

Each institution's review board or national ethics committee approved the study protocol. Because the study involved very little risk of harm to patients, a waiver for informed consent was sought and granted for all participating centres.

Randomisation and masking

After phase 2, the 13 ICUs were randomly assigned (1:1) to the rapid or conventional screening groups. The sequence for allocation was based on a computer-generated randomisation list, generated by an independent data manager who had no other role in the study. We did not match ICUs and no masking was used.

Procedures

Surveillance swabs from perineum, nose, and wounds (if present) were obtained within 2 days of admission to the ICU, then twice per week for 3 weeks, then once per week thereafter, for all patients admitted to ICU for 3 days or more. All surveillance swabs were analysed locally, according to a standardised protocol (appendix). Chromogenic media was used for detection of MRSA (BBL CHROMagar MRSA II; Becton, Dickinson and Company, Franklin Lakes, NJ USA), BBL Enterococcosel Agar with vancomycin 8 μg/mL for detection of VRE (Becton, Dickinson and Company), and Brilliance ESBL 2 for detection of HRE (Oxoid, Cambridge, UK).[15–17] In ICUs assigned to rapid screening, Xpert MRSA and Xpert VanA/VanB (Cepheid, Sunnyvale, CA, USA) were used additionally.[18,19]

All microbiology laboratories were required to complete proficiency panels.[20–22] All first isolates of MRSA, VRE, and HRE from surveillance cultures or blood were shipped to a central laboratory for species confirmation, susceptibility testing, and genotyping. To assess chlorhexidine resistance, the presence of *qacA* and *qacB* genes was investigated by PCR at the central laboratory.[2,23]

After phase 1, we implemented a hand hygiene improvement programme and universal daily body-washing with 0·16 g/L chlorhexidine gluconate for 6 months (phase 2) in all ICUs. We derived the hand hygiene programme from the WHO's Five Moments for Hand Hygiene concept.[2–7,24]

These interventions continued in phase 3 alongside screening and contact precautions for carriers of antimicrobial-resistant bacteria (appendix). During phases 1 and 2, barrier precautions were based on pre-study local isolation protocols and were not part of the study interventions. During phase 1 and phase 2, surveillance cultures were stored and processed with a 2 month delay to maintain masking of ICU personnel to the colonisation status of patients. In phase 3, screening results were immediately disclosed to staff at ICUs. Time from acquisition of swabs to start of processing (time-to-test) and from start of test until reporting of results (time-to-result) were recorded for all surveillance cultures; the sum of both was the turn-around time of tests. Interventions likely to affect outcomes (eg, central-line-associated bloodstream infection bundles or ventilator-associated pneumonia bundles, selective digestive decontamination, enhanced antimicrobial stewardship, or mupirocin use) were not introduced during the study.

Patients' demographics, reason for ICU admission, length of stay in ICU and in hospital, disposition at discharge, and 28 day mortality, as well as occurrence of bactaeremia with *S aureus*, enterococci, and Enterobacteriaceae were recorded for all patients. We collected weekly point prevalence data for bed occupancy, staffing ratios, numbers of patients ventilated, invasive devices, and isolation details (appendix). Two research nurses in each ICU were centrally trained to do hand hygiene observations. 15 observation sessions, of 15–30 min, were done every month throughout the study at the ICUs. The

	Phase 1 (n=2043)	Phase 2 (n=2072)	Phase 3	
			Conventional screening group (n=2348)	Rapid screening group (n=2513)
ICU characteristics				
Beds occupied	84·7% (18·5)	87·9% (16·6)	84·2% (17·1)	86·6% (18·3)
Nurse:patient ratio	0·55 (0·22)	0·53 (0·19)	0·55 (0·20)	0·55 (0·25)
Location before admission to ICU				
Home or private residence	38·2% (36·1–40·4)	35·6% (33·6–37·7)	38·2% (36·3–40·2)	37·2% (35·3–39·1)
Health-care facility	59·1% (56·9–61·2)	60·3% (58·1–62·4)	58·6% (56·6–60·6)	58·6% (56·6–60·5)
Unknown or other	2·7% (2·1–3·5)	4·2% (3·4–5·1)	3·2% (2·6–4·0)	4·3% (3·6–5·1)
Risk factors for colonisation before admission to ICU				
Admitted to a hospital for >24 h in the past year	52·6% (50·4–54·8)	47·6% (45·4–49·7)	56·6% (54·5–58·6)	41·4% (39·4–43·3)
Any type of surgery in the past year	20·3% (18·6–22·1)	22·2% (20·4–24·0)	20·9% (19·3–22·6)	18·9% (17·4–20·5)
Urgent or emergency surgery before admission to ICU	17·4% (15·8–19·1)	15·3% (13·8–17·0)	14·8% (13·4–16·3)	17·4% (16·0–19·0)
Patient history				
Solid tumour	14·2% (12·8–15·8)	12·0% (10·7–13·5)	13·5% (12·2–14·9)	15·8% (14·5–17·3)
Haematological cancer	3·9% (3·2–4·9)	4·1% (3·3–5·0)	4·2% (3·4–5·1)	4·1% (3·4–4·9)
Haemopoietic stem cell or bone marrow transplant	0·7% (0·4–1·2)	0·8% (0·5–1·3)	0·8% (0·5–1·3)	0·8% (0·5–1·2)
Solid organ transplant	2·2% (1·6–2·9)	1·6% (1·2–2·3)	1·8% (1·4–2·5)	1·5% (1·1–2·0)
HIV/AIDS	1·9% (1·4–2·5)	1·4% (0·9–2·0)	1·4% (1·0–2·0)	1·6% (1·2–2·2)
MRSA colonisation in the past year	3·1% (2·2–3·6)	3·1% (2·4–4·0)	2·8% (2·2–3·6)	4·5% (3·8–5·4)
VRE colonisation in the past year	0·2% (0·1–0·4)	0·2% (0·1–0·6)	0·2% (0·1–0·5)	2·1% (1·6–2·7)
HRE colonisation in the past year	2·3% (1·7–3·1)	2·7% (2·1–3·4)	3·2% (2·5–3·9)	3·0% (2·4–3·7)
Patient demographics				
Median age (IQR, years)	65 (50–76)	64 (50–75)	64 (49–76)	65 (51–77)
Men	61·0% (58·9–63·1)	60·0% (57·9–62·1)	60·9% (58·9–62·9)	59·3% (57·4–61·2)
Non-surgical reason for admission to ICU	76·5% (74·6–78·3)	79·8% (78·0–81·5)	81·4% (79·8–82·9)	73·4% (71·7–75·1)
Median APACHE-II score (IQR)*	16 (11–22)	16 (11–22)	15 (10–22)	15 (11–19)
Median SAPS-II (IQR)†	40 (28–54)	38 (27–50)	37 (26–50)	35 (24–48)
Invasive devices (during first 3 days)				
Endotracheal tube	60·4% (58·2–62·5)	60·4% (58·3–62·5)	59·4% (57·4–61·3)	52·1% (50·2–54·1)
Tracheostomy tube	4·2% (3·4–5·2)	4·3% (3·5–5·3)	3·2% (2·6–4·0)	5·8% (5·0–6·8)
Central venous catheter	69·8% (67·7–71·7)	68·3% (66·3–70·3)	61·5% (59·5–63·5)	73·5% (71·7–75·2)
Arterial intravascular catheter	64·2% (62·1–66·3)	63·4% (61·3–65·5)	59·2% (57·2–61·2)	69·0% (67·2–70·8)

Data are mean (95% CI), unless otherwise stated. Data were taken from all patients admitted for at least 3 days. ICU=intensive care unit. APACHE=Acute Physiology and Chronic Health Evaluation. SAPS=Simplified Acute Physiology Score. MRSA=meticillin-resistant *Staphylococcus aureus*. VRE=vancomycin-resistant enterococci. HRE=highly resistant Enterobacteriaceae. *Data available for 709 patients in phase 1, 780 in phase 2, and 1724 in phase 3. †Data available for 1334 patients in phase 1, 1292 in phase 2, and 3134 in phase 3.

Table 1: **Baseline characteristics**

sessions were randomly scheduled within three 4 h periods (0800–1200 h, 1200–1600 h, and 1600–2000 h).

We checked 10% of all electronic case report forms against data collected at each ICU, and checked all procedures for consistency once during phase 1 and once during phase 2. Data were collected through an online data entry system, consisting of an independently managed secure data processing centre, including plausibility checks for data entry.

Colonisation was defined as growth on chromogenic plates and acquisition was based on chromogenic agar results for all phases and both screening groups. If a patient was colonised according to the last screening culture, we assumed that colonisation persisted until discharge from ICU. If a patient was not colonised at the last screening culture, the period at risk ended on that day. Colonisation and bacteraemia were classed as ICU-acquired if detected on or after the third day of admission to the ICU, after a negative swab. We did not follow up patients after discharge from ICU.

The primary endpoint was the number of patients who acquired MRSA, VRE, or HRE carriage per 100 patient-days at risk in ICU. Secondary outcomes included incidence density rate of ICU-acquired colonisation and bacteraemia for each of MRSA, VRE, and HRE; compliance with hand hygiene practices; length of stay in ICU; length of stay in hospital; and 28 day mortality. The appendix shows further secondary outcomes.

Patients admitted for fewer than 3 days were not deemed at risk for ICU-acquired colonisation and

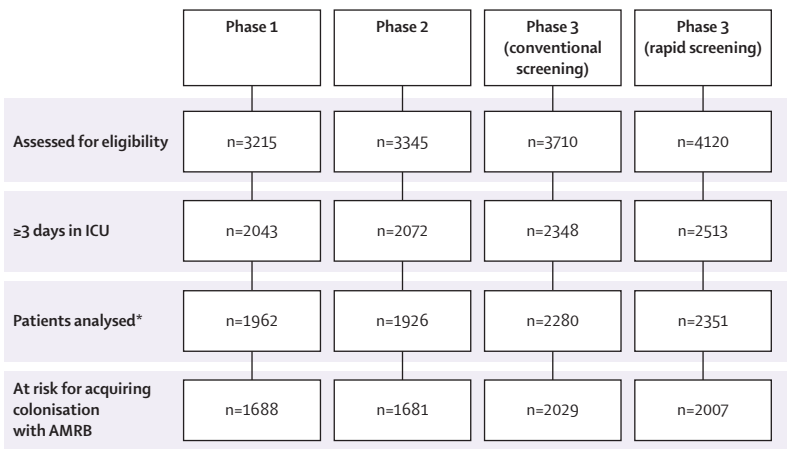

Figure 1: **Study profile**
Patients at risk for acquiring colonisation with AMRB excludes all patients colonised at admission with any of MRSA, VRE, HRE, or in whom a first (admission) swab was taken after the first 2 days of ICU stay and was positive. AMRB=antimicrobial-resistant bacteria. ICU=intensive care unit. MRSA=meticillin-resistant *Staphylococcus aureus*. VRE=vancomycin-resistant enterococci. HRE=highly resistant Enterobacteriaceae. *Admitted for at least 3 days, for whom admission and discharge data were available and of whom at least one nasal, rectal, or wound swab was obtained during ICU admission.

	Phase 1	Phase 2	Phase 3
At ICUs using conventional screening	n=979	n=1020	n=2280
Any (%)	13·5% (11·5–15·8)	12·5% (10·6–14·6)	10·3% (9·1–11·6)
MRSA (%)	5·4% (4·2–7·0)	3·7% (2·7–5·1)	4·1% (3·3–5·0)
VRE (%)	3·3% (2·3–4·6)	2·9% (2·1–4·2)	1·1% (0·7–1·6)
HRE			
Total (%)	6·8% (5·4–8·6)	7·0% (5·6–8·7)	6·0% (5·1–7·1)
Escherichia coli (%)	4·0% (2·9–5·4)	2·8% (2·0–4·1)	3·7% (3·0–4·5)
Proteus, *Providencia*, or *Morganella* spp (%)	0·3% (0·1–0·9)	0·4% (0·2–1·0)	0·2% (0·1–0·5)
Klebsiella, *Enterobacter*, *Serratia*, or *Citrobacter* spp (%)	3·4% (2·4–4·7)	4·8% (3·7–6·3)	2·7% (2·1–3·4)
At ICUs using rapid screening	n=983	n=906	n=2351
Any (%)	12·3% (10·4–14·5)	11·0% (9·2–13·2)	14·1% (12·7–15·5)
MRSA (%)	3·3% (2·3–4·6)	4·6% (3·5–6·2)	3·3% (2·6–4·1)
VRE (%)	3·5% (2·5–4·8)	2·2% (1·4–3·4)	5·8% (4·9–6·8)
HRE			
Total (%)	7·0% (5·6–8·8)	5·7% (4·4–7·5)	7·7% (6·7–8·8)
Escherichia coli (%)	2·7% (1·9–4·0)	2·2% (1·4–3·4)	3·8% (3·1–4·6)
Proteus, *Providencia*, or *Morganella* spp (%)	0·3% (0·1–0·9)	0·0% (0·0–0·4)	0·2% (0·1–0·5)
Klebsiella, *Enterobacter*, *Serratia*, or *Citrobacter* spp (%)	4·8% (3·6–6·3)	3·6% (2·6–5·1)	4·2% (3·5–5·1)

Data are mean (95% CI). Excludes patients for whom both the admission swab was not obtained during the first 2 days after admission, and the first swab taken during ICU admission was positive. MRSA=meticillin-resistant *Staphylococcus aureus*. VRE=vancomycin-resistant enterococci. HRE=highly resistant Enterobacteriaceae. ICU=intensive care unit.

Table 2: **Carriage of antimicrobial-resistant bacteria at admission to ICU**

bacteraemia, and were excluded from the analyses of ICU-acquired endpoints, though they were subject to the interventions. For secondary outcomes, patients were deemed at risk for acquisition of individual pathogens if not colonised or infected with that pathogen at hospital admission.

Statistical analysis

We calculated that 960 patients per ICU would be needed to show a 10% absolute difference in the probability of colonisation between the randomised groups with a two-sided test and assuming a type I error of 0·05, a type II error of 0·2, and an intracluster correlation coefficient of 0·05. We assessed outcomes with a multilevel Poisson segmented regression analysis, allowing for random variation between ICUs for baseline levels and trends. We assessed both step changes in acquisition rate per 100 patient-days at risk and changes in trends of acquisition rate per 100 patient-days at risk (rate of change of the log weekly acquisition rate) after the introduction of each intervention.[14]

Potential confounding factors—calendar month and patient and ward characteristics—were fitted as covariates. We did a post-hoc exploratory analysis with time-dependent Cox regression to assess the effects of colonisation pressure on acquisition. We did the analyses with STATA (version 11), and SPSS (version 17).

This study is registered with ClinicalTrials.gov, number NCT00976638.

Role of the funding source

The sponsors had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We screened 14 390 patients for eligibility, of whom 8976 were admitted to the ICU for at least 3 days (table 1). 8519 patients had at least one nasal, rectal, or wound swab during ICU admission and were therefore analysed (figure 1, table 2). ICUs varied from completely open to all single-patient rooms.

We obtained at least one nasal swab from 8517 (95%) of 8976 patients, a perineal swab from 8501 (95%) of 8976 patients, and a wound swab from 931 (10%) of 8976 patients. Of 41 558 hand hygiene opportunities, mean compliance was 52% in phase 1, 69% in phase 2, and 77% in phase 3 (figure 2, appendix p 11). We found no evidence of a change of behaviour of health-care workers as a result of observation (ie, the Hawthorne effect; data not shown). Based on 1188 point-prevalence measurements, median adherence to chlorhexidine body-washing was 0% in phase 1, 100% in phase 2, and 100% in phase 3 (appendix).

In ICUs assigned to rapid screening, proportions of patients for whom contact precautions were taken increased for all antimicrobial-resistant bacteria compared with phase 2. In ICUs assigned to conventional screening, only MRSA-related and VRE-related contact precautions increased, consistent with protocol (appendix). The proportion of patients in single rooms varied from 15% to 22%. This proportion exceeds the proportion of carriers,

which was less than 10% except during phase 3 in the rapid screening group (13%). Therefore, the scarcity of single rooms was unlikely to have decreased the quality of isolation procedures during phase 3. In phase 3, median turn-around time was 48 h for chromogenic tests, and 24 h for PCR (appendix, table 3).

We analysed 64 997 swabs in total. At admission to ICU, 296 (3·6%) of 8184 patients were colonised with MRSA, 384 (4·7%) of 8243 were colonised with VRE, and 1014 (12·8%) of 7943 were colonised with HRE. Molecular analysis of first isolates at the central laboratory confirmed identification for 508 of 553 (92%) isolates for MRSA. For VRE, 346 of 672 (51%) isolates were *vanA* or *vanB* containing *Enterococcus faecium* and *Enterococcus faecalis*, and 235 (35%) were *Enterococcus gallinarum* and *Enterococcus casseliflavus*. Of 2129 HRE isolates, 1966 (92%) produced extended-spectrum β lactamases, of which 571 (29%) were also resistant to carbapenems, and 241 (12%) produced AmpC.

The baseline acquisition rate of antimicrobial-resistant bacteria and trends varied widely between centres (appendix), with a baseline trend (weekly incidence rate ratio) of 1·014 (95% CI 0·996–1·031; table 3). Trend in acquisition of antimicrobial-resistant bacteria decreased during phase 2 with no evidence of a stepwise change in incidence between phases 1 and 2. For phase 3, there was no incremental effect on acquisition of antimicrobial-resistant bacteria (table 3, figure 3). When comparing the rapid and conventional screening groups, we found no evidence of differences in trends of acquisition of antimicrobial-resistant bacteria, though there was evidence of a stepwise difference in the rapid screening group associated with a higher acquisition rate (table 3). However, using a combined test of both possible effects (step changes and changes to trend), we found no strong evidence to reject the null hypothesis of no overall difference between rapid and conventional groups (p=0·06; likelihood ratio test).

Trends in acquisition of MRSA rose during phase 1 and fell during phase 2, resulting in a mean weekly decrease of 3·6%, with no substantial step change in phase 2. No substantial step change occurred during phase 3, while trends in MRSA acquisition increased (table 3). Step changes and changes in trends of MRSA acquisition were similar in the conventional screening and rapid screening groups (table 3, appendix). For HRE and VRE, we found no evidence of step changes in acquisition or trends in either phase 2 or phase 3; acquisition in each screening group was also much the same (table 3, appendix). Cox regression confirmed the results of the Poisson model and suggested that trends in acquisition during each phase could not be wholly explained by changes in colonisation pressure. This analysis also provided some evidence that the phase 2 intervention led to a trend for reduced acquisition of VRE (appendix). Much the same results were obtained for only MRSA and VRE grouped together in an unplanned post-hoc analysis (data not shown).

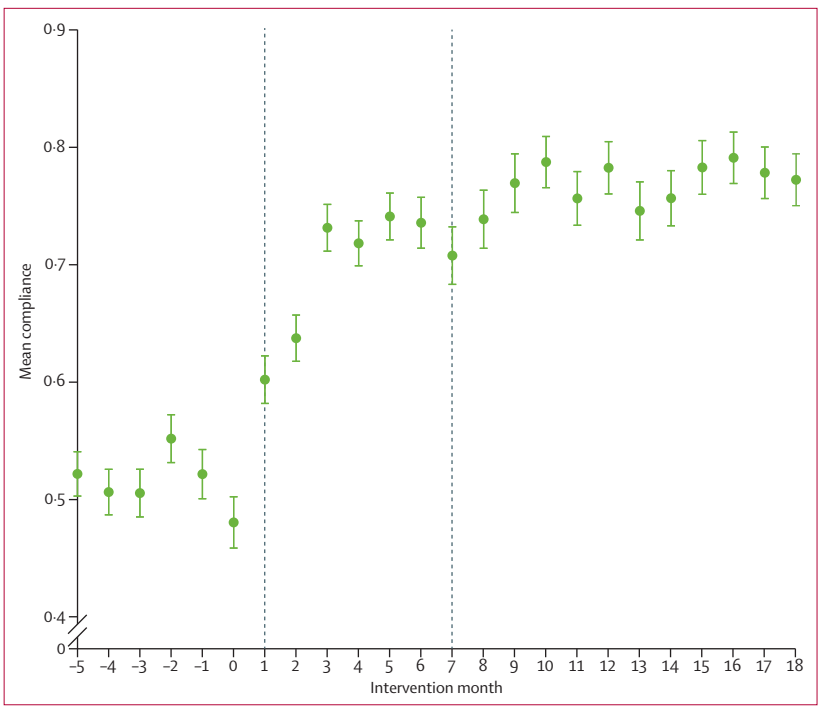

Figure 2: **Mean hand hygiene compliance per month**
Hand hygiene improvement intervention introduced at month 0. Error bars are 95% CIs.

The total number of ICU-acquired first bacteraemias recorded during the trial was 72 HRE, 28 MRSA, and nine VRE (*E faecium* and *E faecalis* only). Overall ICU-acquired bacteraemia caused by antimicrobial-resistant bacteria did not differ significantly between phases or between intervention groups in phase 3 (appendix). The trend in ICU-acquisition of HRE bacteraemia fell in phase 1, but not in phase 2, phase 3, or in the screening groups. For MRSA and VRE, numbers were too low to do statistical analyses.

Mean length of stay in ICU for patients at risk for acquisition of antimicrobial-resistant bacteria was 8 days in phase 1. Trend in phase 2 was 0·988 (95% CI 0·982–0·994); a net reduction of 26% (16–48) at the end of phase 2. For phase 3, trend for length of stay in ICU was 1·180 (95% CI 1·006–1·384) for ICUs using rapid screening compared with 1·082 (0·921–1·270) for those using conventional screening. Rapid screening, but not conventional screening, was also associated with a stepwise increase for phase 3. There was no evidence that hospital length of stay and mortality at day 28 were affected by any of the interventions (appendix). We assessed 223 MRSA isolates for *qacA* or *qacB*: we detected the genes in 14 of 110 isolates from phase 1 and in 16 of 113 isolates from phase 3 (p=0·75; data not shown).

Discussion

Improved hand hygiene combined with universal chlorhexidine body-washing was associated with reduced

	Antimicrobial-resistant bacteria	MRSA	VRE	HRE
Phase 1 trend	1·014 (0·996–1·031; p=0·12)	1·042 (1·010–1·075; p=0·01)	1·000 (0·971–1·030; p=0·99)	1·012 (0·992–1·032; p=0·25)
Phase 2 step change	0·955 (0·676–1·348; p=0·79)	1·159 (0·654–2·053; p=0·61)	0·884 (0·481–1·626; p=0·69)	0·831 (0·559–1·235; p=0·36)
Phase 2 change in trend	0·976 (0·954–0·999; p=0·04)	0·925 (0·890–0·962; p<0·001)	0·982 (0·945–1·020; p=0·36)	0·994 (0·968–1·021; p=0·66)
Phase 3 step change	0·634 (0·349–1·153; p=0·14)	0·755 (0·252–2·257; p=0·62)	0·651 (0·209–2·031; p=0·46)	0·525 (0·263–1·048; p=0·07)
Phase 3 change in trend	1·015 (0·998–1·032; p=0·09)	1·057 (1·029–1·086; p<0·001)	1·015 (0·984–1·048; p=0·34)	0·991 (0·971–1·011; p=0·35)
Phase 3 step change (rapid *vs* conventional screening)	1·696 (1·090–2·638; p=0·02)	1·734 (0·768–3·916; p=0·19)	1·735 (0·711–4·234; p=0·23)	1·691 (1·012–2·828; p=0·05)
Phase 3 change in trend (rapid *vs* conventional screening)	0·996 (0·984–1·007; p=0·46)	0·985 (0·966–1·005; p=0·15)	0·993 (0·969–1·018; p=0·59)	1·000 (0·986–1·014; p=0·99)
Likelihood ratio test (rapid *vs* conventional screening)	p=0·06	p=0·34	p=0·47	p=0·10

Data are IRR (95% CI) unless stated otherwise. IRR <1 represents a decrease in acquisition, whereas IRR >1 represents an increase. Cluster effects were accounted for in the analyses, and potential confounding factors (sex, age, month, invasive devices, nurse-to-patient staffing ratio, location before ICU admission, reason for admission, APACHE/SAPS, hospital, and number of days-at-risk for acquisition) were fitted as covariates. MRSA=meticillin-resistant *Staphylococcus aureus*. VRE=vancomycin-resistant enterococci. HRE=highly resistant Enterobacteriaceae. IRR=incidence rate ratio. APACHE=Acute Physiology and Chronic Health Evaluation. SAPS=Simplified Acute Physiology Score.

Table 3: **Weekly acquisition of any antimicrobial-resistant bacteria, MRSA, VRE, and HRE**

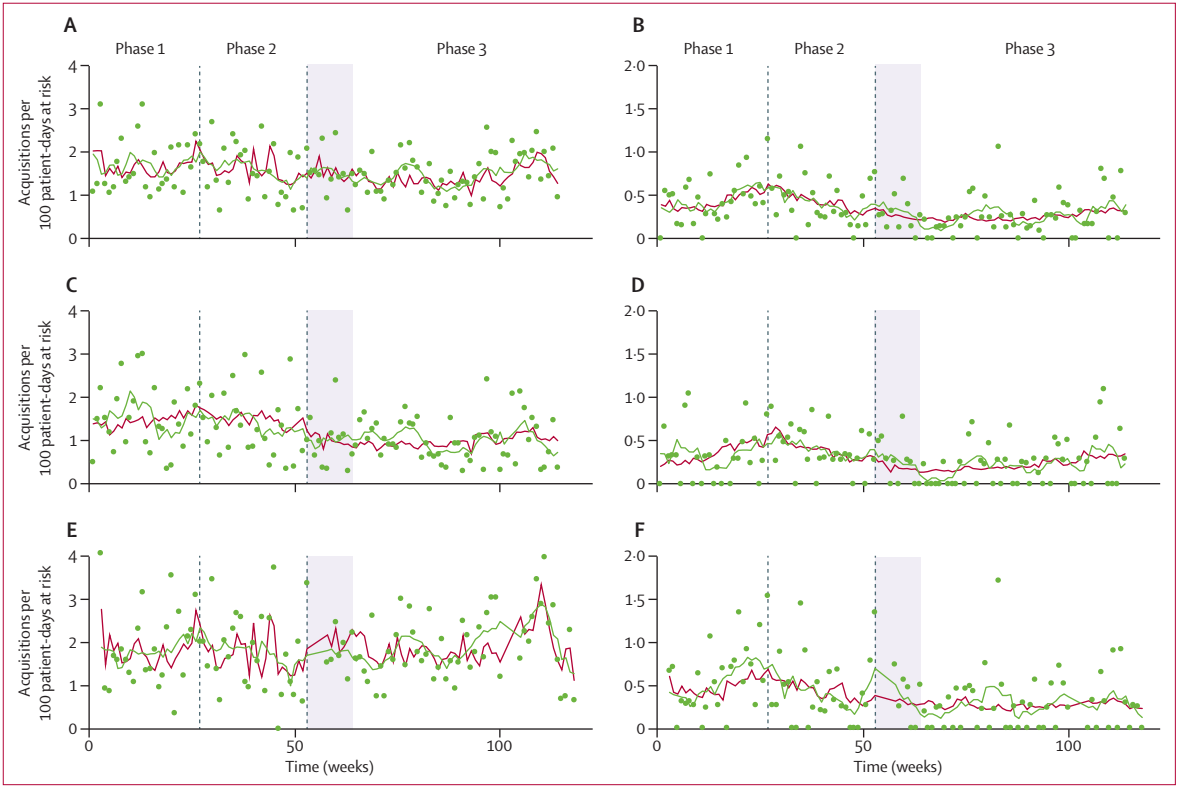

Figure 3: **Acquisition of antimicrobial-resistant bacteria and meticillin-resistant *Staphylococcus aureus* per 100 patient-days at risk**
For all antimicrobial bacteria in both screening groups (A), for MRSA in both screening groups (B), for all antimicrobial bacteria in the conventional screening group (C), for MRSA in the conventional screening group (D), for all antimicrobial bacteria in the rapid screening group (E), and for MRSA in the rapid screening group (F). Shaded area is the start of phase 3. Green dots are data; green lines are 7 week moving average. Red lines are expected values from the multilevel Poisson segmented regression model. Cluster effects were accounted for, and potential confounding factors (sex, age, month, invasive devices, nurse-to-patient staffing ratio, location before ICU admission, reason for admission, APACHE and SAPS score, hospital, and number of days-at-risk for acquisition) were fitted as covariates. APACHE=Acute Physiology and Chronic Health Evaluation. SAPS=Simplified Acute Physiology Score.

acquisition of antimicrobial-resistant bacteria, mainly by reduction of MRSA acquisition. The same interventions did not reduce acquisition of HRE or VRE. Implementation of contact precautions for carriers identified by either chromogenic or PCR screening had no incremental effect on acquisition. Optimum hand hygiene and universal chlorhexidine body-washing was also associated with reduced length of stay in ICU, and

addition of PCR-based screening was associated with increased length of stay in ICU.

Three cluster randomised studies of ICUs in the USA have evaluated similar interventions. Huskins and colleagues[25] showed no change in acquisition of MRSA and VRE after universal screening of patients and pre-emptive isolation followed by barrier precautions for identified carriers. However, average turn-around time of admission screening was 5·2 days, implying that many screening results were not available before patient discharge.[18,19,25]

In a cluster-crossover study of nine ICUs, Climo and coworkers[8] compared daily bathing with chlorhexidine-impregnated washcloths to non-antimicrobial washcloths. The intervention reduced acquisition of VRE, but not MRSA, and was associated with a significant reduction in primary bloodstream infections, primarily caused by a reduced incidence of coagulase-negative staphylococci bacteraemia. Moreover, the analysis did not account for clustering effects and might therefore have overestimated the statistical significance of the findings. In the third study,[9] 74 ICUs were randomly assigned to one of three groups: MRSA screening and isolation; targeted decolonisation; and universal decolonisation with mupirocin nasal ointment combined with chlorhexidine body-washing. Universal decolonisation was associated with significant reductions of clinical cultures yielding MRSA, and all-cause bloodstream infections, but not MRSA bloodstream infections.

None of these studies addressed the beneficial effects of hand hygiene improvement. In our study, the gradual decrease in acquisition of antimicrobial-resistant bacteria in phase 2 coincided with a gradual increase in hand hygiene compliance, suggesting that hand hygiene improvement might have been an important component of the intervention since chlorhexidine body-washing was successfully implemented immediately in phase 2 (appendix). However, our study design precludes assessment of the relative importance of these two interventions.

Our findings add to the growing body of evidence that, in high endemicity settings, screening for MRSA carriage followed by implementation of barrier precautions is of little effectiveness for prevention of transmission.[9,25–28] The failure to reduce HRE acquisitions might be explained—at least in part—by differences in bacterial epidemiology. Whereas HRE mainly colonise the digestive tract, MRSA and VRE can also colonise the skin and environment. Thus, patient-to-patient transmission might not be the main route of acquisition for HRE in ICUs, and other prevention methods will be needed to reduce colonisation and infections with HRE, such as antibiotic stewardship programmes or intestinal decolonisation with non-absorbable antibiotics (panel).[13,14,29–31]

Our study has some limitations. With 13 ICUs in eight countries, many differences in resistance and unit characteristics existed. However, in unplanned explanatory subgroup analyses, intervention effects did not differ significantly between wards with high and low median prevalence of MRSA, VRE, or HRE at admission.

***Panel:* Research in context**

Systematic review

We searched PubMed with the terms ("clinical trials as topic"[MeSH Terms]) AND (("anti-infective agents"[Pharmacological Action] OR "anti-infective agents"[MeSH Terms] OR ("anti-infective"[All Fields] AND "agents"[All Fields]) OR "anti-infective agents"[All Fields] OR "antimicrobial" AND resistance) AND ("intensive care"[MeSH Terms]) AND ("infection control"[MeSH Terms])) which returned 66 articles, of which we excluded those testing drug prophylaxis (eg, selective digestive decontamination or surgical prophylaxis) or testing prevention of specific infections (eg, catheter-related or respiratory infections) or non-resistant microorganisms and studies done outside intensive care units (ICUs). Related citations and authors' personal references lists were also searched. We identified eight articles, including four systematic reviews. One was a systematic review[32] of screening for meticillin-resistant *Staphylococcus aureus* (MRSA), which included 48 studies, of which 14 were done in ICUs, but did not include the most recent and largest study by Huang and colleagues.[9] This meta-analysis concluded that the available evidence was insufficient to assess the effect of screening of ICU patients for MRSA carriage on MRSA acquisition, and evidence was insufficient to support or refute that, compared with no screening, screening for MRSA carriage in ICU patients decreases healthcare-associated MRSA infection or bloodstream infection. An individual-patient randomised controlled trial not included in this review found no effect of screening and isolation on MRSA acquisition rates.[33] Further evidence against routine screening has been provided by the study by Huang and colleagues,[9] showing no significant reduction in MRSA acquisition or bloodstream infection with screening and isolation, but reduced rates with decolonisation strategies using chlorhexidine and mupirocin. Three systematic reviews[24,34,35] of chlorhexidine bathing were done before publication of the study by Climo and coworkers,[8] the results of which favoured the intervention when studying rates of acquisition of MRSA and vancomycin-resistant enterococci, without evidence of efficacy against multidrug-resistant Gram-negative bacteria. There was only one randomised controlled trial of isolation and segregation of colonised patients, which showed no efficacy of this measure on MRSA acquisition rate.[36] No controlled study addressed the effectiveness of hand hygiene or the preventive efficacy of the above measures on rates of acquisition of multidrug-resistant Gram-negative bacteria in ICU patients.

Interpretation

Our study addresses the effect of hand hygiene in combination with chlorhexidine bathing and of screening and isolation on the prevention of acquisition of major antimicrobial-resistant pathogens (multidrug-resistant bacteria, including MRSA, vancomycin-resistant enterococci, and highly resistant Enterobacteriaceae) in ICUs. Improved hand hygiene and chlorhexidine bathing are associated with a reduction in acquisition, mainly through reduced acquisition of MRSA, whereas no effect on highly resistant Enterobacteriaceae was evidenced. Screening and isolation of carriers did not further reduce acquisition of multidrug-resistant bacteria, whether screening was done with rapid testing or conventional testing. Our results show the efficacy of improved hand hygiene to reduce MRSA acquisition rates, and concur with other studies[7,8] of the efficacy of chlorhexidine body-washing. Our finding of a lack of added preventive efficacy of screening and isolation of carriers is also consistent with several large recent controlled studies[9,25] showing little or no efficacy of such an approach to reduce acquisition of MRSA or VRE in ICUs; however, this finding might not apply to settings with lower hand hygiene compliance. Lastly, the absence of an effect of any of our interventions on highly resistant Enterobacteriaceae suggests that new methods to control this emerging threat—eg, selective digestive decontamination—should be investigated.

Furthermore, the effectiveness of interventions did not vary with differences according to baseline trends or levels (data not shown). The 95% CIs for primary and secondary outcomes were generally small. Because the participating ICUs represent typical ICU populations, we believe that their heterogeneity and the consistent results for high and low prevalence wards add to the external validity of our results.

Absence of screening at admission for all patients could have biased the results if missing screens did not occur at random. However, only new colonisation on day 3 or later was deemed acquired in the ICU. Of the patients admitted for at least 3 days (and thus at risk for acquisition), 95% had admission and discharge data available and at least one nasal, rectal, or wound swab during ICU stay. Of the patients admitted for at least 5 days, 96% had at least one screening swab after admission. Any such bias, if present, is therefore likely to be small.

We did not expect the large changes in length of stay, which could have affected the number of acquisitions of antimicrobial-resistant bacteria (and therefore the Poisson regression results). However, the very similar results obtained by Cox regression analysis (which takes the acquisition rate into account) suggest that changes in rates cannot be explained by changes in length of stay. Knowledge of antimicrobial-resistant bacteria carriage in phase 3 might have caused some delay in discharge of patients. The increasing length of stay during phase 3 affected both groups but was larger in the rapid screening group. This difference might be because more patients were identified as carriers in this group and such patients were identified earlier. We cannot comment on the risk of transmission of antimicrobial-resistant bacteria after ICU discharge, because it was not measured.

All participating laboratories used standardised procedures to process samples, and completed quality assessments for detection of MRSA, VRE, and HRE.[20–22] Confirmation rates at the central laboratory were high for MRSA and HRE. For VRE only 51% of isolates contained *vanA* or *vanB*. However, analyses using only confirmed *vanA* or *vanB* data did not change our results (data not shown).

A further limitation is that improved hand hygiene combined with universal chlorhexidine body-washing was not protected by randomisation and is potentially vulnerable to maturation effects. However, the primary analysis adjusted for seasonal effects, and accounted for ICU-specific levels and trends in the baseline period. Moreover, visual inspection of MRSA outcomes in the two study groups shows a similar decrease during phase 2. Finally, patient isolations were assessed from weekly point-prevalence, and not monitored on a daily patient-level basis and adherence to contact precautions was not audited.

Contributors

MJMB, CB-B, BSC, and LPGD designed the study. MJMB and CB-B supervised the study. LPGD searched the published work and supervised data collection. BSC and LPGD provided the figures. MJMB, CB-B, BSC, MJDD, and LPGD analysed and interpreted data. MJMB, CB-B, BSC, and LPGD wrote the report. All other authors collected and interpreted data, and helped to revise the report.

Participating staff

Data collection—E Aires, A Antoniadou, A Armaganidis, F Blairon, J Carneiro, D Chaskou, P Coppadoro, A-P Dias, I Drinovec, M Elia, V Exarchou, A Flet, J Fournier, N Gillet, A Jaklič, M Jereb, A Kane, E Karkali, J Kieffer, P Kirpach, C Landelle, F Landercy, C Lawrence, P Legrand, V Lopes, E Magira, F Marco, J A Martínez, A Melbārde-Kelmere, B Misset, R Monte, E Moreno, J C Nguyen, M Novak, D Orazi, E Papadomichelakis, J Papaparaskevas, M Paris, J Pavleas, F Pimenta, R Piñer, A Radouan, M-G Ramunno, M Reis, I Rinaldi, E Ronco, A San Jose, K Seme, A Skiada, S Trapassi, M Tronci, M Verachten, J Vila, K Vrankar, M Winkler, S Zagavierou; *data monitoring and collection*—M Hopman; *data management*—F Leus, J Schotsman, J Zwerver.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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