Contact precautions in single-bed or multiple-bed rooms for patients with extended-spectrum β-lactamase-producing Enterobacteriaceae in Dutch hospitals: a cluster-randomised, crossover, non-inferiority study

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Summary

Background Use of single-bed rooms for control of extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae is under debate; the added value when applying contact precautions has not been shown. We aimed to assess whether an isolation strategy of contact precautions in a multiple-bed room was non-inferior to a strategy of contact precautions in a single-bed room for preventing transmission of ESBL-producing Enterobacteriaceae.

Methods We did a cluster-randomised, crossover, non-inferiority study on medical and surgical wards of 16 Dutch hospitals. During two consecutive study periods, either contact precautions in a single-bed room or contact precautions in a multiple-bed room were applied as the preferred isolation strategy for patients with ESBL-producing Enterobacteriaceae cultured from a routine clinical sample (index patients). Eligible index patients were aged 18 years or older, had no strict indication for barrier precautions in a single-bed room, had a culture result reported within 7 days of culture and before discharge, and had no wardmate known to be colonised or infected with an ESBL-producing Enterobacteriaceae isolate of the same bacterial species with a similar antibiogram. Hospitals were randomly assigned in a 1:1 ratio by computer to one of two sequences of isolation strategies, stratified by university or non-university hospital. Allocation was masked for laboratory technicians who assessed the outcomes but not for patients, treating doctors, and infection-control practitioners enrolling index patients. The primary outcome was transmission of ESBL-producing Enterobacteriaceae to wardmates, which was defined as rectal carriage of an ESBL-producing Enterobacteriaceae isolate that was clonally related to the index patient's isolate in at least one wardmate. The primary analysis was done in the per-protocol population, which included patients who were adherent to the assigned room type. A 10% non-inferiority margin for the risk difference was used to assess non-inferiority. This study is registered with Nederlands Trialregister, NTR2799.

Findings 16 hospitals were randomised, eight to each sequence of isolation strategies. All hospitals randomised to the sequence single-bed room then multiple-bed room and five of eight hospitals randomised to the sequence multiple-bed room then single-bed room completed both study periods and were analysed. From April 24, 2011, to Feb 27, 2014, 1652 index patients and 12 875 wardmates were assessed for eligibility. Of those, 693 index patients and 9527 wardmates were enrolled and 463 index patients and 7093 wardmates were included in the per-protocol population. Transmission of ESBL-producing Enterobacteriaceae to at least one wardmate was identified for 11 (4%) of 275 index patients during the single-bed room strategy period and for 14 (7%) of 188 index patients during the multiple-bed room strategy period (crude risk difference 3·4%, 90% CI –0·3 to 7·1).

Interpretation For patients with ESBL-producing Enterobacteriaceae cultured from a routine clinical sample, an isolation strategy of contact precautions in a multiple-bed room was non-inferior to a strategy of contact precautions in a single-bed room for preventing transmission of ESBL-producing Enterobacteriaceae. Non-inferiority of the multiple-bed room strategy might change the current single-bed room preference for isolation of patients with ESBL-producing Enterobacteriaceae and, thus, broaden infection-control options for ESBL-producing Enterobacteriaceae in daily clinical practice.

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Introduction

Health-care-associated infections are a leading cause of morbidity and mortality worldwide.[1,2] Extended-spectrum

β-lactamase (ESBL)-producing Enterobacteriaceae have emerged as common pathogens causing health-care-associated infections and they restrict therapeutic

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See **Online** for appendix

Research in context

Evidence before this study

Our study was designed in 2010 in response to national and international debate on the need for single-bed rooms when nursing patients with extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae under contact precautions. We searched PubMed on Dec 31, 2010, for original research articles published up to that date that compared use of single-bed and multiple-bed rooms, both in combination with contact precautions, with the occurrence or transmission of antimicrobial-resistant bacteria as an outcome. No language restrictions were applied. We used the search terms ("single room[s]" OR "single-bed room[s]" OR "private room[s]") AND ("isolation" OR "contact precautions") AND ("antibiotic" OR "antimicrobial") AND ("resistance" OR "resistant"). Our search yielded 55 articles of which three met our selection criteria. We repeated this search on Dec 4, 2018, yielding 38 additional articles, of which none met our selection criteria. The studies reviewed were all observational studies, were targeted at Gram-positive microorganisms (eg, meticillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* spp), and results were inconsistent. No studies on the added value of single-bed rooms to applying contact precautions for patients with ESBL-producing Enterobacteriaceae were identified.

Added value of this study

To the best of our knowledge, our randomised study of isolation strategies for patients with ESBL-producing Enterobacteriaceae is the first to assess the added value of single-bed rooms when applying contact precautions. An important strength of our study is its pragmatic design, reflecting current Dutch clinical practice and control policy for ESBL-producing Enterobacteriaceae.

Implications of all the available evidence

Our study in patients with ESBL-producing Enterobacteriaceae cultured from a routine clinical sample provides evidence that an isolation strategy of contact precautions in a multiple-bed room is non-inferior to a strategy of contact precautions in a single-bed room for preventing transmission of ESBL-producing Enterobacteriaceae to wardmates. Non-inferiority of the multiple-bed room strategy might change the current single-bed room preference for isolation of patients with ESBL-producing Enterobacteriaceae and, thus, broaden infection-control options for ESBL-producing Enterobacteriaceae in daily clinical practice.

options.[3,4] To control the spread of ESBL-producing Enterobacteriaceae within hospitals, infection-control guidelines recommend applying contact precautions in addition to standard precautions for patients who are colonised or infected with ESBL-producing Enterobacteriaceae, preferably in a single-bed room.[5–7] For endemic settings, the guideline of the European Society for Clinical Microbiology and Infectious Diseases restricts this recommendation to ESBL-producing Enterobacteriaceae other than *Escherichia coli*.[7]

Use of single-bed rooms has become controversial because of the suggested deleterious effects on quality of care and the occurrence of adverse events.[8,9] A few studies have reported on the added value of single-bed rooms for control of antimicrobial resistance, but results were inconsistent. In an observational German study,[10] a lower frequency of hospital-acquired meticillin-resistant *Staphylococcus aureus* (MRSA) infections was reported for intensive-care units (ICUs) that routinely nursed patients with MRSA in single-bed rooms compared with ICUs that used both single-bed and multiple-bed rooms. However, in a before-and-after study at two ICUs in the UK,[11] actively moving patients with MRSA to single-bed rooms did not affect the frequency of hospital-acquired MRSA carriage. Yet, in a Korean before-and-after study,[12] the frequency of hospital-acquired carriage of vancomycin-resistant *Enterococcus* spp (VRE) was reduced when contact precautions for patients with VRE were applied in single-bed rooms compared with multiple-bed rooms. Data to show the added value of single-bed rooms when applying contact precautions for control of nosocomial spread of antimicrobial-resistant Gram-negative bacteria are currently not available. Data showing non-inferiority of multiple-bed rooms for isolation of patients with ESBL-producing Enterobacteriaceae would broaden infection-control options for ESBL-producing Enterobacteriaceae in daily clinical practice.

We aimed to assess whether an isolation strategy of contact precautions in a multiple-bed room would be non-inferior to a strategy of contact precautions in a single-bed room for patients in non-ICU, non-haematology wards with ESBL-producing Enterobacteriaceae cultured from a routine clinical sample, in terms of preventing transmission of ESBL-producing Enterobacteriaceae to wardmates.

Methods

Study design

We did a pragmatic, cluster-randomised, crossover, non-inferiority study on medical and surgical wards of six university hospitals, nine non-university teaching hospitals, and one non-university general hospital in the Netherlands (appendix pp 5, 6). Cluster-randomisation with hospitals as clusters was used to overcome confounding by indication and to prevent contamination between isolation strategies.[13] Crossover of strategies at the hospital level was aimed at reducing between-hospital variability and, thus, increasing statistical efficiency.[14]

The study protocol was reviewed by the Medical Research and Ethics Committee of the Elisabeth-TweeSteden

Hospital (Tilburg, Netherlands; METC/jv/2010.234). The study was judged to be beyond the scope of the Medical Research Involving Human Subjects Act and a waiver of written informed consent was granted.

Patients

For this study, two groups of patients were included. The first group comprised index patients, who were individuals with ESBL-producing Enterobacteriaceae cultured from a routine clinical sample. The second group consisted of wardmates of index patients. To minimise enrolment bias, all consecutive index patients were screened for eligibility by infection-control practitioners on the day the laboratory reported the culture result. Index patients were ineligible if they were younger than 18 years, had a strict indication for barrier precautions in a single-bed room (appendix p 7), had no culture result reported within 7 days after the culture was obtained or before discharge, had a wardmate known to be colonised or infected with an ESBL-producing Enterobacteriaceae isolate of the same bacterial species with a similar antibiogram, or were enrolled previously. Eligible index patients were enrolled after obtaining verbal informed consent for data collection. Obtaining informed consent for the nursing of index patients according to the assigned isolation strategy was not needed because patients were not randomised individually and both isolation strategies were already used in clinical practice in all participating hospitals.[5]

For each hospital, the targeted maximum number of index patients available for analysis was 50 per study period. As a result, the duration of the study periods differed per hospital and was dependent on the enrolment rate (appendix p 3). In 2012, the maximum duration of study periods, which was initially set at 6 months, was extended to 18 months to compensate for low enrolment.

All patients who were present in the index patient's ward during screening for rectal carriage of ESBL-producing Enterobacteriaceae that followed enrolment of each index patient were eligible to be enrolled as wardmates. Wardmates younger than 18 years were not eligible. Eligible wardmates were enrolled after providing verbal informed consent for obtaining a perianal swab and data collection.

In case of an outbreak with ESBL-producing Enterobacteriaceae or another infectious agent that required a change in infection-control measures, enrolment of index patients was temporarily discontinued on the outbreak ward until the outbreak was resolved. Reasons for ineligibility, non-enrolment, and loss to follow-up of index patients and wardmates were documented.

Randomisation and masking

During two consecutive study periods, either contact precautions in a single-bed room or contact precautions in a multiple-bed room (two to six beds) were applied as the preferred isolation strategy for index patients. Hospitals were randomly assigned in a 1:1 ratio to one of two sequences of the two isolation strategies (appendix p 3). Both study periods were preceded by a 2-month washout period during which the assigned isolation strategy for the subsequent study period was implemented, to limit carryover effects between study periods. The random allocation sequence was computer-generated by an investigator with no clinical involvement in the study, using a permuted block design (block size of two and four) and stratification by type of hospital (university or non-university). Use of sequentially numbered sealed opaque envelopes enabled concealment of the allocation sequence at the hospital level until the last hospital was randomised.

Patients, treating doctors, and infection-control practitioners enrolling index patients were aware of the assigned isolation strategy but were unaware of the results of the screening of wardmates for ESBL-producing Enterobacteriaceae. As a result, screening cultures that grew ESBL-producing Enterobacteriaceae were not followed by institution of contact precautions. Laboratory technicians at the central laboratories that processed cultures and did molecular typing were unaware of the assigned isolation strategy.

Procedures

Throughout both study periods, all index patients were nursed under contact precautions—either pre-emptive or from the day the culture was reported to grow ESBL-producing Enterobacteriaceae—until discharge. Contact precautions comprised wearing gloves for all direct contacts with the patient or the patient's immediate environment or belongings. Contact precautions were applied in addition to standard precautions, which included hand hygiene and use of personal protective equipment (ie, gloves and gown) when anticipating contact with blood or body fluids. Dutch infection-control guidelines do not provide recommendations on the sharing of a toilet and bathroom with other patients when barrier precautions are indicated. Yet, sharing of a toilet and bathroom among patients was judged to be incompatible with the single-bed room strategy and was, thus, not allowed for patients in single-bed room isolation. Patients in multiple-bed room isolation could have either a private or shared toilet and bathroom.

For all index patients and wardmates, routine clinical culture data, demographic data, and hospital location data were retrieved from the medical record. Use of a private or shared toilet and bathroom, strategy adherence, and reasons for non-adherence were registered for all index patients at enrolment and every day during follow-up. Strategy adherence was defined as adherence to the assigned room type—ie, single bed or multiple bed. For index patients, unprotected ward stay was defined as stay on the ward from obtaining the routine clinical culture that grew ESBL-producing Enterobacteriaceae until the institution of contact precautions, whereas protected ward stay was defined as the period after institution of

contact precautions until the screening of wardmates for ESBL-producing Enterobacteriaceae or discharge, whichever came first. For wardmates, exposure to the index patient was defined as presence on the ward during the index patient's protected or unprotected ward stay.

Screening of wardmates for ESBL-producing Entero-bacteriaceae was done on day 7 (range 5–9) after enrolment of each index patient. Perianal and, if applicable, gastrointestinal stoma swabs were pre-enriched in a selective tryptic soy broth (TSB-VC; Cepheid, Apeldoorn, Netherlands) and subsequently cultured on a selective ESBL screening agar plate (EbSA; Cepheid) at local microbiology laboratories (appendix p 2).[15] All bacterial isolates obtained from clinical and perianal cultures were sent to the central microbiology laboratory (Amphia Hospital, Breda, Netherlands) for species identification with Vitek MS (bioMérieux, Marcy l'Etoile, France) and for phenotypic confirmation of ESBL production using the combination disk diffusion method, with cefotaxime, ceftazidime, and cefepime as indicator cephalosporins (Rosco, Taastrup, Denmark). Whole-genome shotgun sequencing of all phenotypically confirmed ESBL-producing Entero-bacteriaceae isolates was done on either a MiSeq or a HiSeq 2500 sequencer (Illumina, San Diego, CA, USA) at the central molecular microbiology laboratory (University Medical Center Groningen, Groningen, Netherlands). We used CLC genomics workbench 7.0.4 (Qiagen, Hilden, Germany) for de-novo assembly, and Ridom SeqSphere+ software version 3.0 (Ridom, Münster, Germany) for whole-genome multilocus sequence typing (MLST) and core-genome MLST. Clonal relatedness of isolates was assessed using previously proposed genetic distance thresholds for whole-genome and core-genome MLST data.[16] ESBL-encoding genes were identified with the online bioinformatics tool ResFinder version 2.1 (Center for Genomic Epidemiology, Technical University Denmark, Lingby, Denmark).[17]
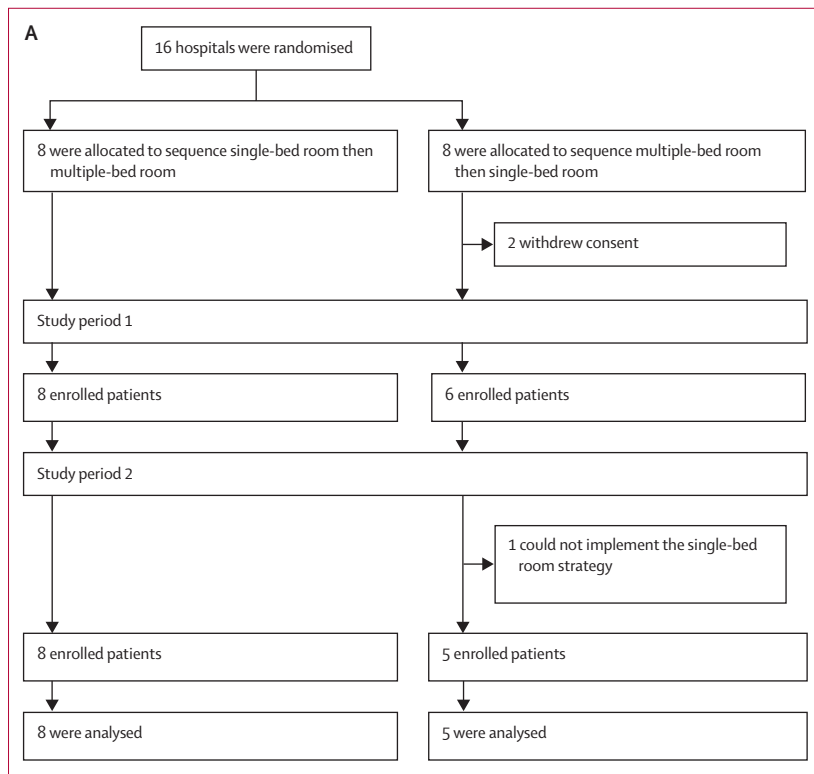
Outcomes

The primary outcome, analysed at the patient level, was transmission of ESBL-producing Enterobacteriaceae to wardmates, which was defined as rectal carriage in at least one wardmate of an ESBL-producing Enterobacteriaceae isolate that was clonally related to the index patient's isolate on day 7 (range 5–9) after enrolment of the index patient. Hospital-level prespecified secondary outcomes were the number of patients hospitalised with (all-source) clinical cultures and blood cultures with ESBL-producing Enterobacteriaceae. The prevalence of rectal carriage of ESBL-producing Enterobacteriaceae, the length of hospital stay, and 30-day mortality in wardmates were analysed as post-hoc patient-level secondary outcomes. All outcomes were considered safety outcomes.

Transmission of mobile genetic elements, which was a prespecified secondary outcome, could not be assessed because a method to reliably reconstruct plasmids from short-read sequence data was unavailable.[18] Our attempt to develop such a method is the reason we are reporting study results 4 years after study end. Other outcomes specified in the study protocol do not relate to the comparison of isolation strategies and were not deemed relevant to this Article; they will be reported elsewhere.

As post-hoc analyses, the primary analysis was stratified by microorganism and sensitivity analyses were done in which analysis of the primary outcome was restricted to index patients without unprotected ward stay, and thresholds for genetic distance based on core-genome MLST were used to define transmission of ESBL-producing Enterobacteriaceae. Furthermore, post-hoc analyses were done of the effect of unprotected ward stay of index patients on the risk of transmission of ESBL-producing Enterobacteriaceae and the prevalence of rectal carriage of ESBL-producing Enterobacteriaceae among wardmates. Moreover, the effect of sharing the index patient's room on the prevalence of rectal carriage of ESBL-producing Enterobacteriaceae among wardmates was assessed post hoc. Finally, the microorganism-specific risk of transmission (ie, the proportion of index patients' isolates transmitted to at least one wardmate) and the microorganism-specific burden of transmission (ie, the number of transmission events) were assessed, also as post-hoc endpoints.

For the **study protocol** see https://www.dropbox.com/s/bdthecyoqpkhmcx/2018.12.18%20SoM%20-%20onderzoeksprotocol%20%28LID%29.pdf?dl=0

(Figure 1 continues on next page)
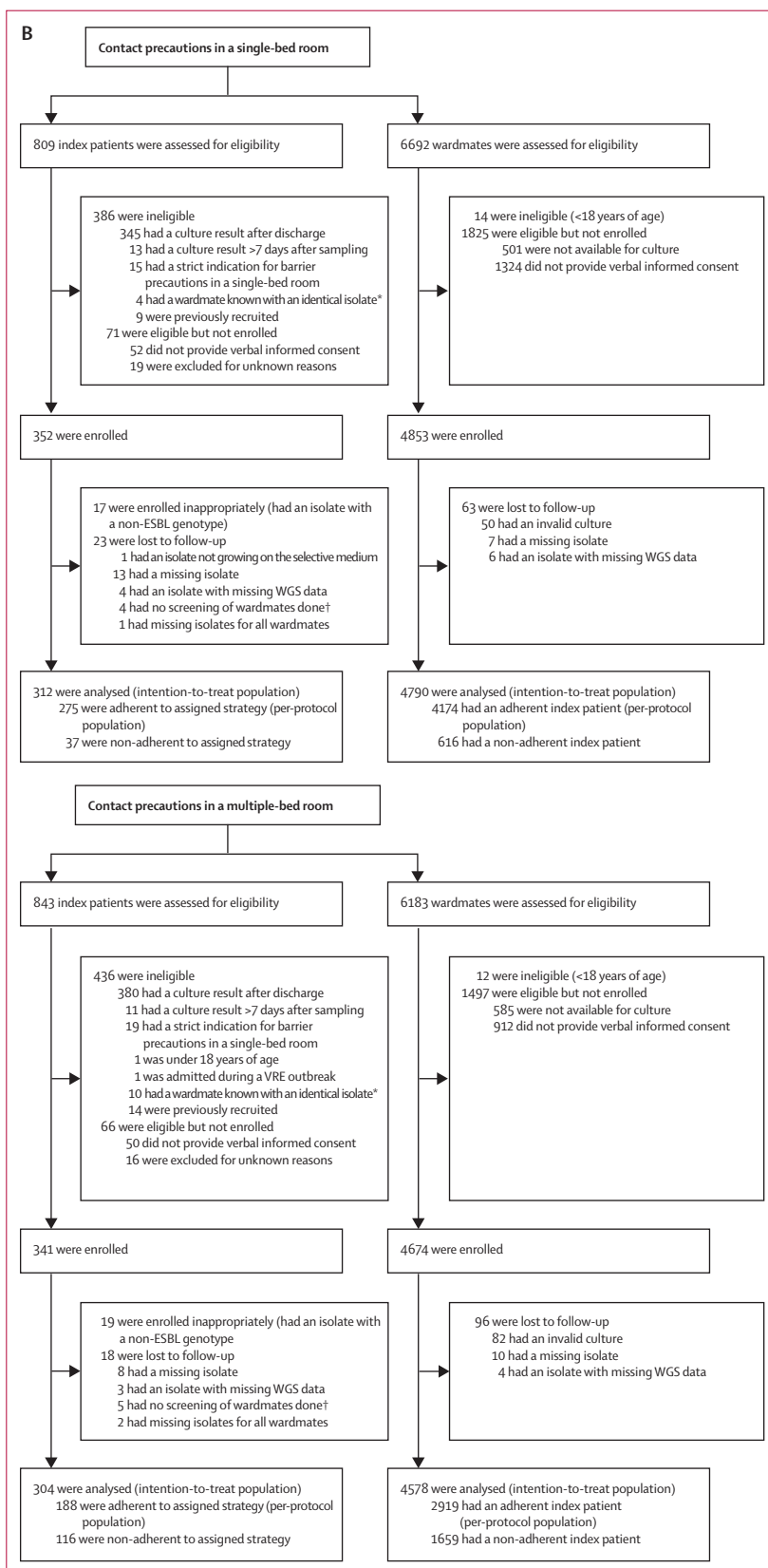
Statistical analysis

The required number of patients per study arm was calculated to be 241, based on an expected risk of transmission of ESBL-producing Enterobacteriaceae to at least one wardmate of 10% for the single-bed room strategy, a non-inferiority margin of 10% for the risk difference between strategies, a one-sided α of 5%, power of 90%, and expected frequencies of non-adherence of 15% and 5% for the single-bed and multiple-bed room strategies, respectively (appendix p 2). No adjustments for clustering were made. Because a crossover design was used and no large differences in care practices were expected between study periods, the intracluster correlation for cluster period was expected to be negligible. This assumption was checked by assessing the intracluster correlation coefficient for cluster period in the intention-to-treat population using a generalised linear mixed model with a binomial distribution and identity link, robust error estimation, and a random intercept for study period per hospital. The required sample size of 241 differs from the 296 calculated in the study protocol, which was based on an incorrect formula (appendix p 2).

Analyses were done in the (complete case) per-protocol population, which included all strategy-adherent patients for whom the primary outcome could be assessed (primary analysis), and the (complete case) intention-to-treat population, which included all enrolled patients for whom the primary outcome could be assessed. Generalised linear models with a binomial (for binary outcomes) or normal (for continuous outcomes) distribution and robust error estimation were used to estimate crude and adjusted risk differences (identity link) and relative risks (log link) for the primary and secondary patient-level outcomes. Adjusted analyses were adjusted for unprotected ward days of the index patient (primary outcome) and unprotected exposure to the index patient (post-hoc secondary outcome). For the primary outcome, two-sided 90% CIs were calculated, the upper limit of which was used to assess non-inferiority of the multiple-bed room isolation strategy. For all other outcomes, 95% CIs were calculated. Paired-sample t tests were done for the analysis of hospital-level secondary outcomes. Post-hoc analyses were done using the same generalised linear model approach as used for the analyses of primary and patient-level secondary outcomes. All analyses were done with SPSS Statistics, version 24.0 (IBM, Armonk, NY, USA).

This study is registered in the Nederlands Trialregister, NTR2799.

Figure 1: Trial profile
Cluster-level (A) and patient-level (B) profiles include patients' recruitment for 13 hospitals that completed both study periods. ESBL=extended-spectrum β-lactamase. VRE=vancomycin-resistant *Enterococcus* spp. WGS=whole-genome sequencing. *The identity of isolates was based on bacterial species and antibiogram. †No screening of wardmates for rectal carriage with ESBL-producing Enterobacteriaceae was done within the required time window of 5–9 days after enrolment of the index patient.

	Intention-to-treat population		Per-protocol population	
	Contact precautions in a single-bed room (n=312)	Contact precautions in a multiple-bed room (n=304)	Contact precautions in a single-bed room (n=275)	Contact precautions in a multiple-bed room (n=188)
Hospital and ward				
Hospital type				
Non-university	143 (46%)	127 (42%)	138 (50%)	87 (46%)
University	168 (54%)	177 (58%)	137 (50%)	101 (54%)
Ward type				
Medical	167 (54%)	154 (51%)	139 (51%)	104 (55%)
Surgical	145 (46%)	150 (49%)	136 (49%)	84 (45%)
Routine clinical culture with ESBL-producing Enterobacteriaceae				
Indication				
Screening	156 (50%)	171 (56%)	145 (53%)	104 (55%)
(Suspected) infection	156 (50%)	133 (44%)	130 (47%)	84 (45%)
Microorganism*				
Citrobacter spp	2 (1%)	2 (1%)	1 (<1%)	1 (<1%)
Enterobacter cloacae complex	24 (7%)	17 (5%)	21 (7%)	9 (4%)
Escherichia coli	250 (76%)	255 (78%)	225 (78%)	158 (79%)
Klebsiella aerogenes	0 (0%)	1 (<1%)	0 (0%)	1 (<1%)
Klebsiella oxytoca	2 (1%)	3 (1%)	2 (1%)	2 (1%)
Klebsiella pneumoniae	46 (14%)	45 (14%)	38 (13%)	27 (14%)
Morganella morganii	1 (<1%)	2 (1%)	1 (<1%)	2 (1%)
Proteus mirabilis	2 (1%)	0 (0%)	2 (1%)	0 (0%)
Raoultella spp	0 (0%)	1 (<1%)	0 (0%)	0 (0%)
ESBL gene type†				
CTX-M	299 (90%)	309 (93%)	267 (90%)	191 (93%)
GES	0 (0%)	2 (1%)	0 (0%)	2 (1%)
SHV	23 (7%)	17 (5%)	20 (7%)	8 (4%)
TEM	12 (4%)	5 (2%)	9 (3%)	5 (2%)
At enrolment				
Age (years)	67 (56–74)	67 (56–76)	67 (56–75)	68 (56–77)
Sex				
Male	174 (56%)	180 (59%)	152 (55%)	112 (60%)
Female	138 (44%)	124 (41%)	123 (45%)	76 (40%)
Antibiotic use	221 (71%)	206 (68%)	195 (71%)	136 (72%)
Wounds	142 (46%)	152 (50%)	130 (47%)	80 (43%)
Intravascular catheter	232 (74%)	215 (71%)	201 (73%)	133 (71%)
Indwelling urinary catheter	129 (41%)	150 (49%)	119 (43%)	79 (42%)
Urinary incontinence	19 (6%)	9 (3%)	17 (6%)	3 (2%)
Faecal incontinence	29 (9%)	31 (10%)	26 (9%)	18 (10%)
Bedridden	61 (20%)	80 (26%)	58 (21%)	38 (20%)
Ward stay‡				
Unprotected ward stay	203 (65%)	170 (56%)	179 (65%)	110 (59%)
Protected ward days	6 (4–7)	6 (4–7)	6 (4–7)	6 (4–7)
Protected ward days (sum)	727	581	632	381
Unprotected ward days	2 (0–4)	1 (0–4)	2 (0–4)	2 (0–4)
Contact precautions with shared toilet and bathroom§	34 (11%)	176 (58%)	0 (0%)	176 (94%)

(Table 1 continues on next page)

Role of the funding source
The funder 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 data in the study and had final responsibility for the decision to submit for publication.

Results
After randomisation and before patients' enrolment, two hospitals withdrew in response to a hospital-wide outbreak of OXA-48 carbapenemase-producing Entero-bacteriaceae in a non-participating Dutch hospital in May, 2011 (appendix p 6).[19] A third hospital withdrew at the time of crossover to the second (single-bed room) study period because of an unanticipated renovation of all single-bed rooms that did not allow for a private toilet and bathroom. In 2012, when enrolment seemed to be lower than anticipated, it was decided to additionally recruit two university hospitals and two non-university hospitals.

13 hospitals completed both study periods and assessed 1652 index patients for eligibility from April 24, 2011, to Feb 27, 2014 (figure 1). Of these index patients, 830 (50%) were eligible for enrolment. The main reason for ineligibility was the time to report cultures that grew ESBL-producing Enterobacteriaceae; 725 (44%) patients were already discharged from the hospital at the time the culture result was reported. Of 830 index patients eligible for enrolment, 693 (83%) were enrolled, 102 (12%) did not provide informed consent, and 35 (4%) were not enrolled for unknown reasons. Enrolment was inappropriate for 36 (5%) of 693 index patients, for whom the ESBL genotype of the cultured isolate could not be confirmed. Of 657 index patients enrolled appropriately, 616 (94%) were available for analysis. The most frequent reason for loss to follow-up was unavailability of the index patient's isolate (n=21 [3%]).

For the 616 index patients analysed, 12875 wardmates were assessed for eligibility, of whom 12849 (>99%) were eligible for enrolment (figure 1). Of the eligible wardmates, 9527 (74%) were enrolled; perianal swabs could not be obtained from 1086 (8%), and 2236 (17%) did not provide informed consent. Of 9527 wardmates enrolled, 9368 (98%) were available for analysis. Invalidity (negative growth control) of the perianal culture (n=132 [1%]) was the main reason for loss to follow-up. For index patients and wardmates, reasons for ineligibility, non-enrolment, and loss to follow-up were similar across strategies and study periods (appendix p 4).

Characteristics of analysed index patients—including the ESBL-producing microorganism, the ESBL gene type, and several aspects relating to the institution of contact precautions and the screening of wardmates for ESBL-producing Enterobacteriaceae—were similar across isolation strategies (table 1), except for the percentage of patients with at least 1 day of unprotected ward stay and the number of unprotected ward days. Characteristics of wardmates were comparable across isolation strategies (table 2), apart from a slightly higher percentage of wardmates in the single-bed room strategy period than in the multiple-bed room strategy period

with unprotected exposure to the index patient with an ESBL-producing Enterobacteriaceae.

Adherence to the assigned room type was 88% (275 of 312) and 62% (188 of 304) for index patients in the single-bed and multiple-bed room strategy periods, respectively (figure 1). The most frequent reasons for non-adherence to the single-bed room strategy was unavailability of a single-bed room (35 of 312 [11%]; appendix p 9). During the multiple-bed room strategy period, having a medical indication to be nursed in a single-bed room (62 of 304 [20%]) was the main reason for non-adherence to the assigned room type.

Transmission of ESBL-producing Enterobacteriaceae to wardmates could not be assessed for 41 (6%) of 693 enrolled index patients; these patients were excluded from all analyses (figure 1). For the (complete case) per-protocol population, transmission of ESBL-producing Enterobacteriaceae to at least one wardmate was identified for 11 (4%) of 275 index patients in the single-bed room strategy period and 14 (7%) of 188 index patients in the multiple-bed room strategy period (crude risk difference 3·4%, 90% CI –0·3 to 7·1; adjusted risk difference 3·4%, –0·2 to 6·9; figure 2, table 3). Transmission of ESBL-producing Enterobacteriaceae was identified for 15 (5%) of 312 index patients in the (complete case) intention-to-treat population during the single-bed room strategy period compared with 18 (6%) of 304 index patients during the multiple-bed room strategy period (crude risk difference 1·1%, 90% CI –1·9 to 4·1; adjusted risk difference 1·6%, 90% CI –1·1 to 4·3).

In generalised linear mixed-model analyses, the intracluster correlation coefficient for cluster period in the intention-to-treat population was less than 0·0005 (95% CI $2·9 \times 10^{-5}$ to 0·006) for transmission of ESBL-producing Enterobacteriaceae to wardmates. Sensitivity analyses for the primary outcome that either were restricted to patients without unprotected ward stay (figure 2, table 3) or that used core-genome MLST-based thresholds for genetic distance to define transmission of ESBL-producing Enterobacteriaceae confirmed the findings of the primary analysis (appendix p 10). Analysis of the primary outcome stratified by microorganism resulted in slightly higher estimates for the effect of the isolation strategy for *Klebsiella pneumoniae* than for *E coli*, but CIs were wide and largely overlapping (appendix p 11).

Rectal carriage of ESBL-producing Enterobacteriaceae could not be assessed for 159 (2%) of 9527 wardmates; these patients were excluded from all analyses (figure 1). In wardmates in the (complete case) per-protocol population, the prevalence of rectal carriage of ESBL-producing Enterobacteriaceae was similar during the single-bed room and multiple-bed room strategy periods (table 3).

For both isolation strategies, the median length of hospital stay in wardmates was 11 days and 30-day mortality was 4% (table 3). Similar estimates were found for wardmates in the (complete case) intention-to-treat population.

	Intention-to-treat population		Per-protocol population	
	Contact precautions in a single-bed room (n=312)	Contact precautions in a multiple-bed room (n=304)	Contact precautions in a single-bed room (n=275)	Contact precautions in a multiple-bed room (n=188)
(Continued from previous page)				
Screening of wardmates for ESBL-producing Enterobacteriaceae				
Days after enrolment	7 (6–8)	7 (6–8)	7 (6–8)	7 (6–8)
Wardmates hospitalised	21 (16–26)	20 (16–25)	21 (16–26)	20 (16–25)
Wardmates enrolled	15 (11–20)	15 (11–19)	15 (12–19)	16 (11–20)
Response (%)¶	77% (62–88)	80% (67–90)	75% (60–88)	79% (67–90)

Data are n (%) or median (IQR). ESBL=extended-spectrum β-lactamase. *Numbers include multiple microorganisms for some index patients. †Numbers include multiple ESBL genes for some ESBL-producing Enterobacteriaceae isolates. An overview of all ESBL genes identified is provided in the appendix (p 8). ‡Ward stay concerned stay on the ward after obtaining the clinical culture with ESBL-producing Enterobacteriaceae. §Shared toilet and bathroom in the single-bed room period pertained to index patients in the non-adherent population. ¶Response was calculated as the number of wardmates enrolled divided by the number of wardmates hospitalised.

Table 1: Characteristics of index patients in the intention-to-treat and per-protocol population

	Intention-to-treat population		Per-protocol population	
	Contact precautions in a single-bed room (n=4790)	Contact precautions in a multiple-bed room (n=4578)	Contact precautions in a single-bed room (n=4174)	Contact precautions in a multiple-bed room (n=2919)
Hospital type				
Non-university	2131 (44%)	1953 (43%)	2029 (49%)	1374 (47%)
University	2659 (56%)	2625 (57%)	2145 (51%)	1545 (53%)
Sex				
Male	2571 (54%)	2527 (55%)	2261 (54%)	1571 (54%)
Female	2219 (46%)	2051 (45%)	1913 (46%)	1348 (46%)
Age (years)	65 (54–75)	66 (54–75)	65 (54–75)	65 (54–75)
Exposure to the index patient				
No exposure	676 (14%)	491 (11%)	575 (14%)	373 (13%)
Protected exposure only	3067 (64%)	3292 (72%)	2712 (65%)	1985 (68%)
Protected and unprotected exposure	1047 (22%)	795 (17%)	887 (21%)	561 (19%)
Days of exposure to the index patient				
No exposure	0 (0–2)	0 (0–2)	0 (0–2)	0 (0–2)
Protected exposure	3 (1–5)	3 (1–6)	3 (1–5)	3 (1–6)
Unprotected exposure (median [range])	0 (0–7)	0 (0–7)	0 (0–7)	0 (0–7)
Sharing a multiple-bed room with the index patient during contact precautions*	29 (1%)	184 (4%)	0 (0%)	184 (6%)
Sharing a toilet and bathroom with the index patient during contact precautions*	27 (1%)	177 (4%)	9 (<1%)	177 (6%)

Data are n (%) or median (IQR), unless otherwise stated. ESBL=extended-spectrum β-lactamase. *Sharing a multiple-bed room or toilet and bathroom with the index patient in the single-bed room period pertained to index patients in the non-adherent population.

Table 2: Characteristics of wardmates in the intention-to-treat and per-protocol population

For the single-bed room strategy period, the mean number of patients hospitalised with a clinical culture with ESBL-producing Enterobacteriaceae was 115 per 100 000 bed-days (SD 99·6) versus 122 per 100 000 bed-days (113·7) for the multiple-bed room strategy period

(mean paired difference 6·8 per 100 000 bed-days, 95% CI −6·0 to 19·5). The mean number of patients hospitalised with a blood culture with ESBL-producing Enterobacteriaceae was 11 per 100 000 bed-days (SD 18·5)

Figure 2: Non-inferiority plots for the primary outcome
The figures show two-sided 90% CIs for crude and adjusted differences in risk of transmission of ESBL-producing Enterobacteriaceae in the per-protocol and intention-to-treat populations, and the risk difference for index patients without unprotected ward stay. The prespecified non-inferiority margin (indicated by the dotted line) was 10%. Adjusted analyses were adjusted for unprotected ward days of the index patient. ESBL=extended-spectrum β-lactamase.

for the single-bed room strategy period and 15 per 100 000 bed-days (26·3) for the multiple-bed room strategy period (mean paired difference 4·2 per 100 000 bed-days, 95% CI −1·4 to 9·7).

For 373 (61%) of 616 index patients, protected ward stay was preceded by at least 1 day of unprotected ward stay (table 1). Likewise, 1842 (20%) of 9368 wardmates were exposed to the index patient who was positive for ESBL-producing Enterobacteriaceae before contact precautions were instituted (table 2). Transmission of ESBL-producing Enterobacteriaceae to at least one wardmate was identified for 25 (7%) of 373 index patients with unprotected ward stay, compared with eight (3%) of 243 index patients for whom contact precautions were instituted directly at admission (risk difference 3·4%, 95% CI 0·0 to 6·8). The prevalence of rectal carriage of ESBL-producing Enterobacteriaceae was 6% (70 of 1167) in wardmates who were not exposed to the index patient compared with 8% (503 of 6359) in wardmates who were exposed to the index patient only after contact precautions had been initiated (risk difference 1·9%, 95% CI 0·4 to 3·4) and 11% (204 of 1842) in wardmates who were exposed to the index patient before and after contact precautions had been instigated (5·1%, 3·1 to 7·1).

Among wardmates who did not have unprotected exposure to the index patient, rectal carriage of an ESBL-producing Enterobacteriaceae isolate that was clonally related to the index patient's isolate was observed
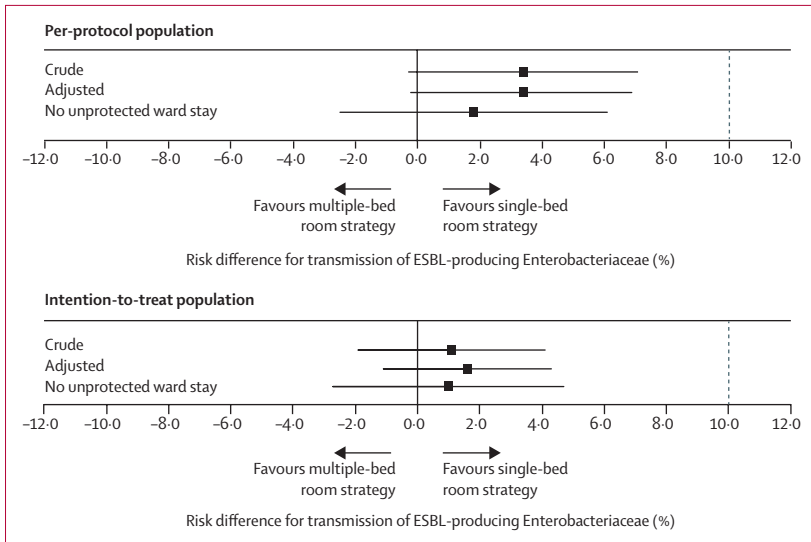
	Contact precautions in a single-bed room	Contact precautions in a multiple-bed room	Risk difference (90% CI)	Risk difference (95% CI)	Relative risk (95% CI)
Transmission of ESBL-producing Enterobacteriaceae to wardmates					
All index patients: per-protocol population, crude	11/275 (4%)	14/188 (7%)	3·4% (−0·3 to 7·1)	3·4% (−1·0 to 7·9)	1·86 (0·86 to 4·01)
All index patients: per-protocol population, adjusted*	..	..	3·4% (−0·2 to 6·9)	3·4% (−0·8 to 7·6)	1·95 (0·91 to 4·18)
All index patients: intention-to-treat population, crude	15/312 (5%)	18/304 (6%)	1·1% (−1·9 to 4·1)	1·1% (−2·4 to 4·7)	1·23 (0·63 to 2·40)
All index patients: intention-to-treat population, adjusted*	..	..	1·6% (−1·1 to 4·3)	1·6% (−1·7 to 4·8)	1·33 (0·69 to 2·56)
Index patients without unprotected ward stay: per-protocol population	2/96 (2%)	3/78 (4%)	1·8% (−2·5 to 6·1)	1·8% (−3·4 to 6·9)	1·85 (0·32 to 10·77)
Index patients without unprotected ward stay: intention-to-treat population	3/109 (3%)	5/134 (4%)	1·0% (−2·7 to 4·7)	1·0% (−3·5 to 5·4)	1·36 (0·33 to 5·55)
Rectal carriage of ESBL-producing Enterobacteriaceae in wardmates					
All wardmates: per-protocol population, crude	322/4174 (8%)	256/2919 (9%)	..	1·1% (−0·3 to 2·4)	1·14 (0·97 to 1·33)
All wardmates: per-protocol population, adjusted†	..	..	..	1·0% (−0·3 to 2·3)	1·16 (0·99 to 1·35)
All wardmates: intention-to-treat population, crude	377/4790 (8%)	400/4578 (9%)	..	0·9% (−0·3 to 2·0)	1·11 (0·97 to 1·27)
All wardmates: intention-to-treat population, adjusted†	..	..	..	0·9% (−0·2 to 2·0)	1·14 (1·00 to 1·30)
Wardmates of index patients with unprotected ward stay: per-protocol population	117/1448 (8%)	94/1206 (8%)	..	−0·1% (−2·1 to 2·0)	0·99 (0·76 to 1·29)
Wardmates of index patients with unprotected ward stay: intention-to-treat population	130/1665 (8%)	173/2046 (9%)	..	0·6% (−1·1 to 2·4)	1·08 (0·87 to 1·35)
Length of hospital stay in wardmates (days)					
Per-protocol population	11 (6–21)	11 (6–22)	..	0·3 (−0·8 to 1·5)	1·02 (0·96 to 1·08)
Intention-to-treat population	11 (6–22)	11 (5–22)	..	0·1 (−0·9 to 1·1)	1·01 (0·96 to 1·06)
30-day mortality in wardmates					
Per-protocol population‡	155/4133 (4%)	123/2890 (4%)	..	0·5% (−0·4 to 1·4)	1·14 (0·90 to 1·43)
Intention-to-treat population§	174/4742 (4%)	180/4525 (4%)	..	0·3% (−0·5 to 1·1)	1·08 (0·88 to 1·33)

Data are n/N (%) or median (IQR), unless otherwise stated. ESBL=extended-spectrum β-lactamase. *Analyses were adjusted for unprotected ward days of the index patient. †Analyses were adjusted for unprotected exposure days to the index patient. ‡30-day mortality data were missing for 70 wardmates. §30-day mortality data were missing for 101 wardmates.

Table 3: Effect of isolation strategy on patient-level outcomes

in two (1%) of 160 roommates, both with shared toilet and bathroom, compared with 17 (<1%) of 6199 wardmates who did not share the index patient's room or toilet and bathroom (risk difference 1·0%, 95% CI −0·1 to 3·5).

The number of ESBL-producing Enterobacteriaceae transmission events was 22 in the single-bed room strategy period and 23 in the multiple-bed room strategy period, ranging from none to three per index patient for both strategies (appendix p 12). *K pneumoniae* had a nearly threefold higher risk of transmission than did *E coli* (relative risk 2·92, 95% CI 1·40–6·08). The greatest burden of transmission, however, was seen for *E coli*, which accounted for 28 (62%, 95% CI 48–75) of 45 transmission events. $bla_{CTX-M-15}$ was the most frequently involved ESBL gene (n=29 [64%]; appendix p 13).

Only 37 (5%) of 777 wardmates with a screening culture that grew ESBL-producing Enterobacteriaceae had a routine clinical culture with ESBL-producing Enterobacteriaceae at any time during admission, indicating an undetected ratio of 0·95 (95% CI 0·93–0·97)—ie, 95% of rectal carriers of ESBL-producing Enterobacteriaceae were not detected by routine clinical cultures.

Discussion

In this pragmatic study in patients admitted to non-ICU, non-haematology wards with ESBL-producing Enterobacteriaceae cultured from a routine clinical sample, an isolation strategy of contact precautions in a multiple-bed room was non-inferior to a strategy of contact precautions in a single-bed room for preventing transmission of ESBL-producing Enterobacteriaceae to wardmates. No differences were noted between isolation strategies in the prevalence of rectal carriage of ESBL-producing Enterobacteriaceae, length of hospital stay, and 30-day mortality in wardmates, nor in the number of patients hospitalised with clinical cultures or blood cultures with ESBL-producing Enterobacteriaceae.

Post-hoc analyses showed that unprotected ward stay of patients with ESBL-producing Enterobacteriaceae—ie, before contact precautions were instituted—increased the risk for transmission of ESBL-producing Enterobacteriaceae to wardmates; likewise, unprotected exposure to a patient with ESBL-producing Enterobacteriaceae increased the prevalence of rectal carriage of ESBL-producing Enterobacteriaceae in wardmates. Most transmission events were attributable to *E coli*.

To the best of our knowledge, our randomised study is the first to assess isolation strategies for patients with ESBL-producing Enterobacteriaceae. Observational studies of the added value of single-bed rooms when applying contact precautions were targeted at Gram-positive microorganisms (eg, MRSA and VRE) and results were inconsistent.[10–12] Use of contact precautions for control of antimicrobial resistance is under debate,[20] but the observed role of unprotected ward stay in the transmission of ESBL-producing Enterobacteriaceae in our study suggests that contact precautions are effective in the control of ESBL-producing Enterobacteriaceae.

Current European recommendations to limit ESBL-producing Enterobacteriaceae control measures in endemic settings to non-*E coli* are based on studies that have shown lower transmission rates for *E coli* than for *K pneumoniae*.[7,21,22] In our study, the observed risk of transmission was indeed lower for *E coli*. Most transmission events, however, were attributable to *E coli*, which shows the prevention paradox for control of ESBL-producing Enterobacteriaceae—ie, the highest burden of transmission of ESBL-producing Enterobacteriaceae is attributable to a microorganism with a relatively low risk of transmission.[23] This paradox implies that both the intrinsic transmission capacity and the prevalence of ESBL-producing bacterial species should be considered when designing infection-control policies.

In previous studies, roommates of patients with ESBL-producing Enterobacteriaceae were reported to be at risk for acquiring ESBL-producing Enterobacteriaceae.[22,24] Yet, these studies included only roommates with unprotected exposure to patients with ESBL-producing Enterobacteriaceae and did not compare their risk of acquisition with risk in wardmates who did not share the index patient's room. For wardmates in our study, sharing the index patient's room during contact precautions did not increase the risk of acquiring the index patient's ESBL-producing Enterobacteriaceae isolate, although the number of events in roommates was low, which precludes firm conclusions.

The strengths of this study include the pragmatic design, reflecting current Dutch clinical practice and control policy for ESBL-producing Enterobacteriaceae; the participation of 16 university and non-university hospitals from different regions of the Netherlands; and the crossover of isolation strategies at the hospital level to avoid cluster imbalance.

The primary outcome was transmission of the index patient's ESBL-producing Enterobacteriaceae isolate to at least one wardmate. The number of transmission events was not considered as an outcome to prevent more transmissible isolates or outbreaks from driving the results. Clonal relatedness of ESBL-producing Enterobacteriaceae isolates was based on whole-genome MLST, a highly discriminatory molecular typing technique.[16] A post-hoc sensitivity analysis using more commonly used—but slightly less discriminatory—core-genome MLST-based thresholds for genetic distance yielded identical results. Although plasmid-mediated horizontal transfer of ESBL-genes was prespecified as a secondary outcome, currently available analytical methods did not allow reliable reconstruction of plasmids based on the short-read sequence data obtained in this study.[18] The discriminatory power of plasmid replicon typing was considered too low to reliably assess relatedness of plasmids. The number of isolation days for ESBL-producing Enterobacteriaceae at the hospital level and the transmission index—ie, the number of patients with acquired ESBL-producing Enterobacteriaceae

in clinical cultures (secondary cases) divided by the number of primary patients with ESBL-producing Enterobacteriaceae—were prespecified as secondary outcomes, but could not be assessed because of constraints on use of data from patients who were not enrolled and, thus, did not provide informed consent.

Our study has several limitations. It was designed to compare use of single-bed and multiple-bed rooms when nursing patients with ESBL-producing Enterobacteriaceae under contact precautions. Although unprotected ward stay—preceding institution of contact precautions—was found to increase the risk for transmission of ESBL-producing Enterobacteriaceae, the data did not allow a head-to-head comparison of contact precautions with standard precautions only.

The risk of post-randomisation bias is inherent to cluster-randomised studies.[25] The pattern of non-enrolment and the characteristics of index patients and wardmates were similar among strategies, except for a slight difference in unprotected ward stay and unprotected exposure to the index patient, respectively. Adjustment for unprotected ward days (index patients) and unprotected exposure days (wardmates) changed the findings only minimally. Missingness of data on the ESBL status of index patients and wardmates was infrequent and assumed to be completely at random. Complete case analyses were, therefore, considered to provide unbiased estimates with limited effect on the precision of the results.[26]

To reflect daily clinical practice, non-adherence to room type was allowed for medical and logistical reasons. Non-adherence to the multiple-bed room strategy was substantially more frequent than expected and might have diluted the effect of isolation strategy in the intention-to-treat analysis. Furthermore, the most frequently reported reason for non-adherence was the presence of a medical indication for nursing the patient in a single-bed room, which is probably associated with risk for transmission and, thus, could have biased the results towards non-inferiority in the per-protocol analysis as well. On the other hand, the effect of unprotected ward stay in adherent patients is expected to be higher for the multiple-bed room strategy than for the single-bed room strategy, which might have strengthened the effect of isolation strategy in the per-protocol analysis and, thus, could have biased the results towards inferiority, as was suggested by the results of the sensitivity analyses in index patients without unprotected ward stay.

Other aspects of the study with the potential to affect the assay sensitivity—ie, the ability to show a difference in transmission between isolation strategies—include poor compliance with standard and contact precautions, suboptimum microbiological and typing methods, and biased assessment of outcomes.[27] Although compliance with standard and contact precautions was not assessed, the low overall rate of transmission of ESBL-producing Enterobacteriaceae does not suggest major breaches in compliance. Also, the observed prevalence of rectal carriage of ESBL-producing Enterobacteriaceae during hospitalisation, being similar to that reported in other Dutch studies,[28,29] confirms the previously reported high sensitivity of the microbiological methods used to detect rectal carriage of ESBL-producing Enterobacteriaceae.[15] Thresholds for genetic distance that were used in this study to define clonally related isolates were previously proposed and set to have 100% sensitivity to identify epidemiologically related isolates, with a negligible probability of misclassifying unrelated isolates.[16] Lastly, the risk of biased assessment of outcomes was minimised by masking laboratory technicians to the assigned isolation strategy.

Non-inferiority of the multiple-bed room strategy was apparent in all analyses. Yet, the conclusions of a non-inferiority study are highly dependent on the choice of the non-inferiority margin. For this study, the non-inferiority margin was based on the best available data at the start of the study. A non-inferiority margin of 10% for the risk difference was chosen based on an expected 10% risk of transmission for the single-bed room strategy and a maximum risk of 20% that would be clinically acceptable.[30] The 5% risk of transmission observed for the single-bed room strategy was substantially lower than expected and could be attributable to the 79% observed response for screening of wardmates for ESBL-producing Enterobacteriaceae and the timing of this screening at 5–9 days after institution of contact precautions for the index patient. The choice of this time window for screening was a trade-off between the probability that exposed wardmates were still present during screening and the probability to detect transmission of the index patient's ESBL-producing Enterobacteriaceae isolate, which requires acquisition and gastrointestinal passage of the isolate. The lower-than-expected risk of transmission noted in our study suggests that the non-inferiority margin of 10% might have been too liberal. Yet, the observed 90% CI for the adjusted risk differences for the primary outcome would have satisfied non-inferiority for a margin of at least 8% in the per-protocol analysis and at least 5% in the intention-to-treat analysis.

Finally, our study was done on non-ICU, non-haematology wards in Dutch hospitals that adhered to national infection-control guidelines. This study setting might affect generalisability to other situations.

Non-inferiority of the multiple-bed room strategy could change the current single-bed room preference for isolation of patients with ESBL-producing Enterobacteriaceae and, thus, broaden infection-control options for ESBL-producing Enterobacteriaceae in daily clinical practice. Moreover, the observed role of unprotected ward stay in the nosocomial spread of ESBL-producing Enterobacteriaceae, together with the high frequency of undetected rectal carriage of ESBL-producing Enterobacteriaceae in patients during hospitalisation, suggest that current control measures for ESBL-producing Enterobacteriaceae can be optimised. Lastly, the large

contribution of *E coli* to the burden of transmission of ESBL supports current Dutch recommendations to target infection-control measures at all ESBL-producing Enterobacteriaceae, including *E coli*.

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For **raw data** see https://www.ebi.ac.uk/ena/data/search?query=prjeb15226