Drug Resistant Infections
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SLIDE 1-TITLE

SLIDE 2

Hi. I'm Zack Moore, a medical epidemiologist with the Communicable Disease Branch. In this presentation, I will be discussing drug resistant infections.

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By the end of this presentation, you should be able to:

- Identify basic principles of drug resistance
- Distinguish vancomycin-intermediate staph aureus from vancomycin-resistant staph aureus and identify vancomycin-resistant staph aureus as a public health emergency
- Locate resources for investigation and control of other drug resistant infections that are not reportable in NC but still represent a threat to public health. Although there are many such infections, I will only address two in this presentation: methicillin-resistant staph aureus or MRSA, and carbapenem-resistant enterobacteriaceae or CRE.

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Each year in the United States, at least 2 million people become infected with bacteria that are resistant to antibiotics and at least 23,000 people die each year as a direct result of these infections. Many more people die from other conditions that were complicated by an antibiotic-resistant infection.

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Bacteria have many mechanisms for developing resistance to antibiotics, some of which are shown in this slide. These mechanisms can confer resistance to a single antibiotic or to entire classes of antibiotics. In some cases, genetic material causing drug-resistance can be spread to other types of bacteria.

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The basic principles of antibiotic resistance are shown in this slide from CDC. In step 1 you see a normal group of bacteria where only a few are drug-resistant, as shown in pink. In step 2 the bacteria are exposed to antibiotics, so that only those that were drug-resistant survive. Without the other bacteria to compete with, these drug-resistant bacteria grow and take over, as shown in step 3. Finally in step 4, some of these drug-resistant bacteria start transferring their resistance to other bacteria.

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It's important to understand that anytime antibiotics are used, this puts pressure on bacteria that promotes antibiotic resistance. Research has shown that as much as 50% of the time, antibiotics are prescribed when they are not needed or they are misused. As public health professionals, we should always be aware that the use of antibiotics by any one person affects others in the community and makes it less likely that antibiotics will be effective in the future.

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The first drug-resistant infections I will cover are vancomycin-intermediate *Staphylococcus aureus*, or VISA, and vancomycin-resistant *Staphylococcus aureus*, or VRSA. Currently, reduced susceptibility to vancomycin among staph aureus is the only type of drug resistance that is reportable by law in NC.

Staph aureus are classified as vancomycin susceptible, intermediate, or resistant based on the minimum inhibitory concentration or MIC required to suppress bacterial growth. The MIC can be determined by several different tests. In the broth microdilution method illustrated here, bacteria are placed into tubes of broth containing increasing amounts of vancomycin; 1mcg/mL, 2mcg/mL, 4mcg/mL, etc. If the bacteria can grow, the broth turns cloudy (like the tubes on the left). If the bacteria can't grow, the broth stays clear (like the tubes on the right). The MIC is the lowest concentration of vancomycin needed to stop the bacteria from growing. In this hypothetical example, the MIC would be 8mcg/mL.

An MIC of 4–8 indicates vancomycin intermediate staph (or VISA), and an MIC of greater than 16 indicates vancomycin-resistant staph (or VRSA). Vancomycin resistance is important because vancomycin is one of very few options for treating staph that are resistant to other drugs.

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Although VISA and VRSA sound similar, they actually develop in different ways and require very different public health responses.

VISA usually develops in patients who have had prolonged exposure to vancomycin. This exposure causes a thickened cell wall to develop around the organism. This change is often reversible if the vancomycin is stopped. While VISA is still uncommon, several cases are reported in North Carolina each year.

VRSA develops when staph pick up drug resistance genes from other bacteria in the patient's body- usually from vancomycin resistant enterococci (or VRE). These genes make the organism highly resistant to vancomycin, and this resistance can spread to other organisms and other patients. VRSA is very rare; only a small number of cases have ever been identified in the United States, and none have ever been reported in North Carolina.

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Vancomycin-resistant staph aureus is a true public health emergency, which requires immediate action and immediate notification of the Communicable Disease Branch.

It is important to confirm the lab results, including the specific MIC value. VRSA reports are usually due to errors in organism identification or susceptibility testing. Therefore, the isolates should always be sent to the state laboratory of public health for confirmation.

CDC guidelines for investigation and control of VISA and VRSA are available in the "Local Health Department Investigation Steps" section of the on-line CD manual.

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Next, I will discuss a two other epidemiologically important drug resistant infections, MRSA and CRE. Although neither of these are individually reportable in North Carolina, local health departments should investigate and report outbreaks of public health significance. Consultation is available from your CD nurse consultant or from the communicable disease branch epidemiologist on call.

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Methicillin-resistant staph aureus, or MRSA, is a type of staph that is not killed by methicillin or by other antibiotics that are commonly-used for staph infections.

MRSA poses a significant public health burden. In a study of 11 emergency departments nationwide conducted during 2004, MRSA was found to be the leading identifiable cause of skin and soft tissue infections. The CDC has estimated that 94,000 invasive MRSA infections occur in the US each year, with most of these being linked to healthcare settings. These infections result in an estimated 19,000 deaths.

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MRSA can found in many locations in the body and in the environment. It is commonly found in the nose; other sites include the skin, intestines, and throat. Most people who are colonized with MRSA will never develop any illness from it.

MRSA infections occur when the bacteria finds a way to penetrate the body's natural barriers. This is usually through a break in the skin, sometimes through minor cuts or scrapes that are too small to notice. Staph can also penetrate into the lungs if breathing surfaces are inflamed from colds or flu. Secondary infection with MRSA is one of the leading causes of influenza-associated deaths in children.

Once MRSA has penetrated, it can cause a wide variety of problems. Skin and soft tissue infections are the most common, including cellulitis and boils or abscesses.

However, MRSA can infect any organ system in the body, and less frequently causes infection of the bloodstream, bones, joints, lungs, heart or other organs. Disseminated infections can be difficult to treat and sometimes fatal.

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These photographs from the Texas Dept. of Health show a typical MRSA skin lesion with a central collection of pus surrounded by an area of redness and swelling. The drainage from the lesions is highly infectious and can be a source of transmission to others if not covered appropriately. MRSA skin infections are often mistaken for spider bites, particularly in the early stages.

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Studies have shown that MRSA is often transmitted by direct skin-to-skin contact, and particularly by contact with draining lesions, like those on the previous slides, or with soiled bandages.

Transmission can also occur through shared contact with personal items- such as razors, towels, and sports equipment- that have come in contact with skin lesions.

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Other potential routes that have NOT been shown to play a major role in transmission include coughing and sneezing, and contact with non-personal items such as pencils, paper, or books.

Since MRSA cases can cause alarm, particularly in school settings, it's important to emphasize that just being in a room with an infected person does not pose a significant risk of infection.

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This slide lists six basic control and prevention measures to consider in outbreak situations. First, it is important to enhance surveillance to make sure that all cases have been identified. This is important in order to understand the scope of the outbreak and to identify contacts.

Patients should be referred for testing and treatment. Healthcare providers should be encouraged to obtain cultures if possible, and to use appropriate antibiotics. The NC Consensus Guidelines for Management of Suspected Community-Associated MRSA are a good resource for providers, and are available on-line.

Provide education about the importance of good wound care, including avoiding contact with other people's wounds or bandages.

Basic hygiene should be promoted, particularly thorough hand-washing and not sharing personal items.

Exclusion of patients from certain activities may be necessary in some situations if draining lesions can't be adequately covered. Examples could include toddlers who won't leave dressings in place or athletes whose dressings might be displaced during competition.

Finally, efforts should be made to achieve and maintain a clean environment to prevent spread from contaminated surfaces, particularly those that come in contact with bare skin. However, remember that environmental cleaning is NOT a substitute for appropriate hygiene measures.

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Detailed information about MRSA prevention and control is available from NC DPH and from the CDC at the websites listed here.

http://epi.publichealth.nc.gov/cd/diseases/mrsa.html

Centers for Disease Control and Prevention

www.cdc.gov/MRSA

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Next I will briefly discuss carbapenem-resistant enterobacteriaceae, or CRE, a growing public health threat recently designated as "threat level urgent" by CDC.

Enterobacteriaceae are a family of bacteria that normally live in water, soil, and the human gut. These bacteria are a common cause of healthcare and community infections. Two members of the enterobacteriaceae family, *E. coli, K. pneumoniae*, accounted for 20% of all healthcare associated infections reported in 2009 and 2010.

CRE are enterobacteriaceae that have become resistant to carbapenems, a class of broad-spectrum antibiotics considered the "last resort" for treatment of serious gram-negative infections.

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Until recently, enterobacteriaceae were rarely resistant to carbapenems. In recent years, there has been a dramatic increase in the proportion of enterobacteriaceae that are found to be resistant because they produce carbapenemases; enzymes that break down carbapenems. These carbapenemase enzymes also confer resistance to other beta-lactam antibiotics, such as penicillins and cephalosporins. This can make these infections difficult or in some cases impossible to treat. To make matters worse, the genes for many carbapenemases are carried on mobile genetic elements called plasmids, which means they can be easily transferred to other nonresistant bacteria.

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This map shows the rapid spread of one important type of carbapenemase called KPC that was first reported in NC in 2001. By 2012, it had been reported from all across the country.

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A survey conducted by the Division of Public Health in 2012 found that more than half of North Carolina hospitals had cared for at least one patient colonized or infected with CRE over the

preceding 18 months. Currently, the Division of Public Health is working with partners to conduct periodic surveys to track CRE in both acute and long-term care facilities.

Resources for prevention and control of CRE are available on both the Communicable Disease Branch and CDC websites at the addresses listed here.

http://epi.publichealth.nc.gov/cd/diseases/cre.html

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

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Many other drug resistant threats that require urgent public health attention were not covered here in the interest of time. More information about these threats is available through the CDC and CDB websites or through consultation with the epidemiologist on call.

- Drug-resistant *Clostridium difficile*
- Drug resistant *Neisseria gonorrhea*
- Vancomycin-resistant enterococcus (VRE)
- Multidrug-resistant tuberculosis (MDR TB) and extensively drug-resistant tuberculosis (XDR TB)
- Drug-resistant *Streptococcus pneumoniae (*DRSP),
- Etc.

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In conclusion, drug resistant infections are a growing threat created largely by misuse and overuse of antibiotics.

Thankfully, vancomycin resistant staph aureus remains rare so far, but reports of possible VRSA cases require urgent investigation.

Finally, although MRSA, CRE and other drug resistant infections are not individually reportable at present, these infections may require public health interventions to address public concerns and prevent spread.