BMJ Open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2015-009029
Article Type:	Research
Date Submitted by the Author:	12-Jun-2015
Complete List of Authors:	Birgand, Gabriel Leroy, Christophe; AP-HP, Hôpital Louis Mourier, Emergency department Nerome, Simone; AP-HP, Hôpital Beaujon, Infection Control Unit Nguyen, Liem Binh Luong; AP-HP, Hôpital Beaujon, Internal medicine department Lolom, Isabelle; AP-HP, Hôpital Bichat-Claude Bernard, Infection Control Unit Armand-Lefevre, Laurence; AP-HP, Hôpital Bichat-Claude Bernard, Bacteriology Laboratory Ciotti, Celine; AP-HP, Hôpital Beaujon, Infection Control Unit Le corre, Bertrand; AP-HP, Hôpital Beaujon, Internal medicine department marcade, geraldine; AP-HP, Hôpital Louis Mourier,, Infection Control Unit fihman, vincent; AP-HP, Hôpital Louis Mourier,, Infection Control Unit Nicolas-Chanoine, Marie-Helene; AP-HP, Hôpital Beaujon,, Bacteriology Laboratory Pelat, Camille; INSERM, IAME, UMR 1137 perozziello, anne; AP-HP, Hôpital Bichat-Claude Bernard, Medical Information Systems Program (PMSI) Fantin, Bruno; AP-HP, Hôpital Beaujon, Internal medicine department yazdanpanah, yazdan; AP-HP, Hôpital Bichat-Claude Bernard, Infectious diseases department Ricard, jean-damien; AP-HP, Hôpital Louis Mourier, Intensive care unit Lucet, Jean-Christophe; AP-HP, Hôpital Bichat-Claude Bernard, Infection Control Unit
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Health economics, Infectious diseases, Health services research
Keywords:	Microbiology < BASIC SCIENCES, EPIDEMIOLOGY, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Human resource management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Infection control < INFECTIOUS DISEASES

Intended category: Research article

Costs associated with implementation of a strict national policy for controlling spread of highly resistant microorganisms

Gabriel Birgand [1,2,3]; Christophe Leroy [4]; Simone Nerome [5]; Liem Binh Luong Nguyen [10]; Isabelle Lolom [3]; Laurence Armand-Lefevre [1,2,6]; Céline Ciotti [5]; Bertrand Lecorre [10]; Géraldine Marcade [7]; Vincent Fihman [7]; Marie-Hélène Nicolas-Chanoine [8]; Camille Pelat [1,2,]; Anne Perozziello [9]; Bruno Fantin [10]; Yazdan Yazdanpanah [1,2, 11]; Jean-Damien Ricard [1,2,12*]; Jean-Christophe Lucet [1,2,3*]

* Equally supervised the study

[1] INSERM, IAME, UMR 1137, F-75018 Paris, France

[2] Univ Paris Diderot, IAME, UMR 1137, Sorbonne Paris Cité, F-75018 Paris, France

[3] AP-HP, Hôpital Bichat-Claude Bernard, Infection Control Unit, F-75018 Paris, France

[4] AP-HP, Hôpital Louis Mourier, Emergency department, F-92700 Colombes, France

[5] AP-HP, Hôpital Beaujon, Infection Control Unit, F-92110 Clichy, France

[6] AP-HP, Hôpital Bichat-Claude Bernard, Bacteriology Laboratory, F-75018 Paris, France

[7] AP-HP, Hôpital Louis Mourier, Infection Control Unit, F-92700 Colombes, France

[8] AP-HP, Hôpital Beaujon, Bacteriology Laboratory, F-92110 Clichy, France

[9] AP-HP, Hôpital Bichat-Claude Bernard, Medical Information Systems Program (PMSI), F-75018 Paris, France;

[10] AP-HP, Hôpital Beaujon, Internal medicine department, F-92110 Clichy, France

[11] AP-HP, Hôpital Bichat-Claude Bernard, Infectious diseases department, F-75018 Paris, France

[12] AP-HP, Hôpital Louis Mourier, Intensive care unit, F-92700 Colombes, France

Keywords: Cost, highly resistant bacteria, infection control, search and isolate, glycopeptide-resistant enterococci, carbapenemase-producing enterobacteriacae, strict contact precautions

Running title: Costs due to highly resistant bacteria

Corresponding author: Gabriel Birgand, Unité d'Hygiène et de Lutte contre l'Infection nosocomiale, GH Bichat-Claude Bernard, 46 rue Henri Huchard, 75877 Paris Cedex 18, France.

Tel: +33 140 256 199; Fax: +33 140 258 811; E-mail: gbirgand@gmail.com

Word count: 3253

Abstract

Objective

To assess costs associated with implementation of a strict "search and isolate" strategy for controlling highly-drug-resistant organisms (HDRO).

Design

Review of data from 2-year prospective surveillance (01/2012 to 12/2013) of HDRO.

Setting

Three university hospitals located in northern Paris.

Methods

Episodes were defined as single cases or outbreaks of glycopeptide-resistant enterococci (GRE) or carbapenemase-producing enterobacteriacae (CPE) colonization. Costs were related to staff reinforcement, costs of screening cultures, contact precautions and interruption of new admissions. Univariate analysis, along with simple and multiple linear regression analyses were conducted to determine variables associated with cost of HDRO management.

Results

Overall, 41 consecutive episodes were included, 28 single cases and 13 outbreaks. The cost (mean ± SD) associated with management of a single case identified within and/or 48 h after admission was €4,443 ± 11,552 and €11,445 ± 15,743, respectively ($p<0.01$). In an outbreak, the total cost varied from €14,864 ± 17,734 for an episode with one secondary case (€7,432 ± 8,867 per case) to €136,525 ± 151,231 (€12,845 ± 5,129 per case) when more than one secondary case occurred. In episodes of single cases, contact precautions and microbiological analyses represented 51 and 30% of overall cost, respectively. In outbreaks, cost related to interruption of new admissions represented 77 to 94% of total costs, and had the greatest financial impact ($R^2 = 0.98$, $p<0.01$).

Conclusion

In HDRO episodes occurring at three university hospitals, interruption of new admissions constituted the most costly measure in an outbreak situation.

Article summary: Strengths and limitations of this study

- Multicenter study to estimate costs of a strict policy for controlling HDRO spread with data collected prospectively, enabling detailed cost analysis in a large panel of situations.
- Provides a basis for minimizing the financial burden of a "search and isolate" strategy. Early identification of patients suspected of being colonized and rapid implementation of contact precautions represented the least expensive scenario.
- The study raises the question of having, or creating, dedicated areas, thus enabling continuity of care together with cost-savings.
- The study did not include: loss of revenue due to systematic placement of colonized patients in a single room, costs linked to prolongation of the hospital stay of case patients and time spent by the infection control team in managing episodes.
- Cost estimations were based on local levels of hospital reimbursement.

INTRODUCTION

Hospitals are increasingly plagued by microorganisms highly-drug-resistant (HDRO) to antimicrobials [1]. These HDRO include carbapenamase-producing *Enterobacteriaceae* (CPE) and glycopeptide-resistant enterococci (GRE). In France, the prevalence of GRE and CP-*K. pneumoniae* isolated from blood cultures was 0.8 and 0.5% in 2012, respectively [2–4].

In France, guideline based on a "search and isolate" strategy have been issued for the control of emerging HDROs [5]. They are based on two assumptions: 1) most HDRO-positive patients are asymptomatic carriers with high risk of spreading before outbreak identification; and 2) standard or contact precautions do not reliably halt HDRO transmission in all circumstances.

Infection control measures are gradually implemented according to risk analysis. In case of immediate enforcement of strict contact precautions (identification of a colonized patient upon hospital admission, notably if repatriated or recently hospitalized abroad in the past 12 months), weekly cross-sectional screening of ward patients is recommended, with no additional control measures [5,6].

In an outbreak situation, i.e. with at least one secondary case, measures are upgraded and consist of a strict "search and isolate" strategy, as follows: (a) HDRO-positive patients are cohorted and cared for by dedicated staff; (b) secondary cases are detected via repeated rectal sampling of contact patients, i.e. patients cared for by the same nursing staff as the HDRO-positive patient; (c) contact patients are cohorted and cared for by dedicated staff until three weekly screening tests are negative; (d) HDRO-positive and contact patients are discharged home whenever possible; and (e) the ward with the HDRO-positive patients

neither transfers patients to other wards or healthcare facilities (HCF) nor admits new patients until after three negative weekly screening tests of contact patients.

These strict recommendations are difficult to implement and require additional human and material resources. Moreover, interruption of admission to and transfer from the involved ward lead to a decrease in hospital medical service utilization and therefore a loss of hospital income [7]. Costs associated with each different epidemiological situation and the determinants of these costs are not known. The purpose of this study was to assess costs associated with implementation of national recommendations for controlling HDRO spread in three university hospitals and to identify determinants of these costs.

PATIENTS AND METHODS

Setting

This study was performed in a French university healthcare group located in northern Paris, the 950-bed Bichat-Claude-Bernard Hospital, the 470-bed Beaujon Hospital and the 490-bed Louis-Mourier Hospital, providing primary, tertiary and long term care with a large panel of surgical and medical specialities. This group of hospital takes part of a public health institution (AP-HP) representing 10% of all public hospital beds in France. These three hospitals are situated in the highly exposed area with a high proportion of patients originating from a foreign country [8,9]. None of these hospitals has a dedicated ward for housing/regrouping case patients. Case patients were therefore admitted to the ward matching their pathology. In outbreak situations, however, case patients from different wards could be housed in the ward with the highest case number.

Design and data collection on resources used

We reviewed data from 2-year prospective surveillance of HDRO occurrence (01/2012-12/2013). We defined an episode as consisting of new identification of HDRO in a clinical or screening sample, unrelated to previous situations. An outbreak was defined as at least two CPE cases (i.e. one index case and at least one secondary case among the contact patients) occurring in a given hospital, with a clear epidemiological link (stay during the same period of time in the same unit) and involving indistinguishable CPE strain based on species, antibiotic susceptibility and resistance gene. We distinguished four types of episodes, from simple situations with low epidemic risk to complex situations with confirmed outbreaks: (i) a single case suspected within 48 h after hospital admission; (ii) a single case suspected more than 48 h after hospital admission; (iii) an outbreak with only one secondary case; and (iv) an outbreak with more than one secondary case.

For each episode, data were prospectively collected, including characteristics of the epidemic (type of HDRO and resistance mechanism, type of ward, dates of admission and discharge of case patients, date of positive results and implementation of contact precautions, number of contact patients); human resources (nursing staff reinforcement allocated to a ward during an episode, either for cohorting colonized patients, i.e. placing the patient in a dedicated location on the ward with dedicated HCW, or for decreasing the workload of the unit by globally increasing the nurse-to-patient ratio); material for the three weekly screening protocol and patient care; and duration of interruption of new admissions.

Cost analysis

Costs were considered from a hospital perspective. For human resources, staff reinforcement was calculated based on the number of supplementary hours put in by nurses and nursing assistants on the basis of their hourly salary. (Table 1)

Table 1: Methods of cost analyses

Type	Variables collected	Value
Loss of income	Number of hospital bed days lost	
	Mean cost billed per hospital day per specialty	
	Medical units	335 to 601 €
	Surgical units	306 to 940 €
	ICU	609 to 2078 €
Staff reinforcement	Cost of 1 h of a nursing assistant	24.6 €
	Cost of 1 h of a nurse	30.5 €
Cost of micro-analysis [7]	Negative culture for GRE	13.9 €
	Cepheid Xpert *van*A/*van*B	37.3 €
	Positive culture for GRE strain	117.8 €
	Negative culture for CPE	7.7 €
	Negative culture for CPE, + for ESBLPE	21 €
	Positive culture for CPE	115 €
Cost of contact precautions	Cumulative number of hospital days, HDRO patients	

[12]	Cost of gloves	0.05 € /pair
	Cost of gowns	0.3 € each
	Cost of nursing contact (1 min) *Papia et al.*	0.26 €
	Number of patient contacts per day	30
	Cost per HDRO patient per day	18.5 €

For the laboratory sector, methods for detecting CPE and GRE in screening samples have been described elsewhere [10][11]. Unit costs for resources used to screen were computed based on use of the following resources: selective chromogenic plates or PCR-based method, identification tests and susceptibility tests, depending on the above-described situations. Personnel costs for laboratory tests were calculated on the basis of the hourly salary of a senior staff member and the estimated time required for each step. Unit cost of PCR screening included acquisition of the GeneXpertTM machine and XpertTM *van*A/*van*B test cartridges and performing cultures for GRE on a *van*A/*van*B-positive sample or samples without PCR results (invalid tests) [7].Cost of contact precautions included that of gloves and gowns used for case patients, assuming an average of 30 patient contacts per day of isolation and nursing costs for additional time to donning and discarding gloves and gown (1 min) [12].

Finally, to estimate the decrease in hospital service use, we first computed the difference between admission capacity, assuming 100% bed occupancy, and the number of patients admitted when a HDRO-positive patient was identified in the ward. Next, we estimated costs attributable to decreased occupancy, by multiplying the number of missed patient-days by the mean cost of a hospital day, depending on the type of pathology and the ward. According to the French reimbursement system, the mean cost per hospital day was the total cost related to hospital stay in the previous year in the affected ward divided by the

number of patient-days [13]. Total cost related to missed hospital days in a ward was estimated using the French diagnosis-related group system according to which patients are classified into statistically and clinically homogeneous groups on the basis of their clinical and demographic data.

Statistical analysis

Categorical independent variables were described using proportions and continuous variables via medians and 25th-75th percentiles. For costs, means with standard deviation were used to take into account outliers and data dispersion. Univariate comparisons used a Wilcoxon rank or Chi-2 test as required. Statistics on categorical variables were based on two-way analysis of variance (ANOVA). After univariate analysis, simple and multiple linear regression analyses were carried out, with overall cost as the dependent variable, to determine those costs most strongly associated with the overall financial burden. The overall percentage of explained variance of the model was described by the adjusted R^2 of observed costs. Predictive values of models built were tested using the method of "Leave One Out Cross-Validation" (jack-knife). This method assesses the predicted costs in one episode based on the model built with all other episodes. We analyzed observed versus predicted costs for all episodes, and specifically for outbreaks, by giving the mean and median predictive error per episode and the mean relative predictive error. Statistical analyses were done with R software, version 2.15.2.

Ethics Committee Approval

Because of the observational and blinded nature of the study, the institutional review board of the Bichat-Claude Bernard Hospital waived the requirement for informed consent. According to this statement, written consents of patients were not collected. Patient information was de-identified by attributing a number. The study has been approved by the ethical committee of the Bichat-Claude Bernard Hospital group.

RESUTS

Characteristics of HDRO episodes

Overall, we observed 41 HDRO episodes (34 at Bichat-Claude Bernard, 6 at Beaujon and 1 at Louis Mourier Hospital), with a total of 113 colonized patients (Table 2).

Table 2: Characteristics of episodes with highly resistant organisms according to type of episode.

Description of episode characteristics	Total N=41	A single case (suspicion ≤48 h after admission) N=14	A single case (suspicion >48 h after admission) N=14	Episode with 1 secondary case N=6	Episode with > 1 secondary case N=7
Number of episodes per hospital, n (%)					
Bichat-Claude Bernard	34 (83)	10 (71)	13 (93)	6 (100)	5 (70)
Beaujon	6 (15)	4 (29)	1 (7)	0	1 (15)
Louis Mourier	1 (3)	0	0	0	1 (15)
Year, n (%)					
2012	24 (58)	6 (43)	8 (57)	6 (100)	4 (57)
2013	17 (42)	8 (57)	6 (43)	0	3 (43)

Type of HDRO, n (%)					
GRE	19 (46)	10 (71)	8 (57)	1 (17)	0
CPE	20 (49)	3 (21)	6 (43)	5 (83)	6 (86)
GRE + CPE	2 (5)	1 (8)	0	0	1 (14)
Type of ward at identification, n (%)					
ICU	7 (17)	4 (29)	2 (14)	1 (17)	0
Medical	23 (56)	8 (57)	6 (43)	3 (50)	6 (86)
Surgical	10 (24)	2 (14)	6 (43)	2 (33)	0
Rehabilitation	1 (3)	0	0	0	1 (14)
Time from admission to suspicion, days, median (IQR)	4 (1-26)	0 (0-1)	12.5 (5-33)	14 (4-26)	42 (3-75)
Time from admission to HDRO+ result, days, median (IQR)	6 (3-26)	0.5 (0-3)	12.5 (5-33)	14 (7-26)	42 (6-75)

Number of contact patients, median (IQR); min-max	32 (13-65)	5 (0-21); 0-65	34 (19-76); 0-260	48.5 (32-53); 19-262	66 (53-152); 48-237
Number of secondary cases, median (IQR); min-max	-	0	0	1	3 (2-22); 2-29
Suspension of admissions, days median (IQR); min-max	0 (0-3)	0 (0-0); 0-10	1 (0-3); 0-7	3 (0-3); 0-7	8 (6-12); 0-62

We observed 24 episodes in 2012 and 17 in 2013. Index cases were colonized with GRE in 19 (46%) episodes, CPE in 20 (49%) and with both HDRO in 2 (5%) episodes. HDRO were cultured from clinical samples in 13 (12%) patients, 9 with GRE and 4 with CPE. Among the 41 episodes, 14 (34%) were single cases suspected within 48 h after admission; 14 (34%) were single cases suspected more than 48 h after admission; 6 (15%) were with one secondary case; and 7 (17%) were outbreaks with more than one secondary case. Patients colonized with GRE were single cases in 7/19 cases and generated 12 outbreaks (among which one carried both GRE and CPE). These outbreaks resulted in a median of one secondary case (IQR, 0-2; range, 0-29). Episodes with CPE were single cases in 18/19 situations and with one secondary case in the remaining episode. The difference in the number of secondary cases was significant between GRE and CPE ($p<0.01$). The affected wards included medical (23 episodes), surgical (10 episodes), intensive care (7 episodes) and rehabilitation (one episode) wards.

The median time from hospital admission to suspicion of a first case was 4 days (IQR: 1-26). This duration was significantly longer in outbreak situations, 21 (4-62) days vs. 2 (0-12.5) days in single cases ($p<0.01$). In eight episodes, the suspected patient was placed in a contact precaution state upon hospital admission, the risk of cross transmission was considered low and contact patients were not followed. For the 33 other episodes, the median number of contact patients was 32 (IQR: 13-65). The number of contact patients was higher for GRE than for CPE episodes, 52 (15-76) and 24 (0-37), respectively, ($p=0.06$).

The median duration of episodes was 3 days (IQR, 0-10). Interruption of new admissions was decided for 20 episodes, with a median duration of 0 days (IQR, 0-3, range 0-62). This median duration of interruption was significantly higher if case patients were suspected and isolated more than 48 h after admission (2 days) than for suspected patients identified at hospital admission (1 day)($p=0.02$) and for outbreaks with only one secondary

case (3 days) as compared to outbreaks with more than one secondary case (16 days) (p=0.02).

Costs associated with HDRO episodes

Concerning human resources, the nursing staff was reinforced in 16 episodes, among which 10 (62%) were outbreak episodes. Nursing assistants represented the main reinforced staff category, with a mean of 61 supplementary h per episode (range, 0-1603). Nurses were requested in 15 episodes, with a mean number of 38 supplementary h. The mean cost associated with staff reinforcement was €2,686 (SD, €8,861), varying from 0 to €55,081. (Table 3)

Table 3: Resources used in, and costs associated with, episodes of highly-resistant organisms per type of episodes

Costs in €1000s	Total N=41		One single case (suspicion ≤48h after admission) N=14		One single case (suspicion >48h after admission) N=14		Episode with 1 secondary case N=6		Episode with > 1 secondary case N=7	
	Average (SD)	Min-max	Average (SD)	Min-max	Average (SD)	Min-max	Average (SD)	Min-max	Average (SD)	Min-max
Loss of income, €1,000s	**25.2 (67.3)**	**0-348.5**	**2.5 (9.3)**	**0-34.9**	**9.6 (15.7)**	**0-54.9**	**10.2 (16.2)**	**0-40.6**	**11.5 (13.4)**	**1.5-348.5**
Loss hospital bed days	35 (88.7)	0-520	7.4 (27.8)	0-104	13.6 (23.2)	0-90	19.2 (28.3)	0-67	165 (182)	5-520
Staff reinforcement, €1,000s	**2.7 (8.8)**	**0-55.1**	**0.77 (2.3)**	**0-8.4**	**0.3 (0.6)**	**0-1.9**	**0.7 (1.1)**	**0-2.9**	**12.9 (18.9)**	**0.45-55.1**
Hours of assistant nurses	61.4 (252.7)	0-1603	15.7 (58.7)	0-219.5	4.4 (11.4)	0-42	9.3 (11.9)	0-30	311 (574)	0-1603
Hours of nurses	38.5 (93.5)	0-512	12.8 (32.7)	0-98	5.9 (14.2)	0-48	16,1 (27.6)	0-71	174 (169)	7.5-512
Cost of microbiological analysis, €1000s	**2.0 (3.4)**	**0-19.6**	**0.53 (0.49)**	**0-1.5**	**0.9 (0.64)**	**0.13-2.2**	**2.7 (1.7)**	**0.87-5.5**	**6.7 (6.3)**	**2.3-19.6**
Negative culture for GRE	59.9 (101.6)	0-426	39.7 (33.7)	0-75	65 (52)	10-150	104 (95.7)	17-263	198 (156)	76-426

Cepheid Xpert vanA/vanB	18.4 (45.4)	0-279	0.8 (2.9)	0-11	4.1 (8.8)	0-29	32.7 (21.9)	0-62	70.4 (92.8)	20-279
Positive culture for GRE strain	2.2 (6.2)	0-29	0.2 (0.5)	0-1	0.6 (0.5)	0-1	2 (0)	2-2	10.7 (12.2)	2-29
Negative culture for CPE	20.5 (35.5)	0-137	27 (44)	0-137	49 (35)	0-112	70	70-70	102	102-102
Negative culture for CPE, + for ESBLPE	4.6 (10.3)	0-61	15.5 (19.1)	1-61	7.7 (4.2)	4-17	5	5-5	-	-
Positive culture for CPE	0.12 (0.39)	0-2	0.1 (0.3)	0-1	0.2 (0.4)	0-1	2	2-2	0	0-0
Cost of contact isolation, €1,000s	**0.93 (1.0)**	**0-4.7**	**0.63 (0.74)**	**0.1-3.1**	**0.58 (0.57)**	**0-1.8**	**1.18 (0.44)**	**0.61-1.79**	**1.99 (1.74)**	**0.49-4.69**
Cumulative LOS of HDRO patients	49.4 (55.7)	0-254	34.3 (40.3)	7-166	31.8 (30.7)	0-98	64 (23.9)	33-97	111.5 (102.7)	27-254
Overall cost, €1,000s	**30.9 (77.2)**	**0.3-370.7**	**4.44 (11.5)**	**0.3-44.3**	**11.4 (15.7)**	**0.6-57.2**	**14.8 (17.7)**	**1.4-45.9**	**136.5 (151.2)**	**16.7-370.7**
Cost per case, €1,000s	**8.7 (12.2)**	**0.3-57.2**	**4.44 (11.5)**	**0.3-44.3**	**11.4 (15.7)**	**0.6-57.2**	**7.4 (8.8)**	**0.7-22.9**	**12.8 (5.1)**	**4.1-12.3**

For laboratory resources, the median number of screening samples performed per episode was 69 (IQR, 27-119), with 110 (IQR, 66-152) in GRE episodes and 46 (IQR, 13-74) in CPE episodes. Mean costs of microbiological analysis were €2,050 (SD, €3,428) and €3,423 (SD, €4,479) for GRE episodes and €742 (SD, €872) for CPE episodes (p<0.01).

The median duration of contact precautions for HDRO-colonized patients was 33 (IQR, 17-65) days. The mean cost of protective equipment used for contact isolation was €931 (SD, €1,022).

In wards affected by an episode of HDRO, the duration of interruption of admissions ranged from zero to 694 patient bed-days according to episode, with a mean varying from 7 patient bed-days for episodes with a single case identified at admission to 241 patient bed-days in case of outbreak with more than one secondary case. The mean cost associated with interruption of admissions was estimated at €25,242 (SD, €67,297), varying from zero to €348,468 for the largest outbreak. In single HDRO cases, the mean cost associated with interruption of admissions for the episode was significantly higher when the case patient was suspected >48 h after admission (€9,666) than when it was suspected <48 h (€2,493, p<0.01). In the 13 outbreaks, mean cost associated with interruption of admissions for the episode was €66,516 (SD, €109,557) varying from zero in three situations with one secondary case to €348,468 with 29 secondary cases. The mean cost associated with interruption of admissions was €44,020 for GRE episodes and €6,834 for CPE episodes (p=0.18).

The overall mean cost of infection control measures was €4,443 in a single case identified within 48 h after admission. Mean costs were higher if a single case was identified more than 48 h after the admission, at €11,445 (p<0.01). In an outbreak situation, the mean cost varied from €14,864 (SD, €17,734) for an episode with one secondary case to €136,525 (SD, €151,231) for outbreaks with at least two secondary cases. The mean cost per case was

€7,432 (SD, €8,867) in episodes with one secondary case and €12,845 (SD, €5,129) in other outbreak episodes (P < 0.01).

Analysis by category of cost

Overall, cost associated with interruption of admissions represented the most expensive category, with an average of 38% of total cost, followed by microbiology testing 29%, contact precautions 27% and staff reinforcement 6%.(Figure 1). When outbreaks had one secondary case, cost associated with interruption of admissions represented 53 % of total cost; this proportion increased to 74% when outbreaks had more than one secondary case. In episodes with a single case suspected within the first 48 h of admission, contact precautions and microbiological analyses represented 53 and 34% of average overall cost, respectively.

Linear regression analysis was performed to assess cost determinants using data from the 41 episodes. Individually, cost associated with interruption of admissions was the highest item affecting the cost of infection control strategies (R^2=0.98, p<0.01), followed by microbiological analyses (R^2= 0.76, p<0.01), staff reinforcement (R^2= 0.59, p<0.01) and contact precautions (R^2= 0.25, p<0.01). The linear model, including the duration of interruption of new admissions as an independent variable, predicted the overall cost of episodes, with a median error of €3,394 (IQR: 704-15,942), or 62% of median overall cost. When restricting analysis to the 7 outbreak episodes with at least 2 secondary cases, the same model more accurately predicted overall cost, with a median error of €19,038 (IQR: 16,056-69,486), or 27% of the median overall cost. We used single and multiple linear regression to predict overall cost, using all potential explicative variables, individually or combined**.** None of the models built accurately fit the data.

DISCUSSION

This study was performed to assess the financial burden of implementation of a strict national policy to control spread of HDRO. Mean cost per episode was measured at €4,443 per episode for single cases isolated at admission to €136,525 for outbreaks with at least 2 secondary cases. The mean cost per case varied from €4,443 for a single case to €12,845 in outbreak situations. Interruption of admissions was the most costly measure in an outbreak situation.

To our knowledge, this is the first multicenter study to estimate costs of a strict policy for controlling HDRO spread. Data were collected prospectively, enabling detailed cost analysis in a large panel of situations. Previous studies mainly focused on GRE, and primarily assessed costs related to an outbreak situation [14–16], infection, prolonged length of stay [17–19] or implementation of surveillance [20–23]. Studies focusing on cost associated with outbreak situations measured the overall financial burden, varying from €4, 161 to €40,131 per case [14–16,23]. Methods used were variable, with approximate measures and occasional missed critical cost categories.

Antibiotic resistance has become a worldwide concern, and a recent World Health Organization report warned of a "post-antibiotic era". Strict French national strategy appeared to be effective in controlling the spread of HDRO, as illustrated by European Antimicrobial Resistance Surveillance System data and results from large hospital networks [2,4,24,25]. These guidelines exclude multidrug resistance organisms requiring basic contact precautions by the fact that they have become endemic (Methicillin resistant *Staphylococcus aureus)* or pandemic (extended spectrum beta-lactamase producing *Enterobacteriacae)*

making the search and destroy strategy useless. In emerging situations, we can assume that applying a search and isolated strategy for the control of these organisms would lead to comparable costs. Despite a small proportion of HDRO-positive clinical samples and the fact that very few were infected, this control strategy may be justified by the high colonized-to-infected ratio, with possible spread from unidentified colonized patients. However, these recommendations are costly, difficult to implement on a practical basis and require human/laboratory resources and occasional need for interruption of admissions. The present study provides a basis for minimizing the financial burden of a "search and isolate" strategy.

In our study, early identification of patients suspected of being colonized and rapid implementation of contact precautions represented the least expensive scenario. In this context, ward activity was usually maintained, with costs mainly due to staff reinforcement and laboratory techniques. In situations with delayed identification, suspension of admissions was often decided pending results of screening of contact patients. Along this line, guidelines were issued in order to promptly identify, screen and implement strict contact precautions for patients recently hospitalized in a foreign country [5,26]

In outbreak situations, suspension of admissions was the most expensive measure, with mean costs of every secondary case estimated at €12,845, whereas costs due to human resources were lower. The present study raises the question of having, or creating, dedicated areas, thus enabling continuity of care together with cost-savings. A literature review did not find any study that performed cost-effectiveness/benefit or savings analysis of strict measures for controlling HDRO spread in outbreak situations. This underlines the need for further studies on cost effectiveness of different strategies to control HDRO dissemination and optimize both the financial and medical burden of recommendations.

Our study had limitations. First, we did not include potential loss of revenue due to systematic placement of colonized patients in a single room. Like other French HCF, the three hospitals possess a high rate of single rooms for patient isolation or privacy [27]. Hence, we assumed that a single room was standard in the affected unit. Secondly, costs were estimated based on local levels of hospital reimbursement. Costs of suspension of admissions would be much higher in hospitals with higher daily costs. However, a quick review shown that costs per bed days are very similar as those found in the literature [28–31]. Moreover, the presentation with proportion of the overall cost by category allows a clear interpretation. Thirdly, we did not consider costs linked to prolongation of the hospital stay of case patients. We had previously estimated the average prolongation at 23 days, representing €6,981 to €47,800 per case [32]. In the present study, it was not possible to precisely determine the prolongation of hospital stay, which would have been based on a subjective ward physician estimate. Fourthly, we did not measure time spent by the infection control team in managing episodes. Finally, no statistical model built fit the data, mainly because of the heterogeneity of situations and control measures. Specifically, loss of income varied from 0 to €54,976 for episodes with single cases and represented the most heterogeneous variable, directly linked to the context and risk assessment and control measures decided/set by the infection control team.

In conclusion, cost analysis of a large number of episodes showed that suspension of admission was the most costly measure in an outbreak situation. Further studies are needed to assess the cost-effectiveness of cohorting to control HDRO spread. Early identification and implementation of contact precautions may lead to major cost savings in a context of a strict HDRO policy.

Acknowledgments: We thank the members of the infection control teams for their dedication: S Belorgey, W Guerinot, G Bendjelloul, I Garrigues and F Mignot.

Funding statement: None

Competing interests statement: None for all authors

Author's contribution:

GB: writing, analysis, data collection; CL: writing, analysis, data collection; SN: writing, analysis, data collection; LBLN: writing, analysis, data collection; IL: data collection; LAL: data collection; CC: data collection; BL: data collection; GM: data collection; VF: data collection, writing; MHNC: writing; CP: analysis; AP: data collection, analysis; BF: writing; YY: writing; JDR: writing; JCL: data analysis, writing

Data sharing statement: We state that there is no additional unpublished data from the study.

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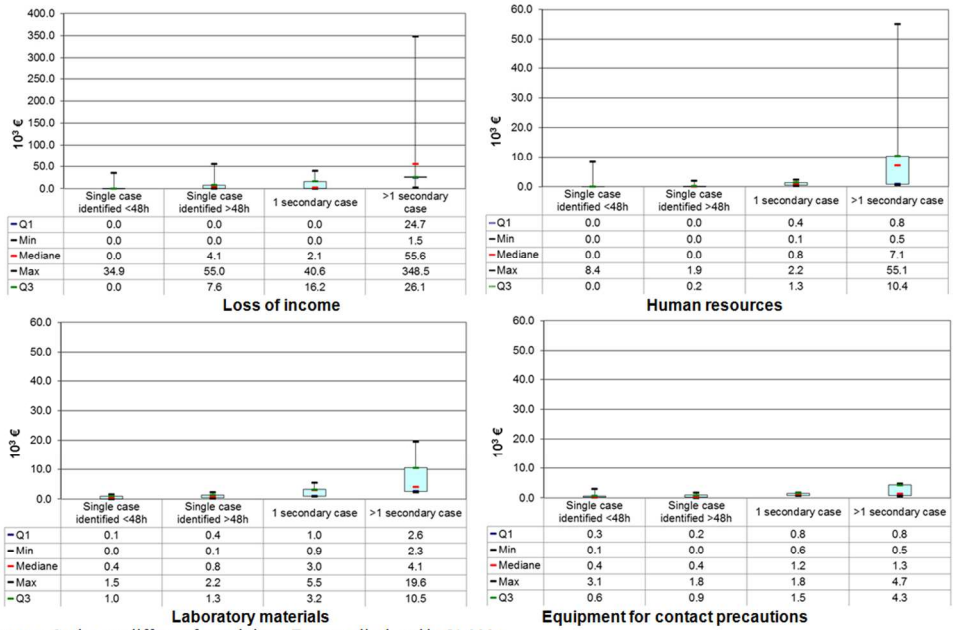
Figure 1: Cost distribution per category of resource and type of episode

Figure 1: Cost distribution per category of resource and type of episode



Loss of income	Single case identified <48h	Single case identified >48h	1 secondary case	>1 secondary case
Q1	0.0	0.0	0.0	24.7
Min	0.0	0.0	0.0	1.5
Mediane	0.0	4.1	2.1	55.6
Max	34.9	55.0	40.6	348.5
Q3	0.0	7.6	16.2	26.1

Human resources	Single case identified <48h	Single case identified >48h	1 secondary case	>1 secondary case
Q1	0.0	0.0	0.4	0.8
Min	0.0	0.0	0.1	0.5
Mediane	0.0	0.0	0.8	7.1
Max	8.4	1.9	2.2	55.1
Q3	0.0	0.2	1.3	10.4

Laboratory materials	Single case identified <48h	Single case identified >48h	1 secondary case	>1 secondary case
Q1	0.1	0.4	1.0	2.6
Min	0.0	0.1	0.9	2.3
Mediane	0.4	0.8	3.0	4.1
Max	1.5	2.2	5.5	19.6
Q3	1.0	1.3	3.2	10.5

Equipment for contact precautions	Single case identified <48h	Single case identified >48h	1 secondary case	>1 secondary case
Q1	0.3	0.2	0.8	0.8
Min	0.1	0.0	0.6	0.5
Mediane	0.4	0.4	1.2	1.3
Max	3.1	1.8	1.8	4.7
Q3	0.6	0.9	1.5	4.3

Footnotes: Scales are different for each item. Data are displayed in €1,000s.

315x215mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1 OK	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2 OK	Explain the scientific background and rationale for the investigation being reported
Objectives	3 OK	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 OK	Present key elements of study design early in the paper
Setting	5 OK	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 OK	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7 OK	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* OK	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 OK	Describe any efforts to address potential sources of bias
Study size	10 OK	Explain how the study size was arrived at
Quantitative variables	11 OK	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 OK	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13* OK	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* OK	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15* OK	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 OK	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 OK	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18 OK	Summarise key results with reference to study objectives
Limitations	19 OK	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 OK	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 OK	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 OK	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Costs associated with implementation of a strict policy for controlling spread of highly resistant microorganisms in France

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009029.R1
Article Type:	Research
Date Submitted by the Author:	03-Sep-2015
Complete List of Authors:	Birgand, Gabriel; INSERM, Univ Paris Diderot, Sorbonne Paris Cité, IAME, UMR 1137; AP-HP, Hôpital Bichat-Claude Bernard, Infection Control Unit Leroy, Christophe; AP-HP, Hôpital Louis Mourier, Emergency department Nerome, Simone; AP-HP, Hôpital Beaujon, Infection Control Unit Luong Nguyen, Liem Binh; AP-HP, Hôpital Beaujon, Internal medicine department Lolom, Isabelle; AP-HP, Hôpital Bichat-Claude Bernard, Infection Control Unit Armand-Lefevre, Laurence; AP-HP, Hôpital Bichat-Claude Bernard, Bacteriology Laboratory Ciotti, Celine; AP-HP, Hôpital Beaujon, Infection Control Unit Le corre, Bertrand; AP-HP, Hôpital Beaujon, Internal medicine department marcade, geraldine; AP-HP, Hôpital Louis Mourier,, Infection Control Unit fihman, vincent; AP-HP, Hôpital Louis Mourier,, Infection Control Unit Nicolas-Chanoine, Marie-Helene; AP-HP, Hôpital Beaujon,, Bacteriology Laboratory Pelat, Camille; INSERM, IAME, UMR 1137; Univ Paris Diderot, Sorbonne Paris Cité, IAME, UMR 1137 perozziello, anne; AP-HP, Hôpital Bichat-Claude Bernard, Medical Information Systems Program (PMSI) Fantin, Bruno; AP-HP, Hôpital Beaujon, Internal medicine department yazdanpanah, yazdan; AP-HP, Hôpital Bichat-Claude Bernard, Infectious diseases department; INSERM, Univ Paris Diderot, Sorbonne Paris Cité, IAME, UMR 1137 Ricard, jean-damien; AP-HP, Hôpital Louis Mourier, Intensive care unit Lucet, Jean-Christophe; AP-HP, Hôpital Bichat-Claude Bernard, Infection Control Unit; INSERM, Univ Paris Diderot, Sorbonne Paris Cité, IAME, UMR 1137
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Health economics, Infectious diseases, Health services research
Keywords:	Microbiology < BASIC SCIENCES, EPIDEMIOLOGY, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Human resource management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Infection control < INFECTIOUS DISEASES

Intended category: Research article

Costs associated with implementation of a strict policy for controlling spread of highly resistant microorganisms in France

Gabriel Birgand [1,2,3]; Christophe Leroy [4]; Simone Nerome [5]; Liem Binh Luong Nguyen [10]; Isabelle Lolom [3]; Laurence Armand-Lefevre [6]; Céline Ciotti [5]; Bertrand Lecorre [10]; Géraldine Marcade [7]; Vincent Fihman [7]; Marie-Hélène Nicolas-Chanoine [8]; Camille Pelat [1,2,]; Anne Perozziello [9]; Bruno Fantin [10]; Yazdan Yazdanpanah [1,2, 11]; Jean-Damien Ricard [1,2,12*]; Jean-Christophe Lucet [1,2,3*]

* Equally supervised the study

[1] INSERM, IAME, UMR 1137, F-75018 Paris, France

[2] Univ Paris Diderot, IAME, UMR 1137, Sorbonne Paris Cité, F-75018 Paris, France

[3] AP-HP, Hôpital Bichat-Claude Bernard, Infection Control Unit, F-75018 Paris, France

[4] AP-HP, Hôpital Louis Mourier, Emergency department, F-92700 Colombes, France

[5] AP-HP, Hôpital Beaujon, Infection Control Unit, F-92110 Clichy, France

[6] AP-HP, Hôpital Bichat-Claude Bernard, Bacteriology Laboratory, F-75018 Paris, France

[7] AP-HP, Hôpital Louis Mourier, Infection Control Unit, F-92700 Colombes, France

[8] AP-HP, Hôpital Beaujon, Bacteriology Laboratory, F-92110 Clichy, France

[9] AP-HP, Hôpital Bichat-Claude Bernard, Medical Information Systems Program (PMSI), F-75018 Paris, France;

[10] AP-HP, Hôpital Beaujon, Internal medicine department, F-92110 Clichy, France

[11] AP-HP, Hôpital Bichat-Claude Bernard, Infectious diseases department, F-75018 Paris, France

[12] AP-HP, Hôpital Louis Mourier, Intensive care unit, F-92700 Colombes, France

Keywords: Cost, highly resistant bacteria, infection control, search and isolate, glycopeptide-resistant enterococci, carbapenemase-producing enterobacteriacae, strict contact precautions

Running title: Costs due to highly resistant bacteria

Corresponding author: Gabriel Birgand, Unité d'Hygiène et de Lutte contre l'Infection nosocomiale, GH Bichat-Claude Bernard, 46 rue Henri Huchard, 75877 Paris Cedex 18, France.

Tel: +33 140 256 199; Fax: +33 140 258 811; E-mail: gbirgand@gmail.com

Word count: 3253

Abstract

Objective

To assess costs associated with implementation of a strict "search and isolate" strategy for controlling highly-drug-resistant organisms (HDRO).

Design

Review of data from 2-year prospective surveillance (01/2012 to 12/2013) of HDRO.

Setting

Three university hospitals located in northern Paris.

Methods

Episodes were defined as single cases or outbreaks of glycopeptide-resistant enterococci (GRE) or carbapenemase-producing enterobacteriacae (CPE) colonization. Costs were related to staff reinforcement, costs of screening cultures, contact precautions and interruption of new admissions. Univariate analysis, along with simple and multiple linear regression analyses were conducted to determine variables associated with cost of HDRO management.

Results

Overall, 41 consecutive episodes were included, 28 single cases and 13 outbreaks. The cost (mean ± SD) associated with management of a single case identified within and/or 48 h after admission was €4,443 ± 11,552 and €11,445 ± 15,743, respectively ($p<0.01$). In an outbreak, the total cost varied from €14,864 ± 17,734 for an episode with one secondary case (€7,432 ± 8,867 per case) to €136,525 ± 151,231 (€12,845 ± 5,129 per case) when more than one secondary case occurred. In episodes of single cases, contact precautions and microbiological analyses represented 51 and 30% of overall cost, respectively. In outbreaks, cost related to interruption of new admissions represented 77 to 94% of total costs, and had the greatest financial impact ($R^2 = 0.98$, $p<0.01$).

Conclusion

In HDRO episodes occurring at three university hospitals, interruption of new admissions constituted the most costly measure in an outbreak situation.

Article summary: Strengths and limitations of this study

- Multicenter study to estimate costs of a strict policy for controlling HDRO spread with data collected prospectively, enabling detailed cost analysis in a large panel of situations.
- Provides a basis for minimizing the financial burden of a "search and isolate" strategy. Early identification of patients suspected of being colonized and rapid implementation of contact precautions represented the least expensive scenario.
- The study raises the question of having, or creating, dedicated areas, thus enabling continuity of care together with cost-savings.
- The study did not include: loss of revenue due to systematic placement of colonized patients in a single room, costs linked to prolongation of the hospital stay of case patients and time spent by the infection control team in managing episodes.
- Cost estimations were based on local levels of hospital reimbursement.

INTRODUCTION

Hospitals are increasingly plagued by microorganisms highly-drug-resistant (HDRO) to antimicrobials (1). These HDRO include carbapenamase-producing *Enterobacteriaceae* (CPE) and glycopeptide-resistant enterococci (GRE). In France, the prevalence of GRE and CP-*K. pneumoniae* isolated from blood cultures was 0.8 and 0.5% in 2012, respectively (2).

In France, guideline based on a "search and isolate" strategy have been issued for the control of emerging HDROs (3). They are based on two assumptions: 1) most HDRO-positive patients are asymptomatic carriers with high risk of spreading before outbreak identification; and 2) standard or contact precautions do not reliably halt HDRO transmission in all circumstances.

Infection control measures are gradually implemented according to risk analysis. In case of immediate enforcement of strict contact precautions (identification of a colonized patient upon hospital admission, notably if repatriated or recently hospitalized abroad in the past 12 months), weekly cross-sectional screening of ward patients is recommended, with no additional control measures (3,4).

In an outbreak situation, i.e. with at least one secondary case, measures are upgraded and consist of a strict "search and isolate" strategy, as follows: (a) HDRO-positive patients are cohorted and cared for by dedicated staff; (b) secondary cases are detected via repeated rectal sampling of contact patients, i.e. patients cared for by the same nursing staff as the HDRO-positive patient; (c) contact patients are cohorted and cared for by dedicated staff until three weekly screening tests are negative; (d) HDRO-positive and contact patients are discharged home whenever possible; and (e) the ward with the HDRO-positive patients neither transfers patients to other wards or healthcare facilities (HCF) nor admits new patients until after three negative weekly screening tests of contact patients.

These strict recommendations are difficult to implement and require additional human and material resources. Moreover, interruption of admission to and transfer from the involved ward lead to a decrease in hospital medical service utilization and therefore a loss of hospital income (5). Costs associated with each different epidemiological situation and the determinants of these costs are not known. The purpose of this study was to assess costs associated with implementation of national recommendations for controlling HDRO spread in three university hospitals and to identify determinants of these costs.

PATIENTS AND METHODS

Setting

This study was performed in a French university healthcare group located in northern Paris, the 950-bed Bichat-Claude-Bernard Hospital, the 470-bed Beaujon Hospital and the 490-bed Louis-Mourier Hospital, providing primary, tertiary and long term care with a large panel of surgical and medical specialities. This group of hospital takes part of a public health institution (AP-HP) representing 10% of all public hospital beds in France. These three hospitals are situated in the highly exposed area with a high proportion of patients originating from a foreign country. None of these hospitals has a dedicated ward for housing/regrouping case patients. Case patients were therefore admitted to the ward matching their pathology. In outbreak situations, however, case patients from different wards could be housed in the ward with the highest case number.

Design and data collection on resources used

We reviewed data from 2-year prospective surveillance of HDRO occurrence (01/2012-12/2013). We defined an episode as consisting of new identification of HDRO in a clinical or screening sample, unrelated to previous situations. An outbreak was defined as at least two CPE cases (i.e. one index case and at least one secondary case among the contact patients) occurring in a given hospital, with a clear epidemiological link (stay during the same period of time in the same unit) and involving indistinguishable CPE strain based on species, antibiotic susceptibility and resistance gene. We distinguished four types of episodes involving CPE or GRE strains, from simple situations with low epidemic risk to complex situations with confirmed outbreaks: (i) a single case suspected within 48 h after hospital admission; (ii) a single case suspected more than 48 h after hospital admission; (iii) an outbreak with only one secondary case; and (iv) an outbreak with more than one secondary case.

For each episode, data were prospectively collected, including characteristics of the epidemic (type of HDRO and resistance mechanism, type of ward, dates of admission and discharge of case patients, date of positive results and implementation of contact precautions, number of contact patients); human resources (nursing staff reinforcement allocated to a ward during an episode, either for cohorting colonized patients, i.e. placing the patient in a dedicated location on the ward with dedicated healthcare workers (HCW), or for decreasing the workload of the unit by globally increasing the nurse-to-patient ratio); material for the three weekly screening protocol and patient care; and duration of interruption of new admissions.

Cost analysis

Costs were considered from a hospital perspective. For human resources, staff reinforcement was calculated based on the number of supplementary hours put in by nurses and nursing assistants on the basis of their hourly salary. (Table 1) The cost calculation was performed until the date of analysis, nine months after the end of the last episode. Costs associated to readmission of contact patients after this date were not considered.

Table 1: Methods of cost analyses

Type	Variables collected	Value
Loss of income	Number of hospital bed days lost	
	Mean cost billed per hospital day per specialty	
	Medical units	335 to 601 €
	Surgical units	306 to 940 €
	ICU	609 to 2078 €
Staff reinforcement	Cost of 1 h of a nursing assistant	24.6 €
	Cost of 1 h of a nurse	30.5 €
Cost of micro-analysis (5)	Negative culture for GRE	13.9 €
	Cepheid Xpert *van*A/*van*B	37.3 €
	Positive culture for GRE strain	117.8 €
	Negative culture for CPE	7.7 €
	Negative culture for CPE, + for ESBLPE	21 €
	Positive culture for CPE	115 €
Cost of contact precautions	Cumulative number of hospital days, HDRO patients	

(6)	Cost of gloves	0.05 € /pair
	Cost of gowns	0.3 € each
	Cost of nursing contact (1 min) *Papia et*	0.26 €
	al.(7)	30
	Number of patient contacts per day	18.5 €
	Cost per HDRO patient per day	

Abbreviation: ESBLPE, extended spectrum beta-lactamase; ICU, intensive care unit; GRE, Glycopeptide resistant enterococci; CPE, carbapenemase producing enterobacteriacae; HDRO, highly drug resistant organism.

For the laboratory sector, methods for detecting CPE and GRE in screening samples have been described elsewhere (8)(9). Unit costs for resources used to screen were computed based on use of the following resources: selective chromogenic plates or PCR-based method, identification tests and susceptibility tests, depending on the above-described situations. Personnel costs for laboratory tests were calculated on the basis of the hourly salary of a senior staff member and the estimated time required for each step. Unit cost of PCR screening included acquisition of the GeneXpertTM machine (Cepheid, Sunnyvale, CA) and XpertTM *van*A/*van*B test cartridges and performing cultures for GRE on a *van*A/*van*B-positive sample or samples without PCR results (invalid tests) (5).Cost of contact precautions included that of gloves and gowns used for case patients, assuming an average of 30 patient contacts per day of isolation and nursing costs for additional time to donning and discarding gloves and gown (1 min) (6).

Finally, to estimate the decrease in hospital service use, we first computed the difference between admission capacity, assuming 100% bed occupancy, and the number of patients admitted when a HDRO-positive patient was identified in the ward. Next, we

estimated costs attributable to decreased occupancy, by multiplying the number of missed patient-days by the mean cost of a hospital day, depending on the type of pathology and the ward. According to the French reimbursement system, the mean cost per hospital day was the total cost related to hospital stay in the previous year in the affected ward divided by the number of patient-days (10). Total cost related to missed hospital days in a ward was estimated using the French diagnosis-related group system according to which patients are classified into statistically and clinically homogeneous groups on the basis of their clinical and demographic data.

Statistical analysis

Categorical independent variables were described using proportions and continuous variables via medians and 25th-75th percentiles. For costs, means with standard deviation were used to take into account outliers and data dispersion. Univariate comparisons used a Wilcoxon rank or Chi-2 test as required. Statistics on categorical variables were based on two-way analysis of variance (ANOVA). After univariate analysis, simple and multiple linear regression analyses were carried out, with overall cost as the dependent variable, to determine those costs most strongly associated with the overall financial burden. The overall percentage of explained variance of the model was described by the adjusted R^2 of observed costs. Predictive values of models built were tested using the method of "Leave One Out Cross-Validation" (jack-knife) (11). This method assesses the predicted costs in one episode based on the model built with all other episodes. We analyzed observed versus predicted costs for all episodes, and specifically for outbreaks, by giving the mean and median predictive error per episode and the mean relative predictive error. Statistical analyses were done with R software, version 2.15.2.

Ethics Committee Approval

Because of the observational and blinded nature of the study, the institutional review board of the Bichat-Claude Bernard Hospital waived the requirement for informed consent. According to this statement, written consents of patients were not collected. Patient information was de-identified by attributing a number. The study has been approved by the ethical committee of the Bichat-Claude Bernard Hospital group.

RESUTS

Characteristics of HDRO episodes

Overall, we observed 41 HDRO episodes (34 at Bichat-Claude Bernard, 6 at Beaujon and 1 at Louis Mourier Hospital), with a total of 113 colonized or infected patients (Table 2).

Table 2: Characteristics of episodes with highly resistant organisms according to type of episode.

Description of episode characteristics	Total N=41	A single case (suspicion ≤48 h after admission) N=14	A single case (suspicion >48 h after admission) N=14	Episode with 1 secondary case N=6	Episode with > 1 secondary case N=7
Number of episodes per hospital, n (%)					
Bichat-Claude Bernard	34 (83)	10 (71)	13 (93)	6 (100)	5 (70)
Beaujon	6 (15)	4 (29)	1 (7)	0	1 (15)
Louis Mourier	1 (3)	0	0	0	1 (15)
Year, n (%)					
2012	24 (58)	6 (43)	8 (57)	6 (100)	4 (57)
2013	17 (42)	8 (57)	6 (43)	0	3 (43)

Type of HDRO, n (%)					
GRE	20 (49)	3 (21)	6 (43)	5 (83)	6 (86)
CPE	19 (46)	10 (71)	8 (57)	1 (17)	0
GRE + CPE	2 (5)	1 (8)	0	0	1 (14)
Type of ward at identification, n (%)					
ICU	7 (17)	4 (29)	2 (14)	1 (17)	0
Medical	23 (56)	8 (57)	6 (43)	3 (50)	6 (86)
Surgical	10 (24)	2 (14)	6 (43)	2 (33)	0
Rehabilitation	1 (3)	0	0	0	1 (14)
Time from admission to suspicion (screening), days, median (IQR)	4 (1-26)	0 (0-1)	12.5 (5-33)	14 (4-26)	42 (3-75)
Time from admission to HDRO+ result, days, median (IQR)	6 (3-26)	0.5 (0-3)	12.5 (5-33)	14 (7-26)	42 (6-75)

Number of contact patients, median (IQR); min-max	32 (13-65)	5 (0-21); 0-65	34 (19-76); 0-260	48.5 (32-53); 19-262	66 (53-152); 48-237
Number of secondary cases, median (IQR); min-max	-	0	0	1	3 (2-22); 2-29
Suspension of admissions, days median (IQR); min-max	0 (0-3)	0 (0-0); 0-10	1 (0-3); 0-7	3 (0-3); 0-7	8 (6-12); 0-62

Abbreviation: ESBLPE, extended spectrum beta-lactamase; ICU, intensive care unit; GRE, Glycopeptide resistant enterococci; CPE, carbapenemase producing enterobacteriacae; HDRO, highly drug resistant organism; IQR, interquartile range.

We observed 24 episodes in 2012 and 17 in 2013. Index cases were colonized with GRE in 20 (49%) episodes, CPE in 19 (46%) and with both HDRO in 2 (5%) episodes. HDRO were cultured from clinical samples in 13 (12%) patients, 9 with GRE and 4 with CPE (p=0.85). Among the 41 episodes, 14 (34%) were single cases suspected within 48 h after admission; 14 (34%) were single cases suspected more than 48 h after admission; 6 (15%) were with one secondary case; and 7 (17%) were outbreaks with more than one secondary case. Patients colonized or infected with GRE were single cases in 10/22 cases and generated 12 outbreaks (among which one carried both GRE and CPE). These outbreaks resulted in a median of one secondary case (IQR, 0-2; range, 0-29). Episodes with CPE were single cases in 18/19 situations and with one secondary case in the remaining episode. The difference in the number of secondary cases was significant between GRE and CPE (p<0.01). The affected wards included medical (23 episodes), surgical (10 episodes), intensive care (7 episodes) and rehabilitation (one episode) wards.

The median time from hospital admission to suspicion of a first case was 4 days (IQR: 1-26). It was 1 day (0-8) and 14 days (3-42) for CPE and GRE, respectively (p=0.01). This duration was significantly longer in outbreak situations, 21 (4-62) days vs. 2 (0-12.5) days in single cases (p<0.01). In eight episodes, the suspected patient was placed in a contact precaution state upon hospital admission, the risk of cross transmission was considered low and contact patients were not followed. For the 33 other episodes, the median number of contact patients was 32 (IQR: 13-65). The number of contact patients was higher for GRE than for CPE episodes, 52 (15-76) and 24 (0-37), respectively, (p=0.06).

The median duration of episodes was 3 days (IQR, 0-10). Interruption of new admissions was decided for 20 episodes. The median duration of interruption in outbreak situations (≥ 1 secondary case) was 4.5 days (IQR, 1.5-8, range 0-62). This median duration of interruption was significantly higher if case patients were suspected and isolated more than

48 h after admission (2 days) than for suspected patients identified at hospital admission (1 day)(p=0.02) and for outbreaks with only one secondary case (3 days) as compared to outbreaks with more than one secondary case (16 days) (p=0.02).

Costs associated with HDRO episodes

Concerning human resources, the nursing staff was reinforced in 16 episodes, among which 10 (62%) were outbreak episodes. Nursing assistants represented the main reinforced staff category, with a mean of 61 supplementary h per episode (range, 0-1603). Nurses were requested in 15 episodes, with a mean number of 38 supplementary h. The mean cost associated with staff reinforcement was €2,686 (SD, €8,861), varying from 0 to €55,081. (Table 3)

Table 3: Resources used in, and costs associated with, episodes of highly-resistant organisms per type of episodes

	Total N=41		One single case (suspicion ≤48h after admission) N=14		One single case (suspicion >48h after admission) N=14		Episode with 1 secondary case N=6		Episode with > 1 secondary case N=7	
	Median (IQR)	Min-max	Average (SD)	Min-max	Average (SD)	Min-max	Average (SD)	Min-max	Average (SD)	Min-max
Loss of income, €1,000s	**25.2 (67.3)**	**0-348.5**	**2.5 (9.3)**	**0-34.9**	**9.6 (15.7)**	**0-54.9**	**10.2 (16.2)**	**0-40.6**	**115 (134)**	**1.5-348**
Loss hospital bed days	35 (88.7)	0-520	7.4 (27.8)	0-104	13.6 (23.2)	0-90	19.2 (28.3)	0-67	165 (182)	5-520
Staff reinforcement, €1,000s	**2.7 (8.8)**	**0-55.1**	**0.77 (2.3)**	**0-8.4**	**0.3 (0.6)**	**0-1.9**	**0.7 (1.1)**	**0-2.9**	**12.9 (18.9)**	**0.45-55.1**
Hours of assistant nurses	61.4 (252.7)	0-1603	15.7 (58.7)	0-219.5	4.4 (11.4)	0-42	9.3 (11.9)	0-30	311 (574)	0-1603
Hours of nurses	38.5 (93.5)	0-512	12.8 (32.7)	0-98	5.9 (14.2)	0-48	16,1 (27.6)	0-71	174 (169)	7.5-512
Cost of microbiological analysis, €1000s	**2.0 (3.4)**	**0-19.6**	**0.53 (0.49)**	**0-1.5**	**0.9 (0.64)**	**0.13-2.2**	**2.7 (1.7)**	**0.87-5.5**	**6.7 (6.3)**	**2.3-19.6**

For GRE strains, number of:										
Negative culture	59.9 (101.6)	0-426	39.7 (33.7)	0-75	65 (52)	10-150	104 (95.7)	17-263	198 (156)	76-426
Cepheid Xpert *van*A/*van*B	18.4 (45.4)	0-279	0.8 (2.9)	0-11	4.1 (8.8)	0-29	32.7 (21.9)	0-62	70.4 (92.8)	20-279
Positive culture	2.2 (6.2)	0-29	0.2 (0.5)	0-1	0.6 (0.5)	0-1	2 (0)	2-2	10.7 (12.2)	2-29
For CPE strains, number of:										
Negative culture	20.5 (35.5)	0-137	27 (44)	0-137	49 (35)	0-112	70	70-70	102	102-102
Negative culture, + for ESBLPE	4.6 (10.3)	0-61	15.5 (19.1)	1-61	7.7 (4.2)	4-17	5	5-5	-	-
Positive culture	0.12 (0.39)	0-2	0.1 (0.3)	0-1	0.2 (0.4)	0-1	2	2-2	0	0-0
Cost of contact isolation, €1,000s	**0.93 (1.0)**	**0-4.7**	**0.63 (0.74)**	**0.1-3.1**	**0.58 (0.57)**	**0-1.8**	**1.18 (0.44)**	**0.61-1.79**	**1.99 (1.74)**	**0.49-4.69**
Cumulative LOS of HDRO patients	49.4 (55.7)	0-254	34.3 (40.3)	7-166	31.8 (30.7)	0-98	64 (23.9)	33-97	111.5 (102.7)	27-254
Overall cost, €1,000s	**30.9 (77.2)**	**0.3-370.7**	**4.44 (11.5)**	**0.3-44.3**	**11.4 (15.7)**	**0.6-57.2**	**14.8 (17.7)**	**1.4-45.9**	**136.5 (151.2)**	**16.7-370.7**
Cost per case, €1,000s	**8.7 (12.2)**	**0.3-57.2**	**4.44 (11.5)**	**0.3-44.3**	**11.4 (15.7)**	**0.6-57.2**	**7.4 (8.8)**	**0.7-22.9**	**12.8 (5.1)**	**4.1-12.3**

Abbreviation: LOS, length of stay; GRE, Glycopeptide resistant enterococci; CPE, carbapenemase producing enterobacteriacae; HDRO, highly drug resistant organism; IQR, interquartile range; SD, standard deviation.

For laboratory resources, the median number of screening samples performed per episode was 69 (IQR, 27-119), with 110 (IQR, 66-152) in GRE episodes and 46 (IQR, 13-74) in CPE episodes. Mean costs of microbiological analysis were €2,050 (SD, €3,428), €3,423 (SD, €4,479) for GRE episodes and €742 (SD, €872) for CPE episodes (p<0.01).

The median duration of contact precautions for HDRO-colonized patients was 33 (IQR, 17-65) days. The mean cost of protective equipment used for contact isolation was €931 (SD, €1,022).

In wards affected by an episode of HDRO, the duration of interruption of admissions ranged from zero to 694 patient bed-days according to episode, with a mean varying from 7 patient bed-days for episodes with a single case identified at admission to 241 patient bed-days in case of outbreak with more than one secondary case. The mean cost associated with interruption of admissions was estimated at €25,242 (SD, €67,297), varying from zero to €348,468 for the largest outbreak. In single HDRO cases, the mean cost associated with interruption of admissions for the episode was significantly higher when the case patient was suspected >48 h after admission (€9,666) than when it was suspected <48 h (€2,493, p<0.01). In the 13 outbreaks, mean cost associated with interruption of admissions for the episode was €66,516 (SD, €109,557) varying from zero in three situations with one secondary case to €348,468 with 29 secondary cases. The mean cost associated with interruption of admissions was €44,020 for GRE episodes and €6,834 for CPE episodes (p=0.18).

The overall mean cost of infection control measures was €4,443 in a single case identified within 48 h after admission. Mean costs were higher if a single case was identified more than 48 h after the admission, at €11,445 (p<0.01). In an outbreak situation, the mean cost varied from €14,864 (SD, €17,734) for an episode with one secondary case to €136,525 (SD, €151,231) for outbreaks with at least two secondary cases. The mean cost per case was

€7,432 (SD, €8,867) in episodes with one secondary case and €12,845 (SD, €5,129) in other outbreak episodes (P < 0.01).

Analysis by category of cost

Overall, cost associated with interruption of admissions represented the most expensive category, with an average of 38% (range 0-97%) of total cost per episode, followed by microbiology testing 29% (0-100%), contact precautions 27% and staff reinforcement 6% per episode.(Figure 1). When outbreaks had one secondary case, cost associated with interruption of admissions represented 53 % of total cost per episode; this proportion increased to 74% when outbreaks had more than one secondary case. In episodes with a single case suspected within the first 48 h of admission, contact precautions and microbiological analyses represented 53 and 34% of average overall cost per episode, respectively. When we aggregated costs for all episodes, the interruption of activity represented 81.7% of the overall cost, followed by the human resources 8.7%, microbiology 6.6% and contact precautions 3%.

Linear regression analysis was performed to assess cost determinants using data from the 41 episodes. Individually, cost associated with interruption of admissions was the highest item affecting the cost of infection control strategies (R^2=0.98, p<0.01), followed by microbiological analyses (R^2= 0.76, p<0.01), staff reinforcement (R^2= 0.59, p<0.01) and contact precautions (R^2= 0.25, p<0.01). The linear model, including the duration of interruption of new admissions as an independent variable, predicted the overall cost of episodes, with a median error of €3,394 (IQR: 704-15,942), or 62% of median overall cost. When restricting analysis to the 7 outbreak episodes with at least 2 secondary cases, the same

model more accurately predicted overall cost, with a median error of €19,038 (IQR: 16,056-69,486), or 27% of the median overall cost per episode. We used single and multiple linear regression to predict overall cost, using all potential explicative variables, individually or combined**.** None of the models built accurately fit the data.

DISCUSSION

This study was performed to assess the financial burden of implementation of a strict national policy to control spread of HDRO. Mean cost per episode was measured at €4,443 per episode for single cases isolated at admission to €136,525 for outbreaks with at least 2 secondary cases. The mean cost per case varied from €4,443 for a single case to €12,845 in outbreak situations. Interruption of admissions was the most costly measure in an outbreak situation.

To our knowledge, this is the first multicenter study to estimate costs of a strict policy for controlling HDRO spread. Data were collected prospectively, enabling detailed cost analysis in a large panel of situations. Previous studies mainly focused on GRE, and primarily assessed costs related to an outbreak situation (12–14), infection, prolonged length of stay (15–17) or implementation of surveillance (18–21). Studies focusing on cost associated with outbreak situations measured the overall financial burden, varying from €4, 161 to €40,131 per case (12–14,21). Methods used were variable, with approximate measures and occasional missed critical cost categories.

Antibiotic resistance has become a worldwide concern, and a recent World Health Organization report warned of a "post-antibiotic era". Strict French national strategy appeared to be effective in controlling the spread of HDRO, as illustrated by European Antimicrobial Resistance Surveillance System data and results from large hospital networks (2,22–24). These guidelines exclude multidrug resistance organisms requiring basic contact precautions by the fact that they have become endemic (Methicillin resistant *Staphylococcus aureus)* or pandemic (extended spectrum beta-lactamase producing *Enterobacteriacae)*

making the search and destroy strategy useless. In emerging situations, we can assume that applying a search and isolated strategy for the control of these organisms would lead to comparable costs. Despite a small proportion of HDRO-positive clinical samples and the fact that very few were infected, this control strategy may be justified by the high colonized-to-infected ratio, with possible spread from unidentified colonized patients. However, these recommendations are costly, difficult to implement on a practical basis and require human/laboratory resources and occasional need for interruption of admissions. The present study provides a basis for minimizing the financial burden of a "search and isolate" strategy.

In our study, early identification of patients suspected of being colonized and rapid implementation of contact precautions represented the least expensive scenario. In this context, ward activity was usually maintained, with costs mainly due to staff reinforcement and laboratory techniques. In situations with delayed identification, suspension of admissions was often decided pending results of screening of contact patients. Along this line, guidelines were issued in order to promptly identify, screen and implement strict contact precautions for patients recently hospitalized in a foreign country (3,25)

In outbreak situations, suspension of admissions was the most expensive measure, with mean costs of every secondary case estimated at €12,845, whereas costs due to human resources were lower. The present study raises the question of having, or creating, dedicated areas, thus enabling continuity of care together with cost-savings. A literature review did not find any study that performed cost-effectiveness/benefit or savings analysis of strict measures for controlling HDRO spread in outbreak situations. This underlines the need for further studies on cost effectiveness of different strategies to control HDRO dissemination and optimize both the financial and medical burden of recommendations.

Our study had limitations. First, we did not include potential loss of revenue due to systematic placement of colonized patients in a single room. Like other French HCF, the three hospitals possess a high rate of single rooms for patient isolation or privacy (26). Hence, we assumed that a single room was standard in the affected unit. Secondly, costs were estimated based on local levels of hospital reimbursement. Costs of suspension of admissions would be much higher in hospitals with higher daily costs. However, a quick review shown that costs per bed days are very similar as those found in the literature (27–30). Moreover, the presentation with proportion of the overall cost by category allows a clear interpretation. Thirdly, we did not consider costs linked to prolongation of the hospital stay of case patients. We had previously estimated the average prolongation at 23 days, representing €6,981 to €47,800 per case (31). In the present study, it was not possible to precisely determine the prolongation of hospital stay, which would have been based on a subjective ward physician estimate. Fourthly, we did not measure time spent by the infection control team in managing episodes. Fifthly, the setting of this study (three hospitals in one country) imposes the caution regarding the generalizability of crude costs. However, distributions of expenses should remain approximately the same whatever the hospital and the country. Sixthly, the loss of activity was estimated based on a 100% bed occupancy. This assumption appear to be contestable, but the proportion of free bed-days was so small that we considered them as negligible. Finally, no statistical model built fit the data, mainly because of the heterogeneity of situations and control measures. Specifically, loss of income varied from 0 to €54,976 for episodes with single cases and represented the most heterogeneous variable, directly linked to the context and risk assessment and control measures decided/set by the infection control team.

In conclusion, cost analysis of a large number of episodes showed that suspension of admission was the most costly measure in an outbreak situation. Further studies are needed to assess the cost-effectiveness of cohorting to control HDRO spread. Early identification and implementation of contact precautions may lead to major cost savings in a context of a strict HDRO policy.

Acknowledgments: We thank the members of the infection control teams for their dedication: S Belorgey, W Guerinot, G Bendjelloul, I Garrigues and F Mignot.

Funding statement: None

Competing interests statement: None for all authors

Author's contribution:

GB: writing, analysis, data collection; CL: writing, analysis, data collection; SN: writing, analysis, data collection; LBLN: writing, analysis, data collection; IL: data collection; LAL: data collection; CC: data collection; BL: data collection; GM: data collection; VF: data collection, writing; MHNC: writing; CP: analysis; AP: data collection, analysis; BF: writing; YY: writing; JDR: writing; JCL: data analysis, writing

Data sharing statement: We state that there is no additional unpublished data from the study.

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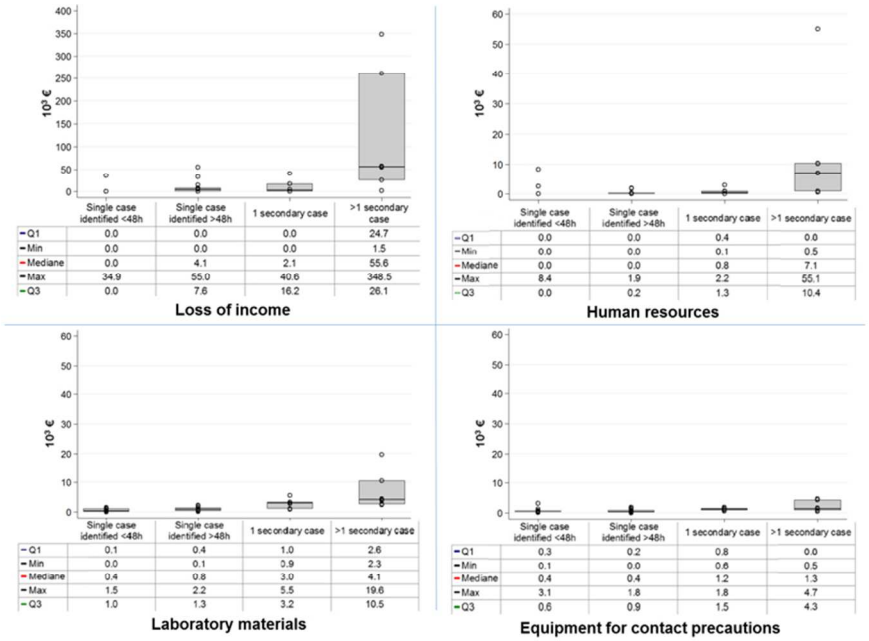
Figure 1: Cost distribution per category of resource and type of episode

Figure 1: Cost distribution per category of resource and type of episode



Loss of income	Single case identified <48h	Single case identified >48h	1 secondary case	>1 secondary case
Q1	0.0	0.0	0.0	24.7
Min	0.0	0.0	0.0	1.5
Mediane	0.0	4.1	2.1	55.6
Max	34.9	55.0	40.6	348.5
Q3	0.0	7.6	16.2	26.1

Human resources	Single case identified <48h	Single case identified >48h	1 secondary case	>1 secondary case
Q1	0.0	0.0	0.4	0.0
Min	0.0	0.0	0.1	0.5
Mediane	0.0	0.0	0.8	7.1
Max	8.4	1.9	2.2	55.1
Q3	0.0	0.2	1.3	10.4

Laboratory materials	Single case identified <48h	Single case identified >48h	1 secondary case	>1 secondary case
Q1	0.1	0.4	1.0	2.6
Min	0.0	0.1	0.9	2.3
Mediane	0.4	0.8	3.0	4.1
Max	1.5	2.2	5.5	19.6
Q3	1.0	1.3	3.2	10.5

Equipment for contact precautions	Single case identified <48h	Single case identified >48h	1 secondary case	>1 secondary case
Q1	0.3	0.2	0.8	0.0
Min	0.1	0.0	0.6	0.5
Mediane	0.4	0.4	1.2	1.3
Max	3.1	1.8	1.8	4.7
Q3	0.6	0.9	1.5	4.3

Footnotes: Scales are different for each item. Data are displayed in €1,000s.

Figure 1: Cost distribution per category of resource and type of episode
246x172mm (96 x 96 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1 OK	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2 OK	Explain the scientific background and rationale for the investigation being reported
Objectives	3 OK	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 OK	Present key elements of study design early in the paper
Setting	5 OK	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 OK	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7 OK	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* OK	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 OK	Describe any efforts to address potential sources of bias
Study size	10 OK	Explain how the study size was arrived at
Quantitative variables	11 OK	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 OK	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13* OK	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* OK	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15* OK	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 OK	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 OK	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18 OK	Summarise key results with reference to study objectives
Limitations	19 OK	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 OK	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 OK	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 OK	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Costs associated with implementation of a strict policy for controlling spread of highly resistant microorganisms in France

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2015-009029.R2
Article Type:	Research
Date Submitted by the Author:	23-Oct-2015
Complete List of Authors:	Birgand, Gabriel; INSERM, Univ Paris Diderot, Sorbonne Paris Cité, IAME, UMR 1137; AP-HP, Hôpital Bichat-Claude Bernard, Infection Control Unit Leroy, Christophe; AP-HP, Hôpital Louis Mourier, Emergency department Nerome, Simone; AP-HP, Hôpital Beaujon, Infection Control Unit Luong Nguyen, Liem Binh; AP-HP, Hôpital Beaujon, Internal medicine department Lolom, Isabelle; AP-HP, Hôpital Bichat-Claude Bernard, Infection Control Unit Armand-Lefevre, Laurence; AP-HP, Hôpital Bichat-Claude Bernard, Bacteriology Laboratory Ciotti, Celine; AP-HP, Hôpital Beaujon, Infection Control Unit Le corre, Bertrand; AP-HP, Hôpital Beaujon, Internal medicine department marcade, geraldine; AP-HP, Hôpital Louis Mourier,, Infection Control Unit fihman, vincent; AP-HP, Hôpital Louis Mourier,, Infection Control Unit Nicolas-Chanoine, Marie-Helene; AP-HP, Hôpital Beaujon,, Bacteriology Laboratory Pelat, Camille; INSERM, IAME, UMR 1137; Univ Paris Diderot, Sorbonne Paris Cité, IAME, UMR 1137 perozziello, anne; AP-HP, Hôpital Bichat-Claude Bernard, Medical Information Systems Program (PMSI) Fantin, Bruno; AP-HP, Hôpital Beaujon, Internal medicine department yazdanpanah, yazdan; AP-HP, Hôpital Bichat-Claude Bernard, Infectious diseases department; INSERM, Univ Paris Diderot, Sorbonne Paris Cité, IAME, UMR 1137 Ricard, jean-damien; AP-HP, Hôpital Louis Mourier, Intensive care unit Lucet, Jean-Christophe; AP-HP, Hôpital Bichat-Claude Bernard, Infection Control Unit; INSERM, Univ Paris Diderot, Sorbonne Paris Cité, IAME, UMR 1137
Primary Subject Heading:	Infectious diseases
Secondary Subject Heading:	Epidemiology, Health economics, Infectious diseases, Health services research
Keywords:	Microbiology < BASIC SCIENCES, EPIDEMIOLOGY, Health economics < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Human resource management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Organisation of health services < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Infection control < INFECTIOUS DISEASES

Intended category: Research article

Costs associated with implementation of a strict policy for controlling spread of highly resistant microorganisms in France

Gabriel Birgand [1,2,3]; Christophe Leroy [4]; Simone Nerome [5]; Liem Binh Luong Nguyen [10]; Isabelle Lolom [3]; Laurence Armand-Lefevre [6]; Céline Ciotti [5]; Bertrand Lecorre [10]; Géraldine Marcade [7]; Vincent Fihman [7]; Marie-Hélène Nicolas-Chanoine [8]; Camille Pelat [1,2,]; Anne Perozziello [9]; Bruno Fantin [10]; Yazdan Yazdanpanah [1,2, 11]; Jean-Damien Ricard [1,2,12*]; Jean-Christophe Lucet [1,2,3*]

* Equally supervised the study

[1] INSERM, IAME, UMR 1137, F-75018 Paris, France

[2] Univ Paris Diderot, IAME, UMR 1137, Sorbonne Paris Cité, F-75018 Paris, France

[3] AP-HP, Hôpital Bichat-Claude Bernard, Infection Control Unit, F-75018 Paris, France

[4] AP-HP, Hôpital Louis Mourier, Emergency department, F-92700 Colombes, France

[5] AP-HP, Hôpital Beaujon, Infection Control Unit, F-92110 Clichy, France

[6] AP-HP, Hôpital Bichat-Claude Bernard, Bacteriology Laboratory, F-75018 Paris, France

[7] AP-HP, Hôpital Louis Mourier, Infection Control Unit, F-92700 Colombes, France

[8] AP-HP, Hôpital Beaujon, Bacteriology Laboratory, F-92110 Clichy, France

[9] AP-HP, Hôpital Bichat-Claude Bernard, Medical Information Systems Program (PMSI), F-75018 Paris, France;

[10] AP-HP, Hôpital Beaujon, Internal medicine department, F-92110 Clichy, France

[11] AP-HP, Hôpital Bichat-Claude Bernard, Infectious diseases department, F-75018 Paris, France

[12] AP-HP, Hôpital Louis Mourier, Intensive care unit, F-92700 Colombes, France

Keywords: Cost, highly resistant bacteria, infection control, search and isolate, glycopeptide-resistant enterococci, carbapenemase-producing enterobacteriacae, strict contact precautions

Running title: Costs due to highly resistant bacteria

Corresponding author: Gabriel Birgand, Unité d'Hygiène et de Lutte contre l'Infection nosocomiale, GH Bichat-Claude Bernard, 46 rue Henri Huchard, 75877 Paris Cedex 18, France.

Tel: +33 140 256 199; Fax: +33 140 258 811; E-mail: gbirgand@gmail.com

Word count: 3253

Abstract

Objective

To assess costs associated with implementation of a strict "search and isolate" strategy for controlling highly-drug-resistant organisms (HDRO).

Design

Review of data from 2-year prospective surveillance (01/2012 to 12/2013) of HDRO.

Setting

Three university hospitals located in northern Paris.

Methods

Episodes were defined as single cases or outbreaks of glycopeptide-resistant enterococci (GRE) or carbapenemase-producing enterobacteriacae (CPE) colonization. Costs were related to staff reinforcement, costs of screening cultures, contact precautions and interruption of new admissions. Univariate analysis, along with simple and multiple linear regression analyses were conducted to determine variables associated with cost of HDRO management.

Results

Overall, 41 consecutive episodes were included, 28 single cases and 13 outbreaks. The cost (mean ± SD) associated with management of a single case identified within and/or 48 h after admission was €4,443 ± 11,552 and €11,445 ± 15,743, respectively ($p<0.01$). In an outbreak, the total cost varied from €14,864 ± 17,734 for an episode with one secondary case (€7,432 ± 8,867 per case) to €136,525 ± 151,231 (€12,845 ± 5,129 per case) when more than one secondary case occurred. In episodes of single cases, contact precautions and microbiological analyses represented 51 and 30% of overall cost, respectively. In outbreaks, cost related to interruption of new admissions represented 77 to 94% of total costs, and had the greatest financial impact ($R^2 = 0.98$, $p<0.01$).

Conclusion

In HDRO episodes occurring at three university hospitals, interruption of new admissions constituted the most costly measure in an outbreak situation.

Article summary: Strengths and limitations of this study

- Multicenter study to estimate costs of a strict policy for controlling HDRO spread with data collected prospectively, enabling detailed cost analysis in a large panel of situations.
- Provides a basis for minimizing the financial burden of a "search and isolate" strategy. Early identification of patients suspected of being colonized and rapid implementation of contact precautions represented the least expensive scenario.
- The study raises the question of having, or creating, dedicated areas, thus enabling continuity of care together with cost-savings.
- The study did not include: loss of revenue due to systematic placement of colonized patients in a single room, costs linked to prolongation of the hospital stay of case patients and time spent by the infection control team in managing episodes.
- Cost estimations were based on local levels of hospital reimbursement.

INTRODUCTION

Hospitals are increasingly plagued by microorganisms highly-drug-resistant (HDRO) to antimicrobials (1). These HDRO include carbapenamase-producing *Enterobacteriaceae* (CPE) and glycopeptide-resistant enterococci (GRE). In France, the prevalence of GRE and CP-*K. pneumoniae* isolated from blood cultures was 0.8 and 0.5% in 2012, respectively (2).

In France, guideline based on a "search and isolate" strategy have been issued for the control of emerging HDROs (3). They are based on two assumptions: 1) most HDRO-positive patients are asymptomatic carriers with high risk of spreading before outbreak identification; and 2) standard or contact precautions do not reliably halt HDRO transmission in all circumstances.

Infection control measures are gradually implemented according to risk analysis. In case of immediate enforcement of strict contact precautions (identification of a colonized patient upon hospital admission, notably if repatriated or recently hospitalized abroad in the past 12 months), weekly cross-sectional screening of ward patients is recommended, with no additional control measures (3,4).

In an outbreak situation, i.e. with at least one secondary case, measures are upgraded and consist of a strict "search and isolate" strategy, as follows: (a) HDRO-positive patients are cohorted and cared for by dedicated staff; (b) secondary cases are detected via repeated rectal sampling of contact patients, i.e. patients cared for by the same nursing staff as the HDRO-positive patient; (c) contact patients are cohorted and cared for by dedicated staff until three weekly screening tests are negative; (d) HDRO-positive and contact patients are discharged home whenever possible; and (e) the ward with the HDRO-positive patients neither transfers patients to other wards or healthcare facilities (HCF) nor admits new patients until after three negative weekly screening tests of contact patients.

These strict recommendations are difficult to implement and require additional human and material resources. Moreover, interruption of admission to and transfer from the involved ward lead to a decrease in hospital medical service utilization and therefore a loss of hospital income (5). Costs associated with each different epidemiological situation and the determinants of these costs are not known. The purpose of this study was to assess costs associated with implementation of national recommendations for controlling HDRO spread in three university hospitals and to identify determinants of these costs.

PATIENTS AND METHODS

Setting

This study was performed in a French university healthcare group located in northern Paris, the 950-bed Bichat-Claude-Bernard Hospital, the 470-bed Beaujon Hospital and the 490-bed Louis-Mourier Hospital, providing primary, tertiary and long term care with a large panel of surgical and medical specialities. This group of hospital takes part of a public health institution (AP-HP) representing 10% of all public hospital beds in France. These three hospitals are situated in the highly exposed area with a high proportion of patients originating from a foreign country. None of these hospitals has a dedicated ward for housing/regrouping case patients. Case patients were therefore admitted to the ward matching their pathology. In outbreak situations, however, case patients from different wards could be housed in the ward with the highest case number.

Design and data collection on resources used

We reviewed data from 2-year prospective surveillance of HDRO occurrence (01/2012-12/2013). We defined an episode as consisting of new identification of HDRO in a clinical or screening sample, unrelated to previous situations. An outbreak was defined as at least two CPE cases (i.e. one index case and at least one secondary case among the contact patients) occurring in a given hospital, with a clear epidemiological link (stay during the same period of time in the same unit) and involving indistinguishable CPE strain based on species, antibiotic susceptibility and resistance gene. We distinguished four types of episodes involving CPE or GRE strains, from simple situations with low epidemic risk to complex situations with confirmed outbreaks: (i) a single case suspected within 48 h after hospital admission; (ii) a single case suspected more than 48 h after hospital admission; (iii) an outbreak with only one secondary case; and (iv) an outbreak with more than one secondary case.

For each episode, data were prospectively collected, including characteristics of the epidemic (type of HDRO and resistance mechanism, type of ward, dates of admission and discharge of case patients, date of positive results and implementation of contact precautions, number of contact patients); human resources (nursing staff reinforcement allocated to a ward during an episode, either for cohorting colonized patients, i.e. placing the patient in a dedicated location on the ward with dedicated healthcare workers (HCW), or for decreasing the workload of the unit by globally increasing the nurse-to-patient ratio); material for the three weekly screening protocol and patient care; and duration of interruption of new admissions.

Cost analysis

Costs were considered from a hospital perspective. For human resources, staff reinforcement was calculated based on the number of supplementary hours put in by nurses and nursing assistants on the basis of their hourly salary. (Table 1) The cost calculation was performed until the date of analysis, nine months after the end of the last episode. Costs associated to readmission of contact patients after this date were not considered.

Table 1: Methods of cost analyses

Type	Variables collected	Value
Loss of income	Number of hospital bed days lost	
	Mean cost billed per hospital day per specialty	
	Medical units	335 to 601 €
	Surgical units	306 to 940 €
	ICU	609 to 2078 €
Staff reinforcement	Cost of 1 h of a nursing assistant	24.6 €
	Cost of 1 h of a nurse	30.5 €
Cost of micro-analysis (5)	Negative culture for GRE	13.9 €
	Cepheid Xpert *van*A/*van*B	37.3 €
	Positive culture for GRE strain	117.8 €
	Negative culture for CPE	7.7 €
	Negative culture for CPE, + for ESBLPE	21 €
	Positive culture for CPE	115 €
Cost of contact precautions	Cumulative number of hospital days, HDRO patients	

(6)	Cost of gloves	0.05 € /pair
	Cost of gowns	0.3 € each
	Cost of nursing contact (1 min) *Papia et*	0.26 €
	al.(7)	30
	Number of patient contacts per day	18.5 €
	Cost per HDRO patient per day	

Abbreviation: ESBLPE, extended spectrum beta-lactamase; ICU, intensive care unit; GRE, Glycopeptide resistant enterococci; CPE, carbapenemase producing enterobacteriacae; HDRO, highly drug resistant organism.

For the laboratory sector, methods for detecting CPE and GRE in screening samples have been described elsewhere (8)(9). Unit costs for resources used to screen were computed based on use of the following resources: selective chromogenic plates or PCR-based method, identification tests and susceptibility tests, depending on the above-described situations. Personnel costs for laboratory tests were calculated on the basis of the hourly salary of a senior staff member and the estimated time required for each step. Unit cost of PCR screening included acquisition of the GeneXpertTM machine (Cepheid, Sunnyvale, CA) and XpertTM *van*A/*van*B test cartridges and performing cultures for GRE on a *van*A/*van*B-positive sample or samples without PCR results (invalid tests) (5).Cost of contact precautions included that of gloves and gowns used for case patients, assuming an average of 30 patient contacts per day of isolation and nursing costs for additional time to donning and discarding gloves and gown (1 min) (6).

Finally, to estimate the decrease in hospital service use, we first computed the difference between admission capacity, assuming 100% bed occupancy, and the number of patients admitted when a HDRO-positive patient was identified in the ward. Next, we

estimated costs attributable to decreased occupancy, by multiplying the number of missed patient-days by the mean cost of a hospital day, depending on the type of pathology and the ward. According to the French reimbursement system, the mean cost per hospital day was the total cost related to hospital stay in the previous year in the affected ward divided by the number of patient-days (10). Total cost related to missed hospital days in a ward was estimated using the French diagnosis-related group system according to which patients are classified into statistically and clinically homogeneous groups on the basis of their clinical and demographic data.

Statistical analysis

Categorical independent variables were described using proportions and continuous variables via medians and 25th-75th percentiles. For costs, means with standard deviation were used to take into account outliers and data dispersion. Univariate comparisons used a Wilcoxon rank or Chi-2 test as required. Statistics on categorical variables were based on two-way analysis of variance (ANOVA). After univariate analysis, simple and multiple linear regression analyses were carried out, with overall cost as the dependent variable, to determine those costs most strongly associated with the overall financial burden. The overall percentage of explained variance of the model was described by the adjusted R^2 of observed costs. Predictive values of models built were tested using the method of "Leave One Out Cross-Validation" (jack-knife) (11). This method assesses the predicted costs in one episode based on the model built with all other episodes. We analyzed observed versus predicted costs for all episodes, and specifically for outbreaks, by giving the mean and median predictive error per episode and the mean relative predictive error. Statistical analyses were done with R software, version 2.15.2.

Ethics Committee Approval

Because of the observational and blinded nature of the study, the institutional review board of the Bichat-Claude Bernard Hospital waived the requirement for informed consent. According to this statement, written consents of patients were not collected. Patient information was de-identified by attributing a number. The study has been approved by the ethical committee of the Bichat-Claude Bernard Hospital group.

RESUTS

Characteristics of HDRO episodes

Overall, we observed 41 HDRO episodes (34 at Bichat-Claude Bernard, 6 at Beaujon and 1 at Louis Mourier Hospital), with a total of 113 colonized or infected patients (Table 2).

Table 2: Characteristics of episodes with highly resistant organisms according to type of episode.

Description of episode characteristics	Total N=41	A single case (suspicion ≤48 h after admission) N=14	A single case (suspicion >48 h after admission) N=14	Episode with 1 secondary case N=6	Episode with > 1 secondary case N=7
Number of episodes per hospital, n (%)					
Bichat-Claude Bernard	34 (83)	10 (71)	13 (93)	6 (100)	5 (70)
Beaujon	6 (15)	4 (29)	1 (7)	0	1 (15)
Louis Mourier	1 (3)	0	0	0	1 (15)
Year, n (%)					
2012	24 (58)	6 (43)	8 (57)	6 (100)	4 (57)
2013	17 (42)	8 (57)	6 (43)	0	3 (43)

Type of HDRO, n (%)					
GRE	20 (49)	3 (21)	6 (43)	5 (83)	6 (86)
CPE	19 (46)	10 (71)	8 (57)	1 (17)	0
GRE + CPE	2 (5)	1 (8)	0	0	1 (14)
Type of ward at identification, n (%)					
ICU	7 (17)	4 (29)	2 (14)	1 (17)	0
Medical	23 (56)	8 (57)	6 (43)	3 (50)	6 (86)
Surgical	10 (24)	2 (14)	6 (43)	2 (33)	0
Rehabilitation	1 (3)	0	0	0	1 (14)
Time from admission to suspicion (screening), days, median (IQR)	4 (1-26)	0 (0-1)	12.5 (5-33)	14 (4-26)	42 (3-75)
Time from admission to HDRO+ result, days, median (IQR)	6 (3-26)	0.5 (0-3)	12.5 (5-33)	14 (7-26)	42 (6-75)

Number of contact patients, median (IQR); min-max	32 (13-65)	5 (0-21); 0-65	34 (19-76); 0-260	48.5 (32-53); 19-262	66 (53-152); 48-237
Number of secondary cases, median (IQR); min-max	-	0	0	1	3 (2-22); 2-29
Suspension of admissions, days median (IQR); min-max	0 (0-3)	0 (0-0); 0-10	1 (0-3); 0-7	3 (0-3); 0-7	8 (6-12); 0-62

Abbreviation: ESBLPE, extended spectrum beta-lactamase; ICU, intensive care unit; GRE, Glycopeptide resistant enterococci; CPE, carbapenemase producing enterobacteriacae; HDRO, highly drug resistant organism; IQR, interquartile range.

We observed 24 episodes in 2012 and 17 in 2013. Index cases were colonized with GRE in 20 (49%) episodes, CPE in 19 (46%) and with both HDRO in 2 (5%) episodes. HDRO were cultured from clinical samples in 13 (12%) patients, 9 with GRE and 4 with CPE (p=0.85). Among the 41 episodes, 14 (34%) were single cases suspected within 48 h after admission; 14 (34%) were single cases suspected more than 48 h after admission; 6 (15%) were with one secondary case; and 7 (17%) were outbreaks with more than one secondary case. Patients colonized or infected with GRE were single cases in 10/22 cases and generated 12 outbreaks (among which one carried both GRE and CPE). These outbreaks resulted in a median of one secondary case (IQR, 0-2; range, 0-29). Episodes with CPE were single cases in 18/19 situations and with one secondary case in the remaining episode. The difference in the number of secondary cases was significant between GRE and CPE (p<0.01). The affected wards included medical (23 episodes), surgical (10 episodes), intensive care (7 episodes) and rehabilitation (one episode) wards.

The median time from hospital admission to suspicion of a first case was 4 days (IQR: 1-26). It was 1 day (0-8) and 14 days (3-42) for CPE and GRE, respectively (p=0.01). This duration was significantly longer in outbreak situations, 21 (4-62) days vs. 2 (0-12.5) days in single cases (p<0.01). In eight episodes, the suspected patient was placed in a contact precaution state upon hospital admission, the risk of cross transmission was considered low and contact patients were not followed. For the 33 other episodes, the median number of contact patients was 32 (IQR: 13-65). The number of contact patients was higher for GRE than for CPE episodes, 52 (15-76) and 24 (0-37), respectively, (p=0.06).

The median duration of episodes was 3 days (IQR, 0-10). Interruption of new admissions was decided for 20 episodes. The median duration of interruption in outbreak situations (≥ 1 secondary case) was 4.5 days (IQR, 1.5-8, range 0-62). This median duration of interruption was significantly higher if case patients were suspected and isolated more than

48 h after admission (2 days) than for suspected patients identified at hospital admission (1 day)(p=0.02) and for outbreaks with only one secondary case (3 days) as compared to outbreaks with more than one secondary case (16 days) (p=0.02).

Costs associated with HDRO episodes

Concerning human resources, the nursing staff was reinforced in 16 episodes, among which 10 (62%) were outbreak episodes. Nursing assistants represented the main reinforced staff category, with a mean of 61 supplementary h per episode (range, 0-1603). Nurses were requested in 15 episodes, with a mean number of 38 supplementary h. The mean cost associated with staff reinforcement was €2,686 (SD, €8,861), varying from 0 to €55,081. (Table 3)

Table 3: Resources used in, and costs associated with, episodes of highly-resistant organisms per type of episodes

	Total N=41		One single case (suspicion ≤48h after admission) N=14		One single case (suspicion >48h after admission) N=14		Episode with 1 secondary case N=6		Episode with > 1 secondary case N=7	
	Median (IQR)	Min-max	Average (SD)	Min-max	Average (SD)	Min-max	Average (SD)	Min-max	Average (SD)	Min-max
Loss of income, €1,000s	**25.2 (67.3)**	**0-348.5**	**2.5 (9.3)**	**0-34.9**	**9.6 (15.7)**	**0-54.9**	**10.2 (16.2)**	**0-40.6**	**115 (134)**	**1.5-348**
Loss hospital bed days	35 (88.7)	0-520	7.4 (27.8)	0-104	13.6 (23.2)	0-90	19.2 (28.3)	0-67	165 (182)	5-520
Staff reinforcement, €1,000s	**2.7 (8.8)**	**0-55.1**	**0.77 (2.3)**	**0-8.4**	**0.3 (0.6)**	**0-1.9**	**0.7 (1.1)**	**0-2.9**	**12.9 (18.9)**	**0.45-55.1**
Hours of assistant nurses	61.4 (252.7)	0-1603	15.7 (58.7)	0-219.5	4.4 (11.4)	0-42	9.3 (11.9)	0-30	311 (574)	0-1603
Hours of nurses	38.5 (93.5)	0-512	12.8 (32.7)	0-98	5.9 (14.2)	0-48	16,1 (27.6)	0-71	174 (169)	7.5-512
Cost of microbiological analysis, €1000s	**2.0 (3.4)**	**0-19.6**	**0.53 (0.49)**	**0-1.5**	**0.9 (0.64)**	**0.13-2.2**	**2.7 (1.7)**	**0.87-5.5**	**6.7 (6.3)**	**2.3-19.6**

For GRE strains, number of:										
Negative culture	59.9 (101.6)	0-426	39.7 (33.7)	0-75	65 (52)	10-150	104 (95.7)	17-263	198 (156)	76-426
Cepheid Xpert *van*A/*van*B	18.4 (45.4)	0-279	0.8 (2.9)	0-11	4.1 (8.8)	0-29	32.7 (21.9)	0-62	70.4 (92.8)	20-279
Positive culture	2.2 (6.2)	0-29	0.2 (0.5)	0-1	0.6 (0.5)	0-1	2 (0)	2-2	10.7 (12.2)	2-29
For CPE strains, number of:										
Negative culture	20.5 (35.5)	0-137	27 (44)	0-137	49 (35)	0-112	70	70-70	102	102-102
Negative culture, + for ESBLPE	4.6 (10.3)	0-61	15.5 (19.1)	1-61	7.7 (4.2)	4-17	5	5-5	-	-
Positive culture	0.12 (0.39)	0-2	0.1 (0.3)	0-1	0.2 (0.4)	0-1	2	2-2	0	0-0
Cost of contact isolation, €1,000s	**0.93 (1.0)**	**0-4.7**	**0.63 (0.74)**	**0.1-3.1**	**0.58 (0.57)**	**0-1.8**	**1.18 (0.44)**	**0.61-1.79**	**1.99 (1.74)**	**0.49-4.69**
Cumulative LOS of HDRO patients	49.4 (55.7)	0-254	34.3 (40.3)	7-166	31.8 (30.7)	0-98	64 (23.9)	33-97	111.5 (102.7)	27-254
Overall cost, €1,000s	**30.9 (77.2)**	**0.3-370.7**	**4.44 (11.5)**	**0.3-44.3**	**11.4 (15.7)**	**0.6-57.2**	**14.8 (17.7)**	**1.4-45.9**	**136.5 (151.2)**	**16.7-370.7**
Cost per case, €1,000s	**8.7 (12.2)**	**0.3-57.2**	**4.44 (11.5)**	**0.3-44.3**	**11.4 (15.7)**	**0.6-57.2**	**7.4 (8.8)**	**0.7-22.9**	**12.8 (5.1)**	**4.1-12.3**

Abbreviation: LOS, length of stay; GRE, Glycopeptide resistant enterococci; CPE, carbapenemase producing enterobacteriacae; HDRO, highly drug resistant organism; IQR, interquartile range; SD, standard deviation.

For laboratory resources, the median number of screening samples performed per episode was 69 (IQR, 27-119), with 110 (IQR, 66-152) in GRE episodes and 46 (IQR, 13-74) in CPE episodes. Mean costs of microbiological analysis were €2,050 (SD, €3,428), €3,423 (SD, €4,479) for GRE episodes and €742 (SD, €872) for CPE episodes (p<0.01).

The median duration of contact precautions for HDRO-colonized patients was 33 (IQR, 17-65) days. The mean cost of protective equipment used for contact isolation was €931 (SD, €1,022).

In wards affected by an episode of HDRO, the duration of interruption of admissions ranged from zero to 694 patient bed-days according to episode, with a mean varying from 7 patient bed-days for episodes with a single case identified at admission to 241 patient bed-days in case of outbreak with more than one secondary case. The mean cost associated with interruption of admissions was estimated at €25,242 (SD, €67,297), varying from zero to €348,468 for the largest outbreak. In single HDRO cases, the mean cost associated with interruption of admissions for the episode was significantly higher when the case patient was suspected >48 h after admission (€9,666) than when it was suspected <48 h (€2,493, p<0.01). In the 13 outbreaks, mean cost associated with interruption of admissions for the episode was €66,516 (SD, €109,557) varying from zero in three situations with one secondary case to €348,468 with 29 secondary cases. The mean cost associated with interruption of admissions was €44,020 for GRE episodes and €6,834 for CPE episodes (p=0.18).

The overall mean cost of infection control measures was €4,443 in a single case identified within 48 h after admission. Mean costs were higher if a single case was identified more than 48 h after the admission, at €11,445 (p<0.01). In an outbreak situation, the mean cost varied from €14,864 (SD, €17,734) for an episode with one secondary case to €136,525 (SD, €151,231) for outbreaks with at least two secondary cases. The mean cost per case was

€7,432 (SD, €8,867) in episodes with one secondary case and €12,845 (SD, €5,129) in other outbreak episodes (P < 0.01).

Analysis by category of cost

Overall, cost associated with interruption of admissions represented the most expensive category, with an average of 38% (range 0-97%) of total cost per episode, followed by microbiology testing 29% (0-100%), contact precautions 27% and staff reinforcement 6% per episode.(Figure 1). When outbreaks had one secondary case, cost associated with interruption of admissions represented 53 % of total cost per episode; this proportion increased to 74% when outbreaks had more than one secondary case. In episodes with a single case suspected within the first 48 h of admission, contact precautions and microbiological analyses represented 53 and 34% of average overall cost per episode, respectively. When we aggregated costs for all episodes, the interruption of activity represented 81.7% of the overall cost, followed by the human resources 8.7%, microbiology 6.6% and contact precautions 3%.

Linear regression analysis was performed to assess cost determinants using data from the 41 episodes. Individually, cost associated with interruption of admissions was the highest item affecting the cost of infection control strategies (R^2=0.98, p<0.01), followed by microbiological analyses (R^2= 0.76, p<0.01), staff reinforcement (R^2= 0.59, p<0.01) and contact precautions (R^2= 0.25, p<0.01). The linear model, including the duration of interruption of new admissions as an independent variable, predicted the overall cost of episodes, with a median error of €3,394 (IQR: 704-15,942), or 62% of median overall cost. When restricting analysis to the 7 outbreak episodes with at least 2 secondary cases, the same

model more accurately predicted overall cost, with a median error of €19,038 (IQR: 16,056-69,486), or 27% of the median overall cost per episode. We used single and multiple linear regression to predict overall cost, using all potential explicative variables, individually or combined**.** None of the models built accurately fit the data.

DISCUSSION

This study was performed to assess the financial burden of implementation of a strict national policy to control spread of HDRO. Mean cost per episode was measured at €4,443 per episode for single cases isolated at admission to €136,525 for outbreaks with at least 2 secondary cases. The mean cost per case varied from €4,443 for a single case to €12,845 in outbreak situations. Interruption of admissions was the most costly measure in an outbreak situation.

To our knowledge, this is the first multicenter study to estimate costs of a strict policy for controlling HDRO spread. Data were collected prospectively, enabling detailed cost analysis in a large panel of situations. Previous studies mainly focused on GRE, and primarily assessed costs related to an outbreak situation (12–14), infection, prolonged length of stay (15–17) or implementation of surveillance (18–21). Studies focusing on cost associated with outbreak situations measured the overall financial burden, varying from €4, 161 to €40,131 per case (12–14,21). Methods used were variable, with approximate measures and occasional missed critical cost categories.

Antibiotic resistance has become a worldwide concern, and a recent World Health Organization report warned of a "post-antibiotic era". Strict French national strategy appeared to be effective in controlling the spread of HDRO, as illustrated by European Antimicrobial Resistance Surveillance System data and results from large hospital networks (2,22–24). These guidelines exclude multidrug resistance organisms requiring basic contact precautions by the fact that they have become endemic (Methicillin resistant *Staphylococcus aureus)* or pandemic (extended spectrum beta-lactamase producing *Enterobacteriacae)*

making the search and destroy strategy useless. In emerging situations, we can assume that applying a search and isolated strategy for the control of these organisms would lead to comparable costs. Despite a small proportion of HDRO-positive clinical samples and the fact that very few were infected, this control strategy may be justified by the high colonized-to-infected ratio, with possible spread from unidentified colonized patients. However, these recommendations are costly, difficult to implement on a practical basis and require human/laboratory resources and occasional need for interruption of admissions. The present study provides a basis for minimizing the financial burden of a "search and isolate" strategy.

In our study, early identification of patients suspected of being colonized and rapid implementation of contact precautions represented the least expensive scenario. In this context, ward activity was usually maintained, with costs mainly due to staff reinforcement and laboratory techniques. In situations with delayed identification, suspension of admissions was often decided pending results of screening of contact patients. Along this line, guidelines were issued in order to promptly identify, screen and implement strict contact precautions for patients recently hospitalized in a foreign country (3,25)

In outbreak situations, suspension of admissions was the most expensive measure, with mean costs of every secondary case estimated at €12,845, whereas costs due to human resources were lower. The present study raises the question of having, or creating, dedicated areas, thus enabling continuity of care together with cost-savings. A literature review did not find any study that performed cost-effectiveness/benefit or savings analysis of strict measures for controlling HDRO spread in outbreak situations. This underlines the need for further studies on cost effectiveness of different strategies to control HDRO dissemination and optimize both the financial and medical burden of recommendations.

Our study had limitations. First, we did not include potential loss of revenue due to systematic placement of colonized patients in a single room. Like other French HCF, the three hospitals possess a high rate of single rooms for patient isolation or privacy (26). Hence, we assumed that a single room was standard in the affected unit. Secondly, costs were estimated based on local levels of hospital reimbursement. Costs of suspension of admissions would be much higher in hospitals with higher daily costs. However, a quick review shown that costs per bed days are very similar as those found in the literature (27–30). Moreover, the presentation with proportion of the overall cost by category allows a clear interpretation. Thirdly, we did not consider costs linked to prolongation of the hospital stay of case patients. We had previously estimated the average prolongation at 23 days, representing €6,981 to €47,800 per case (31). In the present study, it was not possible to precisely determine the prolongation of hospital stay, which would have been based on a subjective ward physician estimate. Fourthly, we did not measure time spent by the infection control team in managing episodes. Fifthly, the setting of this study (three hospitals in one country) imposes the caution regarding the generalizability of crude costs. However, distributions of expenses should remain approximately the same whatever the hospital and the country. Sixthly, the loss of activity was estimated based on a 100% bed occupancy. This assumption appear to be contestable, but the proportion of free bed-days was so small that we considered them as negligible. Finally, no statistical model built fit the data, mainly because of the heterogeneity of situations and control measures. Specifically, loss of income varied from 0 to €54,976 for episodes with single cases and represented the most heterogeneous variable, directly linked to the context and risk assessment and control measures decided/set by the infection control team.

In conclusion, cost analysis of a large number of episodes showed that suspension of admission was the most costly measure in an outbreak situation. Further studies are needed to assess the cost-effectiveness of cohorting to control HDRO spread. Early identification and implementation of contact precautions may lead to major cost savings in a context of a strict HDRO policy.

Acknowledgments: We thank the members of the infection control teams for their dedication: S Belorgey, W Guerinot, G Bendjelloul, I Garrigues and F Mignot.

Funding statement: None

Competing interests statement: No, there are no competing interests.

Author's contribution:

All authors participated in data collection, analysis and writing of the manuscript

Data sharing statement: We state that there is no additional unpublished data from the study.

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Figure 1: Cost distribution per category of resource and type of episode

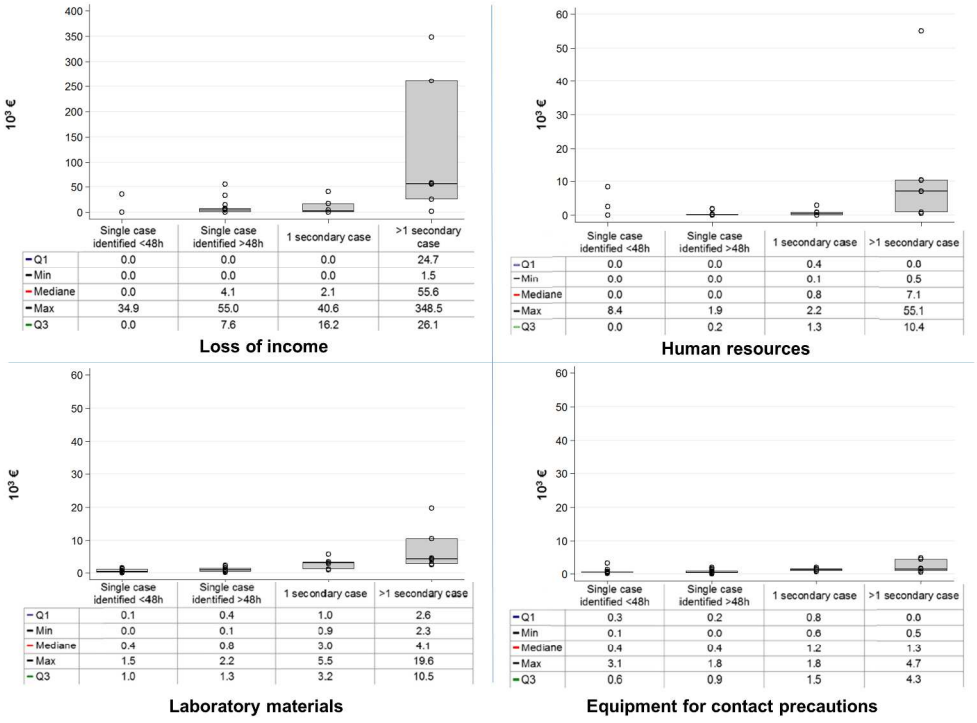

Figure 1: Cost distribution per category of resource and type of episode
278x209mm (300 x 300 DPI)

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1 OK	(*a*) Indicate the study's design with a commonly used term in the title or the abstract
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found
Introduction		
Background/rationale	2 OK	Explain the scientific background and rationale for the investigation being reported
Objectives	3 OK	State specific objectives, including any prespecified hypotheses
Methods		
Study design	4 OK	Present key elements of study design early in the paper
Setting	5 OK	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection
Participants	6 OK	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7 OK	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable
Data sources/ measurement	8* OK	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group
Bias	9 OK	Describe any efforts to address potential sources of bias
Study size	10 OK	Explain how the study size was arrived at
Quantitative variables	11 OK	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12 OK	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

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Results		
Participants	13* OK	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14* OK	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15* OK	*Cohort study*—Report numbers of outcome events or summary measures over time
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16 OK	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17 OK	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18 OK	Summarise key results with reference to study objectives
Limitations	19 OK	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20 OK	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21 OK	Discuss the generalisability (external validity) of the study results
Other information		
Funding	22 OK	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.