Cette présentation a été effectuée le 26 novembre 2013, au cours des « 4es Journées sur la prévention des infections nosocomiales (Jour 2) - 10 ans de prévention et de contrôle des infections : qu'avons-nous appris pour guider nos actions? » dans le cadre des 17es Journées annuelles de santé publique (JASP 2013). L'ensemble des présentations est disponible sur le site Web des JASP à la section Archives au : http//jasp.inspq.qc.ca/.

SIGNALEMENT DES ENTÉROBACTÉRIES PRODUCTRICES DE CARBAPÉNÉMASES (EPC) DE D'AUTRES BMR – RÉGION DE MONTRÉAL

TERRY-NAN TANNENBAUM
DIRECTION DE SANTÉ PUBLIQUE
AGENCE DE LA SANTÉ ET DES SERVICES SOCIAUX DE MONTRÉAL

JAPI 2013

REMERCIEMENTS

- Membres de la Table régionale de prévention des infections nosocomiales (TRPIN) de Montréal
- Dre Adréanne Jean, Résidente stagiaire
- Laboratoire de santé publique du Québec (LSPQ)
- Direction de santé publique de l'Agence de la santé et des services sociaux de Montréal (DSP de l'Agence de Montréal)

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CONTEXTE : HISTORIQUE

- Proposition d'un centre hospitalier de soins généraux et spécialisés (CHSGS) à la TRPIN en 2010 suite à une éclosion de KPC
- Discussions à la TRPIN (à partir de février 2012)
- Début projet pilote (octobre 2012)

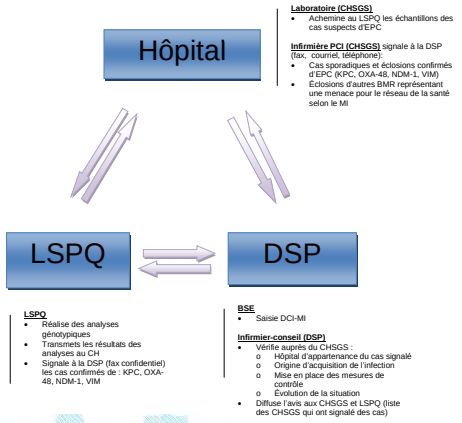
OBJECTIF DU SYSTÈME DE SIGNALEMENT

- Mettre en place un système pour informer les CH de courte durée (CHSGS) de la région de Montréal de la présence d'EPC ou autres BMR (avis) dans des autres CHSGS

LE SIGNALEMENT

- Concerne tous les CHSGS
- Fait à la fois par le LSPQ et les hôpitaux
- Sont inclus :
  - Colonisations et infections
  - Les cas sporadiques ou les éclosions confirmés d'EPC :
    - résultat génotypique (LSPQ)
    - Mécanismes de résistance ciblés : KPC, NDM-1, OXA-48, VIM
  - Les éclosions d'autres BMR qui peuvent représenter une menace pour le réseau

PROCESSUS DE SIGNALEMENT



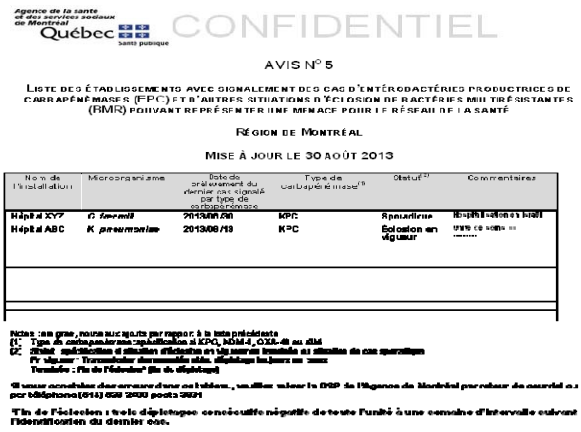
RENSEIGNEMENTS FOURNIS PAR LE LSPQ

- Informations démographiques
- Mécanismes de résistance : KPC, NDM, OXA-48, VIM
- Nom de l'établissement de santé demandant le test
- Date et site de prélèvement

RENSEIGNEMENTS FOURNIS PAR LES CHSGS

- Agent en cause
- Cas sporadique ou éclosion
- Source d'acquisition
- Unité(s) touchée(s)
- Nombre de patients atteints
- Nombre de décès
- Mesures de contrôle en place
- Autres informations complémentaires

L'AVIS



CONFIDENTIEL

AVIS N° 5

LISTE DES ÉTABLISSEMENTS AVEC SIGNALEMENT DES CAS D'ENTÉROBACTÉRIES PRODUCTRICES DE CARBAPÉNÈMASES (EPC) ET D'AUTRES SITUATIONS D'ÉCLOSION DE BACTÉRIES MULTIRÉSISTANTES (BMR) POUVANT REPRÉSENTER UNE MENACE POUR LE RÉSEAU DE LA SANTÉ

RÉGION DE MONTRÉAL

MISE À JOUR LE 30 AOÛT 2013

Nom de l'installation	Microorganisme	Date du prélèvement du dernier cas signalé par type de carbapénémase	Type de carbapénémase[1]	Statut[2]	Commentaires
Hôpital XYZ	*E. faecalis*	2013/08/20	KPC	Sporadique	Hospitalisation en [illegible]
Hôpital ABC	*K. pneumoniae*	2013/08/19	KPC	Éclosion en vigueur	Unité de soins [illegible]

Notes : en gras, nouveau ajouté par rapport à la liste précédente

(1) Type de carbapénémase : spécification si KPC, NDM-1, OXA-48 ou autre

(2) Statut : spécification d'absence d'éclosion en cas de cas sporadiques ou d'éclosion de cas sporadiques

Fin d'éclosion : Transmission documentée stable, dépistage hebdomadaire sur [illegible]

Terminée : Fin de l'éclosion* (fin du dépistage)

*Si vous constatez des erreurs dans cette liste, veuillez aviser la DSP de l'Agence de Montréal par courriel à [illegible] par téléphone (514) 528 2400 poste 3521

*Fin de l'éclosion : trois dépistages consécutifs négatifs de toute l'unité à une semaine d'intervalle suivant l'identification du dernier cas.

Veuillez prendre note que cette liste ne se substitue pas à la communication entre les établissements.

DIFFUSION DE L'AVIS

- Cible
  - Infirmières PCI
  - Microbiologistes-infectiologues
  - LSPQ (professionnels du programme)
- Fréquence
  - À chaque nouveau signalement
  - 1 fois/mois si pas de changement
- 7 diffusions à date

BILAN DES SIGNALEMENTS DES EPC

Du 20 décembre 2012 au 31 octobre 2013 :

- 43 cas signalés/10 CHSGS
- 2 éclosions dans 2 CHSGS (3 cas chacune)
- Âge :
  - Moyenne = 69 ans; Médiane = 71 ans
  - Intervalle = 23 à 95 ans
  - 72% (31/43) des cas âgés >= 60 ans
- Sexe :
  - Homme = 25 (58%)
  - Femme = 18 (42%)

BILAN DES SIGNALEMENTS DES EPC

- Dépistage (rectum/selles) = 19 (44%)
- Spécimens cliniques = 24 (56%)
- Sites de prélèvement des spécimens cliniques
  - expectorations/endotrachéales (10), pus (5), urine (6), sang (1), drain (1), plaie/site chirurgical (1)
- Hospitalisation = 39 cas
  - 25 (58%) cas au moment du signalement
  - 14 (33%) cas congé de l'hôpital
- Évolution des cas
  - Décès = 11% (4/36)
  - Vivant = 89% (32/36)
  - Inconnue = 7

BILAN DES SIGNALEMENTS DES EPC

- Origine présumée d'acquisition
  - Inconnue = 18
  - Nosocomiale reliée à l'installation déclarante = 17 (dont 6 cas reliés à une éclosion)
  - Étranger = 8
    - Hospitalisation à l'étranger (12 derniers mois) = 5
    - Voyage à l'étranger (12 derniers mois) = 2
    - Soins à l'étranger sans hospitalisation (12 derniers mois) = 1

BILAN DES SIGNALEMENTS DES EPC

- Délai moyen de 14 jours entre le prélèvement et le signalement à la DSP de l'Agence de Montréal

- Nombre de signalements
  - 1 à 7 cas par mois
  - Pas de tendance à la hausse
  - Majorité reliée à 3 CHSGS

ESPÈCES D'EPC IDENTIFIÉES

Espèces d'EPC	KPC	OXA-48	VIM	NDM	N. Total*	%
Klebsiella pneumoniae	17	1		4	22	41,5%
Enterobacter cloacae	8				8	15,1%
Escherichia coli	4	1		2	7	13,2%
Citrobacter freundii	6				6	11,3%
Klebsiella oxytoca	4				4	7,5%
Serratia marcescens	2				2	3,8%
Kluyvera sp.	2				2	3,8%
Enterobacter aerogenes	1				1	1,9%
Raoultella terrigena	1				1	1,9%
Total	**45**	**2**	**0**	**6**	**53**	**100%**

* 3 souches identifiées chez 1 patient et 2 souches identifiées chez 8 patients.

Source : DSP de l'Agence de Montréal

PAYS ÉTRANGERS EN LIEN AVEC LES CAS D'EPC SIGNALÉS

Pays	Nombre de cas
Bangladesh	1
Égypte	1
Éthiopie	1
Grèce	1
Inde	1
Israël	1
Pakistan	1
Émirats Arabes Unis	1
Total	**8**

Source : DSP de l'Agence de Montréal

SIGNALEMENTS D'ACINETOBACTER BAUMANNII

- 7 cas signalés par 2 CHSGS
- 2 cas de co-infection avec EPC (NDM)
- 2 éclosions (6 cas) dans un CHSGS

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- Sommaire des résultats
  - 43 cas de l'EPC signalés Nombre sur 10 mois
  - 10 CHSGS : 2 éclosions notifiées à date
  - KPC est le mécanisme de résistance le plus fréquent (36/43 cas)
  - Au moins 4 décès
- Enjeux
  - Exhaustivité limitée par le dépistage fait
  - Politique de dépistage variable (sondage en cours)
  - Informations recueillies partielles
  - Présence des cas dans les centres de réadaptation

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CONCLUSIONS

- Système apprécié par le réseau
- Intérêt d'élargir aux autres régions
- Intérêt d'élargir aux autres pathogènes
- Pertinence du programme de surveillance de l'INSPQ
- Importance d'agir pour prévenir la propagation de ces pathogènes

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Québec

MERCI

20

Québec

CONTEXTE

- Problème en émergence
- Pathogènes virulents avec options thérapeutiques limitées
- Éclosions rapportées dans 2 CHSGS montréalais en 2010
- Transmission nosocomiale de NDM-1 en Ontario en 2011
- Programme provincial de surveillance de laboratoires en place depuis 2010 : majorité des cas recensés proviennent des laboratoires de Montréal

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OBJECTIF DE LA PRÉSENTATION

- Partager l'expérience de la région de Montréal sur la mise en place d'un système de signalement des EPC et d'autres BMR
  - Processus de mise en place
  - Bilan des signalements
  - Enjeux associés

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SYSTÈMES DE SURVEILLANCE EXISTANTS

- Au Canada (Québec, Ontario, CB) et États-Unis : surveillance labo sur une base volontaire des souches pour détection des carbapénémases
- En France:
  - Depuis 2006, surveillance des ESBL par le groupe Raisin
    - Récupère des données sur l'antibiorésistance (et non le mécanisme)
    - Depuis 2010, le Raisin fait des enquêtes épidémiologiques

Source : présentation de Dre Adréanne Jean, R5 maladies infectieuses et microbiologie (stagiaire DSP), 23 avril 2013.

LE SIGNALEMENT (CHSGS)

FICHE DE SIGNALEMENT D'UN CAS OU D'UNE ÉCLOSION D'ENTÉROBACTÉRIES PRODUCTRICES DE CARBAPÉNÉMASES (EPC) OU D'UNE ÉCLOSION D'AUTRES BACTÉRIES MULTIRÉSISTANTES (BMR) POUVANT REPRÉSENTER UNE MENACE POUR LE RÉSEAU DE LA SANTÉ MONTRÉALAIS

ÉTABLISSEMENT DE SANTÉ

Nom de l'installation :

AGENT EN CAUSE :

☐ Cas sporadique d'EPC (confirmation génotypique LSPQ)
→ Gène codant pour ☐ KPC ☐ OXA-48 ☐ NDM-1 ☐ VIM

☐ Éclosion d'EPC (confirmation génotypique LSPQ)
→ Gène codant pour ☐ KPC ☐ OXA-48 ☐ NDM-1 ☐ VIM

☐ Éclosion d'une autre BMR pouvant représenter une menace pour le réseau de la santé selon l'avis du microbiologiste infectiologue (MI) [ex : Acinetobacter avec profil de résistance aberrant] (confirmation phénotypique ou génotypique)
→ Précisez l'agent :

ÉTAT DE LA SITUATION DE L'ÉCLOSION

☐ Nouvelle éclosion dans une installation
→ Unité (s) touchée (s) :

☐ Nouvelle unité de soins affectée dans une installation déjà en éclosion
→ Unité (s) touchée (s) :

Nombre de patients atteints : Colonisés : Infectés :
Complications Décès :

Date de la mise en place des mesures de contrôle *(année/mois/jour) :*

Date probable d'admission du cas index *(année/mois/jour) :*

Date du prélèvement du cas index *(année/mois/jour) :*

Nom de la personne déclarante (ou à rejoindre pour obtenir plus d'informations):

Numéro de téléphone :
Date du signalement (année/mois/jour) :
Commentaires :
Veuillez transmettre la fiche complétée par fax au 514 528-2461

DIFFUSION DE L'AVIS

Si vous constatez des erreurs dans ce tableau, veuillez aviser la DSP de l'Agence de Montréal par retour de courriel ou par téléphone (514) 528-2400 poste 3831

*Fin de l'éclosion : trois dépistages consécutifs négatifs de toute l'unité à une semaine d'intervalle suivant l'identification du dernier cas.

Veuillez prendre note que cette liste ne se substitue pas à la communication entre les établissements.

Proposition de mesures à mettre en place pour les contacts d'entérobactéries productrices de carbapénémase

Considérant :

- Que l'avis et les recommandations de l'INSPQ au regard de la prévention et contrôle de la transmission des entérobactéries productrices de carbapénémase dans les milieux de soins aigus du Québec ne précisent pas la fréquence et l'intervalle de temps entre les dépistages pour les contacts.
- Qu'il n'y a pas de consensus au regard du portage et du temps d'incubation.
- Que les milieux de soins qui recevront la liste des établissements ayant identifié des cas d'EPC se questionneront sur les mesures à mettre en place pour les contacts transférés.

Afin d'éviter des problèmes au moment du transfert des contacts (ex : retard, refus, appels..), La TRPIN propose :

D'appliquer les précautions additionnelles contre la transmission par contact en attente des résultats de dépistage et faire un dépistage (écouvillon rectal) des contacts aux jours 0, 7 et 14

De plus, si le patient demeure hospitalisé, assurer une surveillance et répéter le prélèvement 3 à 4 jours après le début de la prise d'antibiotique.

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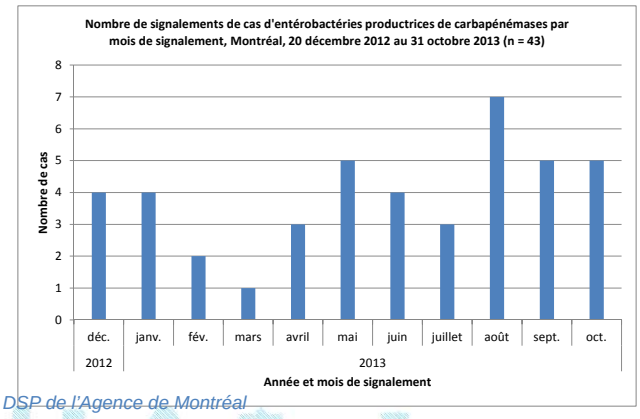
NOMBRE DE SIGNALEMENTS



Source : DSP de l'Agence de Montréal

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Cette présentation a été effectuée le 26 novembre 2013, au cours des « 4es Journées sur la prévention des infections nosocomiales (Jour 2) - 10 ans de prévention et de contrôle des infections : qu'avons-nous appris pour guider nos actions? » dans le cadre des 17es Journées annuelles de santé publique (JASP 2013). L'ensemble des présentations est disponible sur le site Web des JASP à la section Archives au : http//jasp.inspq.qc.ca/.

L'épidémiologie des bactéries multirésistantes : données internationales

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Infectious Diseases Service, JGH
Associated professor of medicine, McGill University

Yves.Longtin@mcgill.ca

Hôpital général juif
Jewish General Hospital

Infection Prevention and Control Unit

Objectives

- Review the international epidemiology of drug-resistant enterobacteriaceae
- Provide the background to Dr. Savard's presentation

Remerciements

- Dr. Christian Lavallée
- Dr. Debby Ben David
- Dr. Jean Longtin
- PHAC

Disclosures

- None to declare

Antibiotics:
Miracle drugs, it started out so well, but ….

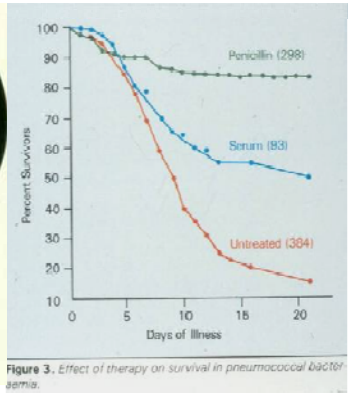

Figure 3. Effect of therapy on survival in pneumococcal bacteremia.

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Multi-resistant pathogens

http://www.cdc.gov/drugresistance/threat-report-2013/

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Startling numbers

- Threats
  - C. difficile
  - Carbapenem-resistant Enterobacteriaceae
  - Drug-resistant Neisseria gonorrheae
  - Multi-drug resistant Acinetobacter
  - Vancomycin-resistant Enterococcus
  - Methicillin-resistant S.aureus

Antibiotic Resistance Threats in the United States, 2013, CDC

Startling numbers

- Consequences
  - 2 million infections/year
  - 23'000 deaths
  - 250'000 C.difficile infections
  - $20 billion excess direct health care costs
  - $35 billion loss of productivity

Antibiotic Resistance Threats in the United States, 2013, CDC

Why worry?

- MDRO are dangerous
  - More difficult to treat
  - May be more virulent
  - Increase mortality
  - Increase morbidity
- Resource-intensive
  - More expensive antibiotics
  - Increase length of hospitalization
  - Increase demand for isolation-facilities
- Derived problems
  - Drug toxicity
  - Poorer quality of care due to single room isolation

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4 core actions for halting resistance

1. Preventing infections and the spread of resistance
2. Tracking resistance patterns
3. Developing new antibiotics and diagnostic tests
4. Improving antibiotic use

Antibiotic Resistance Threats in the United States, 2013, CDC

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4 core actions for halting resistance

1. Immunization
2. Infection prevention in healthcare setting
3. Food safety
4. Hand hygiene

1. Preventing infections and the spread of resistance
2. Tracking resistance patterns
3. Developing new antibiotics and diagnostic tests
4. Improving antibiotic use

Antibiotic Resistance Threats in the United States, 2013, CDC

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4 core actions for halting resistance

1. Preventing infections and the spread of resistance
2. Tracking resistance patterns
3. Developing new antibiotics and diagnostic tests
4. Improving antibiotic use

2012. Generating Antibiotic Incentives Now (GAIN) Act

Extends commercial value of ABx

Antibiotic Resistance Threats in the United States, 2013, CDC

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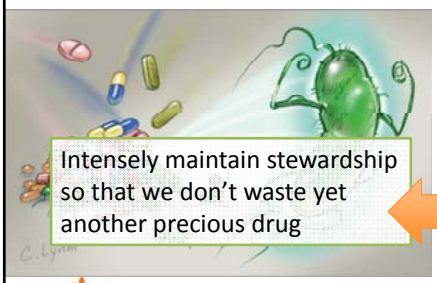
4 core actions for halting resistance

1. Preventing infections and the spread of resistance
2. Tracking resistance patterns
3. Developing new antibiotics and diagnostic tests
4. Improving antibiotic use

Intensely maintain stewardship so that we don't waste yet another precious drug



Antibiotic Resistance Threats in the United States, 2013, CDC

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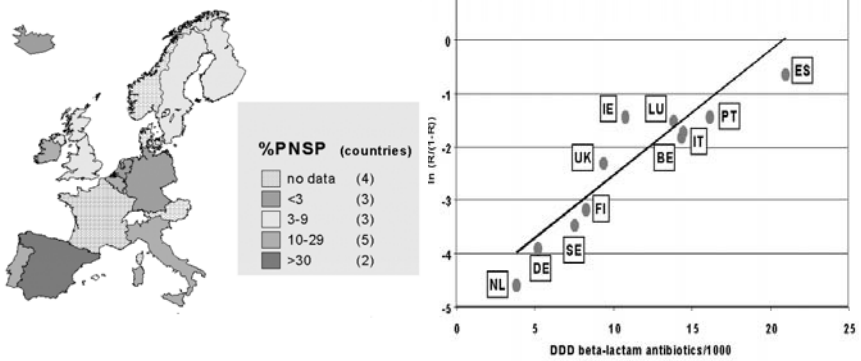
A direct relationship between antibiotic consumption and antibiotic resistance



Bronzwaer et al. Emerg Infect Dis 2002; 8: 278-82

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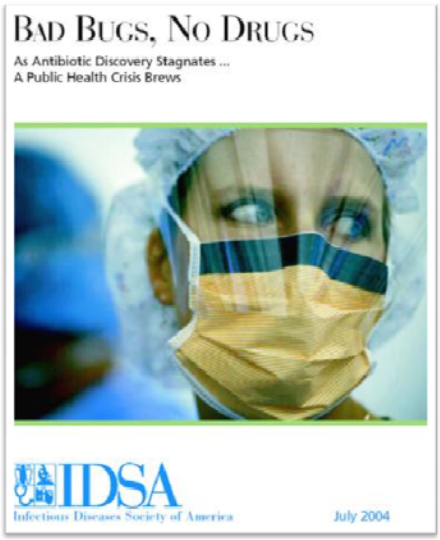

http://www.idsociety.org/pa/IDSA_Paper4_final_web.pdf.

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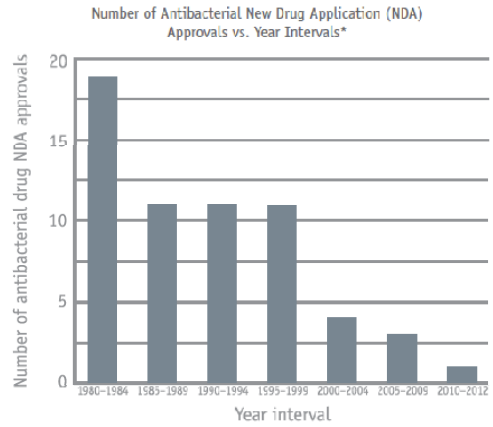
Tomorrow's Antibiotics: The Drug Pipeline

The number of new antibiotics developed and approved has steadily decreased in the past three decades, leaving fewer options to treat resistant bacteria.



*intervals from 1980–2009 are 5 year intervals; 2010–2012 is a 3 year interval. Drugs are limited to systemic agents.
Data courtesy of FDA's Center for Drug Evaluation and Research (CDER).

http://www.cdc.gov/drugresistance/threat-report-2013/

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Drug resistance in Enterobacteriaceae

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Enterobacteriaceae

- **Normal human gut flora & environmental organisms**
- **More than 70 species**
- **Range of human infections: UTI, wound infections, pneumonia, bacteremia**

E. coli and *Klebsiella* species

- *E. coli* causes 75-90% of acute uncomplicated outpatient UTIs [1]
- *E. coli* and *Klebsiella* species (especially *K. pneumoniae*) are also important causes of healthcare associated infections (HAIs)
  - Together they accounted for 15% of all HAIs reported to CDC in 2007.

1. Prim Care. 2008 Jun;35(2):345-67

Pathogens Reported to NHSN 2009-2010

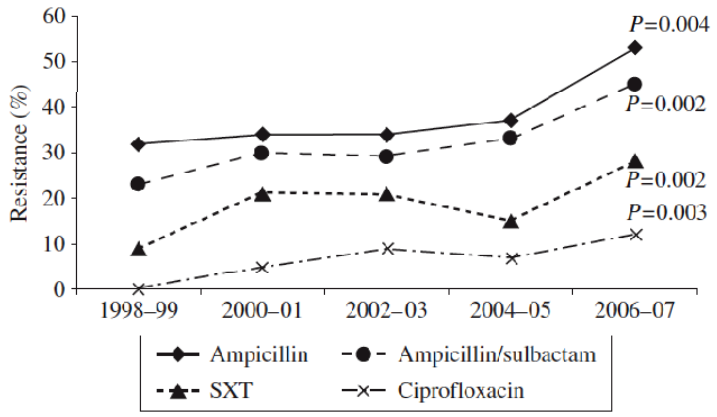
	Overall percentage (rank)	CLABSI	CAUTI	VAP	SSI
E. coli	12% (2)	4%	27%	6%	9%
K. pneumoniae	8% (4)	8%	11%	10%	4%
P. aeruginosa	8% (5)	4%	11%	17%	6%
Enterobacter spp.	5% (8)	5%	4%	9%	4%

Sievert D, et al. Infect Control Hosp Epidemiol 2013; 34: 1-14

Enterobacteriaceae

- **β-lactam antibiotics have long been the mainstay of treating infections caused by Enterobacteriaceae**
- **However, resistance to β-lactams emerged several years ago and has continued to rise**
- **Resistance to β-lactams has been a concern for decades**
  - β-lactamases
  - Extended-spectrum β-lactamases
  - Carbapenemases

Escherichia coli



Al-Hasan et al. Antimicrobial resistance trends of *Escherichia coli* bloodstream isolates. *J Antimicrob Chemother* 2009.

ESBL

Béta-lactamases à spectre élargi – BLSE (ESBL en anglais)

- B-lactamase qui détruit plusieurs sortes de B-lactames
  - Ex. Penicilline, cefazoline, cefuroxime, ceftriaxone…
    - (les ATB de choix contre les EB)
  - Exception: carbapenemes (mero, imi…)
- Différents types (>120)
- Plasmidiques (la plupart)
  - Sur matériel génétique extra-chromosomique
  - donc *transmissibles* de souches en souches donc inquiétant en milieu hospitalier…

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Béta-lactamases à spectre élargi – BLSE (ESBL en anglais)

- B-lactamase qui détruit plusieurs sortes de B-lactames
  - Ex. Penicilline, cefazoline, cefuroxime, ceftriaxone…
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  - Exception: carbapenemes (mero, imi…)
- Différents types (>120)
- Plasmidiques (la plupart)

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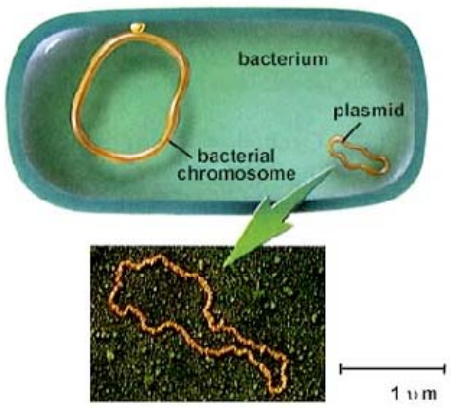
β-lactamase à spectre étendu (*BLSE*)

Mais aussi résistance Pour:

- Aminoglycosides
- Fluoroquinolones
- Tetracyclines
- TMP/SMX

Enterobacteriaceae



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β-lactamase à spectre étendu (*BLSE*)

- Epidemiologie
  - Mondiale
  - En forte augmentation
  - Plus prévalent dans certains pays/continents que d'autres
    - Très élevé Amérique du Sud, Europe
    - Moins élevé en Am. Du Nord
- Colonisation >> infection

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USA

PUBLIC HEALTH THREAT

An estimated 140,000 healthcare-associated Enterobacteriaceae infections occur in the United States each year. CDC estimates that bloodstream infections caused by ESBL-containing Enterobacteriaceae result in upwards of $40,000 in excess hospital charges per occurrence. Approximately 26,000 infections and 1,700 deaths are attributable to ESBLs.

	Percentage of Enterobacteriaceae healthcare-associated infections resistant to extended spectrum cephalosporins	Estimated number of infections	Estimated number of deaths attributed
ESBL-producing *Klebsiella* spp.	23%	17,000	1,100
ESBL-producing *E. coli*	14%	9,000	600
Totals		26,000	1,700

For more information about data methods and references, please see technical appendix.

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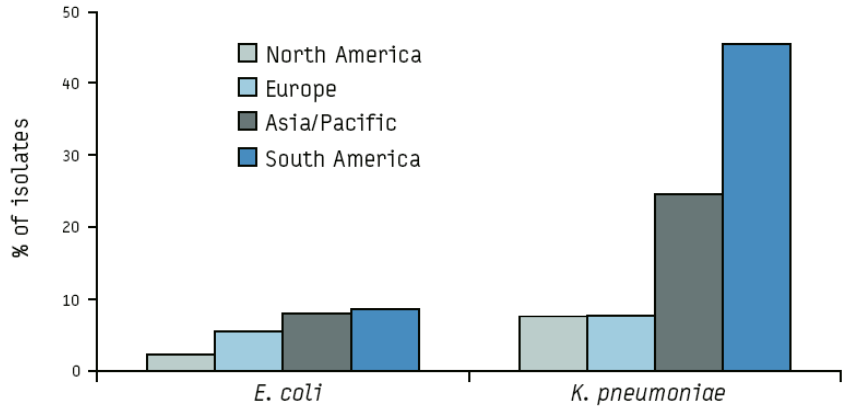
Frequency of ESBL-producing *Escherichia coli* and *Klebsiella pneumoniae* isolates reported in the TEST surveillance study (2004-2006) in different geographic areas [27]



EUROSURVEILLANCE Vol . 13 · Issue 47 · 20 November 2008 ·

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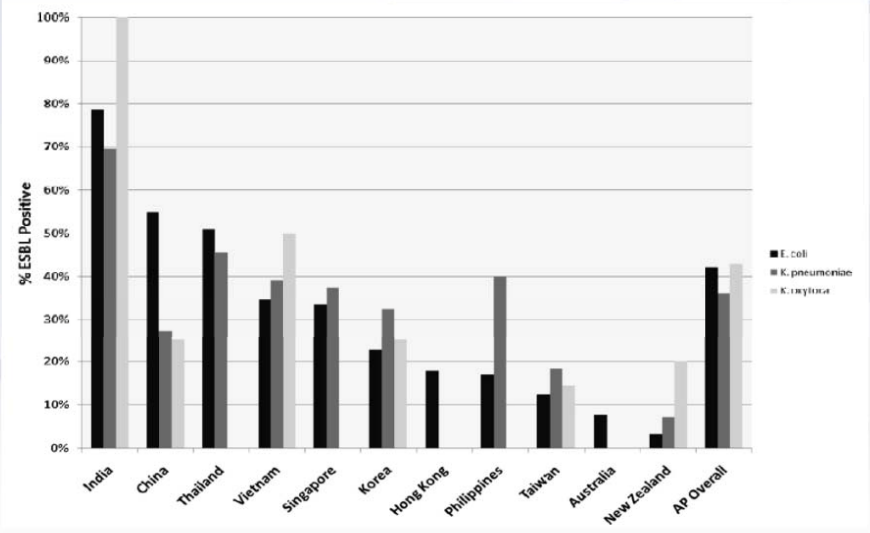
PUBLIC HEALTH AGENCY *of* CANADA | AGENCE DE LA SANTÉ PUBLIQUE *du* CANADA

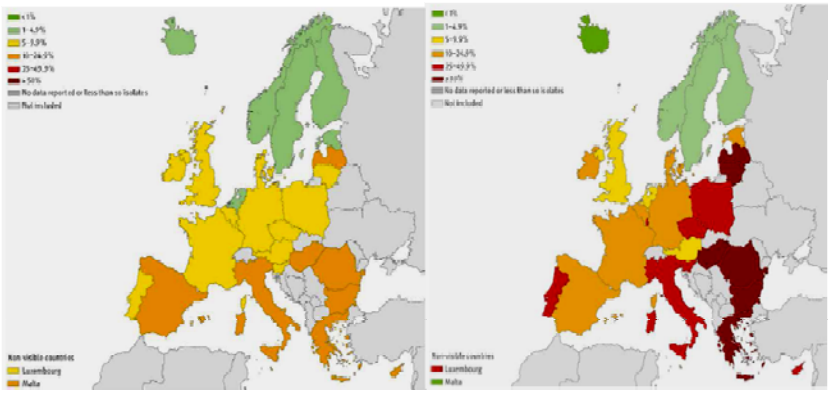
24

ESBL+ve isolates, Asia-Pacific 2007; intra-abdominal infection



Hawser *et al.*, *AAC* 2009; **53**: 3280

ESBL producing *E. coli* & *Klebsiella pneumoniae*



E.coli *K. pneumoniae*

http://www.salute.gov.it/imgs/C_17_pubblicazioni_1404_allegato.pdf

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MDR GNRs in the Community

- **ESBLs**
  - 40 patients with CTX-M *E. coli* from urine in a facility in Texas
    - 30/40 were isolated from outpatients, 7 (18%) had no documented contact with the healthcare system in previous 6 months and no comorbidities
  - Swedish travelers – 100 travelers outside of Northern Europe
    - 24 came back with ESBL in stool
    - 7/8 to India, 10/31 to Asia
    - Development of gastroenteritis a risk factor
    - 5/21 persistently colonized

Lewis JS, et al. Poster Presentation, 49th ICAAC 2009, San Francisco
Tangden T et al. AAC 2010: 3564-3568

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Dissemination by International Traveling

- **ESBLs**
  - Swedish travelers – 100 travelers outside of Northern Europe
    - 24 came back with ESBL in stool
    - 7/8 to India, 10/31 to Asia
    - Development of gastroenteritis a risk factor
    - 5/21 persistently colonized

Lewis JS, et al. Poster Presentation, 49th ICAAC 2009, San Francisco
Tangden T et al. AAC 2010: 3564-3568

Prospective ESBL Colonization Study

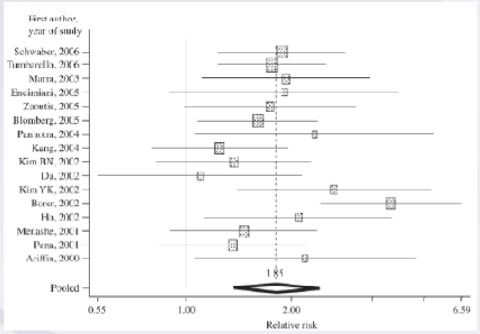
Continent or region	No. of travelers	No. (%) of travelers positive for ESBL-producing isolates
Africa	25	1 (4)
Asia (India excluded)	31	10 (32)
Central America	6	0 (0)
India	8	7 (88)
Middle East	14	4 (29)
North America	2	0 (0)
South America	1	0 (0)
Southern Europe	16	2 (13)

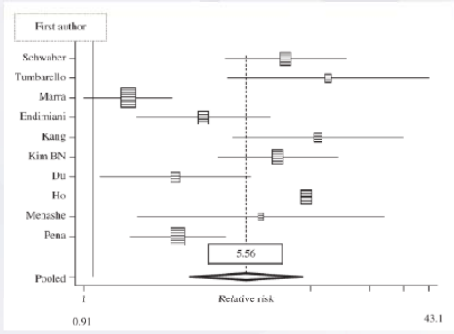
[a] The rate of acquisition of ESBL-producing strains was highest for travelers visiting India ($P < 0.001$). Three participants visited more than one continent, and therefore, the sum of travelers in this table exceeds the actual number of 100.

- 24% of 100 travelers came back with ESBL
- ESBL pos carriers more likely to have gastroenteritis during the trip (P = 0.003)
- 13/24 were CTX-M-15 all from India
- 2/24 carried ESBL after 6 months

Tangden et al. AAC 2010. 54:3564–3568

Meta-analysis of ESBL vs non-ESBL Risk for Bacteremia





Mortality

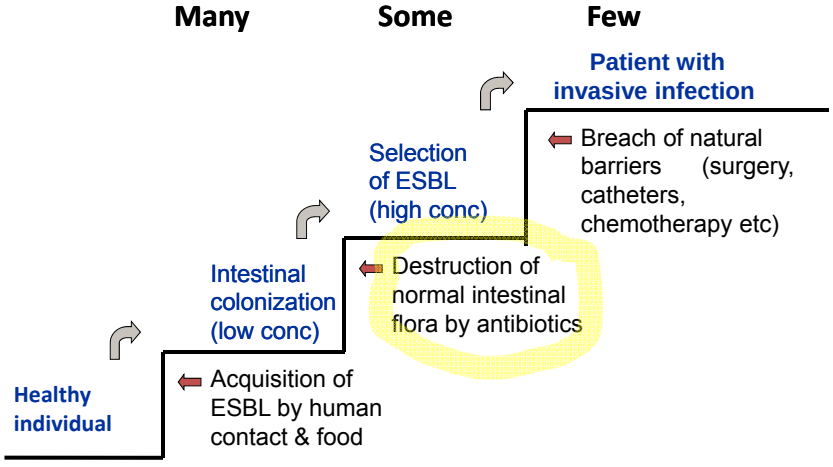
~2X more likely to die with an ESBL bacteremia

Inappropriate Therapy

~6X more likely to receive the wrong antibiotic

Schwaber and Carmeli JAC 2007. 60:913-20.

ESBL: The steps from contamination to infection



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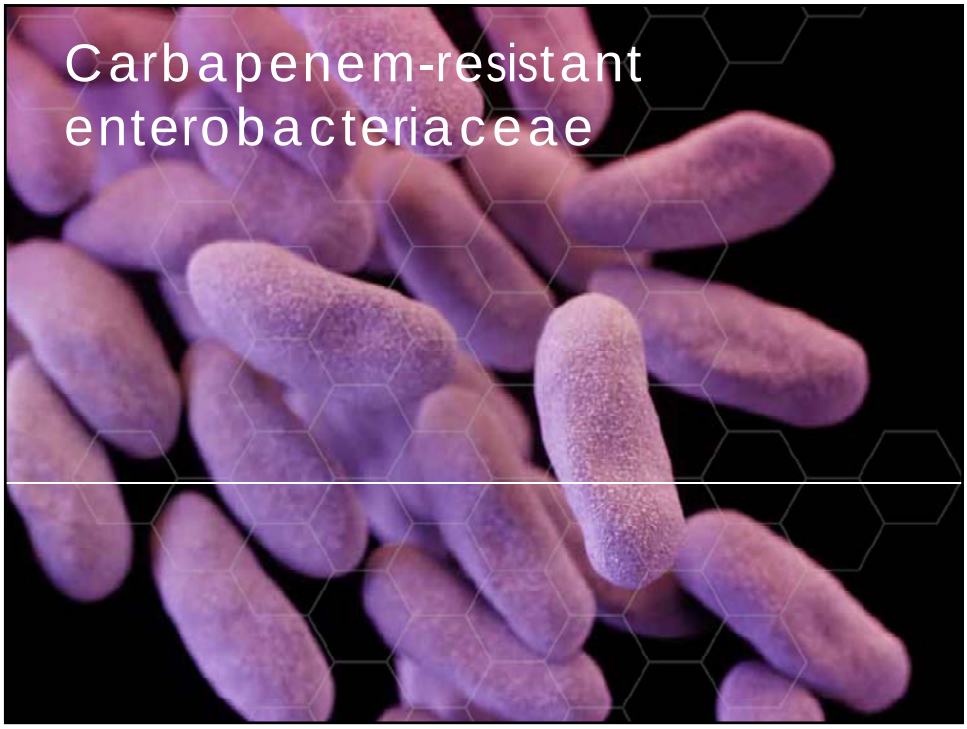

The Last Line of Defense

- Fortunately, our most potent β-lactam class, carbapenems, remained effective against almost all *Enterobacteriaceae* (even ESBL-producing)
  - Meropenem, Ertapenem, Imipenem

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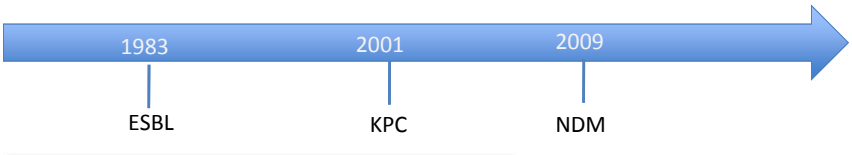

Novel Carbapenem-Hydrolyzing β-Lactamase, KPC-1, from a Carbapenem-Resistant Strain of *Klebsiella pneumoniae*

VIM
IMP

Knothe H et al. Infection 1983;11(6):315–317.

MMWR 2013; 62: 165-70

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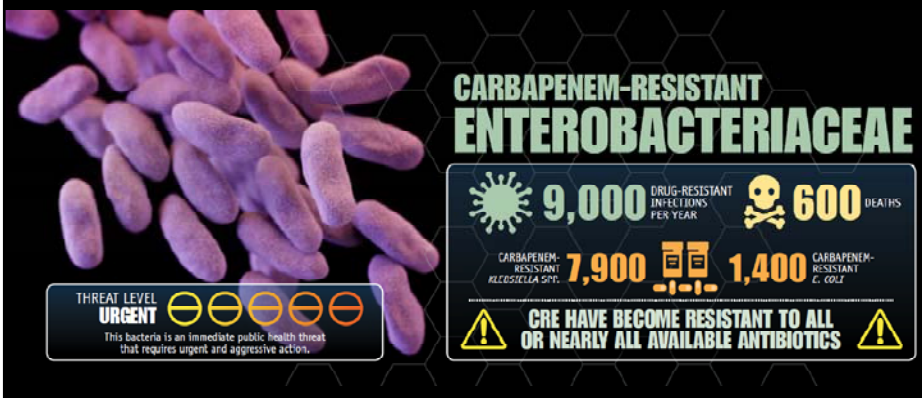

http://www.cdc.gov/drugresistance/threat-report-2013/

PUBLIC HEALTH THREAT

An estimated 140,000 healthcare-associated Enterobacteriaceae infections occur in the United States each year; about 9,300 of these are caused by CRE. Up to half of all bloodstream infections caused by CRE result in death. Fortunately, bloodstream infections account for a minority of all healthcare-associated infections caused by Enterobacteriaceae. Each year, approximately 600 deaths result from infections caused by the two most common types of CRE, carbapenem-resistant *Klebsiella* spp. and carbapenem-resistant *E. coli*.

	Percentage of Enterobacteriaceae healthcare-associated infections resistant to carbapenems	Estimated number of infections	Estimated number of deaths attributed
Carbapenem-Resistant *Klebsiella* spp.	11%	7,900	520
Carbapenem-resistant *E. coli*	2%	1,400	90

For more information about data methods and references, please see technical appendix.

http://www.cdc.gov/drugresistance/threat-report-2013/

Mechanisms of Carbapenem-Resistance in Enterobacteriaceae (CRE)

- **Before 2000: Extended – spectrum cephalosporinase + porin loss**
  - Extended-spectrum β-lactamases (ESBLs)
  - AmpC-type enzymes
- **1986-1990 in NNIS 2.3% of *Enterobacter* NS to imipenem**
  - Did not increase over the time period unlike imipenem NS *Pseudomonas* Carbapenemase production
- **Since 2000: carbapenemases**

Gaynes and Culver. ICHE 1992 13:10-14

Carbapenemases

TABLE I. General classification of carbapenemases and frequency of isolation

Molecular class[a] (functional group[b])	Enzymes	Inhibited by CLA	Inhibited by EDTA	ATM	Organisms	Gene location	Epidemiological relevance
A (2f)	Sme-1 to Sme-3, IMI-1 to IMI-3, NmcA, SFC-1	±	–	R	*Serratia marcescens* and *Enterobacter cloacae*	Ch	±
	KPC-2[c] to KPC-13	±	–	R	*Enterobacteriaceae, Pseudomonas aeruginosa, Acinetobacter baumannii*	Pl	++++
	GES-1 to GES-20	+	–	S/R	*Enterobacteriaceae, P. aeruginosa, A. baumannii*	Pl	+
B (3)	IMP-1 to IMP-33, VIM-1 to VIM-33, NDM-1 to NDM-6, SPM-1, SIM, GIM, IND-1 to IND-7, AIM, DIM, KHM	–	+	S	*Enterobacteriaceae, P. aeruginosa*, and other GNNFB	Pl/Ch	±/+++
D (2df)[d]	OXA-23 group (OXA-23, OXA-27, OXA-49)	±	–[e]	S	*A. baumannii, P. aeruginosa, Enterobacteriaceae*	Pl/Ch	++
	OXA-24 group (OXA-24, OXA-25, OXA-26, OXA-40, OXA-72)						
	OXA-40 group (OXA-40, OXA-143)						
	OXA-58						
	OXA-48 group (OXA-48, OXA-54, OXA-181)						

ATM, aztreonam; Ch, chromosomal; CLA, clavulanate; GNNFB, gram-negative non fermentative bacilli; Pl, plasmid; R, resistant; S, susceptible.
[a]Ambler classification.
[b]Bush, Jacoby and Medeiros classification.
[c]KPC-1 was later found to be identifical to KPC-2.
[d]Only class D carbapenemases representative of different groups have been included.
[e]Some OXA enzymes may be slightly inhibited by EDTA.

Principales carbapenemases: KPC, VIM, IMP, NDM, OXA

Canton R et al. Clin Microbiol Infect 18, 413-431

Carbapenemases

Enzyme	Classification	Activity
KPC	Class A	Hydrolyzes all β-lactam agents
NDM-1	Class B: metallo-β-lactamse (MBL)	Hydrolyzes all β-lactam agents except aztreonam
IMP		
VIM		
OXA	Class D	Hydrolyzes carbapenems but not active against 3rd generation cephalosporins

Carbapenemases

Enzyme	Number identified to date in US	Classification	Activity
KPC		Class A	Hydrolyzes all β-lactam agents
NDM-1	29 (10 states)	Class B: metallo-β-lactamse (MBL)	Hydrolyzes all β-lactam agents except aztreonam
IMP	3 (1 state)		
VIM	3 (2 states)		
OXA	3 (2 states)	Class D	Hydrolyzes carbapenems but not active against 3rd generation cephalosporins

CRE

- **Enterobacteriaceae resistant to carbapenems mainly by means of :**
  - KPC
  - VIM
  - IMP
  - NDM-1
- **Different resistance genes had different epicenters**
  - Followed by different extents of global dissemination
    - KPC: USA
    - VIM: Greece
    - OXA-48: Turkey

Savard P et al. Infect Control Hospit Epidemiol. 2013

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Why are CRE Clinically and Epidemiologically Important?

- **Cause infections associated with high mortality rates**
- **Resistance is highly transmissible**
  - Between organisms – plasmids
  - Between patients
- **Treatment options are limited**
  - Pan-resistant strains identified
  - Could be decades before new agents are available to treat
- **Potential for spread into the community**
  - *E. coli* common cause of community infection

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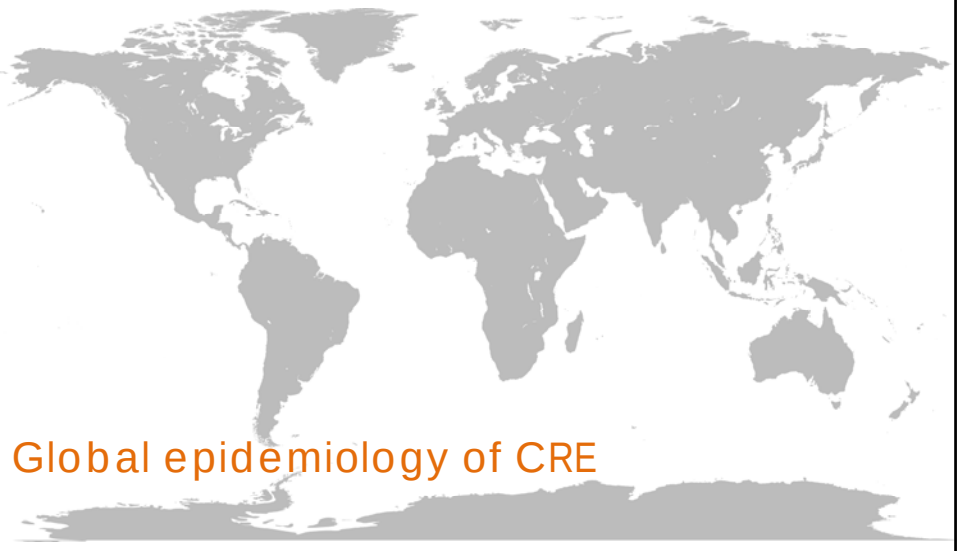

Global epidemiology of CRE

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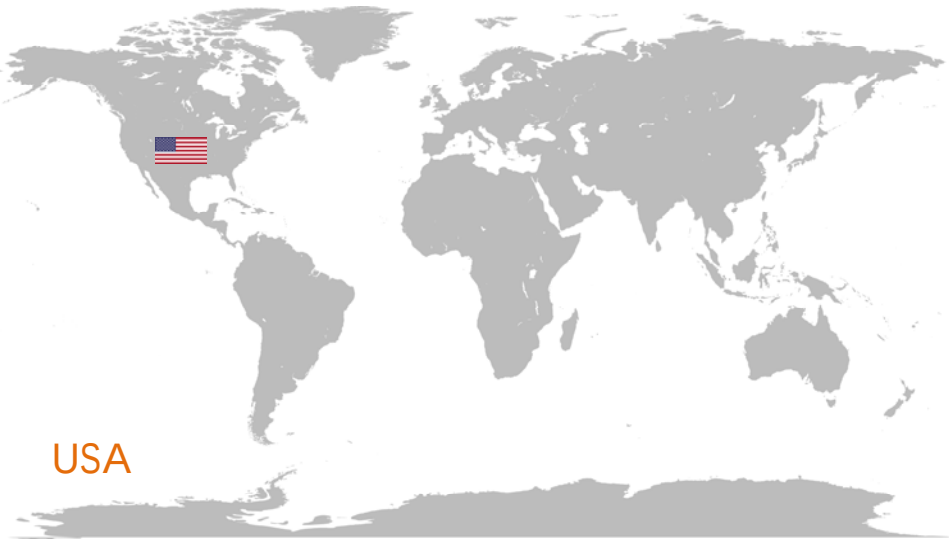

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Klebsiella Pneumoniae Carbapenemase

- KPC is a class A β-lactamase
  - Several KPC types have been described (1-8)
  - Confers resistance to all β-lactams including extended-spectrum cephalosporins and carbapenems
- Is the predominant mechanisms of carbapenem resistance in Enterobacteriaceae (CRE) in the US.
- Occurs primarily in *Klebsiella pneumoniae*
  - Also reported in other Enterobacteriaceae
  - Case reports of KPC in *Pseudomonas aeruginosa*

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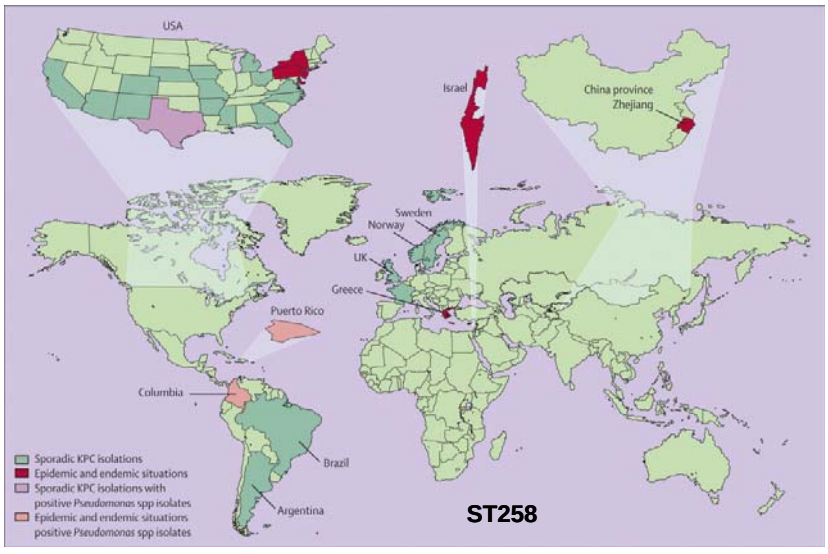
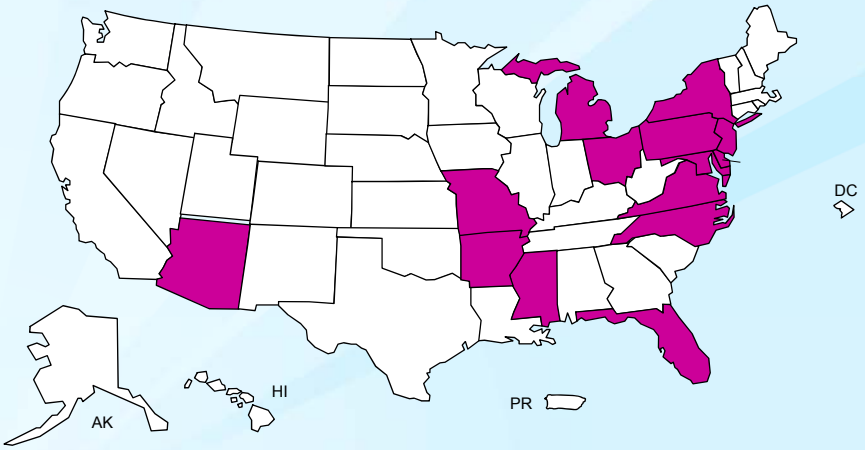
KPC Enzymes

- Located on plasmids- self-sustaining genetic elements outside of the chromosome
- KPC gene (*bla*$_{KPC}$) reported on plasmids with:
  - Extended spectrum β-lactamases
  - Aminoglycoside resistance
  - Fluoroquinolone resistance
- *bla*$_{KPC}$ is usually flanked by transposon sequences- mobile genetic elements



Lancet Infect Dis 2009;9:228-36

Carbapenemase-producing CRE in the United States



Nov. 2008

Patel, Rasheed, Kitchel. 2009. Clin Micro News
CDC, unpublished data

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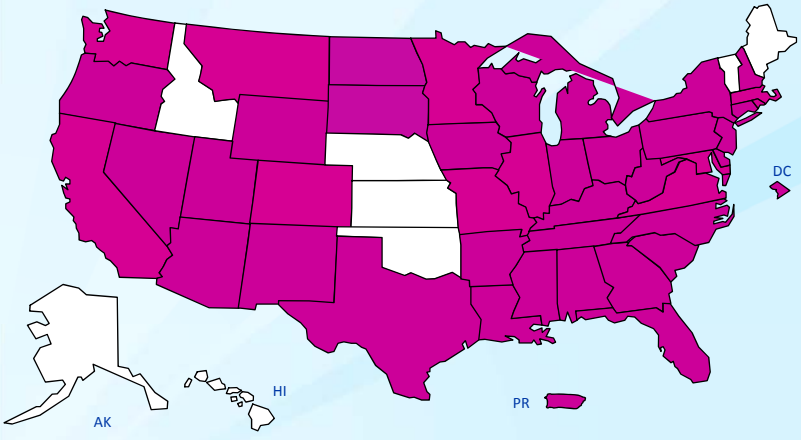
KPC-producing CRE in the United States



Patel, Rasheed, Kitchel. 2009. Clin Micro News
MMWR MMWR Morb Mortal Wkly Rep. 2010 Jun 25;59(24):750.
MMWR Morb Mortal Wkly Rep. 2010 Sep 24;59(37):1212.
CDC, unpublished data

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Change in CRE incidence, 2001-2011

	National Nosocomial infection Surveillance system, Number (%) of isolates			National Healthcare Safety Network, Number (%) of isolates		
	2001			2011		
Organism	Isolates	Tested	Non-susceptible	Isolates	Tested	Non-susceptible
Klebsiella pneumoniae* and *oxytoca	654	253 (38.7)	4 (1.6)	1,902	1,312 (70.0)	136 (10.4)
E. coli	1,424	421 (29.6)	4 (1.0)	3,626	2,348 (64.8)	24 (1.0)
Enterobacter aerogenes* and *cloacae	553	288 (52.1)	4 (1.4)	1,045	728 (69.7)	26 (3.6)
Total	2,631	962 (36.6)	12 (1.2)	6,573	4,388 (66.8)	186 (4.2)

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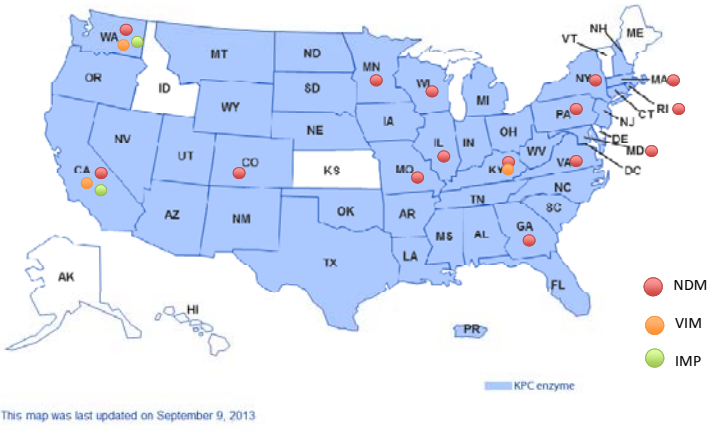
States with reported cases of CRE - 2013



This map was last updated on September 9, 2013

http://www.cdc.gov/hai/organisms/cre/TrackingCRE.html

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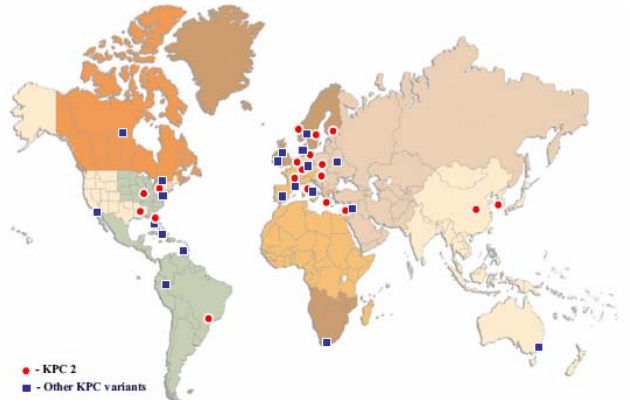
Worldwide Distribution of KPC



Walsh. 2010. International Journal of Antimicrobial Agents

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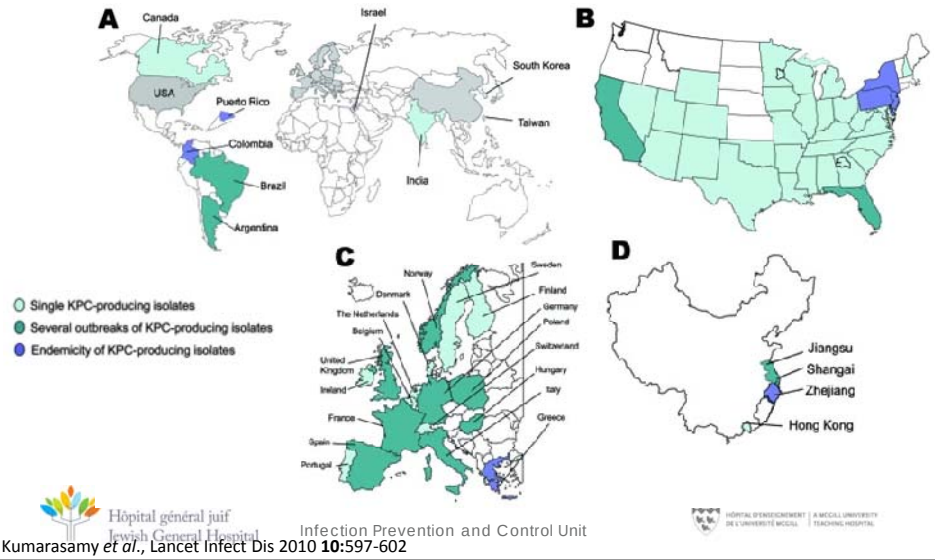
Worldwide Distribution of *Klebsiella pneumoniae* carbapenemase producers



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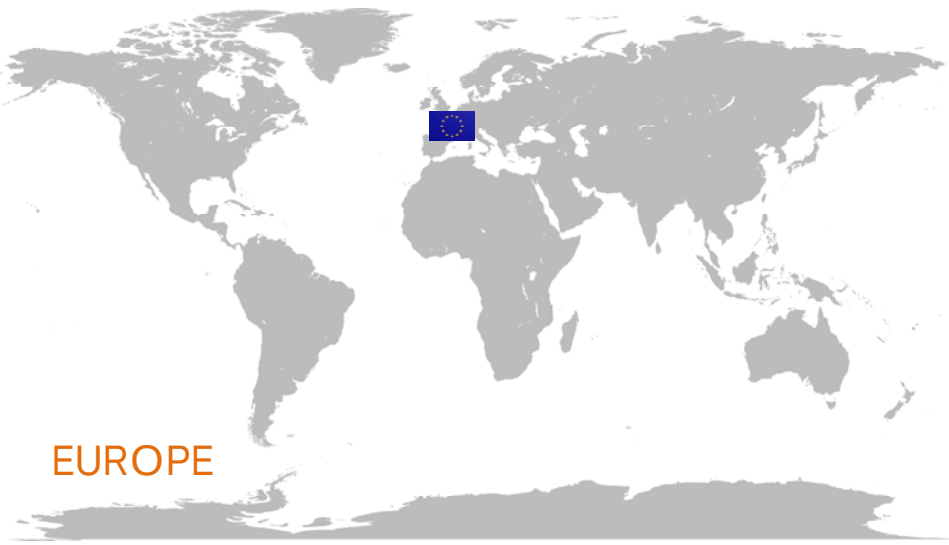
Kumarasamy *et al.*, Lancet Infect Dis 2010 **10:**597-602



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Types of carbapenemase - Europe

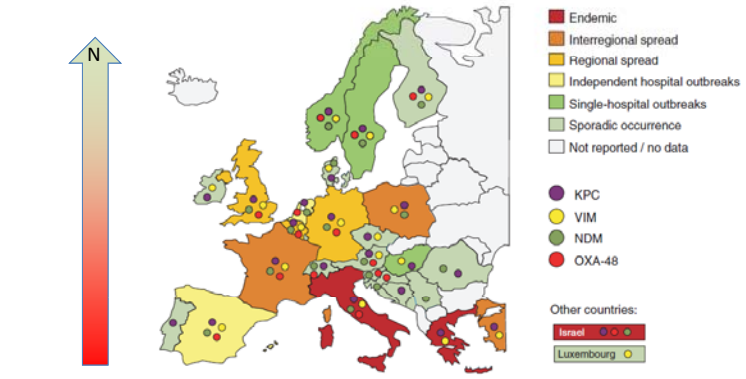

FIG. 1. European situation regarding carbapenemase-producing *Enterobacteriaceae*, using an epidemiological scale of nationwide expansion (data have been updated from reference 17) and carbapenemase types in different countries or geographical areas known until January 2012.

Canton R et al. Clin Microbiol Infect 18, 413-431

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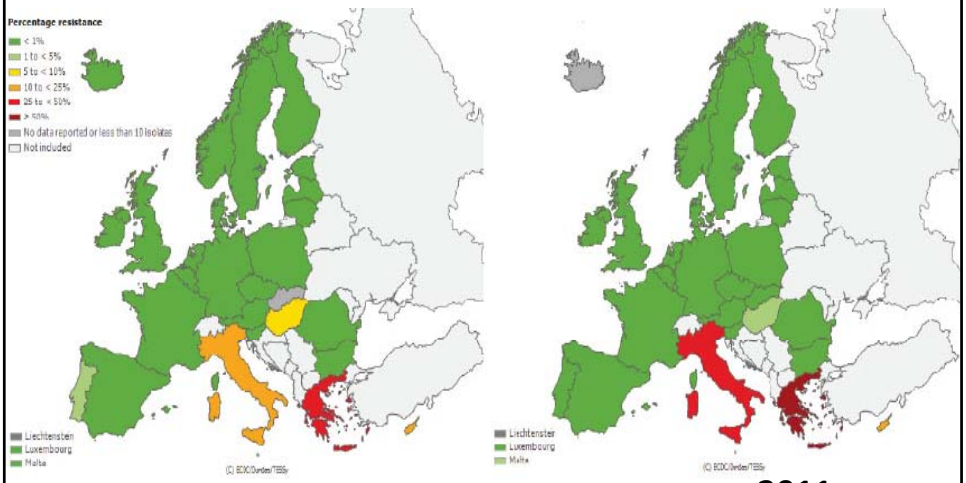
Klebsiella pneumoniae: percentage of invasive isolates with resistance to carbapenems.



Hungary (2006): 0%
Italy (2006): 1.3%

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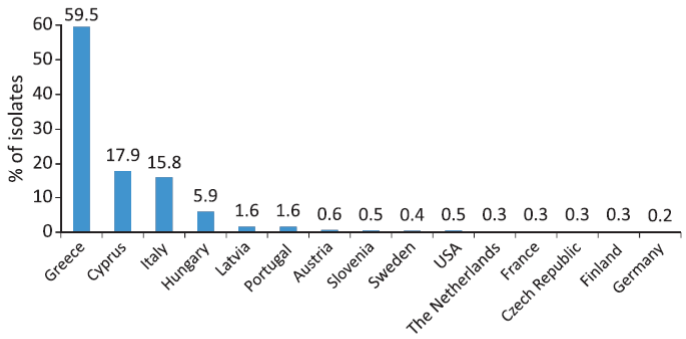

FIG. 2. Rates of non-susceptibility (intermediate plus resistant) of *Klebsiella pneumoniae* to carbapenems in European countries. Data were obtained from the EARS-Net database (2010). (http://ecdc.europa.eu/en/activities/surveillance/EARS-Net/database/Pages/database.aspx). Only those countries with non-susceptible isolates are included.

Canton R et al. Clin Microbiol Infect (2013)18, 413-431

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Transmission of CRE from Greece to other European countries

2007-2010

Country	Year	Total Number of Patients	Origin of Patients	Number of Secondary Cases	Probability of the Greek Origin	References	Mechanisms of Resistance
Belgium	2009	3	3 patients transferred from Greek hospitals	0	Confirmed	Rogaerts et al. 2010 [19]	*bla*KPC-2
Denmark	2009	2	2 patients transferred from Greek hospitals	0	Confirmed	Hammerum et al. 2010 [20]	*bla*KPC-2
Finland	2009	1	1 patient transferred from Crete	0	Confirmed	Osterlund et al. 2010 [21]	*bla*KPC-2
France	No data	8	1 patient transferred from Crete	7	Confirmed	Naas et al. 2010 [22]	*bla*KPC-2
France	2007	1	1 patient transferred from Crete	0	Confirmed	Cuzon et al. 2008 [23]	*bla*KPC-2
France	2009	1	1 patient transferred from Greek hospital	0	Confirmed	Barbier et al. 2010 [24]	*bla*KPC-2
France	2009	4	1 patient transferred from Greek hospital	3	Confirmed	Kassis-Chikhani et al. 2010 [25]	*bla*KPC-2
Germany	2007-2008	9	1 patient treated in Greece	8	Hypothetical	Wendt *et al.* 2010 [26]	*bla*KPC-2
Hungary	2008	7	1 patient transferred from Greek hospital	6	Confirmed	Tóth et al. 2010 [27]	*bla*KPC-2
Norway	2007	6	4 patients transferred from Greek hospitals	2	Confirmed	Samuelsen et al. 2009 [28]	*bla*KPC-2
Sweden	No data	1	1 patient transferred from Greek hospital	0	Confirmed	Tegmark Wisell et al. 2007 [29]	*bla*KPC-2
The Netherlands	No data	14	African immigrants travelling via Greece	No data	Hypothetical	Mouton et al. 2010 [30]	*bla*KPC-2

Wernli et al. PLOS1 2011

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Why do different families of carbapenemases have such different degrees of epidemiological success?

1. **Pathogen**
   bla$_{KPC}$ gene is present in *K. pneumoniae*,
   a leading nosocomial pathogen with high rates of GI carriage among hospitalized patients

2. **Clone**
   presence of the blaKPC gene in a ST258, a highly transmissible & fit strain

The molecular mechanisms behind the success of the KPC-producing ST-258 clone remained obscure

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KPC-producing *K. pneumoniae* - Italian experience

late 2008

The first reported cases of KPC-Kp (ST258)

Giani *et al* – JCM 2009
Rossolini GM – unpublished

early 2011

ST258, ST512 (CC258)

Fontana *et al* – BMC Res Notes 2010
Marchese *et al* – J Chemother 2010
Ambretti *et al* – New Microb 2010
Gaibani *et al* – Eurosurv 2011
Mezzatesta *et al* – CMI 2011
Agodi *et al* – JCM 2011
Richter *et al* – JCM 2011
Di Carlo *et al* – BMC Gastroenterol 2011
Rossolini GM – unpublished

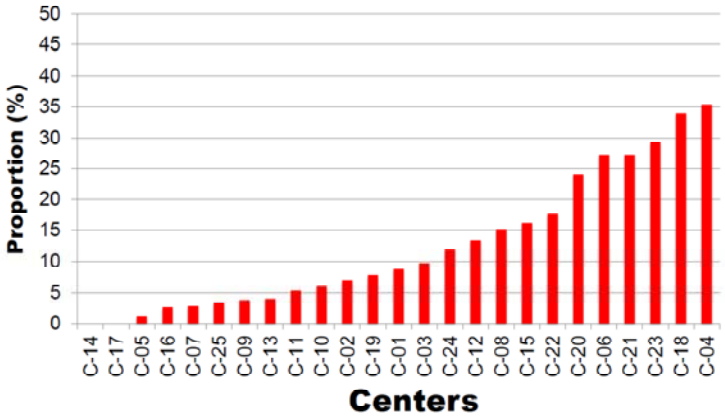
late 2012

ST512
ST258

ST101
ST15
ST147-like

AMCLI – CoSA CRE network
Frasson *et al* – JCM 2012
ARISS-CoSA study – unpublished

Carbapenen-resistant *K. pneumoniae*



AMCLI-CoSA – Italian National CRE Surveillance 2011

Belgium

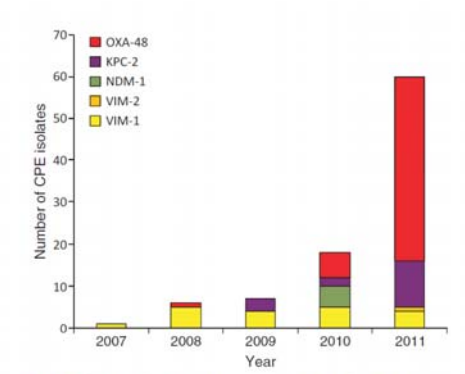


FIG. 3. Evolution of the carbapenemase-producing *Enterobacteriaceae* (CPE) isolates in Belgium (92 isolates referred to the National Reference Centre, Belgium, January 2007–December 2011) (data have been updated from reference 150).

- **Belgium**
  - oxa-48 predominant
    - K.pneumoniae 69%
    - E. cloacae 15%
    - E.coli 6%
  - 70% cases have no travel history!
  - Mainly asympto. bacteriuria in elderly
  - Oxa-48 also dominant in the Netherlands and Germany

Canton R et al. Clin Microbiol Infect 18, 413-431

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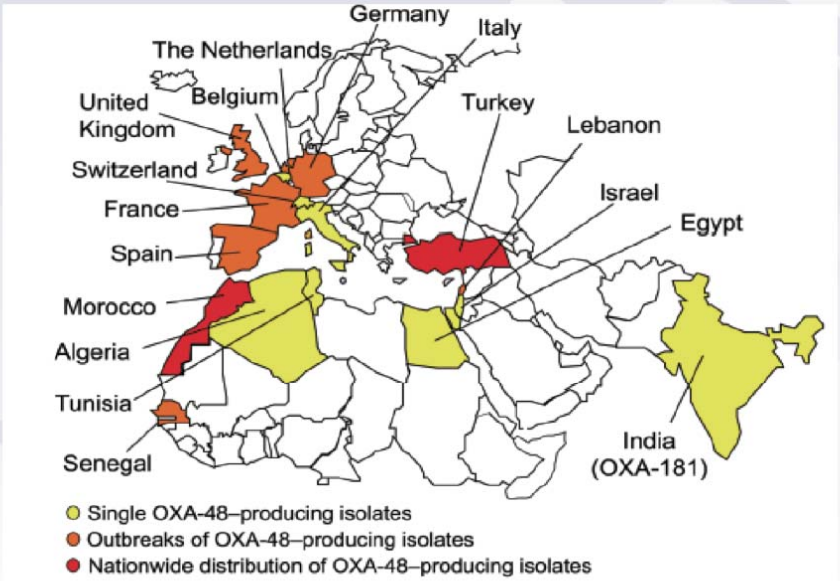
PUBLIC HEALTH AGENCY *of* CANADA | AGENCE DE LA SANTÉ PUBLIQUE *du* CANADA

15

OXA-48 Global Distribution



Nordmann et al. 2011. EID 17:1791-1798

OXA-48

- First described in Turkey
  - Poirel et al. 2004. AAC. 48:15–22
- Focused around Mediterranean countries
- Most difficult to detect of the carbapenemases
  - Low MICs to carb and cephalosporins
  - No inhibitors (ie. clav, EDTA)
  - Under reporting?

UK

N= number of individual isolates

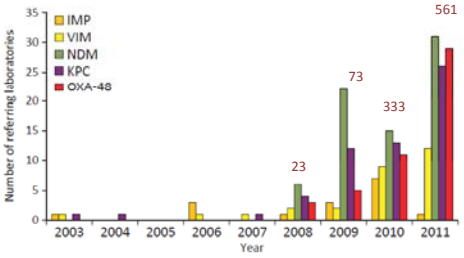


FIG. 4. Numbers of UK laboratories referring at least one carbapenemase-producing *Enterobacteriaceae* (CPE) isolate to the Antibiotic Resistance Monitoring and Reference Laboratory (ARMRL) (Health Protection Agency). Additionally, in 2010 and 2011, two and one laboratories, respectively, referred IMI-producing CPE isolates, respectively. In 2011, one laboratory referred at least one CPE isolate producing both KPC and VIM enzymes.

- **NO coordinated surveillance of CRE by Public Health**
- **The main center of NDM-1 in Europe**
  - Only 46% with travel history in South Asia (!)
  - Only 60% of cases with travel to South Asia had contact with Health Care
- **Types of CRE:**
  - *Klebsiella* 80%
  - *E.coli* 10%
  - *Enterobacter* 8%
  - Other 2% (*Citrobacter, Morgannella, Providencia, Raoutella, Serratia*)
- **Regional specificities**
  - London: oxa-48
  - N-W England: 75% of all KPC-2
- **Horizontal transfer documented**
  - pKpQIL-like plasmid transfering KPC gene from *K.pneumoniae* to *E.coli* and *Enterobacter*
  - Oxa-48-encoding plasmid tranfering from *K.pneumonia* to other *Enterobacteriaceae*

Canton R et al. Clin Microbiol Infect 18, 413-431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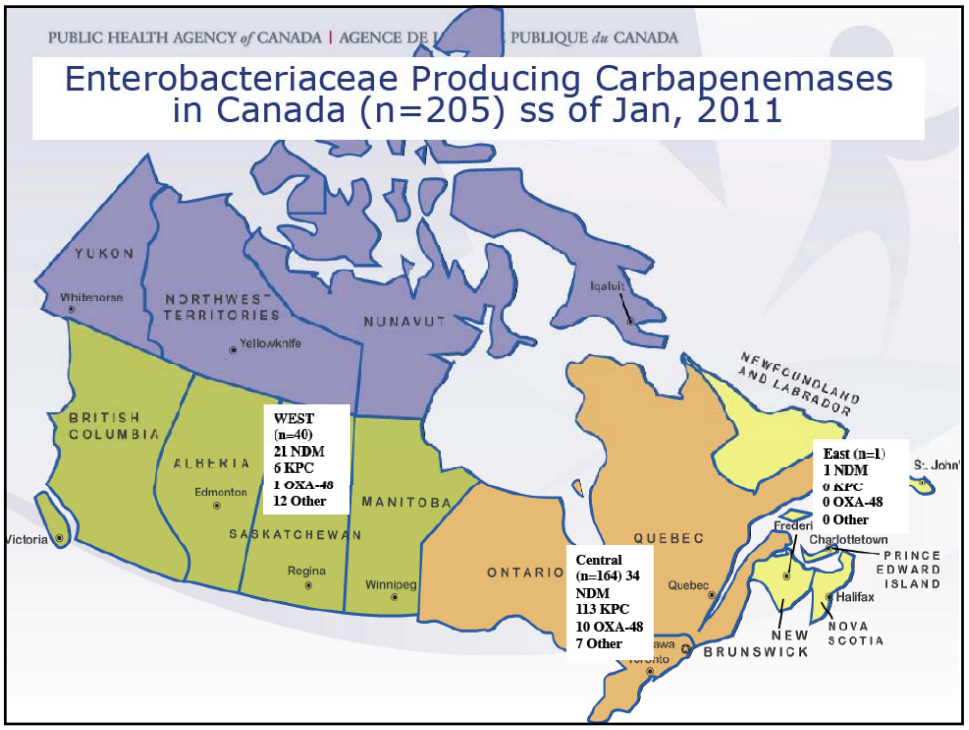
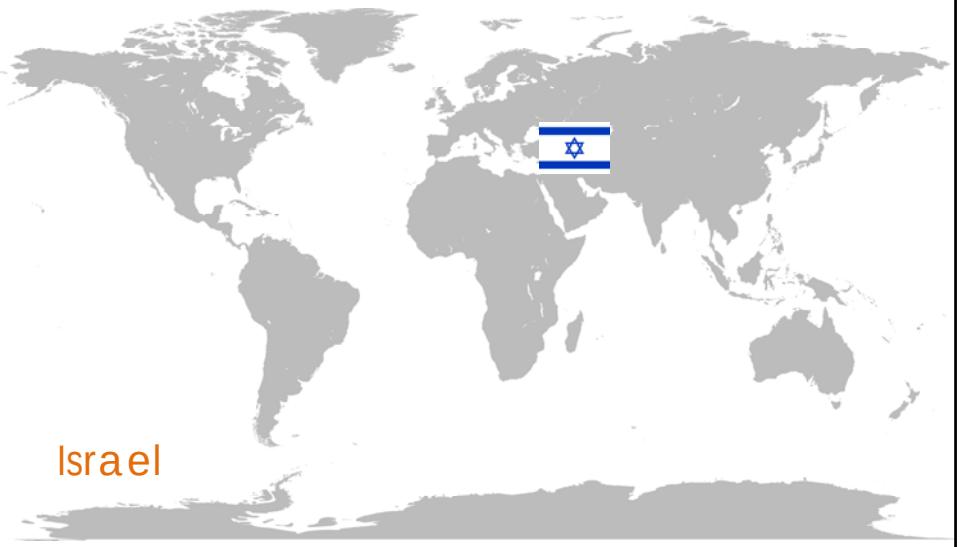

PUBLIC HEALTH AGENCY of CANADA | AGENCE DE
PUBLIQUE du CANADA
Enterobacteriaceae Producing Carbapenemases in Canada (n=205) ss of Jan, 2011
YUKON
Whitehorse
NORTHWEST TERRITORIES
Yellowknife
NUNAVUT
Iqaluit
BRITISH COLUMBIA
ALBERTA
Edmonton
SASKATCHEWAN
Regina
MANITOBA
Winnipeg
ONTARIO
QUEBEC
Quebec
NEWFOUNDLAND AND LABRADOR
PRINCE EDWARD ISLAND
Charlottetown
Halifax
NOVA SCOTIA
NEW BRUNSWICK
Victoria
WEST (n=40) 21 NDM 5 KPC 1 OXA-48 12 Other
Central (n=164) 34 NDM 113 KPC 10 OXA-48 7 Other
East (n=1) 1 NDM 0 KPC 0 OXA-48 0 Other



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The Israeli Story

Israel demographics

- Population: ~ 8 million
- Density: ~ 349/km² (CA: ~3.46/km²)
- Acute-care beds: 30 hospitals ~ 15,000 (=1.9 beds/1000 pop.)
- Long-term-care beds: ~30,000 (13 LTACH)

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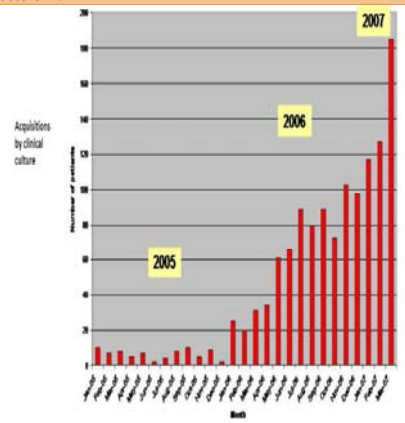
The Israeli Story

- Late 2005 –KPC-producing *K. pneumoniae* ST-258 introduced to Israeli hospitals
- 2006 –outbreak began: ~700 cases
- 01/01/2007 -04/30/2007: ~600 cases
- Local attempts to contain- failed!

Nationwide epidemic curve prior to intervention

carbapenem resistance in *Klebsiella* bacteremia 0% → 22%



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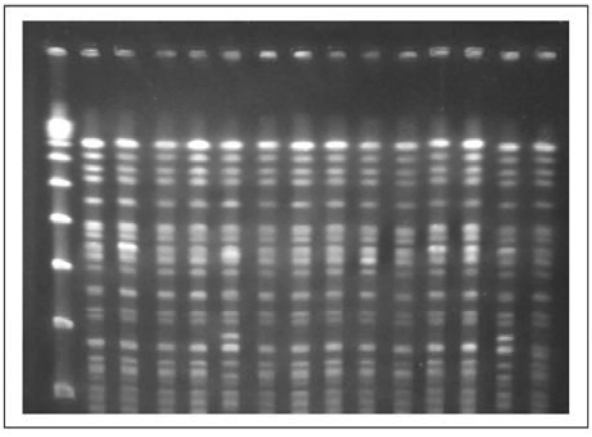
A clonal outbreak, involving acute-care hospitals and long-term care facilities



Navon-Venezia et al, AAC 2009

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Microscopic perspective

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ROLE OF LONG-TERM CARE

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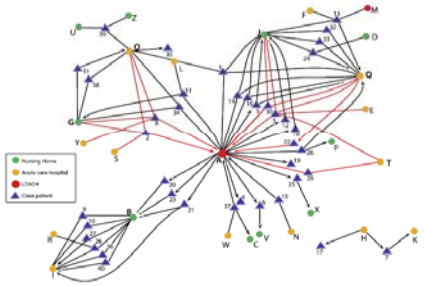
KPC outbreak in Chicago, 2008

An outbreak investigation of KPC-producing *Enterobacteriaceae* among patients of acute and LTACHs

- 4 adjacent counties in Indiana and Illinois
- Jan-Dec 2008

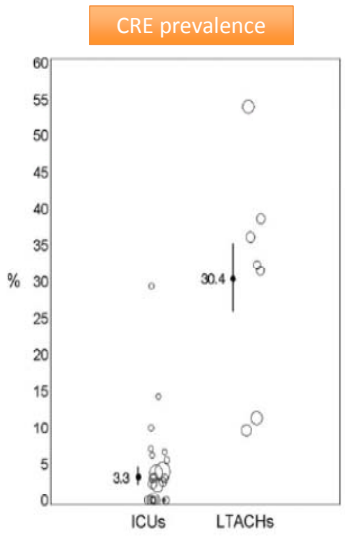


- Most cases - 24 (60%) of 40 cases linked to LTACH-A, at least 10 patients (25%) acquired KPC there
- Of 16 cases not linked to LTACH-A, 12 (75%) were linked to 3 nursing homes
- Of 40 KPC patients, only 4 definitively acquired KPC in acute care hospital

Won et al. Clin Infect Dis 2011; 53:532-540

2 year later...

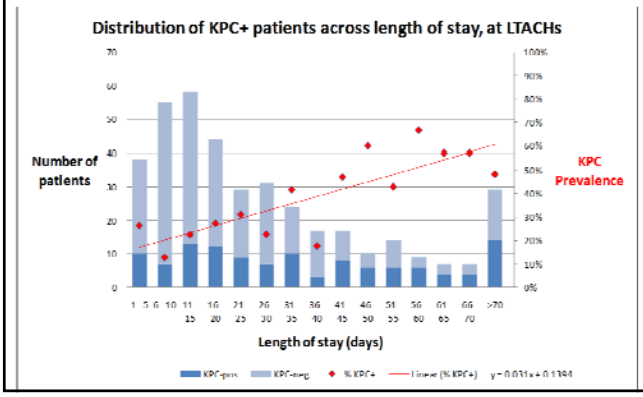
- A cross-sectional single-day point prevalence survey were conducted in:
  - 24 /25 short-stay acute care hospitals
  - and all 7 LTACHs in Chicago



Lin et al. CID 2013:57 (1 November) • Lin et al

KPC Point Prevalence Survey - Chicago

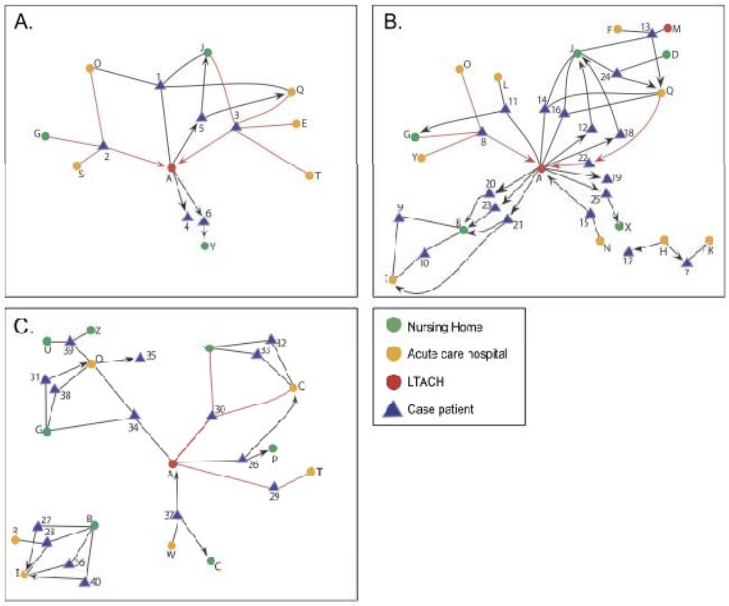
- **Hospitals with >10 ICUs and 7 LTACHs**
- **Two point prevalence surveys (2010 and 2011)**
- **Results**
  - All LTACHs and 15/24 hospitals had at least one patient with KPC
  - In acute care 3.3% of patients colonized (30/909)
  - In LTACH – 30.4% of patients colonized (119/391)



Lin M et al. ID Week 2012 San Diego #396

Lin et al. CID 2013:57 (1 November) • Lin et al

Social Network Analysis



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Long-term Acute Care Hospitals
A major CRE Reservoir

- Several recent studies have reported high rates of CRE carriage among patients hospitalized in LTACH
  - 50% of patients with CRE in an acute care facility were admitted from LTACH

Perez. Antimicrob Chemother 2010; 65:1807

  - Point prevalence studies conducted among LTCF residents have detected colonization prevalence as high as 16-49%

Chitnis ICHE. 2012;33:984
Ben-David. ICHE 2011;32:845

In Israel, the current **nosocomial** CRE attack rate in acute care hospital is low ~1/1000 admissions

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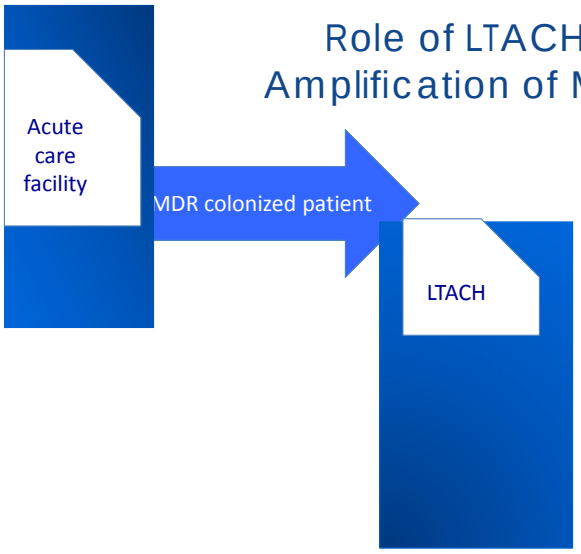
Role of LTACH in Amplification of MDRO



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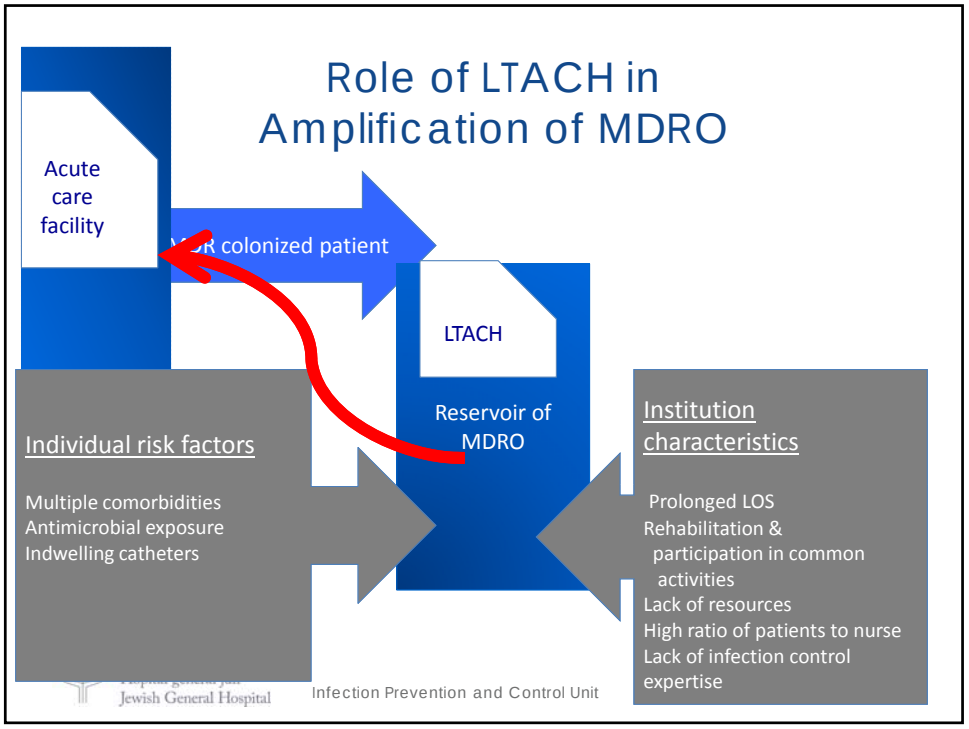

MDR GNRs in the Community

- **NDM**
  - Identified in *K. pneumoniae* in river in Hanoi, Viet Nam
  - Cause of community-onset infections in India
    - In one survey, isolates from 2 sites often from community acquired UTIs
  - Gene for NDM detected in 2/50 drinking water samples and 51/171 water seepage samples from New Delhi
- **OXA-48**
  - Found in 2/4 "puddles" sampled Morocco

Isozumi R et al. EID 2012: 1383-4
Kumarasamy K Lancet ID 2010;
Walsh TR Lancet ID 2011:355-362
Potron et al. 2011. AAC epub August 2011.

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Why are CRE Clinically and Epidemiologically Important?

- **Cause infections associated with high mortality rates**

Risk Factors for and Outcomes of Carbapenem Resistant *K. pneumoniae* (CRKP) Infections

- Two case control studies done by Patel et al. at Mount Sinai in NYC, where CRKP (KPC producers) are now endemic
  - 99 patients with invasive CRKP infections (mostly bloodstream) compared to 99 patients with invasive carbapenem susceptible *K. pneumoniae* infections
  - Patients who survived invasive CRKP infections compared to those who did not.

Patel et al. Infect Control Hosp Epidemiol 2008;29:1099-1106

Pre-infection Length of Stay

	CRKP (n=99)	CSKP (n=99)	p-value
Pre-infection LOS			
Mean	25.1 ± 25	6.44 ± 10	
Median	21	1	p<0.001
Range	0-129	0-59	

Patel et al. Infect Control Hosp Epidemiol 2008;29:1099-1106

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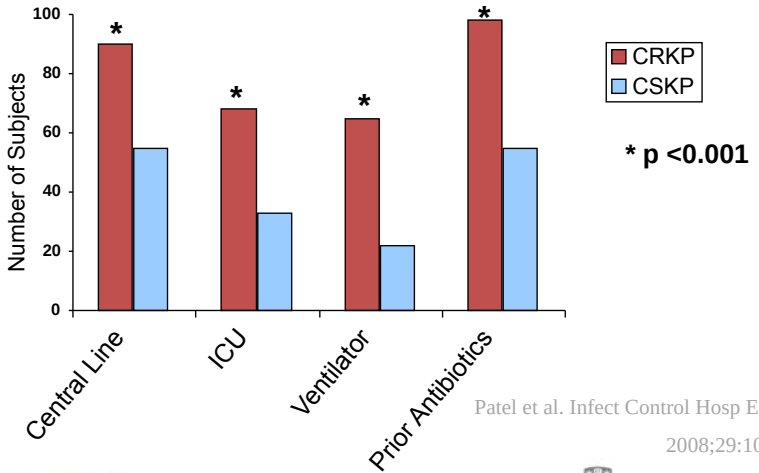
Healthcare-Associated Factors



Patel et al. Infect Control Hosp Epidemiol 2008;29:1099-1106

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Independent Predictors of CRKP

	CRKP (n=99)	CSKP (n=99)	OR[95%CI]	p-value
Cephalosporins	63	31	2.65[1.45-6.12]	0.02
Carbapenems	54	6	14.97[5.29-42.35]	<0.001
Transplant	41	14	3.71[1.41-9.73]	0.008
Pre-infection LOS (days)	25.19	6.44	1.05[1.01-1.08]	0.01
Ventilator	65	22	2.44[1.06-5.61]	0.04

Patel et al. Infect Control Hosp Epidemiol 2008;29:1099-1106

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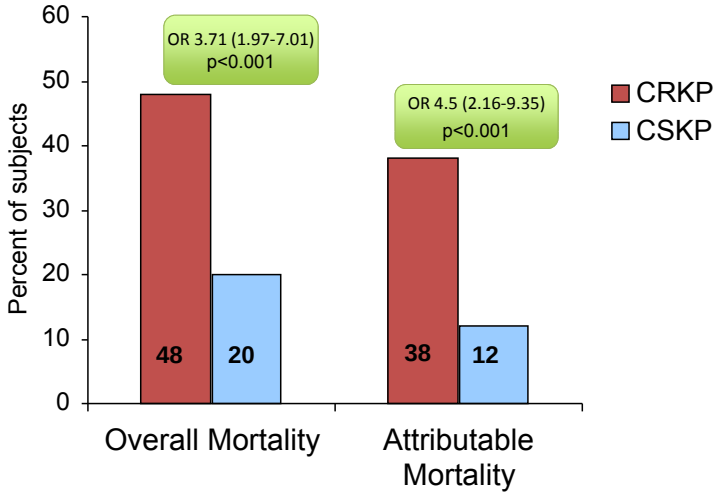
Mortality



Patel et al. Infect Control Hosp Epidemiol 2008;29:1099-1106

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Predictors of Mortality- Therapeutic Interventions

	Expired (n=48)	Survived (n=51)	OR [95% CI]	p-value
Adjunct Therapy*	29(60%)	44(86%)	0.24 [0.09-0.65]	p= 0.004
Appropriate Antibiotics**	35(73%)	31(61%)	1.74[0.74-4.06]	p=0.20
Delay to Appropriate Antibiotic (days)	3.2	3.2	1 .00 [0.81-1.24]	p=0.98

*Procedure to remove the probable focus of infection (e.g. abscess drainage, catheter removal)

**Antibiotics to which the isolate is susceptible *in vitro*

Patel et al. Infect Control Hosp Epidemiol 2008;29:1099-1106

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Morbidity and mortality

- Extremely ill patients acquire CRKP infections
  - Long hospital stay, ventilators, transplant, prior antibiotics
- CRKP associated with high in-hospital mortality
  - In-hospital mortality with CRKP infection was 48%
  - Attributable mortality approaches 38%
- Experience with antimicrobial treatment alone was disappointing.

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How Does This Compare?

- Increase in mortality risk associated with MRSA bacteremia, relative to MSSA bacteremia: OR: 1.93; $p < 0.001$.[1]
- Mortality of MRSA infections was higher than MSSA: relative risk [RR]: 1.7; 95% confidence interval: 1.3–2.4).[2]

1 Clin. Infect. Dis.36(1),53–59 (2003).
2 Infect. Control Hosp. Epidemiol.28(3),273–279 (2007).

Why are CRE Clinically and Epidemiologically Important?

- **Cause infections associated with high mortality rates**
- **Resistance is highly transmissible**
  - Between organisms – plasmids
  - Between patients

Why are CRE Clinically and Epidemiologically Important?

- **Cause infections associated with high mortality rates**
- **Resistance is highly transmissible**
  - Between organisms – plasmids
  - Between patients
- **Treatment options are limited**
  - Pan-resistant strains identified
  - Could be decades before new agents are available to treat

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Nouvelles menaces

New Threats

- Carbapenem-resistant *K pneumoniae* is coresistant to almost all classes of antimicrobials
- Colistin, one of the few remaining therapeutic options available to treat these infections
- A number of facilities have recently reported clusters of colistin resistant K. pneumoniae

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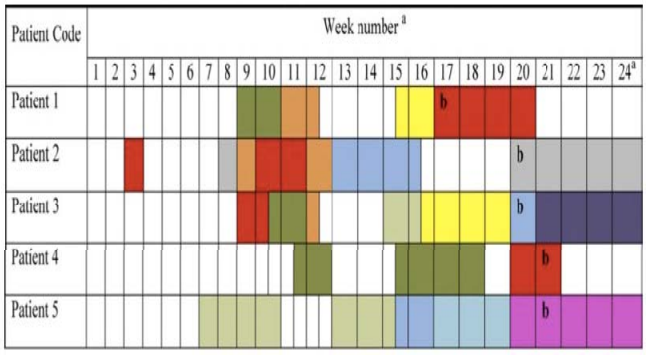
Outbreak of Colistin-Resistant Carbapenem-Resistant *K. pneumoniae* *in* Metropolitan Detroit, Michigan



Marchaim et al. Antimicrobial agents and chemotherpy. 2011, p. 593–599

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High rate of colistin resistance among patients with carbapenem-resistant K. pneumoniae infection accounts for an excess of mortality.

Colisitin resistance - 36.1%
Tigecycline resistance -20.4%

	OR (95% CI)	p
Charlson comorbidity score	1.42 (1.15–1.76)	0.001
Hospitalization in intensive-care unit	18.05 (3.90–83.51)	<0.001
Bloodstream infection	4.92 (1.35–17.28)	0.01
Infection due to a colistin-resistant strain	4.15 (1.17–14.74)	0.02

Clinical Microbiology and Infection, Volume 19 Number 1, January 2013

Tigecycline

- May be active against some CRE
- Breakthrough bacteremia against an NDM-1 positive *E.coli* documented

Stone NRH et al. J Antimicrob Chemother 2011; 66: 2677–2678.

Pan-Resistant Enterobacteriaceae

- **Report from New York City of 2 "Panresistant *K. pneumoniae***
  - 1 patient died
  - 1 had continuing asymptomatic bacteruria

Table 1. Antimicrobial susceptibility patterns for *Klebsiella pneumoniae* isolates.

Antimicrobial	MIC value, μg/mL	
	Patient 1: urine specimen	Patient 2: blood specimen
Amikacin	≥64	≥64
Ampicillin	≥32	≥32
Aztreonam	≥64	≥64
Cefazolin	≥64	≥64
Cefepime	32	≥16
Ceftriaxone	≥64	≥64
Ciprofloxacin	≥4	≥4
Gentamicin	≥16	≥16
Piperacillin-tazobactam	≥128	≥128
Tobramycin	≥16	≥16
Trimethoprim-sulfa	≥320	≥320
Nitrofurantoin	256	NA
Ertapenem	≥8	≥8
Imipenem	≥16	≥R[a]
Moxifloxacin	NA	≥R[a]
Tigecycline	≥8	≥8
Polymyxin B[b]	4	≥16

NOTE. All susceptibility testing, except for polymyxin B, was done using the Vitek 2 automated system (bioMérieux). MIC, minimum inhibitory concentration; NA, not available.

[a] Antimicrobial agents indicated with "R" instead of an MIC value were read as susceptible by the automated system, but findings were modified on the basis of polymerase chain reaction testing results indicating the presence of *K. pneumoniae* carbapenemase genes.

[b] Tested using Etest.

Elemam A, et al. Clin Infect Dis 2009; 49:271-4

- **Carbapenem-resistance among Enterobacteriaceae is increasing**
  - Appears to be driven primarily by the emergence of carbapenemases
- **Heterogeneously distributed within and across regions**
- **Has the potential to spread widely**
  - Healthcare and community settings
- **Most areas in a position to act to slow emergence**
- **A regional approach to MDRO prevention is required**
  - Public health well-positioned to facilitate and support regional prevention efforts

CRE Screening

- **Used to identify unrecognized CRE colonization among contacts of CRE patients**
- **Stool, rectal, peri-rectal**
- **Link to laboratory protocol http://www.cdc.gov/ncidod/dhqp/pdf/ar/Klebsiella_or_E.coli.pdf**
- **Applicable to both acute and long-term care settings**
- **Description of types**
  - Point prevalence survey
    - Rapid assessment of CRE Prevalence on particular wards/units
    - Might be useful if lab review identifies one or more previously unrecognized CRE patient on a particular unit
  - Screening of epidemiologically linked patients
    - Roommates
    - Patients who shared primary HCP

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Risk for Transmission

- **Observational study of ESBLs, facility screened roommates of ESBL positive patients for evidence of transmission**
  - 1/133 (1.5%) confirmed transmission of same strain type, median overall exposure time 4.3 days
  - In transmissions exposure was for 9 and 10 days
- **NDM outbreak in Canada**
  - 9 cases in 15 months, Index patient had care in India
  - Case-control study of transmission cases compared to exposed patients (roommates, ward mates, environmental contacts) that did not acquire NDM
  - Duration of exposure and exposure to certain antimicrobials (Pen, FQ, macrolides, TMP/SMX, vancomycin, carbapenems) were significant risks
  - Exposure time was 26.5 days vs 6.7 days

Tschudin-Sutter S et al. CID 2012;55:1505-15514
Lowe C et al. ICHE 2013;34:49-55

REGIONAL APPROACH TO CRE PREVENTION

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Inter-Facility Transmission of MDROs (Including CRE)

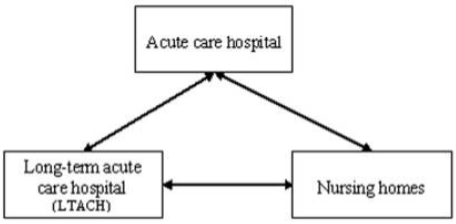


Figure 3. Patient flow among regional health care facilities. Outbreaks of infection with multidrug-resistant organisms have been found to follow the flow of colonized patients across institutions.

Munoz-Price SL. Clin Infect Dis 2009;49:438-43

Regional Approach to MDRO Prevention is Essential

- **Successful regional coordination by public health**
  - VRE control in Siouxland region
  - CRE containment in Israel
- **Public health well placed to facilitate/support regional prevention efforts**
  - Situational awareness
  - Technical and laboratory support

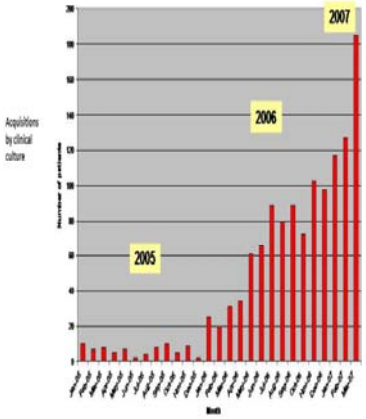
Sohn AH et al. Am J Infect Control 2001;29:53-7
Schwaber MJ et al. Clin Infect Dis 2011;52:848-55

Dr. D. Ben DAvid

The Israeli Story

- Late 2005 –KPC-producing *K. pneumoniae* ST-258 introduced to Israeli hospitals
- 2006 –outbreak began: ~700 cases
- 01/01/2007 -04/30/2007: ~600 cases
- Local attempts to contain- failed!

Nationwide epidemic curve prior to intervention



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What were the causes of this uncontrolled country-wide outbreak?

Common problems in limited income counties

Infrastructure of hospitals
Shortage of isolation & negative pressure rooms
Understaffing
Overcrowding
Heavy workload
Shortages of personal protective equipments,
Late establishment of infection control programme (ICP/400-500 beds)

High HAI infection rates and spread of MDRO

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Israel Experience

- **Initiated National effort to control CRE**
  - Mandatory reporting of patients with CRE
  - Mandatory isolation (CP) of CRE patients
    - Staff and patient cohorting
  - Task Force developed with authority to collect data and intervene

Dr. D. Ben David

The Israeli Intervention

- The National perspective
- A View from the Trenches

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CRE outbreak in Israeli HCW

- A meeting of Israeli infection-control professionals in February 2007 – several hospitals presented the nationwide spread of CRE
- This findings was reported to the Israel Ministry of Health

Dr. D. Ben David

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Task Force on Antimicrobial Resistance and Infection Control,

- March 2007 –
  - Creation a task force
    - professionals from the fields of infection control, clinical microbiology and public health
  - Invested with the statutory authority to collect data from hospitals and to intervene as necessary to contain the outbreak

Dr. D. Ben David

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The principles of the intervention

- Regional coordination
- Assignment of responsibility for containment at each hospital to the hospital director

Dr. D. Ben David

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Goal

- To ensure that every CRE carrier hospitalized in an acute-care facility in Israel would be treated separately from non-carriers
- Compliance with this requirement is monitored daily throughout the country by a central authority

Dr. D. Ben David

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National guidelines

- Placement of carriers in self-contained nursing units
  - containing all materiel needed for their care
  - staffed by dedicated nurses on all shifts

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Feedback

Daily

- Census reports are reviewed on the day of receipt
- Feedback is provided daily (& evenings) to PCI , medical & nursing directors
  - Any deviations from guidelines
  - Suggestions for maximizing compliance and assistance in local outbreaks control

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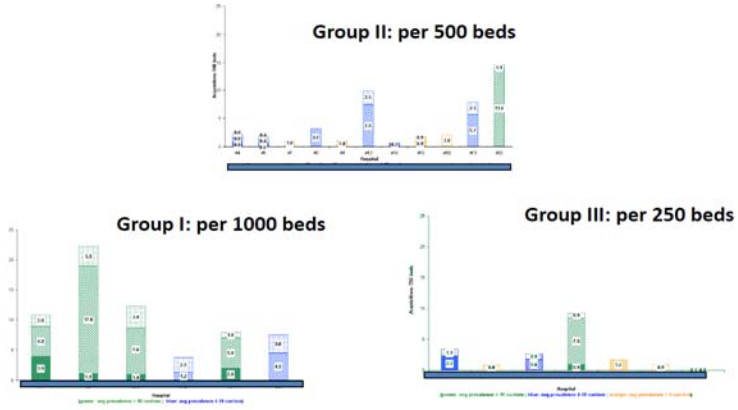
Monthly Feedback



Monthly reports are sent to the medical directors of the hospitals and MOH

Dr. D. Ben David

Real-time communication network

- At all times, the staff of the National Center is aware of the location of every CRE carrier hospitalized in the acute care and LTCF
- All movement of these carriers between facilities and into the outpatient setting is tracked
- The receiving institution (acute, LTCF, HMO) is notified in real time to ensure proper isolation in each setting

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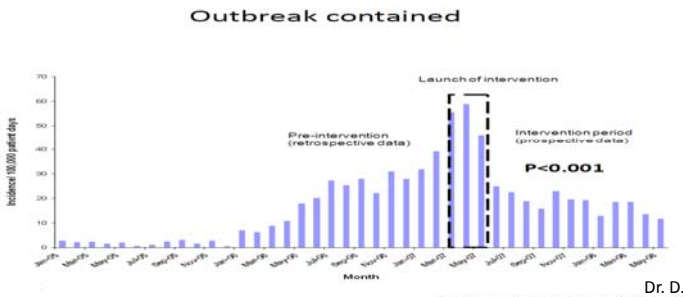
Jewish General Hospital

Infection Prevention and Control Unit

Containment of a Country-wide Outbreak of CRE in Israeli Hospitals via a Nationally Implemented Intervention

Monthly incidence reduced from high of 55.5 cases/100,000 pt-days to 11.7 cases/100,000 pt-days- –79% reduction



Dr. D. Ben David
Clinical Infectious Diseases 2011;52:848–855

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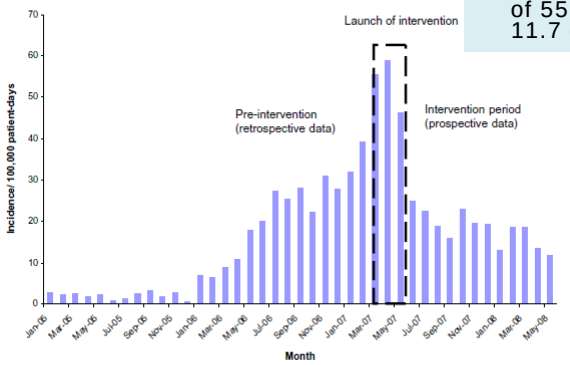

79% decrease from highest and last month

Schwaber et al. CID 2011; 848-855

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Impact of prevalence & compliance

- Incidence was associated with prevalence
  - For each hospitalized carrier, the incidence increased by 0.43
- Compliance with dedicated staffing guideline was associated with lower incidence
  - For each increase of 10% in compliance, there was a decrease in incidence of 0.6 /100,000 patient-days (*P* = .02).

Clinical Infectious Diseases 2011;52:848855

Figured out along the way

- …Adequate isolation of known carriers critical, but not sufficient for effective containment of spread
- Also required: adequate identification of unknown carriers, *meaning* -
  - –Active surveillance
- –Intervention in long-term care, the *BLACK HOLE of CRE carriage*

Israeli Guidelines for Active Surveillance

- Issued June 2008
  - Required in 3 groups
    - Contacts of CRE carriers newly identified on wards
    - High-risk groups on admission
      - Prior hospital admission or LTCF in past year
    - High-risk wards in hospital –at hospital's discretion

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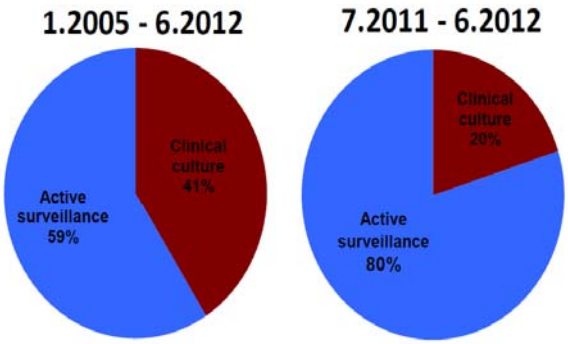
First isolation of CRE



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The CRE battle continues…

- **The Israeli national intervention was implemented late –**
  - **a huge reservoir has developed both in acute care facilities & LTCF**
- **Since the start of the outbreak –**
  - **~17,000 patients identified with CRE**
- **Continued success requires recruitment and continued vigilance at every level in the hospital**
- **<u>No end in sight</u>**

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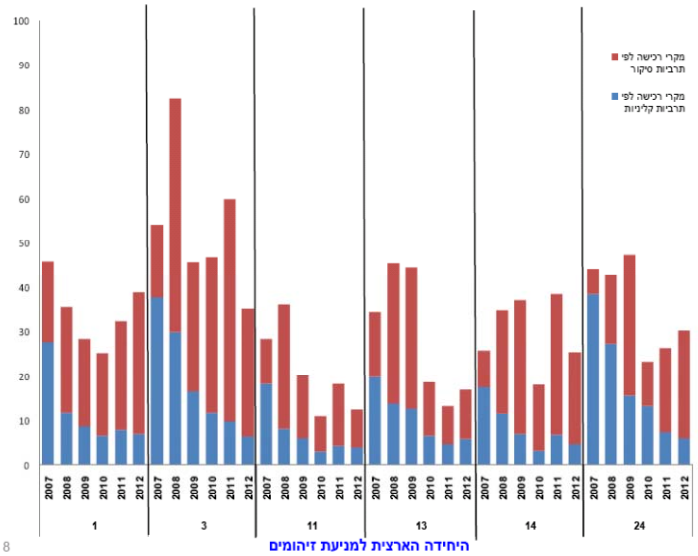
Incidence of CRE/100,000 patient days, Jul 2007 - Dec 2012, acquisitions by clinical culture and active surveillance, Hospital Group I

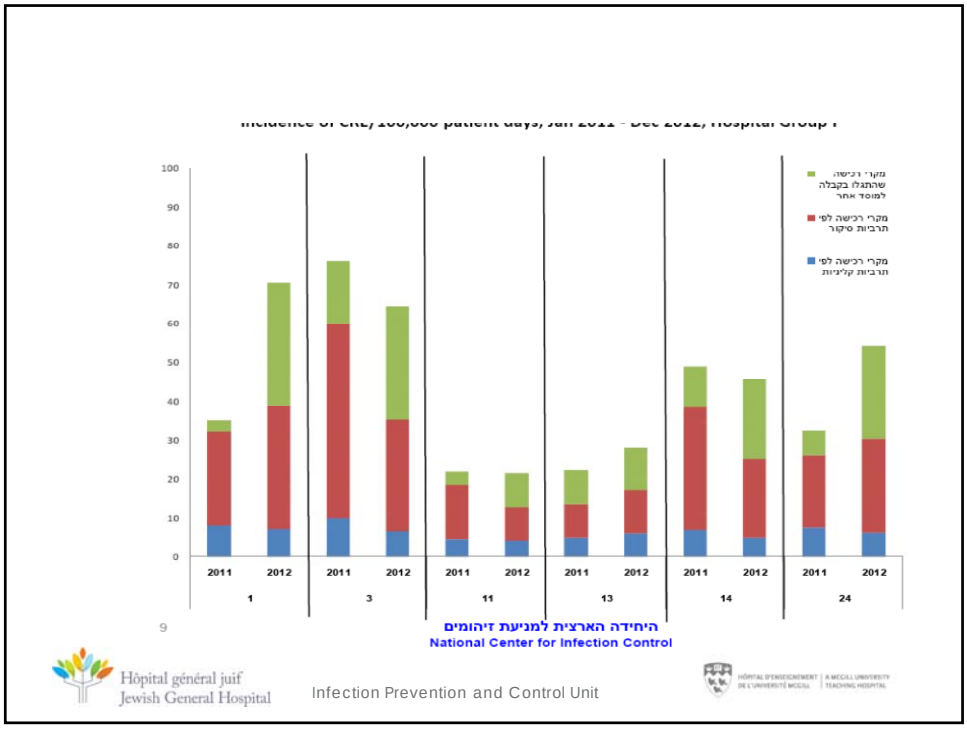


8

היחידה הארצית למניעת זיהומים
National Center for Infection Control

Hôpital général juif
Jewish General Hospital

Infection Prevention and Control Unit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2011
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היחידה הארצית למניעת זיהומים
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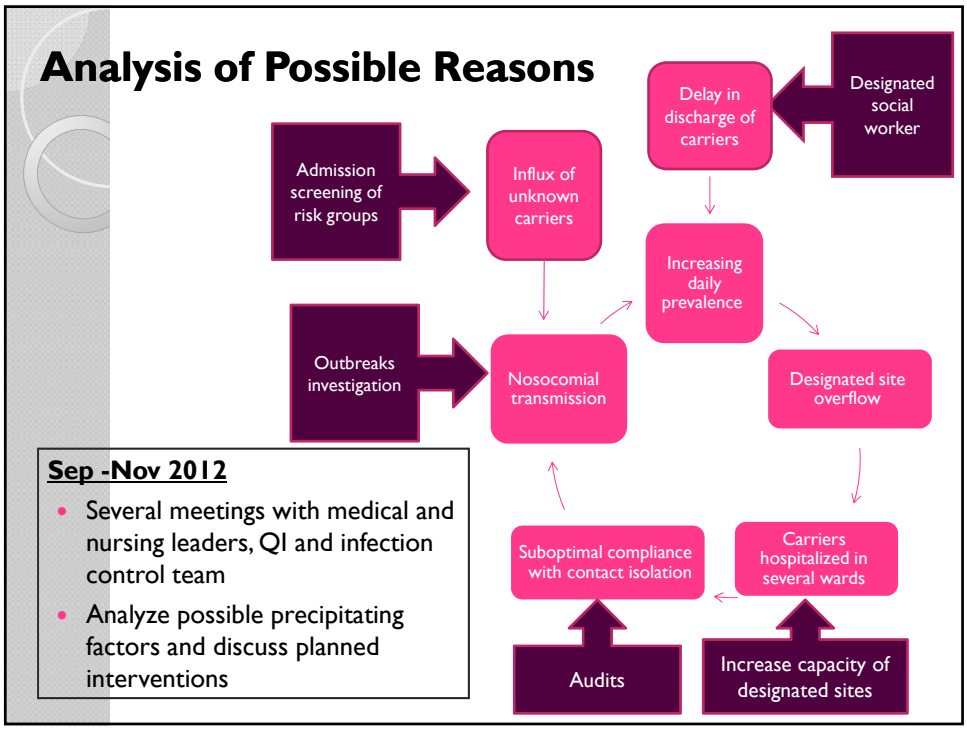
Analysis of Possible Reasons
Admission screening of risk groups
Influx of unknown carriers
Delay in discharge of carriers
Designated social worker
Increasing daily prevalence
Outbreaks investigation
Nosocomial transmission
Designated site overflow
Sep -Nov 2012
Several meetings with medical and nursing leaders, QI and infection control team
Analyze possible precipitating factors and discuss planned interventions
Suboptimal compliance with contact isolation
Carriers hospitalized in several wards
Audits
Increase capacity of designated sites

Summary of Prevention Strategies

- **Core measures:**
  1. Hand hygiene
  2. Contact Precautions
  3. Healthcare personnel education
  4. Minimizing device use
  5. Patient and staff cohorting
  6. Lab notification
  7. Promote antimicrobial stewardship
  8. CRE screening
- **If transmission occurs in the facility:**
  1. Active surveillance
  2. [illegible]ng

www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html

NDM-1 carbapenemases in the UK

- Carbapenemase-producers were sporadic in the UK in 2003-2007
- Isolations of carbapenemase-producers increased in the UK 2008-2009
- First NDM-1 isolated in 2008 in the UK
- In 2009, NDM-1 became the predominant carbapenemase in *Enterobacteriaceae* (44%) in the UK
- 37 isolates of NDM-1 were referred from 25 UK laboratories in 2008-2009 (urines (15), blood (3), burns/wound (4), sputum (2). CL (1), throat (1), unknown (3))
- Average age of UK patients: 60 years (range 1-87) (India: 36 years)
- 17 out of 29 patients with NDM-1 had been in India/Pakistan within the past year (14 had been in hospitals during their travels)
- Most UK carbapenemase-producers concurrently carry additional beta-lactamases (CTXM-15, CMY-4), fluoroquinolone and gentamicin resistance mechanisms

Carbapenemases - Is there a link to medical tourism?

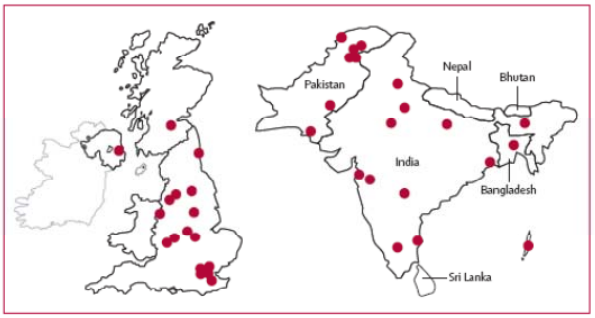

Figure 5: Distribution of NDM-1-producing Enterobacteriaceae strains in Bangladesh, Indian, Pakistan, and the UK

Kumarasamy, Lancet Infection, Aug 2010

Clones and plasmids are transported between continents in the human gut flora – most dissemination is undetected!

Carbapenemases – UK and India

- UK: Non-clonal isolates (NDM-1 on chromosome, variable plasmids, conjugates easily)
- Chennai (South India) : Non-clonal isolates (NDM-1 on plasmids, variation of plasmids, conjugates easily)
- Haryana (North India): Clonal isolates – outbreak?
- There were no genetic links between isolates from India and the UK (possibly due to too few isolates investigated)
- UK is the first Western country to report widespread occurrence of NDM-1
- Most patients in Haryana and Chennai were from community-acquired infections in younger people (mean=36 yrs)
- Non-prescription use of carbapenems in India is of major concern

Spread of NDM-Mediated Carbapenem Resistance

Johnson and Woodford J Med Micro 2013; doi: 10.1099/jmm.0.052555-0

Active Surveillance Cultures

- **Studies suggest that only a minority of patients colonized with CRE will have positive clinical cultures**
  - CRKP Point prevalence study in Israel (5.4% prevalence rate); fewer than 5/16 had a positive clinical culture for CRKP.
  - A study of surveillance cultures at a US hospital found that they identified a third of all positive CRKP patients. Placing these patients in CP resulted in about 1400 days from unprotected exposure.

Weiner-Well et al. J Hosp Infect 2010;74:344-9
Calfee et al. ICHE 2008;29:966-8

Active Surveillance Cultures

- **One study from Israel used surveillance cultures - (ICU) admission and weekly; (non-ICU) patients with epi-links to CRE patients**
  - Found a 4.7-fold reduction in in CRKP infection incidence
- **Kochar et al. used rectal surveillance cultures as part of a multifaceted intervention in an ICU**
  - Found decrease in number of new patients per 1,000 patient days per quarter that were positive for CRKP

Ben-David et al. ICHE 2010; 31:620-6
Kochar et al. ICHE 2009; 30:447-52

Active Surveillance Cultures

- **Potential considerations:**
  - Focus on patients admitted to certain high-risk settings (e.g., ICU) or specific populations (e.g., from LTCF/LTAC)
  - Generally done at admission but can also be done periodically during admission
- **Patients identified as positive on these surveillance cultures should be treated as colonized (i.e., Contact Precautions, etc.)**

Surveillance Sites

- Rectal appears to be most sensitive (68% to 97%)
- In one study rectal better than peri-rectal
- Skin (axillae/inguinal) can also be colonized with CRE and can add to sensitivity if sampled

Data from 6 LTACH

TABLE 2. Sensitivity of Culture of Different Anatomic Sites for *Klebsiella pneumoniae* Carbapenemase–Producing Enterobacteriaceae

	No. of positive cultures (N = 24)	Sensitivity, % (95% CI)
Skin sites		
Inguinal	19	79 (58–93)
Axillary	18	75 (53–90)
Upper back	6	25 (10–47)
Antecubital fossae	6	25 (10–47)
Nonskin sites		
Rectal[a]	21	88 (68–97)
Urine (N = 19)[b]	10	53 (29–76)
Oropharyngeal/tracheal secretions	10	42 (22–63)
Combined sites		
Rectal and inguinal	24	100 (86–100)
Rectal and axillary	23	96 (79–100)
Axillary and inguinal	22	92 (73–99)

NOTE. CI, confidence interval.
[a] Three patients had negative rectal swab cultures but positive cultures of inguinal skin.
[b] Five patients were anuric, so urine was not collected for culture.

Thurlow C et al. ICHE 2013;34:56-61
Weiner-Well Y et al. J Hosp Infect 2010; 74:344-349

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