pennsylvania
DEPARTMENT OF HEALTH
Bureau of Epidemiology

Pennsylvania Epi Notes

Winter/Spring 2016 Volume 5, Issue 1

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Epidemiology of Carbapenem-resistant Enterobacteriaceae (CRE) Isolates

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Background and Epidemiology

Enterobacteriaceae are a family of gram-negative bacteria commonly found in the gastrointestinal tract. Occasionally, these bacteria can spread outside the gut and cause serious infections. Of particular concern are those Enterobacteriaceae called carbapenem-resistant Enterobacteriaceae (CRE), which are resistant to carbapenems, a class of broad-spectrum antibiotics. CRE are non-susceptible to at least one of the carbapenem antibiotics, or produce an enzyme, called a carbapenemase, that makes them resistant to carbapenem antibiotics.[1] In 2012, the Centers for Disease Control and Prevention surveillance case-definition of CRE was updated to include resistance to another group of antibiotics, the third-generation cephalosporins (for example, ceftriaxone, cefotaxime and ceftazidime).[2]

Enterobacteriaceae become resistant to carbapenems due to a number of different carbapenemases. In 2001, a novel CRE, *Klebsiella pneumoniae* carbapenemase (KPC), was identified. The genes coding for this carbapenemase are highly mobile and can be easily transmitted from one bacterium to another, spreading resistance. KPC is now widespread in the United States and has been identified in 47 states, including Pennsylvania.[3] Other less common carbapenemases in the United States include New Delhi Metallo-beta-lactamase (NDM), Verona Integron-Encoded Metallo-beta-lactamase (VIM), Imipenemase Metallo-beta-lactamase (IMP) and Oxacillinase group of beta-lactamase (OXA). The NDM carbapenemase is particularly concerning because it is pan-resistant (meaning it is resistant to many types of antibiotics), is highly transmissible to other bacteria, and can spread through contaminated water sources and environmental surfaces.[4] As of February 2014, the Centers for Disease Control and Prevention reported that 15 states, including Pennsylvania, have reported NDM, three have reported VIM, and two have reported IMP.[3] Although hospitals report CRE infections to CDC's National Healthcare Safety Network (NHSN),[5] CRE is not a mandatory reportable condition to the Pennsylvania Department of Health (although all outbreaks or unusual events are reportable). It is likely that CRE infections in Pennsylvania are under-reported.

The prevention of CRE is epidemiologically important for several reasons. First, these organisms are often resistant to multiple classes of antibiotics. Therefore, treatment options are substantially reduced, making the prevention of infections very important. Second, infections caused by these bacteria are associated with high mortality rates, up to 40-50 percent.[6] Third, many genes encoding for carbapenemase production can be transmitted between bacteria, including to other bacterial species, which can lead to more widespread resistance. Finally, Enterobacteriaceae are a common cause of infections in health care settings as well as in community settings.[1]

(CRE epidemiology continued)

Transmission

In the United States, patients commonly at risk of CRE infection are those who have recently received health care and/or antibiotics. The patients at highest risk for a CRE infection are those who 1) receive care in an intensive care unit, 2) are on a mechanical ventilator, 3) have invasive medical devices such as a catheter, or 4) who have a poor functional status. In addition, outbreaks of CRE infection have been identified in long-term care facilities in the United States. Patients can alternatively be asymptomatically colonized with CRE, making them difficult to identify.[1]

CRE can be transmitted in health care settings by person-to-person contact or touching contaminated fomites, such as environmental surfaces or medical equipment. The 2012 CRE Toolkit[2] provides a number of recommendations to prevent transmission of CRE. Education of health care personnel and best practices in infection control are essential. Hand hygiene is particularly important. Patients with CRE infections should be placed under special contact precautions, and health care workers should wear a new gown and gloves when caring for patients with CRE infections. Patients with CRE infections should remain in single patient rooms or in rooms with other CRE positive individuals (patient cohorting) when possible and should also have their own designated medical team (staff cohorting). Because patients with medical devices are at increased risk of CRE infections, the use of devices, like catheters, should be closely monitored.[2]

Laboratory Testing

Isolates can be tested in several ways to determine if they are producing a carbapenemase. The "modified Hodge test" directly checks for the presence of a carbapenemase.[7] Polymerase chain reaction (PCR) looks for the gene for a specific carbapenemase (e.g., NDM, VIM, OXA, IMP). Additional antibiotic resistance to extended-spectrum cephalosporins, a class of antibiotics separate from carbapenems, can be identified by testing for the presence of Extended Spectrum Beta-Lactamases (ESBLs). If an isolate produces ESBLs in addition to carbapenemases, the organism is resistant to multiple classes of antibiotics and especially difficult to treat.[8]

Methods

The purpose of this study was to evaluate the epidemiology of a convenience sample of human isolates voluntarily submitted by hospitals and commercial laboratories to the Pennsylvania Department of Health Bureau of Laboratories (BOL) from March 2009 through May 2014. All laboratory testing was performed by the Centers for Disease Control and Prevention (CDC). Isolates were excluded from final analysis if the final identification was of a non-gram-negative organism, if the reports were missing or if the organisms were from a non-human source. The unit of analysis for this study was the isolate. Data entry and management were performed using Epi Info version 7.1. Data analysis was performed using EpiInfo version 7.1, SAS version 9.3 and ESRI Arc Map version 10.0.

Isolates were tested for resistance to antibiotics, including four carbapenems: doripenem, ertapenem, imipenem and meropenem. Isolates were also tested

Table 1: Submitting facility and isolate information (N=175)

	N	%
Original Submitting Facility Type		
Hospital	118	67%
Commercial laboratory	55	31%
Public health	2	1%
Original Specimen Source		
Urine	98	56%
Wound	21	12%
Gastrointestinal	16	9%
Blood	10	6%
Respiratory	9	5%
Other	21	12%
Organism		
Klebsiella pneumoniae	91	52%
Enterobacter clocae	27	15%
Escherichia coli	19	11%
Enterobacter aerogenes	14	8%
Psuedomonas aeruginosa	8	5%
Proteus mirabilis	3	2%
Proteus vulgaris	3	2%
Serratia marcescens	3	2%
Morganella morganii	2	1%
Acinetobacter baumannii	1	0.6%
Aeromonas species	1	0.6%
Citrobacter freundii	1	0.6%
Enterobacter amnigenus	1	0.6%
Providencia stuartii	1	0.6%

(CRE epidemiology continued)

using the modified Hodge test and polymerase chain reaction (PCR) tests for CRE resistance enzymes (NDM, VIM, OXA), as well as the presence of Extended Spectrum Beta-Lactamases.

Because most isolates were submitted during and prior to 2012, the pre-2012 surveillance case definition was used for all isolates. Geographic analyses were based on patient county of residence. If county of residence was missing or out of state, the submitting laboratory county was used.

Results and Discussion

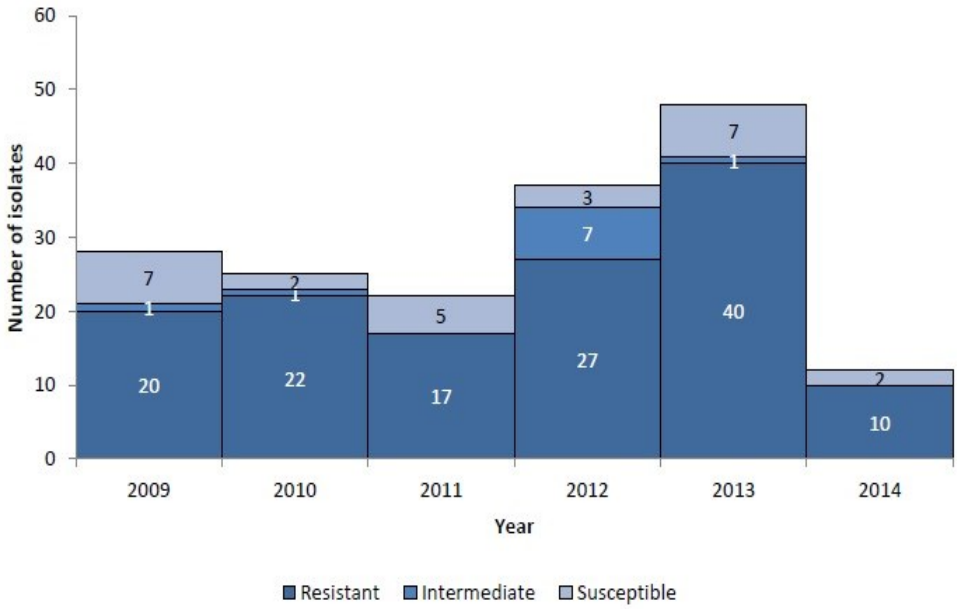
This study evaluated a convenience sample of isolates voluntarily submitted to the Pennsylvania state public health laboratory for CRE testing. From March 2009 to May 2014, 184 isolates were submitted to the BOL. Two isolates were excluded because the organism was not Gram-negative; two were excluded because they were from a non-human source; and five were excluded due to missing data. Final analyses included 175 isolates.

The median patient age was 69 years (range: 2-98 years), and 54 percent of isolates were from female patients. The majority of specimen sources were urine (56 percent) or wounds (12 percent), with only 9 percent of isolates from gastrointestinal sources. Only a small proportion (11 percent) of isolates were from sterile sites (like blood or respiratory specimens), and patient symptom information was unavailable. It is unknown whether isolates collected from non-sterile sites (like urine, wound or gastrointestinal specimens) were from patients who were infected or colonized.

Hospitals were the most frequent isolate submitters (67 percent), followed by commercial laboratories (31 percent). The most commonly identified organisms were *Klebsiella pneumoniae* (52 percent), *Enterobacter cloacae* (15 percent), *Escherichia coli* (11 percent) and *Enterobacter aerogenes* (8 percent). See Table 1.

Figure 1 shows an epidemic curve of submitted isolates and identified resistance, by year. An increasing number of isolates have been submitted since 2012. However, using these data, it cannot be determined whether this means CRE infections are increasing or simply that more isolates were submitted for testing in more recent years.

Figure 1. Carbapenem Resistance among Tested Isolates, by Year (N = 172)*



*Isolates submitted until May, 2014

Figure 2 shows a map of Pennsylvania counties and the number of isolates tested in each county and percent of resistant isolates. Isolates were submitted from 34 of Pennsylvania's 67 counties, including most major population centers but excluding Pittsburgh (Allegheny County) and some neighboring counties. Resistant isolates were identified in 28 counties.

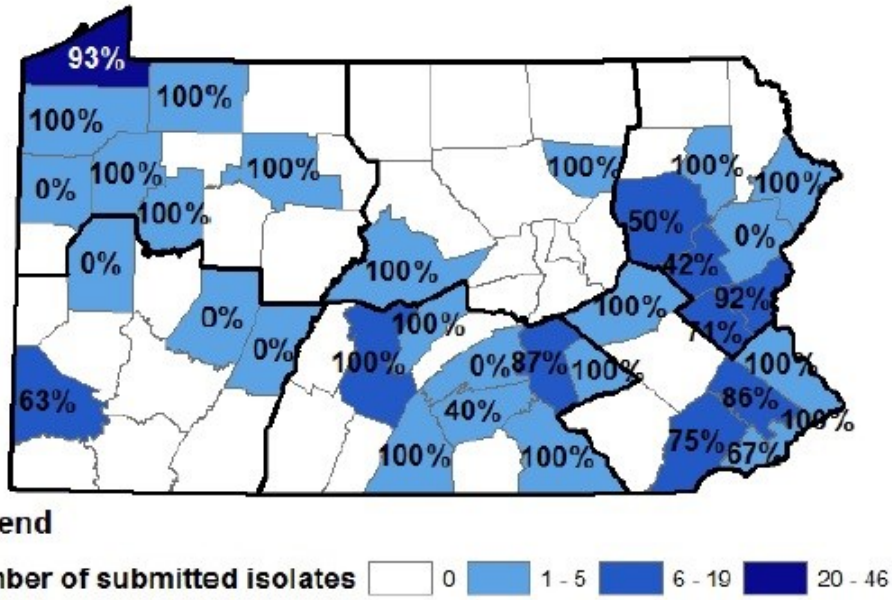
Of tested isolates (172), 79 percent were highly resistant to at least one carbapenem, 6 percent were intermediate and 15 percent were susceptible. See Table 2. Of 145 isolates tested using the modified Hodge test, 120 (83 percent) showed the presence of a carbapenemase. PCR

(CRE epidemiology continued)

results showed that the most commonly identified resistance enzyme was KPC (N = 73, 61 percent). The remaining resistance enzymes were identified infrequently: NDM (N = 6, 10 percent), VIM (N = 1, 100 percent), and OXA (N = 1, 100 percent). See Table 3.

Among fully resistant organisms, as shown in Figure 3, the most common were *Klebsiella pneumoniae* (N = 86, 95 percent), *Enterobacter cloacae* (N = 18, 67 percent), *Escherichia coli* (10, 53 percent), and *Enterobacter aerogenes* (N = 9, 64 percent). Intermediate resistance was identified in *Enterobacter cloacae* (N = 4, 15 percent) and *Enterobacter aerogenes* (N = 3, 21 percent).

Figure 2. Carbapenem Resistance in Pennsylvania by County



The percentages show the percent of resistant isolates within each county.

Table 2: Carbapenem Resistance among Tested Isolates (N=172)

	N	%
Resistant	136	79%
Susceptible	26	15%
Intermediate	10	6%

Limitations

This study has several limitations. Isolates were voluntarily submitted to the Bureau of Laboratories for testing; therefore, isolates included in this study likely underrepresent all CRE identified in Pennsylvania. Additionally, qualitative methods were used to determine carbapenem resistance, and resistance breakpoints changed in 2012.[2] However, most isolates were submitted during and prior to 2012, and, therefore, the pre-2012 case definition was used for all isolates. It is possible that isolates determined to be susceptible prior to 2012 would be considered resistant using the new breakpoints, and, therefore, CRE resistance may have been underestimated. No clinical information was available, so we cannot say why CRE testing was requested or whether patients were infected versus colonized.

Conclusions

In conclusion, carbapenem-resistant Enterobacteriaceae were identified in 42 percent of Pennsylvania counties, and 79 percent percent of tested isolates showed resistance to at least one carbapenem. CRE continues to be an emerging disease in Pennsylvania and throughout the United States. CRE treatment is difficult.

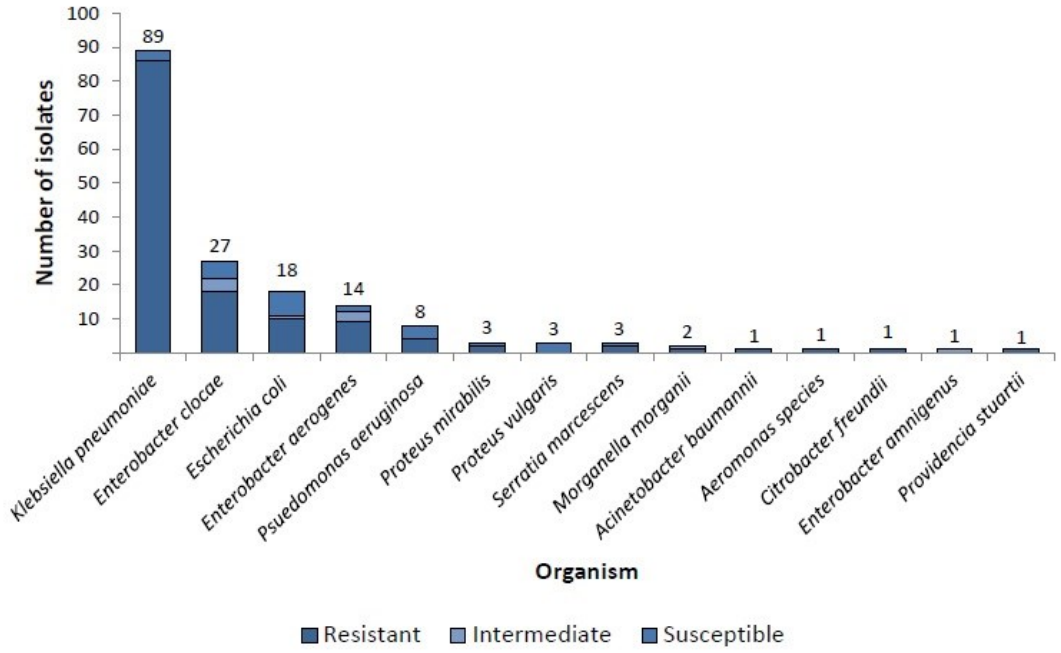
Table 3. Carbapenemase Enzymes and Other Tests

	Isolates Tested	Positive Result		Intermediate Result		Negative Result	
Test	N	N	%	N	%	N	%
Modified Hodge	145	120	83%	4	3%	21	14%
KPC PCR	119	73	61%	NA	NA	46	39%
NDM PCR	63	6	10%	NA	NA	57	90%
OXA PCR	1	1	100%	NA	NA	0	0%
VIM PCR	1	1	100%	NA	NA	0	0%
ESBLs	12	10	83%	NA	NA	2	17%

(CRE epidemiology continued)

Prevention is critical. Providers should review the latest CDC recommendations, including the 2012 CRE Toolkit,[2] a guide for laboratories,[8] and the full 2006 guidelines for "Management of Multidrug-Resistant Organisms in Healthcare Settings" from CDC's Healthcare Infection Control Practices Advisory Committee.[9]

Figure 3. Carbapenem Resistance among Tested Isolates, by Organism (N = 172)



Acknowledgements

We acknowledge the contributions of Lisa Dettinger, Jeffery Miller, Mària Moll, Kirsten Waller, Lindsay Weir and André Weltman, as well as the Centers for Disease Control and Prevention for performing CRE laboratory testing.

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Malaria Surveillance

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Background

Malaria is a serious, sometimes fatal, parasitic disease. The parasite is transmitted through the bite of the *Anopheles* mosquito. There are five parasites associated with malaria transmission — *Plasmodium falciparum* (which is most likely to result in severe disease)*, P. vivax, P. ovule, P. malariae* and *P. knowlesi.* Most *Anopheles* species of mosquitoes are active from dusk until dawn. Exposure to *Anopheles* mosquitoes can be reduced by using insecticide-treated bed nets while sleeping, spraying insecticide indoors and eliminating breeding sites, such as stagnant pools of water, outdoors.[1]

Signs and Symptoms

The signs and symptoms of malaria include fever and flu-like illness including chills, headache, muscle aches and tiredness. Nausea, vomiting and diarrhea are also common symptoms. Jaundice, anemia and enlarged liver and/or spleen may also occur. In more severe cases, kidney failure, seizures, mental confusion, coma and death may occur.[1]

The incubation period is seven to 30 days. The infected person may experience an attack of symptoms lasting six to 10 hours; the symptoms will subside; then the person will experience another attack two to three days later. Malaria is severe if organ failure occurs or if there are blood or metabolic abnormalities.[1]

Prevention and Treatment

Persons traveling to malaria endemic countries are advised to visit their physician prior to departure to obtain prophylactic malarial medications. These will help prevent malaria infection in the event a person is bitten by a mosquito infected with malaria. When in a malaria endemic country, people are advised to use mosquito repellants. Insecticide-treated bed nets may also be advised.[2]

Multiple single and combination drugs are available to treat malaria. The treatment will depend upon the type of malaria, resistance to drugs, the patient's clinical status, any underlying conditions the patient may have, if the patient is pregnant and if the patient has any drug allergies.[2]

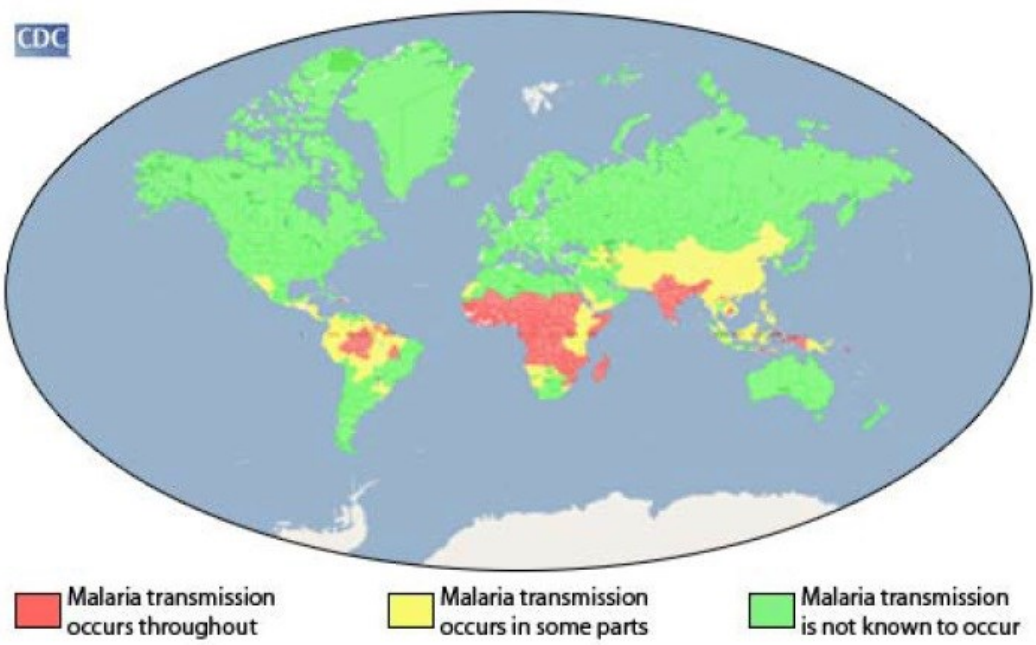
Transmission

Malaria is transmitted in countries with higher temperatures and in areas with rainfall. Countries along the equator tend to have the highest rates of malaria. However, even in countries where malaria is

(Malaria continued)

endemic, transmission does not occur at high altitudes, during cold seasons and in deserts.[3] Figure 1 shows the countries with the greatest risk of transmission.

Figure 1. Malaria Endemic Countries[3]



Malaria is transmitted when an *Anopheles* mosquito bites a person infected with malaria. The *Plasmodium* parasite multiplies in the mosquito. The infected mosquito then bites another person. This person develops malaria.

Some areas of Europe and the United States are susceptible to malaria, as the *Anopheles* mosquito is present in these areas. Malaria transmission in the United States has occurred, although these have been small, isolated outbreaks. Due to economic development and public health measures, malaria is not endemic in the United States, although the risk for reintroduction of the disease remains.[4]

Infected mosquitoes may also be transported to non-endemic countries via aircraft. These mosquitoes can then bite persons in the non-endemic country. It is possible, although rare, for congenital transmission to occur when an infected mother transmits malaria to her offspring during pregnancy. Transfusion-mediated malaria can also occur, whereby the blood of an infected donor is transfused into a person who can then become infected with malaria. This, too, is rare. The great majority of malaria cases in the United States and Pennsylvania are in travelers to endemic countries.[4]

Malaria Surveillance

Malaria in the United States

More than 1,500 cases of malaria are reported annually in the United States. In 2011, 1,925 cases were reported. Five deaths were reported due to malaria. One case was lab-acquired, one was transfusion-associated, two cases were congenital, and there was one whose transmission route was not identified. The remaining cases, 99.7 percent, identified foreign travel as the mode of transmission. Of these, about 67 percent had traveled to Sub-Saharan Africa, 22 percent to Asia, 6.3 percent to Central America or the Caribbean, and 2.1 percent to South America. Six percent had taken prophylactic medications according to recommendations.[5]

Malaria in Pennsylvania, 2003-2013

In the years 2003-2013, 562 malaria cases were reported in Pennsylvania. This is an average of 51 cases per year. Forty percent were female and 60 percent were male. The mean age was 34 years, with the youngest case being one month old and the oldest case 88 years old. Sixty-three percent were hospitalized, and there were eight deaths (1.4 percent).

(Malaria continued)

Table 1 shows the risk factors contributing to malaria cases diagnosed in persons in Pennsylvania. Travel outside of the United States is the most significant risk factor for persons diagnosed with malaria.

Table 2 shows the rate of particular outcomes and complications of malaria. Death occurs in about one percent of malaria cases in Pennsylvania. Anemia is the most common complication.

Figure 2 represents the locations of diagnosed malaria cases in Pennsylvania. Most malaria cases in Pennsylvania are residents of Philadelphia or the southeast area of Pennsylvania.

Figure 3 represents the species most frequently found in malaria specimens in Pennsylvania. The most common species identified in Pennsylvania is P. falciparum.

Figure 4 represents the countries to which Pennsylvania malaria cases have traveled. Most Pennsylvania malaria cases traveled to Southern Asia.

Table 1: Risk Factors Contributing to Pennsylvania Malaria Cases, 2003-2013

Risk	Count	Percent
Blood transfusion or transplant in last 12 mo.*	6/384	2%
Patient took chemophrophylaxis	171/562	30%
Traveled outside U.S. in the past 4 years	524/562	93%

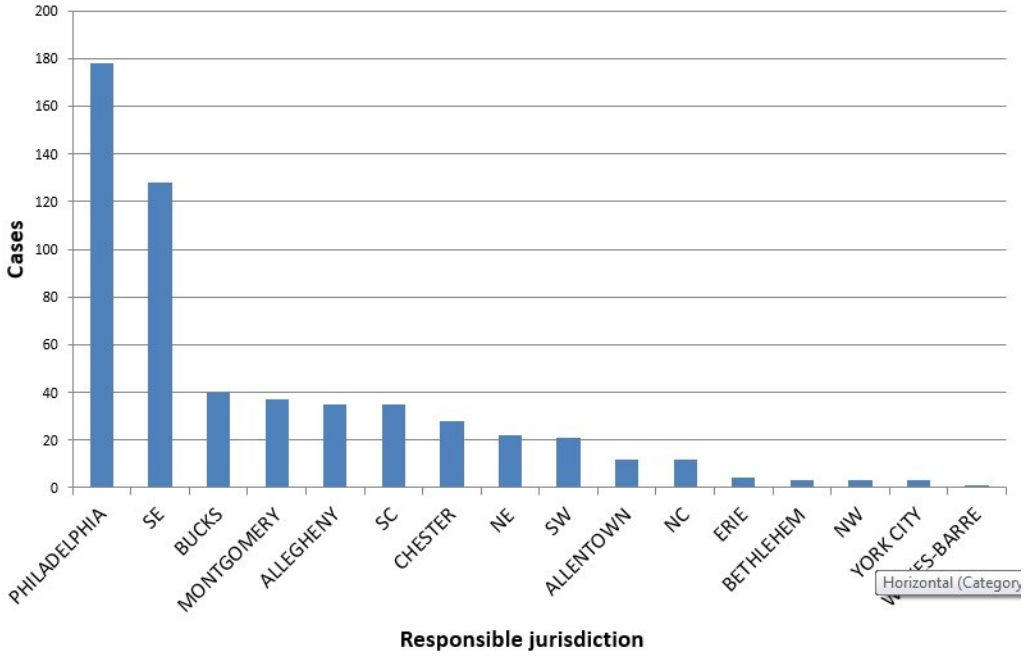
*Data for Philadelphia are incomplete

Table 2: Sequelae of Pennsylvania Malaria Cases, 2003-2013

Sequelae	Count	Percent
Death	8/562	1%
Acute Respiratory Distress Syndrome*	10/384	3%
Anemia*	74/384	19%
Cerebral malaria*	12/384	3%

*Data for Philadelphia are incomplete.

Figure 2: Locations of Confirmed Malaria Cases, Pennsylvania, 2003-2013 (N=562)



(Malaria continued)

Figure 3: Malaria by Species, Pennsylvania, 2003-2013 (N=562)

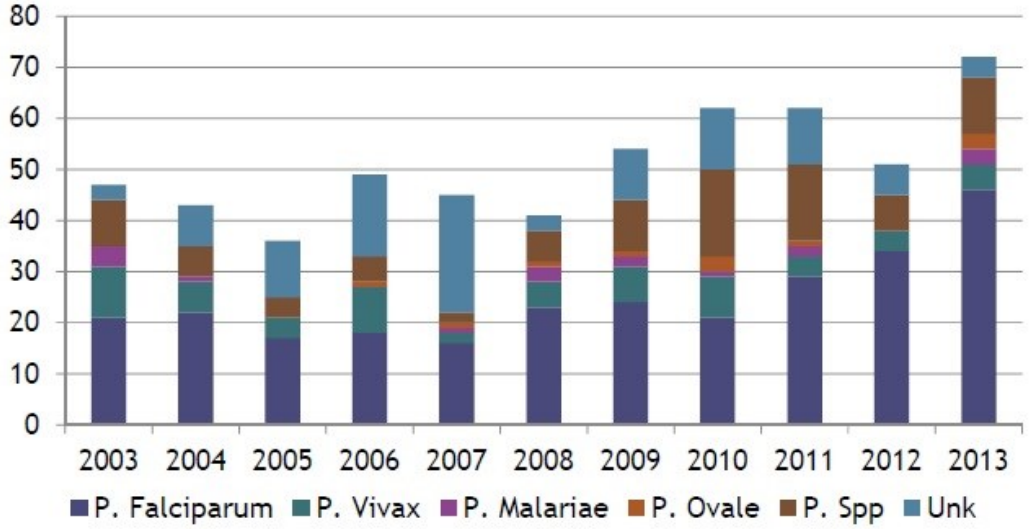
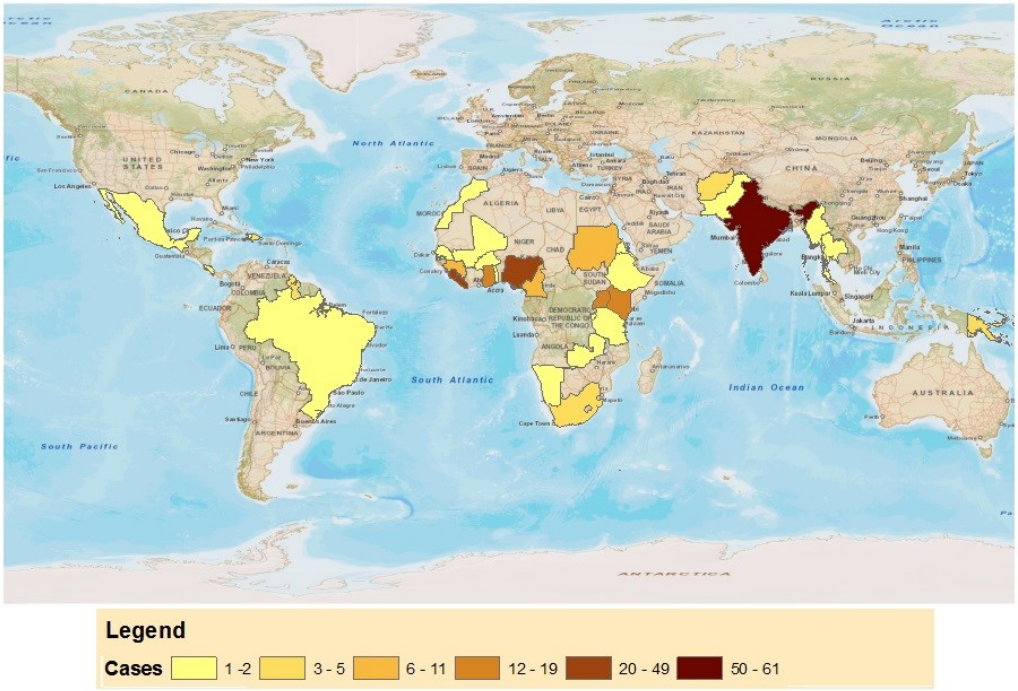


Figure 4: Country of Travel for Malaria Cases, Pennsylvania, excluding Philadelphia, 2003-2013 (N=384)



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3. http://www.cdc.gov/malaria/about/distribution.html
4. http://www.cdc.gov/malaria/about/us_transmission.html
5. http://www.cdc.gov/malaria/about/facts.html

(Pennsylvania Get Smart Program)

Pennsylvania Get Smart Program

Amanda Reiff; Courtney Yealy (Pennsylvania Department of Health)

The Pennsylvania Get Smart Program is focused on efforts to promote judicious antibiotics use in community settings. With support from the CDC, the Get Smart Program is working on a variety of projects in collaboration with multiple partners across the commonwealth. In central Pa, the Get Smart team is working with Penn State University and its College of Medicine to conduct survey research regarding antibiotic prescriptions in children and vaccination coverage in child care. In Pittsburgh, the Get Smart team is collaborating with University of Pittsburgh's School of Pharmacy in community outreach that includes education of appropriate antibiotic use. Other statewide activities include training child care center employees and children in proper hand hygiene.

In the spring of 2015, the Get Smart Program announced its third Annual Get Smart Competition which encourages Pennsylvania children up to 12 years old to show their creativity! Children were encouraged to draw pictures or write stories based on the following themes: importance of proper hand washing, importance of vaccines and knowing when not to use antibiotics. First place winners of the winners of the 2015 Get Smart Drawing Competition can be found below.

The Get Smart Program sponsored two large events this year to observe National Get Smart Week. On Nov. 17, an Antimicrobial Stewardship Seminar was held in State College, Pa. The seminar featured an educational presentation for clinicians and remarks regarding the commonwealth's response to the threat of antimicrobial resistance. The event concluded with the announcement of the 2015 competition winners and a proclamation from the Governor's Office. Penn State Hershey Medical Center and the Children's Hospital hosted an event on Nov. 18 to highlight its stewardship team's activity and discuss quality improvement for appropriate antibiotic use. Details about program activities, including information regarding annual Get Smart competitions, can be found on our website at www.KnowWhenToSayNo.org.

2015 1st Place Winner, Ages 11-12: Eliana Maneval, Richfield, Pa

2015 1st Place Winner, Ages 9-10: Jude Renee Botero, Mechanicsburg, Pa

2015 1st Place Winner, Ages 7-8: Angelina Beshore, York Springs, Pa

2015 1st Place Winner, Ages 5-6: Zakkary Tomcho, Union City, Pa

2015 1st Place Winner, Ages <4: Cheyene Oosterkamp, Union City, Pa

Cases of Select Notifiable Diseases in Pennsylvania *

(as of 3/20/16)

	Total cases reported for previous 5 years				
	2016 †	2015 †	2014	2013	2012
Chlamydia	12,433	53,449	50,536	52,056	54,993
Gonorrhea	2,954	12,850	12,710	13,874	15,390
Pertussis (whooping cough)	231	718	676	531	1,631
Campylobacteriosis	158	1,385	1,349	1,422	1,427
Salmonellosis	118	1,552	1,451	1,573	1,663
Giardiasis	85	648	703	747	651
Shigellosis	77	363	199	138	126
Varicella (chicken pox)	48	326	296	266	294
Cryptosporidiosis	27	195	200	243	287
Legionellosis	23	379	324	434	300

* Confirmed cases only
† Case counts for 2015 and 2016 are provisional and subject to change. Counts for earlier years are for complete years.

Disease Reporting

Health care practitioners, health care facilities and clinical laboratories are required to report certain diseases to the Pennsylvania Department of Health. In addition to the diseases on the list, all disease outbreaks and/or unusual occurrences of disease are reportable within the commonwealth. In most cases, reporting must be done electronically via Pennsylvania's version of the National Electronic Disease Surveillance System (PA-NEDSS). To request a PA-NEDSS account, health care providers may email PA-NEDSS@pa.gov; please include your contact information and the name and address of the facility for which you will be reporting.

New Employees in the Bureau of Epidemiology

Sharon Watkins, PhD

Sharon Watkins, PhD, has been named the new bureau director of the Bureau of Epidemiology and as the state epidemiologist. Dr. Watkins completed her undergraduate studies at Ohio Wesleyan University and completed her doctorate work at Ohio State University, Department of Preventative Medicine at the School of Medicine. Her concentration was Environmental Epidemiology, Perinatal/ Maternal and Child Epidemiology. Prior to accepting a position with the Pennsylvania Department of Health, Dr. Watkins served as the chief of the Bureau of Epidemiology at the Florida Department of Health, and most recently, as the Director of Public Health Research.

She is serving her second elected term on the Council of State and Territorial Epidemiologists Executive Board, a position that allows her to participate in public health issues at the national level.

Under Dr. Watkins' leadership, the Bureau of Epidemiology is focused on strengthening its capacity. Specific projects include the expansion of an environmental health program related to fracking, development of a comprehensive program for the evaluation of healthcare-acquired infections and continued focus on how the bureau can help stem the heroin and prescription drug crisis in Pa. Additionally, programs like Pennsylvania's Get Smart Program and Viral Hepatitis Prevention programs gain statewide attention for use of prevention measures that can stem the spread of disease.

Kelly Kline, MPH

Kelly Kline is the current CSTE Applied Epidemiology Fellow in the Bureau of Epidemiology. She recently graduated from the Yale School of Public Health with her MPH in the epidemiology of microbial diseases. While at Yale, Kelly worked for the Yale Emerging Infections Program as a research assistant on the FoodCORE team. After her fellowship, she plans to work in applied epidemiology at the state level.

For employment opportunities, visit the Pennsylvania State Civil Service Commission website.

Pennsylvania Epi Notes

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