An Ongoing National Intervention to Contain the Spread of Carbapenem-Resistant Enterobacteriaceae

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In 2007, the Israel Ministry of Health initiated a nationwide intervention aimed at containing the spread of carbapenem-resistant Enterobacteriaceae (CRE), primarily manifested by the rapid dissemination of a single clone of *Klebsiella pneumoniae*. Data were gathered from acute and long-term care facilities, and ward-based mandatory guidelines for carrier isolation, patient and staff cohorting, and active surveillance were issued. Guidelines were issued to the microbiology laboratories delineating procedures for identifying CRE and carbapenemase production. A protocol for ruling out continued carriage in known carriers was established. Compliance with national guidelines was overseen via site visits at healthcare facilities, routine reporting of carrier census and isolation status, and the establishment of a network of communications to facilitate reporting on identified carriage, contact tracing and screening, and outbreak investigations. During the intervention, nosocomial CRE acquisition in acute care declined from a monthly high of 55.5 to an annual low of 4.8 cases per 100,000 patient-days ($P < .001$).

**Keywords.** carbapenem-resistant Enterobacteriaceae; *Klebsiella pneumoniae*; outbreak; intervention

In 2006, the Israeli healthcare system began to confront nationwide spread of carbapenem-resistant Enterobacteriaceae (CRE). This was caused predominantly by the clonal spread of *Klebsiella pneumoniae* ST-258, a multi-drug-resistant pathogen producing *K. pneumoniae* carbapenemase (KPC), thought to have been introduced to Israel via the United States in late 2005 [1, 2]. Interventions at the individual hospital level to contain spread met with limited success, and by March 2007 the monthly rate of new nosocomial acquisitions as detected by clinical cultures had reached a high of 185 cases (55.5 cases per 100,000 patient-days) [3]. Several studies documented crude mortality rates ranging from 44% to 70%, with attributable mortality for bacteremia of 50% [4–6].

The Ministry of Health (MOH) was alerted in February 2007 by infection control professionals that the pathogen had become endemic in acute care hospitals [7], the proportion of *K. pneumoniae* blood isolates resistant to carbapenems had reached 22% [8], and the pathogen posed a threat to the entire inpatient healthcare system. In response, the MOH launched a multifaceted intervention on a national scale. This report summarizes the major elements of the intervention to date and its impact on the evolution of the outbreak.

**INITIAL RESPONSE—ACUTE CARE HOSPITALS**

In March 2007, the MOH issued guidelines for control of CRE in Israeli hospitals. The 2 principal elements of the guidelines were the requirements that (1) all patients colonized or infected with CRE be cared for in either isolation rooms or carrier cohorts, physically separated from noncarriers, and (2) carriers be cared for by a dedicated nursing staff, meaning that nurses caring for carriers would not be assigned to care for noncarriers on the same shift. To comply with these
guidelines, hospitals created carrier and nursing cohorts. Concurrently, the MOH established a task force charged with containing the outbreak and invested with the statutory authority to intervene as necessary to do so.

The task force, which the following year became the National Center for Infection Control (NCIC), acted to improve detection of CRE and implementation of infection control measures at acute care hospitals nationwide. The NCIC operated vis-a-vis the hospital directors, meeting and regularly communicating with them and their staff members, advising on actions required, soliciting required data, and providing oversight and feedback. Site visits were conducted, at which isolation measures, environmental cleaning protocols, and laboratory methodology could be observed and addressed.

Hospitals began to report daily a census of all CRE carriers including ward location, isolation status, and information on transfer to other facilities. These reports enabled a mechanism for monitoring and ensuring compliance with the national guidelines, and enabled the NCIC to assure accurate data transfer regarding carrier movement within the healthcare system. A significant association between compliance with the national guidelines and reduction in incidence was demonstrated, and by May 2008 the nationwide monthly incidence of CRE acquisitions had dropped 5-fold to 11.7 per 100,000 patient-days [3].

**BEYOND THE FIRST YEAR**

By the end of the first year, the monthly incidence curve of CRE acquisitions based on clinical culture had leveled off. An influx of carriers with history of exposure to the healthcare system provided sources for continued spread of CRE in acute care hospitals. Moreover, inpatients exposed to these unidentified carriers asymptotically acquired these strains and became a secondary source of transmission. Therefore, the need for proactive screening to detect asymptomatic carriers and isolate them appropriately, as well as for intervention in long-term care facilities, became apparent.

**ACTIVE SURVEILLANCE IN ACUTE CARE SETTINGS**

Individual hospitals initially implemented a variety of strategies for active surveillance using an array of microbiological methods and targeting various populations deemed at risk. To standardize the approach to surveillance, in June 2008 the NCIC issued a requirement to all acute care hospitals to perform active surveillance, via rectal swab, on patients deemed at high risk of CRE carriage. Several categories of high-risk patients have been defined:

1. Ward contacts of patients newly discovered to be CRE carriers. The number of contacts to be screened is determined by the hospital infection control team on a case-by-case basis based on proximity to the index case, duration of exposure, and shared nursing staff. In high-risk units, such as the intensive care unit (ICU) and transplant wards, the entire unit should be screened. When CRE carriers are found among screened contacts, the circle of screening should be expanded.

2. Patients transferred from another medical facility, or having been cared for at such a facility in recent months. These patients should be screened on admission.

3. Patients hospitalized in wards with high incidence and/or prevalence of CRE carriage. These patients are designated for surveillance at each hospital’s discretion.

Although the preferred microbiological method for screening was not initially specified, there is a requirement that the test chosen provides at least a preliminary result within 24 hours, which allows a decision regarding isolation. The implementation of the national surveillance guidelines has resulted in initial detection of CRE carriage in the vast majority of carriers via active surveillance (82% in 2012; Figure 1).

**CRE IN LONG-TERM-CARE FACILITIES**

By 2008, it became apparent that patients admitted from long-term-care facilities (LTCFs) are a source of reintroduction of CRE to acute care hospitals, undermining containment efforts. Therefore, the NCIC extended its nationwide infection control intervention to LTCFs. The primary reason for this decision was to limit the reservoir of CRE in LTCFs to protect the acute care facilities.

The intervention in LTCFs presented challenges beyond those encountered in the acute care setting. First, the infection control infrastructure was far more rudimentary in terms of facilities, staffing, and level of training in basic principles of infection control. Most facilities did not have a physician trained in infectious diseases or infection control, and many did not have a trained infection control nurse. Second, the nature of inpatient care in these facilities, which by definition was of longer duration than that in acute care hospitals and in many cases involved the facility becoming the patient’s home environment, made the implementation of isolation guidelines without compromising such elements of care as rehabilitation protocols and ward-wide social activities particularly difficult.

Targeted interventions were carried out at LTCFs that were identified as a source of influx to acute care facilities per hospital reports on admission screening. In some cases, short-term interventions alone sufficed to contain spread, whereas in others, long-term interventions, including periodic closures, were required.
In addition to these targeted interventions based on temporal need, we conducted systematic interventions in the nation’s 13 post-acute care hospitals (PACHs). These facilities have ventilated, skilled nursing, subacute, and rehabilitation wards, which comprise roughly one-tenth of the long-term-care beds nationwide. The patients in these hospitals were considered to be at highest risk of CRE carriage among the LTCF population, and in addition suffered from medical conditions rendering them most likely to be transferred back into the acute care setting.

The goals of the PACH intervention were as follows: (1) to determine the degree of CRE carriage at these facilities; (2) to map their infection control infrastructure and policies; (3) to determine which CRE containment measures were necessary and feasible; and (4) to bring about the implementation of these measures at all PACHs, in order to reduce the reservoir of CRE carriage in LTCFs and the influx of undetected carriers into the acute care setting.

The results obtained enabled us to issue national, evidence-based guidelines for CRE surveillance and containment in LTCFs according to ward type. These guidelines differ in some ways from those that apply to acute care hospitals. For example, they do not require dedicated nursing for carriers, as patients in wards with a policy of dedicated nursing were not found to be at significantly lower risk of carriage than patients on wards without such a policy. In addition, carriers are not confined to their rooms, and in rehabilitation wards, where carrier prevalence was found to be <3%, even room cohorting for carriers is not required under routine circumstances. The guidelines enable LTCFs to admit CRE carriers without compromising their ability to deliver rehabilitation and enable the socialization required for the well-being of residents of LTCFs.

Site visits were conducted at each of the PACHs. To evaluate infection control practices via uniform criteria, we developed a 16-point Infection Control Score. This score was divided into 4 categories: (1) the presence of an infection control professional on staff; (2) hand hygiene facilities and practices; (3) implementation of standard precautions; and (4) implementation of nationally mandated CRE control measures. During the course of the intervention, the average score among the PACHs increased >2-fold [10]. Follow-up point prevalence surveys of CRE carriage demonstrated that the carriage prevalence among patients not previously known to be carriers dropped from 12.1% in 2008 to 7.9% in 2011 \( (P = .008) \) [14].

![Figure 1. Proportion of newly detected carbapenem-resistant Enterobacteriaceae carriers identified via active surveillance vs clinical cultures by year, 2007–2012. The top portion of the bars represents the yearly proportion identified via surveillance culture. The bottom portion of the bars represents the yearly proportion identified via clinical culture.](https://academic.oup.com/cid/article-abstract/58/5/697/365702)
CRE IN THE COMMUNITY

The epidemiology of CRE outside the inpatient setting is monitored via ongoing surveillance of CRE in community laboratories (responsible for only 3% of CRE detection nationwide) and investigation of newly identified carriage to evaluate the site of acquisition. In addition, all cases of newly identified carriage detected upon hospital admission are investigated. We have also conducted studies on colonization of healthcare workers and family members caring for CRE carriers [11].

On the basis of the data collected, we have concluded that the pathogen at present is almost exclusively healthcare acquired, with no significant community transmission. Thus, the NCIC issued the following guidelines for care of nonhospitalized CRE carriers: At home, patients, family members, and caregivers have no restrictions on activity or specific guidelines for conduct in daily living, although standard hygiene measures are emphasized; in the ambulatory care setting, physical separation of carriers in patient waiting areas is not mandated; however, in treatment areas, use of gloves by the examiner and cleaning and disinfection of the bed are required.

DURATION OF CRE CARRIAGE AND GUIDELINES FOR DISCONTINUATION OF CARRIER STATUS

We investigated duration of CRE carriage outside the acute care setting. Active surveillance upon hospital admission of known CRE carriers demonstrated that 35% remained carriers, the majority of whom underwent screening within 3 months of their identification as carriers [12]. In addition, we found that 70% of prior CRE carriers in LTCFs were no longer CRE positive when cultured at least 90 days following their last positive culture [9]. These findings prompted us to issue a requirement for screening for discontinuation of carrier status for patients hospitalized in LTCFs for >90 days. These guidelines are uniform nationwide, meaning that not only are LTCFs required to implement them after 90 days, the protocol for discontinuation of carrier status is uniform in each facility in which it is undertaken, including those acute care facilities that undertake it on a case-by-case basis at their discretion. The protocol consists of 2 surveillance rectal swabs cultured for CRE, as well as polymerase chain reaction (PCR) performed on enrichment broth for the relevant carbapenemase gene. Negative results on 2 rectal swabs submitted for culture and 1 swab submitted for PCR are required for carrier status to be revoked.

The requirement for 2 negative cultures was validated by data indicating that a single negative culture from a known carrier is insufficient to disprove continued carriage [13]. The requirement for PCR confirmation of negativity in prior carriers is due to the finding of KPC by PCR in approximately 15% of patients with negative cultures for CRE on screening [14]. Once revoked, although the patient is no longer cohorted with other CRE carriers, the history of prior carriage must remain part of the medical record reported on each subsequent admission, due to the possibility of recrudescence. Preliminary data indicate that the proportion of prior carriers who subsequently become carriers again is approximately 15% [13].

LABORATORY GUIDELINES

The clinical microbiology laboratory plays a pivotal role in producing and disseminating the data upon which infection control interventions are undertaken. Therefore, our activities at the national level aim to promote the rapid generation of accurate data that infection control teams can act upon in a timely manner.

Early in the course of the national intervention, we realized the need to distinguish between carbapenemase-producing isolates and CRE with other mechanisms of carbapenem resistance. This distinction has direct ramifications for infection control in that carriers of carbapenemase-producing Enterobacteriaceae (CPE) are cohorted with dedicated staff in acute care hospitals, whereas carriers of non-carbapenemase-producing CRE are placed in contact isolation but are not cohorted with the CPE carriers. In the early phases of the outbreak, as there was no standardized method of distinguishing between CRE with varying mechanisms of resistance that could be uniformly applied at the local laboratory level, we applied the following scheme: K. pneumoniae isolates resistant to all agents tested, with the exception of gentamicin and colistin and with variable resistance to tigecycline (the typical phenotype of the KPC-producing dominant clone in Israel), were considered to be carbapenemase producers, while other CRE isolates had to be tested using specialized tests (phenotypic tests involving hydrolysis or PCR), either locally or at the reference laboratory. Later, as further data and experience accumulated, uniform laboratory guidelines were issued for screening of Enterobacteriaceae for carbapenem resistance and the phenotypic and molecular workup of CRE isolates for carbapenemase production. Laboratory personnel were instructed in the implementation of the guidelines. These requirements undergo periodic updating as new data accumulate.

CRE OTHER THAN KPC-PRODUCING K. PNEUMONIAE

Our national policy for CRE containment has been based primarily on knowledge generated by the study of the epidemiology of KPC-producing K. pneumoniae. However, other carbapenemases are emerging. Following reports of NDM-1–producing Enterobacteriaceae isolates primarily originating from the
Indian subcontinent [15], the NCIC issued guidelines for admission CRE screening of patients who had received medical care in high-risk areas from 2008 onward. Soon after, cases were identified among returning travelers. Later, sporadic cases of carriage of NDM-1–producing Enterobacteriaceae were identified, with no clear source of transmission. One hospital experienced a small-scale outbreak of NDM-producing Providencia rettgeri [16].

OXA-48–producing CRE was initially isolated in non-Israelis receiving care in Israeli hospitals [17]. Subsequently, sporadic isolations occurred in patients with no clear source of transmission. Recently, a large-scale outbreak occurred in a neonatal ICU. This outbreak was contained following intensive intervention [18]. The widespread practice of active surveillance for CRE in Israel likely has an impact on the degree of detection of carriage of non-KPC-producing CPE, and the ability to intervene early to abort potential outbreaks. Much remains unclear regarding the epidemiology of transmission of these non-KPC-producing CPE, thus posing future challenges for containment.

ASSESSMENT OF SUCCESS

National success is dependent on local performance as well as on national activity. Several hospitals have reported successful infection control interventions, carried out in the context of the nationwide intervention. In different settings, the success was attributed primarily to certain components of the national intervention [19, 20]. Others attributed the local success to the institutional intervention generally [21, 22]. From our central perspective, we believe that all components of the Israeli national intervention have been important for success at the regional and national levels.

An essential component of NCIC activities is the nationwide real-time network of communications that has been established, regarding discovery of new CRE carriers and movement of known carriers throughout the healthcare system, with verification of their appropriate conditions of isolation. Via this network, contact tracing and screening, as well as outbreak investigations, are monitored and overseen.

The Israeli national CRE intervention was launched after the predominant pathogen had already become endemic in the healthcare setting. Therefore, we estimated that eradication may not be attainable at that point, and established our goals as containing the outbreak and allowing acute care hospitals to continue to function safely. The intervention led to a reduction in incidence of nosocomial CRE acquisitions detected by clinical culture per 100 000 patient-days in acute care hospitals from a monthly high of 55.5 at the peak of the outbreak to 11.7 within slightly over a year (Figure 2) [3]. Incidence has continued to decline since then, to an annual low of 4.8 in 2012 ($P$ < .001; Figure 3). Similarly, in PACHs new carrier prevalence

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**Figure 2.** 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 preintervention 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). Figure from Schwaber et al [3]; reprinted with permission from Oxford University Press.
dropped by 34% between 2008–2011 [10]. The success of the intervention is reflected as well in a decline in incidence of carbapenem-resistant Klebsiella species and Escherichia coli bacteremia of 37% between 2009 and 2012 (\(P= .001\); Figure 3). Before the national intervention, nonselective carriage prevalence of 5.4% was reported from an acute care hospital [7], whereas at present, focused screening of selected high-risk groups in acute care hospitals yields a carriage prevalence of <2%, and nonselective screening only rarely yields positive results (Carmeli Y, unpublished data). Wards and ICUs have remained open, with closure only rarely needed. Thus, the objective of allowing acute care hospitals to continue to function safely has been achieved.

**CONCLUSIONS**

The nationwide intervention for CRE containment, based on a strategy that includes patient isolation, dedicated staffing in acute care, active surveillance, uniform standards of detection and reporting, and central supervision of adherence to infection control guidelines across the healthcare system, has succeeded in containing spread of a highly transmissible pathogen over several years. The Israeli experience can serve as a model demonstrating that even when CRE has become endemic, its spread can be contained, and safe conditions in the healthcare setting can be reestablished. It remains to be shown whether nationwide eradication of the pathogen can be accomplished after such a late start and the establishment of a large reservoir of carriage. The Israeli experience should serve as a warning to nations in which CRE is still rare or absent to be alert and prepared for its appearance, with a centralized plan for detection and isolation in place.

**Note**

**Potential conflicts of interest.** Both authors: No reported conflicts.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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