MAJOR ARTICLE

Containment of a Country-wide Outbreak of Carbapenem-Resistant *Klebsiella pneumoniae* in Israeli Hospitals via a Nationally Implemented Intervention

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Background. During 2006, Israeli hospitals faced a clonal outbreak of carbapenem-resistant *Klebsiella pneumoniae* that was not controlled by local measures. A nationwide intervention was launched to contain the outbreak and to introduce a strategy to control future dissemination of antibiotic-resistant bacteria in hospitals.

Methods. In March 2007, the Ministry of Health issued guidelines mandating physical separation of hospitalized carriers of carbapenem-resistant Enterobacteriaceae (CRE) and dedicated staffing and appointed a professional task force charged with containment. The task force paid site visits at acute-care hospitals, evaluated infection-control policies and laboratory methods, supervised adherence to the guidelines via daily census reports on carriers and their conditions of isolation, provided daily feedback on performance to hospital directors, and intervened additionally when necessary. The initial intervention period was 1 April 2007–31 May 2008. The primary outcome measure was incidence of clinically diagnosed nosocomial CRE cases.

Results. By 31 March 2007, 1275 patients were affected in 27 hospitals (175 cases per 1 million population). Prior to the intervention, the monthly incidence of nosocomial CRE was 55.5 cases per 100,000 patient-days. With the intervention, the continuous increase in the incidence of CRE acquisition was halted, and by May 2008, the number of new monthly cases was reduced to 11.7 cases per 100,000 patient-days ($P < .001$). There was a direct correlation between compliance with isolation guidelines and success in containment of transmission ($P = .02$). Compliance neutralized the effect of carrier prevalence on new incidence ($P = .03$).

Conclusions. A centrally coordinated intervention succeeded in containing a nationwide CRE outbreak after local measures failed. The intervention demonstrates the importance of strategic planning and national oversight in combating antimicrobial resistance.

Carbapenem-resistant Enterobacteriaceae (CRE) are an emerging threat, because carbapenems are the agents of last resort in treating life-threatening infections caused by drug-resistant Enterobacteriaceae [1]. Until recently, CRE were extremely rare. Over the past decade, outbreaks of infection due to CRE, primarily *Klebsiella pneumoniae*, have occurred in New York City and in other areas of the United States; by 2007, the proportion of carbapenem-resistant isolates among all isolates of *K. pneumoniae* reported to the National Healthcare Safety Network was 10%, and in some areas, the proportion reached as high as 30% [2–4]. These outbreaks have been associated with organisms that produce the plasmid-encoded carbapenemase KPC. In recent years, the occurrence of KPC-producing Enterobacteriaceae outside of the United States has been reported [5–7]. Infection due to CRE is an independent risk factor for heightened mortality among hospitalized patients [8–10].

Received 20 March 2010; accepted 4 January 2011.

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Clinical Infectious Diseases 2011;52(7):848–855

1058-4838/2011/527-0001$37.00
DOI: 10.1093/cid/cir025

In 2006, outbreaks of carbapenem-resistant *K. pneumoniae* were noted at multiple Israeli hospitals. The resistance was mediated by KPC [11, 12], and isolates were mostly susceptible only to colistin and gentamicin. A dominant clone producing KPC-3 was responsible for the outbreaks in numerous facilities and belonged to the genotype of a strain that had been implicated in multiple outbreaks in the United States [13]. Throughout 2006, despite local infection-control efforts, CRE outbreaks continued, with accelerating incidence at multiple hospitals [10, 14], and it became evident in a meeting of Israeli infection-control professionals in February 2007 that the spread of CRE was occurring nationwide. This finding was reported to the Israel Ministry of Health (MOH), and an intervention was planned. The objective of this study was to determine the impact of the intervention on new nosocomial acquisitions of CRE nationwide.

METHODS

Plan of Action

The plan was designed to ensure that every patient identified with CRE carriage who was hospitalized in an acute-care facility in Israel would be treated separately from noncarriers and that compliance with this requirement would be monitored daily throughout the country by a central authority. Enterobacteriaceae resistant to $\geqslant 1$ carbapenems by susceptibility testing were considered to be CRE. The plan was conceived in accordance with the principle that regional coordination of infection-control activities is a key component of containment of spread of resistance [15, 16]. In March 2007, the MOH implemented an intervention that comprised 3 components. The first 2 were mandatory reporting to public health authorities of every patient with a laboratory specimen that grew CRE and mandatory isolation of hospitalized carriers of CRE. A carrier was defined as any patient from whom CRE had been isolated, at any time, in any specimen sent for culture to a clinical microbiology laboratory. Guidelines for hospitals mandated strict adherence to contact isolation measures [17] and placement of patients in self-contained nursing units—either single rooms or cohorts—containing all materiel needed for their care and staffed by dedicated nurses on all shifts (ie, a nurse caring for patients in isolation was not to be assigned to care for noncarriers during the same shift). The requirement of dedicated nursing was based on the premise that staff represented a significant potential vector for transmission to other hospitalized patients [18].

Given the lack of data on carriage duration, hospitals were instructed to re-isolate known carriers at subsequent hospital admissions. The decision to monitor all CRE, rather than carbapenem-resistant *K. pneumoniae* alone, was taken to detect an outbreak caused by carbapenemase-producing Enterobacteriaceae other than *K. pneumoniae* [19–21].

The third component was the creation of the Task Force on Antimicrobial Resistance and Infection Control, which comprised professionals from the fields of infection control, clinical microbiology and public health and which reported directly to the MOH Deputy Director-General. The task force was invested with the statutory authority to collect data from hospitals and to intervene as necessary to contain the outbreak. It began operations on 1 May 2007.

Setting

The intervention was performed in the acute-care hospitals in Israel (area 22,000 km^2, population 7.3 million), comprising $\sim$14,000 beds. All health care facilities in Israel are under MOH regulation.

Data Collection

Data were solicited via e-mail sent by the task force to hospital directors. The task force collected data on hospital infrastructure and activity, including staffing, procedures, infection-control policy, microbiology laboratory operations, and the methods used to identify CRE. Each hospital was required to provide a daily census of CRE carriers, including the patient name and identification number, date of hospital admission, date and anatomical site of first culture sample positive for CRE, and location in the hospital where CRE was likely to have been acquired. The daily census also included a checklist designed to monitor the extent of compliance with isolation guidelines for each carrier, which consisted of the following yes/no questions: (1) labeled for contact isolation; (2) gowns/gloves required; (3) physical separation from noncarriers; and (4) dedicated nursing staff. The daily census included an itemization of changes from the previous census (ie, a list of patients who had died, been transferred to another facility, or had been discharged from the hospital. For transferred patients, the name of the admitting facility was requested. Hospitals with low CRE carrier prevalence (the number of patients with a positive culture during the current hospitalization or in the past) were permitted to send the census in the event of updates in it, rather than sending a daily census. All data were transmitted 0electronically by hospital personnel to the task force.

Site Visits

The task force conducted visits at each hospital, which consisted of discussions with the hospital administration and infection-control and microbiology laboratory staff, as well as visits to selected wards, intensive care units, the emergency department, and the microbiology laboratory. A summary, including points requiring attention to improve the hospital's ability to confront

CRE, was sent to the hospital director following each visit and was copied to the MOH Deputy Director-General.

Feedback

Census reports were reviewed on the day of receipt, and feedback was provided to the appointed hospital representatives addressing deviations from guidelines, suggestions for maximizing compliance, and questions arising in the course of implementation. Monthly feedback on performance, in a format enabling inter-hospital comparison, was provided to hospital directors and the MOH directorate. Performance was measured by incidence of CRE nosocomial cases as determined by clinical culture. A nosocomial case was defined as the first-ever positive culture for CRE taken at least 48 h after hospital admission if the patient came from home and at least 72 h after hospital admission if the patient was transferred from another facility. Feedback was also provided regarding compliance with isolation guidelines as reported in the daily census. Average monthly compliance was defined as the proportion of CRE patient-days of compliance per the total number of CRE patient-days. To ensure confidentiality, hospitals were identified in the monthly reports by code, with individual keys known only to the staff of each hospital and the task force. Reports were stratified by hospital type and average CRE carrier prevalence. When there was evidence of uncontrolled transmission at an individual hospital, the task force conducted a field investigation and issued recommendations that were based on its findings.

Study Period and Data Collection

Retrospective data on first-time CRE patient isolates as of 1 January 2005 were solicited from the hospitals, including patient name and identification number, date and site of culture. The nationwide intervention began with the distribution of the isolation guidelines on 12 March 2007. Daily census reports were collected prospectively beginning in May 2007, and as of 1 June 2007, the majority of hospitals were reporting data. Prior to this date, all CRE isolates were considered to be nosocomially acquired. We examined the following factors in our analysis: (1) CRE colonization pressure as expressed by carrier prevalence [22]; (2) incidence of nosocomial CRE acquisition detected by clinical culture (ie, culture of CRE from a non-gastrointestinal site); (3) degree of compliance; (4) relationship of prevalence to incidence; and (5) impact of compliance on incidence.

Thirty-day mortality was determined by cross-reference of the national carrier database with the national death registry. Analysis and reporting of data collected during the intervention were approved by the jurisdictional ethical review board. In June 2008, the intervention entered a new phase with the issuance of national guidelines for CRE active surveillance. Therefore, the results of the intervention until 31 May 2008 are reported here.

Statistical Analysis

Statistical analysis was performed using SPSS software, version 17 (SPSS). Incidence rates were compared via χ^2 test. Trend analysis using a generalized linear mixed model (GLMM) was performed to examine trends and the influence of various variables on incidence. The unit of observation was hospital-month to allow for differences between hospitals and the effects of time. Variables suspected of influencing incidence were entered into the model and were removed if their P value was $>.05$. Examination of the data led to the finding of an autoregressive structure. Effect modification was searched for by examining interaction terms between significant covariates in the model. For all tests, $P \leq .05$ was considered to be statistically significant.

RESULTS

The intervention included 27 acute-care hospitals comprising 13,040 beds. Thirty-four site visits were paid, including at least 1 visit at each hospital. Retrospective data from 1 January 2005–30 April 2007 were available from 21 hospitals, representing 11,158 beds (86% of the total). During this period, a steep increase in CRE incidence was noted. The monthly average of new cases was as follows: 2005, 6 cases (1.9 cases per 100,000 patient-days); first half of 2006, 39.5 cases (11.8 cases per 100,000 patient-days); second half of 2006, 89 cases (27 cases per 100,000 patient-days); first quarter of 2007, 143 cases (41.9 cases per 100,000 patient-days). The monthly number of new clinical isolations of CRE increased sharply during the latter half of 2006 and the first quarter of 2007, reaching a peak of 185 in March 2007 (55.5 cases per 100,000 patient-days), which was the month in which the national guidelines were issued. The cumulative number of cases during the pre-intervention period was 1275. Approximately 92% of CRE isolates reported to the species level during this period were *K. pneumoniae*; the remainder were *Enterobacter* species (4%), *Escherichia coli* (3%), *Proteus* species (1%), and *Providencia* species (<1%).

Intervention Period–April 2007–May 2008

Incidence The intervention halted the steep increase in incidence observed until April 2007. Beginning in May 2007, a steady and continuous downward trend in incidence was noted, continuing through September 2007, by which time the monthly incidence had decreased to 57 cases (15.9 cases per 100,000 patient-days, 29% of the peak incidence observed in March). In October 2007, the incidence increased to 87 cases (22.6 cases per 100,000 patient-days); from that point, it decreased with monthly variation, reaching a low of 45 cases in May 2008 (11.7 cases per 100,000 patient-days, which was 21% of the March 2007 peak; $P < .001$). The incidence curve is depicted in Figure 1.

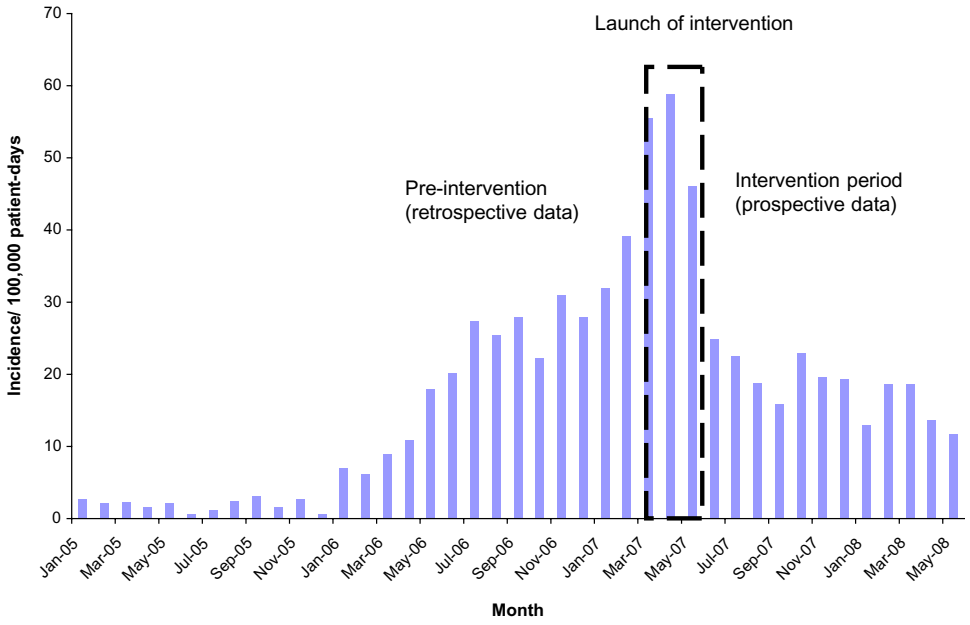

Figure 1. Monthly incidence of carbapenem-resistant Enterobacteriaceae detected by clinical culture per 100,000 patient-days, January 2005–May 2008. The intervention was gradually implemented nationwide from March through May 2007. Data through May 2007 were assembled retrospectively. Data from 1 June 2007 through 31 May 2008 were collected prospectively. The intervention led to a reduction in monthly incidence from a pre-intervention peak of 55.5 cases per 100,000 patient-days in March 2007 to 11.7 cases per 100,000 patient-days in May 2008 ($P < .001$).

Compliance As of 1 May 2007, data on incidence, prevalence, and compliance were collected prospectively. By June, census reports were received by all hospitals, allowing reporting of prospective data. There was almost universal compliance with guidelines during the entire intervention period regarding labeling for contact precautions, use of gowns and gloves, and physical separation. Compliance with dedicated nursing staffing was not uniform throughout, with an upward trend during the study period. Because dedicated staffing was the only component of the compliance checklist with meaningful variation between hospitals and over time, this element was considered to be the marker for compliance with isolation guidelines for the purposes of evaluation of the effect of compliance on incidence.

Multivariable Model The model is represented in Table 1. Incidence was found to be significantly associated with prevalence (ie, the greater the number of CRE carriers hospitalized, the higher the incidence of new acquisitions was likely to be). For each hospitalized carrier, the incidence increased by 0.43 ($P < .001$). Compliance with the dedicated staffing guideline was associated with lower incidence. For each increase of 10% in compliance, there was a decrease in incidence of 0.6 cases per 100,000 patient-days ($P = .02$).

Table 1. Multivariable Model of Variables Affecting Monthly Incidence of Carbapenem-Resistant Enterobacteriaceae (CRE)

Variable	Effect estimate	95% CI	*P*
CRE carrier prevalence	0.43	0.36–0.50	<.001
Compliance with dedicated staffing	−.06	−.11 to −.01	0.02
Months of intervention	−1.10	−1.64 to −0.56	<.001
Intercept	12.16	7.16–17.17	<.001

NOTE. Incidence and prevalence were evaluated per 100,000 patient-days. CI, confidence interval.

Time elapsed from the start of the intervention was also found to be significantly associated with incidence ($P < .001$). The effect of the intervention was sustained over time. For each elapsed month in the intervention period, incidence decreased by 1.1 cases per 100,000 patient-days ($P < .001$). Upon examining interaction terms, we found that compliance modified the effect of prevalence on incidence. The model incorporating this interaction is represented in Table 2. For each 10% increase in compliance, there was a 2% reduction in the association between prevalence and incidence ($P = .03$). The relationship between compliance and incidence is depicted in Figure 2.

Between November 2007 and May 2008, a downward trend in monthly incidence was noted, reaching an all-time low of 45 patients in May 2008 (11.7 cases per 100,000 patient-days). An assessment by the task force as to the reasons for continued nosocomial transmission of CRE despite isolation guidelines led to the arrival at 2 new plans of action: (1) task force intervention in long-term care facilities, and (2) the distribution of guidelines for active CRE surveillance in acute-care hospitals, issued in June 2008. These became part of the nationwide guidelines for

Table 2. Multivariable Model of Variables Affecting Monthly Incidence of Carbapenem-Resistant Enterobacteriaceae (CRE), Including Interaction between Compliance and Prevalence

Variable	Effect estimate	95% CI	*P*
CRE carrier prevalence	0.56	0.43–0.70	<.001
Compliance with dedicated staffing	0.01	−0.07 to 0.10	.72
Months of intervention	−.99	−1.54 to −0.44	.001
Interaction between compliance and prevalence	−.002	−0.004 to −0.0003	.03
Intercept	7.82	1.54–14.10	.02

NOTE. Incidence and prevalence were evaluated per 100,000 patient-days. CI, confidence interval.

containment, thereby defining the next stage of the intervention, which is beyond the scope of this report.

DISCUSSION

CRE are an emerging threat [1, 23] and are associated with high mortality [8–10]. The bla_{KPC} resistance gene family was first reported from the United States in 2001 [24] and has since been implicated in numerous CRE outbreaks worldwide [2, 6, 7, 12, 25–31]. The bla_{KPC-3}-containing strain of *K. pneumoniae* involved in the Israeli outbreak is believed to have been imported from the United States in late 2005 [11–13]. As this strain established a foothold in Israeli hospitals, the health care system was faced with a pathogen exhibiting an exceptional combination of multidrug resistance, virulence, and efficiency of spread. Because of the absence of a national detection system for emergence or spread of drug-resistant bacteria, the nationwide character of the outbreak went unnoted for over a year without concerted intervention.

Although the outbreak was confronted at the local hospital level during 2006, containment was achieved only after national-level intervention. Although success in containment of spread of KPC-producing bacteria has been reported at the local level [32–34], and although guidelines have been issued by national bodies [23, 35], this is the first report of a nationwide intervention to contain a CRE outbreak threatening a country's entire hospital system. We believe that all components of the intervention—adherence to principles of standard precautions and contact isolation [17], physical separation of carriers from noncarriers, and assignment of a dedicated nursing staff to care for carriers on all shifts—were important in halting and reversing the increase in nosocomial incidence of CRE.

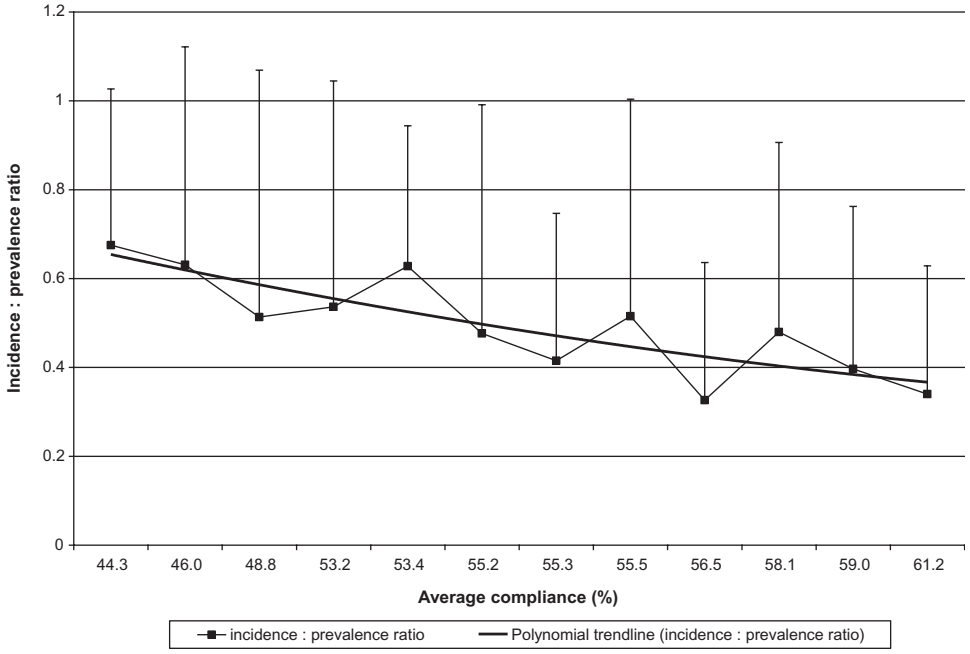

Figure 2. Incidence : prevalence ratio versus average monthly compliance with the dedicated staffing guideline. The graph represents the modifying effect of compliance on the incidence: prevalence ratio. As compliance increases, the risk of new carbapenem-resistant Enterobacteriaceae (CRE) acquisitions posed by hospitalized CRE carriers decreases ($P = .03$). The vertical line above each compliance value is the positive portion of the standard deviation.

Compliance with the national guidelines was directly correlated with success in containment. Because there was near universal compliance with the principles of standard precautions and contact isolation, including physical separation, the observed association between compliance and success in containment reflects differences in compliance with the requirement of dedicated staffing. Our results demonstrate the direct relationship between colonization pressure and nosocomial CRE acquisition, a relationship tempered quantifiably and significantly by adherence to the guideline of dedicated staffing for carriers. Left alone, each hospitalized patient with CRE was associated with 0.43 new nosocomial acquisitions. Because of the intervention, this effect was significantly reduced. Moreover, owing to the additivity of the risk of new acquisitions presented by each hospitalized carrier, compliance becomes increasingly important in containing transmission as prevalence increases.

The rapidity and degree of the response to the national intervention perhaps reflects, in part, the highly efficient spread of this pathogen, against which an effective intervention, in curbing spread at the expected rate, should indeed have a rapid and dramatic effect. Mathematical modeling of infection-control interventions to contain spread of resistant pathogens may predict a longer time to observed effect than we witnessed, although an initial rapid response is to be expected in settings of high endemicity, such as ours [36]. However, published models have not taken into account this particular type of nosocomial pathogen, which is clonal, highly efficient at cross-transmission in the hospital setting, and devoid, at least at the time of the study, of a meaningful reservoir in the community. Indeed, aggressive interventions to curb outbreaks of CRE in the local hospital setting have met with rapid success [34, 37].

We believe that our ability to achieve high-level nationwide compliance was a function of the following elements: (1) implementation of a centrally coordinated infection-control intervention [15, 16]; (2) issuance of mandatory guidelines; (3) daily monitoring by the task force of degree of compliance at all hospitals to all aspects of the guidelines; (4) assignment of responsibility for containment at each hospital to the hospital director; (5) provision of immediate feedback on performance to hospital directors when necessary and on a monthly basis via progress reports, which allowed hospitals to compare their performance with those of other hospitals of similar size and similar patient and activity profiles without compromising patient or institutional confidentiality; (6) scheduled visits by the task force at each hospital at least once during the year and when necessary based on local outbreaks; and (7) dedication to principles of infection control demonstrated by physicians, nurses, administrators, and laboratory personnel. We also believe that the appointment of a task force dedicated to the implementation of the intervention was crucial to success. The inclusion in the task force of experienced professionals in infection control, clinical microbiology, and public health facilitated the acceptance by hospital personnel of the intervention plan.

Our experience highlights the critical nature of effective early detection of outbreaks of drug-resistant bacteria. We therefore recommend that plans for early detection of emerging drug-resistant bacteria be developed and implemented at the national level even prior to their appearance in a region, along with plans for immediate intervention in the event that such bacteria are detected [1]. Although our data demonstrate the ability to contain a nationwide outbreak even when the outbreak is detected late, such containment requires the expenditure of considerably greater resources than when an outbreak is detected at its outset. Moreover, after more than a year of concerted national effort, the outbreak, although contained, was not yet eliminated.

This report is subject to several limitations. First, data until May 2007 are retrospective. From 1 June 2007 onward, the reported data are prospective. This report combines data from the 2 periods in assembling the outbreak picture. Although use of retrospective data may be suboptimal, it is unlikely that such data overestimate the true case number. Second, detection of CRE in the microbiology laboratory may be challenging [38]. Methods of detection may have changed during the course of the study period, perhaps leading to allocation bias. However, the sensitivity of the methods used increased with time, leading to increased identification during the course of the study period, and therefore the magnitude of the result of the intervention, to the extent that it is biased, is underestimated. Third, compliance with infection-control guidelines, although verifiable, is not easily verified nationwide on a daily basis, and the collected data on compliance relied primarily on reports that were filled out by hospital personnel. An assumption of professionalism and trustworthiness was an important aspect of our compliance monitoring. Fourth, enhanced attention to principles of infection control in hospitals as a result of heightened awareness, activity, and feedback has likely had an unmeasured impact on the results reported. Finally, there is no analysis of the economic and opportunity costs associated with the intervention. These include but are not limited to additional staffing and equipment needed to implement the guidelines, lost hospital beds because of the establishment and maintenance of isolation areas, and the dedication of energy and resources at the disposal of the hospitals and the Ministry of Health to containment of the CRE outbreak, perhaps at the expense of other areas that are worthy of attention. A description and analysis of the costs of an intervention on this scale are beyond the scope of this report but should form a basis for future studies.

We have demonstrated containment of a nationwide outbreak of a virulent and rapidly spreading carbapenemase-producing strain of *K. pneumoniae* via a concerted and closely

monitored intervention involving re-emphasis on principles of infection control, physical separation of carriers from non-carriers, and a dedicated nursing staff for carriers. The success of the national-level intervention was dependent on a commitment at the highest levels of health policy planning to confront this outbreak. Despite the success of the intervention, the outbreak is not yet over, and continued vigilance in the implementation of the program remains pivotal to continued containment. The ultimate goal remains the complete cessation of CRE acquisition in the hospital setting.

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Acknowledgments

We thank Ziona Haklai for her contribution to the manuscript.

Potential conflicts of interest. Y.C. is a consultant for MSD, Johnson & Johnson, and Intercell; has received payment for lectures from and is a member of the speaker's bureau of MSD; and has received grant support from Basilea through his institution. All other authors: no conflicts.

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