Big Bad Bacteria: Invasive Bacterial Diseases and VISA/VRSA
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SLIDE 1
Hi. I'm Zack Moore, medical epidemiologist with the Communicable Disease Branch of the North Carolina Division of Public Health. This presentation will cover "Big, Bad Bacteria: Invasive Bacterial Diseases and VISA/VRSA".

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At the conclusion of this presentation, participants should be able to recognize the public health significance of invasive bacterial diseases, locate control measure guidance for these diseases, know which invasive bacteria must be sent to the state lab for serotyping, and identify VRSA as a public health emergency.

SLIDE 3
I will first discuss four invasive bacterial diseases that are reportable in North Carolina: Haemophilus influenzae invasive disease; Invasive meningococcal disease; Pneumococcal meningitis; and Group A streptococcal invasive disease, including toxic shock syndrome. Finally, I will briefly review the problem of vancomycin-intermediate staph aureus, or VISA, and vancomycin-resistant staph aureus, or VRSA.

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When talking about invasive disease, it is important to remember that, with some exceptions, only isolation of the organism from a normally sterile site is considered invasive. Invasive infections occur when pathogens get past the body's normal defenses, such as the skin or the lining of the respiratory tract, and invade into normally sterile sites like the blood stream or spinal fluid. Other sterile sites include joint fluid, bone, pleural fluid, and pericardial fluid. It is important to note that invasive disease does NOT include positive cultures from sputum, throat, or nasopharyngeal swabs. These bacteria are common in the upper respiratory tract and they can cause many noninvasive illnesses, like ear infections and sinus infections. For group A strep, invasive disease also does NOT include cultures from skin, genital tract, or superficial wounds. Invasive means just that – the organism has invaded into a normally sterile site. Some results are difficult to interpret because they are not obviously sterile or non-sterile sites. Examples include cultures from bronchioalveolar lavage fluid, pleural fluid, or surgical specimens. In these cases, it is good to get more clinical information and information about how the specimen was collected to help you decide whether the bacteria was really invasive.

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Three of the pathogens we will discuss – meningococcus, pneumococcus, and haemophilus – have many similarities. All three organisms can colonize the upper respiratory tract. Colonization means that they can be living in or on the body without causing any disease. All three are spread from person to person by respiratory droplets or contact with oral secretions. This means that transmission requires close contact. There is little or no risk of transmission from contaminated environmental surfaces or

through the airborne route. Finally, all three bacteria can invade after viral infections. This happens when respiratory viruses disrupt the lining of the airways, allowing the bacteria to invade. For example, many of the influenza-related deaths that occur each year are caused by secondary bacterial infections.

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The first bacteria I will discuss is Haemophilus influenzae or "H. flu". H. flu can cause a variety of clinical syndromes. Invasive diseases include sepsis, pneumonia, meningitis, and epiglottitis. Noninvasive diseases include ear, eye and sinus infections. H. flu organisms are divided into serotypes a, b, c, d, e, and f, based on proteins found in the capsule that surrounds the organism. Strains without a capsule are called non-typeable. Keep in mind that a "non-typeable" result from the state lab does not mean serotyping could not be performed; it means the organism had no capsule. All serotypes, including non-typeable serotypes, can cause invasive disease. Haemophilus influenza serotype b, or Hib, is the most virulent.

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Hib was the leading cause of bacterial meningitis in children under 5 years of age before vaccine was available. 4-5% of Hib meningitis cases were fatal, and 20% of children who survived had permanent sequelae, such as hearing loss or mental retardation.

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This graph from the CDC shows what happened with reported cases of invasive H. flu disease in children less than 6 years old after the introduction of the Hib vaccine in the late 1980s. As you can see with the yellow line, the incidence of invasive Hib had decreased more than 95% by 1993. As stated previously, other types of H. flu can cause invasive disease; these are represented by the red line. The incidence of invasive H. flu caused by other serotypes has remained stable.

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Antibiotic prophylaxis is only recommended for type b disease. Even for Hib cases, prophylaxis is only recommended for households with an under-immunized child less than 4 years of age or an immunocompromised child in the home. Serotyping results are not usually available when a case is first identified. Since Hib is now rare in the US, we generally do not assume the infection is caused by type b when planning control measures unless the patient is at increased risk of Hib disease. Examples of patients at increased risk might include contacts to known Hib cases, travelers to areas where Hib is still endemic, or unvaccinated children.

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Here are a few tips for reporting H. flu invasive disease to help you avoid common pitfalls. First, H. flu is not influenza. This is a point of confusion for many patients, especially during flu season. Remember that all H. flu serotypes are reportable if they are associated with invasive disease, and that all H. flu isolates from normally sterile sites must be serotyped according to NC law. This usually means the lab must submit

them to the state. Finally, remember that positive latex agglutination tests from spinal fluid are also reportable as probable cases. Latex agglutination tests only pick up type b and are sometimes used for rapid diagnosis or for patients who received antibiotics before spinal fluid could be obtained.

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Let's turn our attention now to meningococcal infections. Neisseria meningitidis, also called meningococcus, can cause several clinical syndromes. It is one of the leading causes of bacterial meningitis in young children, and can also cause a blood stream infection known as meningococcemia. Both meningococcal meningitis and meningococcemia cause significant morbidity and mortality. These conditions can occur as sporadic cases or in outbreaks. There are many strains or serogroups of Neisseria meningitidis. The five serogroups responsible for the vast majority of invasive disease are A, B, C, Y, and W-135. Serogroup A is uncommon in the US. A vaccine is available that protects against four of the five serogroups: A, C, Y and W-135. Routine vaccination is now recommended for all children 11—18 years of age and for adults who are at increased risk, including college freshmen living in dormitories, military recruits, and people with asplenia or certain other immune problems. The vaccine does not protect against serogroup B, which is the leading cause of meningococcal disease in infants.

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One of the frequent signs of meningococcemia is a rash, which often begins as petechiae. In severe cases, the patients can develop purpura, as shown in this picture from the National Foundation of Infectious Diseases website.

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Antibiotic prophylaxis is critically important for close contacts of patients with invasive meningococcal infections, and is recommended for household contacts, childcare contacts, and others with direct exposures to the patient's oral secretions. Note that prophylaxis is NOT recommended for casual contacts, such as office coworkers, elementary, high school or college classmates, or healthcare workers who were not directly exposed to oral secretions. Detailed recommendations are available in the Red Book. Timing of prophylaxis should be based on the index patient's infectious period and the time since last exposure. Patients are considered infectious beginning approximately 7 days before onset until 24 hours after starting appropriate antibiotics. Prophylaxis should be given within 24 hours after the index patient is identified, if possible. Prophylaxis is of limited value if started more than 14 days after the last exposure.

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Invasive meningococcal disease can be reportable, even without a positive culture, if there were gram negative diplococci – like those shown on the right – on a gram stain from a normally sterile site, or if the patient was clinically diagnosed with purpura fulminans. Finally, remember that all meningococcal isolates from normally sterile sites

must be sent to the state laboratory of public health for serogrouping under North Carolina law.

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We are now going to talk about *Streptococcus pneumoniae*, which is also known as pneumococcus. Pneumococcus can cause many clinical syndromes. Invasive pneumococcal diseases include sepsis, pneumonia, and meningitis. Pneumococcal infections are most common during the late winter and early spring. Certain groups are at higher risk of invasive pneumococcal disease, including children less than 2 years of age and adults over 65, as well as people with certain chronic medical conditions. There are many pneumococal serotypes, and vaccines are available to protect against those that are most likely to cause invasive disease. Prevnar (or PCV7) is a conjugate vaccine that protects against seven of these serotypes. A replacement conjugate vaccine has now been approved which covers 13 serotypes. Routine vaccination with Prevnar is recommended for all children less than 2 years of age and for children 2-5 years of age who are at high risk due to medical conditions. Invasive pneumococcal disease has decreased more than 75% since conjugate vaccines became available. Persons over 65 years of age and adults who have chronic medical conditions like diabetes, should receive the pneumococcal polysaccharide vaccine, or PPSV23.

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Only one type of invasive pneumococcal disease is currently reportable in NC, and that is Pneumococcal meningitis. Keep in mind that this is not the same as meningococcal meningitis. There can be some confusion with names of organisms versus names of clinical syndromes, particularly if patients have pneumococcal meningitis, or even meningococcal pneumonia. Since contacts are not generally at increased risk, antibiotic prophylaxis is rarely, if ever, indicated.

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Next I will review Group A strep invasive disease. Group A strep is a very common type of bacteria that often causes strep throat, skin infections, and scarlet fever. It can also cause several types of invasive disease. The first of these is streptococcal toxic shock syndrome, an acute illness characterized by fever, low blood pressure, rash, peeling skin, and multisystem organ involvement which often includes the liver, kidneys, GI tract, and central nervous system.

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The rash of toxic shock syndrome is often described as a sunburn-like rash, as seen in this picture.

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Another clinical finding of toxic shock syndrome is desquamation, or peeling of the skin. This peeling usually involves the palms and soles, as well as fingers and toes. It is important to realize that desquamation, or peeling, is a late finding. This finding may not be present when the initial report is made. Toxic shock syndrome, caused by staph

aureus, is very similar to streptococcal toxic shock and is also reportable in North Carolina. However, that topic is not covered in this presentation.

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Group A strep is also the leading cause of necrotizing fasciitis, often referred to as "flesh-eating bacteria", because of the rapid and severe tissue damage it causes. Some other clinical syndromes include myositis (or muscle infection); bone or joint infections; and pneumonia. Bacteremia can occur in association with superficial skin or wound infections, or with no apparent source.

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Group A strep can also be called *Streptococcus pyogenes* or group A beta hemolytic strep. When investigating and reporting invasive group A strep cases, it's important to remember that not all strep is group A strep. There are many other strep species that cause human illness, including *Streptococcus pneumoniae* and group B strep. Antibiotic prophylaxis is not routinely recommended for contacts to invasive group A strep cases. However, it can be considered for elderly household contacts or others who are at increased risk for invasive group A strep. Prophylaxis can also be considered in outbreak settings. Finally, group A strep is an important cause of post-surgical and postpartum infections. These are sometimes linked to transmission from colonized healthcare workers. To prevent healthcare transmission, it's important to identify these cases by finding out whether patients with invasive group A strep had surgical procedures or delivery within 7 days before the first positive culture. The CDC has published guidance for investigating postpartum and post-surgical cases, and these are available from the Communicable Disease Branch.

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Finally, I will discuss vancomycin-intermediate staphylococcus aureus, or VISA, and vancomycin-resistant staphylococcus aureus, or VRSA. Methicillin-resistant staphylococcus aureus, or MRSA, is covered in a separate presentation. 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 shown here, bacteria are placed into tubes of broth containing increasing amounts of vancomycin; 1 mcg/mL, 2 mcg/mL, 4 mcg/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 8 mcg/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 to other patients. VRSA is very rare; only 12 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. Most VRSA reports are due to errors in organism identification or errors in susceptibility testing. Therefore, the isolates should always be sent to the State Laboratory of Public Health for confirmation. Finally, CDC guidelines for investigation and control of VISA and VRSA are available in the Local Health Department Investigation Steps section of the online Communicable Disease Manual.

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In conclusion, invasive bacterial diseases are an important cause of illness and death in the United States. Although outcomes from these infections have improved greatly, thanks to antibiotics and better supportive care, we must continue to be vigilant in our response to these pathogens. Antimicrobial resistance is an increasing problem. Vancomycin resistance in staph, while still rare, is a growing threat. Careful surveillance for these diseases is essential to help us prevent transmission, to monitor the effectiveness of vaccines, and to track changing patterns of antimicrobial resistance. In public health, we have many opportunities for prevention and control of these diseases. For H. flu, meningococcal and pneumococcal disease, vaccination is the most important. However, education of the public and healthcare providers, and antimicrobial prophylaxis when indicated, are also important tools.

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References for this presentation are listed here.

SLIDE 27
And photography credits.

SLIDE 28
I would like to thank Dr. Kristina Simeonsson for developing an earlier version of this presentation**.**