Surveillance Summary for Carbapenem-Resistant Enterobacteriaceae and Carbapenemase-Producing Organisms, Washington, 2010-2015

Background

Carbapenem-resistant Enterobacteriaceae (CRE), and other multidrug resistant Gram-negative bacteria are increasingly common causes of healthcare associated infections; they are difficult to treat, and result in poorer clinical outcomes. A particular mechanism of carbapenem-resistance, carbapenemase production, results in enzymes that hydrolyze carbapenem antibiotics. This mechanism is usually transmitted on mobile genetic elements (plasmids) that can be passed from one bacterium to another. Carbapenemases are considered an urgent threat by US Centers for Disease Control and Prevention due to their ability to spread exponentially in healthcare settings, tendency to be transmitted between bacterial species along with other resistance genes, and capability to inactivate carbapenems - one of the most powerful classes of antibiotics.

The carbapenemases most frequently identified in Enterobacteriaceae in the United States (in order of frequency) are:

- *Klebsiella pneumoniae* carbapenemase (KPC)
- New Delhi metallo-β-lactamase (NDM)
- Oxacillin-hydrolyzing β-lactamase-48 (OXA-48)
- Verona integron-encoded metallo-β-lactamase (VIM)
- Imipenem-hydrolyzing β-lactamase (IMP)

The first carbapenemase-producing CRE (CP-CRE) reported in Washington was a VIM identified in 2010 in a person who had received healthcare in Greece; a second Washington case occurred soon after. These were also the first cases of VIM ever identified in the United States (http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5937a4.htm). Subsequently, in 2011, a Washington resident was infected with multiple species of bacteria carrying NDM after healthcare in India. In 2012, two additional CP-CRE cases were identified: a patient with NDM and another with KPC who had recently received healthcare in India and California, respectively. A total of 7 CP-CRE isolates from 5 patients were reported prior to statewide surveillance for CRE.

Since October 2012, Washington State Department of Health (DOH) has conducted surveillance for carbapenem-resistant Enterobacteriaceae (CRE) and provided in-state testing for carbapenemases. The Public Health Laboratories (PHL) test for the five most common carbapenemases in the US: KPC, NDM, OXA-48, VIM and IMP. In addition to CP-CRE, surveillance has identified several other carbapenemase-producing organisms (CPO) in other Gram-negative organisms, such as *Acinetobacter* and *Pseudomonas* species.

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Testing for Carbapenemases at the Washington State Public Health Laboratories

All carbapenem-resistant *E. coli*, *Klebsiella* spp., and *Enterobacter* spp. are required to be submitted to PHL for carbapenemase testing, as rare diseases of public health significance. PHL accepts and tests other carbapenem-resistant Gram-negative organisms, such as other genera in the family Enterobacteriaceae, as well as *Acinetobacter* and *Pseudomonas* species, upon request, or if specialized screening tests (e.g.; RAPIDEC® Carba-NP or Rosco Diagnostica Neo-Sensitabs) indicate suspicion for carbapenemase production.

Recommended Actions for Carbapenem-Resistant Enterobacteriaceae and Other Carbapenemase-Producing Organisms

- Infection prevention is essential to prevent spread of carbapenem resistance. Therefore, when any carbapenem-resistant isolate is identified by a clinical lab, healthcare providers and infection prevention staff should be immediately notified so proper treatment and infection prevention measures can be implemented. Contact precautions are recommended for patients in healthcare facilities who are infected or colonized with a carbapenem-resistant organism, whether it produces a carbapenemase or not. General infection control recommendations for CRE in acute and long term care settings are available at: http://www.doh.wa.gov/Portals/1/Documents/5100/420-099-TestingAlgorithmCRE.pdf.
- Information about a patient's infection or colonization with an epidemiologically-important organism, including CRE or other carbapenemase-producer, *Clostridium difficile*, vancomycin-resistant *Enterococcus*, methicillin-resistant *Staph aureus* or other, should be noted in the medical record and communicated to other healthcare providers and facilities receiving the patient in transfer. We recommend using an inter-facility infection prevention form such as: http://www.tpchd.org/files/library/acd8d09cb3afd04b.pdf.
- Results of carbapenemase testing at PHL are communicated to the submitter and local public health department where the patient resides and of the facility where diagnosed. Any person in Washington known to be infected or colonized with a carbapenemase-producing organism should be investigated by public health to attempt to determine the likely source and whether there has been transmission to other patients during healthcare.
- The PHL and DOH Healthcare Associated Infections (HAI) Program staff can offer consultation and assistance with investigations, and perform screening surveillance testing on samples from patients who are epidemiologically-linked to an index case, or who are thought to be otherwise at risk for acquisition. Please contact the HAI Program for information about infection prevention measures for multidrug resistant organisms, carbapenemase testing, CRE or carbapenemase-producing organism (CPO) case investigation, or surveillance screening testing, at 206-418-5500.

Summary of Carbapenem-Resistant Enterobacteriaceae (CRE) and other Carbapenemase-Producing Organisms (CPO)

The Washington CRE surveillance case definition has been modified over time and is described below:

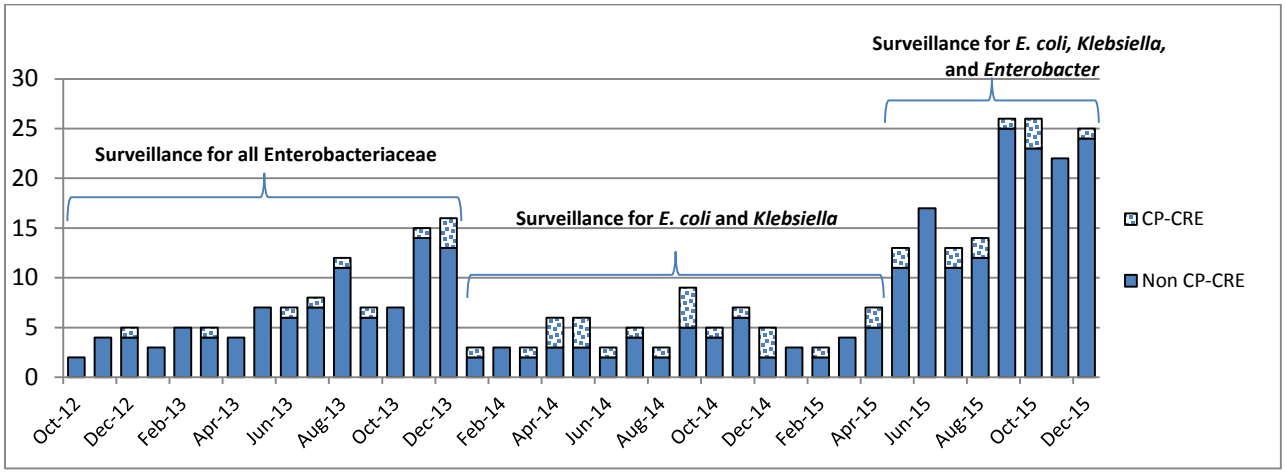
- October 2012-December 2013: Any Enterobacteriaceae resistant to all third-generation cephalosporins tested and non-susceptible to one or more carbapenems.
    - During this period, all submitted isolates had bacterial identification and antibiotic susceptibility confirmed at PHL and only those meeting case-definition after confirmatory testing underwent carbapenemase testing.
- January 2014-April 2015: *E. coli* and *Klebsiella* spp. resistant to all third generation cephalosporins tested and non-susceptible to one or more carbapenems. Other genera in the family Enterobacteriaceae were solicited if the patient had a hospital stay outside of Washington or Oregon in the 6 months prior to diagnosis.
    - During this period, all submitted isolates had identification and susceptibility confirmed at PHL and only those meeting case definition after confirmatory testing underwent carbapenemase testing.
- May-December 2015: *E coli*, *Klebsiella* spp. and *Enterobacter* spp. resistant to any carbapenem.
    - PHL accepted CRE isolates for carbapenemase testing, based on the submitted clinical laboratory antimicrobial susceptibility results, and did not perform confirmatory bacterial identification or susceptibility testing.)

PHL also accepted isolates not meeting these criteria if requested by a healthcare provider or laboratory.

This following summary report includes CRE isolates submitted and/or reported to DOH since surveillance began in October 2012, as well as other non-Enterobacteriaceae carbapenemase-producing Gram-negative organisms identified and reported. Please note that this summary may differ from prior reports due to updated information and deduplication of isolates. This summary includes isolates from residents of Washington diagnosed in-state; residents of Washington diagnosed out-of-state and reported to the department; and residents of other states or countries diagnosed in Washington. For persons with more than one of the same genus-species isolate submitted, we have counted only the first and excluded all subsequent isolates of the same genus, species, and carbapenemase (if any). Any additional isolates submitted of a different genus, species, or carbapenemase from the same person were counted. Screening surveillance isolates were counted only if carbapenem-resistant. For isolates from a single person that produced more than one carbapenemase, each was counted separately.

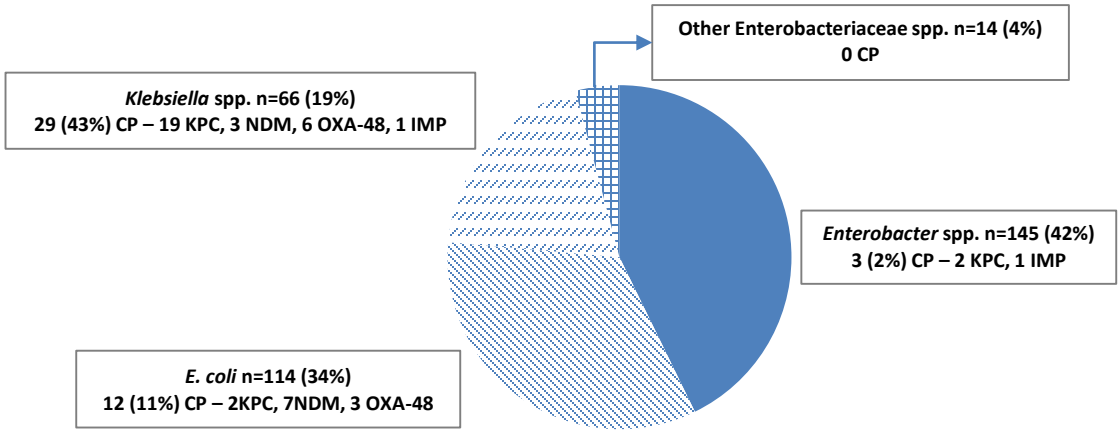
Since October 2012 through December 2015, a total of 339 unique CRE isolates have been reported to DOH (Figure 1) from 330 individual patients. Overall, of 339 CRE isolates, 44 (13%) were carbapenemase-producing CRE (CP-CRE). The total number of CRE isolates and number that were identified as carbapenemase-producers by month are indicated on the figure.

Figure 1. Carbapenem-Resistant Enterobacteriaceae Isolates, Washington October 2012 through December 2015



Of 339 reported CRE isolates, *Enterobacter* spp. were the most common (145 or 42%), followed by *E. coli* (114 or 34%), *Klebsiella* (66 or 19%), and other Enterobacteriaceae such as *Morganella, Proteus, Providencia* and *Serratia* (14 or 4%). (Figure 2) Of the carbapenem-resistant genera submitted, *Klebsiella* spp. were most likely to produce a carbapenemase. Of 66 CR-*Klebsiella* spp. isolates, 29 (43%) were found to produce a carbapenemase, compared to only 12 of 114 (11%) CR-*E. coli* and 3 of 145 (2%) CR-*Enterobacter* spp. None of the "Other Enterobacteriaceae" was found to carry a carbapenemase gene.

Figure 2. Distribution of Carbapenem-Resistant Enterobacteriaceae (CRE) Isolates by Genus and Carbapenemase, Washington October 2012 through December 2015 (N=339)



In addition to carbapenemases in CRE, we have identified several carbapenemases in other non-Enterobacteriaceae Gram-negative bacterial species that were submitted and tested by special request.

This includes 1 *Pseudomonas* with VIM identified in 1 patient, and 1 *Pseudomonas* with both VIM and NDM, and 1 *Acinetobacter* with NDM both from another patient.

Of the 41 case-patients identified as carrying a carbapenemase-producing organism (39 patients with CP-CRE and 2 patients with other CPO), the median age was 63 years with 21 (51%) 18-64 years and 17 (41%) 65 years or older. (Table 1) Males made up slightly more than half the cases (22 or 54%).

Table 1. Demographics of Case-Patients with Carbapenemase-Producing Enterobacteriaceae or Other Carbapenemase-Producing Organism, Washington October 2012 through December 2015

Characteristic	CP-CRE & Other CPO cases N=41, n (%)
Age (years)	Range 0 - 91
0 - 4	3 (7)
5 - 18	0 (--)
18 - 64	21 (51)
>= 65	17 (42)
Male	22 (54)

Each case-patient identified as having a carbapenemase-producing organism (CP-CRE or other CPO) was investigated to attempt to determine the source, and identify ongoing transmission, if any. For 22 KPC cases, 15 (68%) had only healthcare exposures in Washington, while 7 (32%) had out-of-state hospitalizations including in California, Idaho, and Nevada in the 12 months prior to diagnosis. This suggests that there is ongoing transmission of KPC in Washington. (Table 2) Of the 19 individuals with non-KPC carbapenemases, 16 (84%) had either been hospitalized or traveled internationally prior to diagnosis, including two patients who had elective surgical procedures internationally. Interestingly, some had been in the US for more than 12 months prior to their diagnosis, suggesting that carbapenemase colonization may be of long duration. The other 3 (16%) with non-KPC carbapenemases had extensive exposure to healthcare settings in Washington. The continents suspected as potential international sources of carbapenemase include Asia (Central and SE Asia, and the Indian subcontinent), North and West Africa, and North America.

Table 2. Suspected Source Location of Carbapenemase in 41 Case Patients, Washington October 2012, through December 2015

Suspected Source	Carbapenemase N=41	
	KPC n=22	Non-KPC Carbapenemase n=19
In-Washington Healthcare	15 (68%)	3 (16%)
Other US State Healthcare	7 (32%)	--
International Healthcare or Travel	--	16 (84%)

Since carbapenemases present ongoing special infection control challenges in healthcare settings, it is useful to understand the burden of carbapenemase cases according to where they reside and where

they are diagnosed in our state. The table below indicates the number of carbapenemase cases residing and/or diagnosed in Washington. (Table 3)

Table 3. Number of Patients with Carbapenemase-Producing Organism Reported in Washington by Location of Residence and Diagnosis, October 2012 through December 2015

Location	Number of Cases by Location of Residence	Number of Cases by Location of Diagnosis*
Washington Counties		
Benton	4	3
Chelan	1	1
Clark	2	--
Franklin	1	--
Jefferson	1	--
King	12	19
Kitsap	1	--
Lewis	1	--
Okanogan	1	1
Pierce	4	4
Snohomish	3	4
Spokane	3	4
Stevens	--	1
Thurston	1	1
Whatcom	1	1
Yakima	1	1
Other states		
California	1	1
Nevada	3	--
Oregon	--	1

*The diagnosis column totals to 42 rather than 41 because one case had two carbapenemase-producing isolates of different bacterial genus diagnosed in two different counties so were counted in each county where diagnosed.

Since our surveillance has recently identified several carbapenemases outside the Enterobacteriaceae family (*Acinetobacter* and *Pseudomonas* isolates), we plan to adopt voluntary surveillance for carbapenem-resistant *Pseudomonas* spp. Please consider submitting any carbapenem-resistant *Pseudomonas* isolates to PHL for carbapenemase testing.

For any questions or comments about this summary, CRE or CPO case definitions, or epidemiologic investigations, please contact Marisa D'Angeli at 206-418-5595 or marisa.dangeli@DOH.wa.gov. For questions about laboratory testing methods, please contact William Glover at 206-418-5422 or william.glover@DOH.wa.gov.