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The continuing threat of methicillin-resistant Staphylococcus aureus- Past Present Future

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Abstract: Methicillin-resistant *Staphylococcus aureus* has been a major problem in the worldwide health care centres and institutions since the last 60 years . It has been a major pathogen responsible for nosocomial infections and recently has created life-threatening situations. Penicillin resistance was seen a few years after the drug was introduced. To solve this problem another drug of the penicillin family was introduced : the semi-synthetic methicillin or oxacillin. This solved the antibiotic resistance for a while until in 1960 in the UK, strains of *Staphylococcus aureus* were isolated that showed resistance to methicillin thus termed as Methicillin-resistant *Staphylococcus aureus* MRSA or Superbug. In the previous few decades MRSA has shown increased resistance not only to methicillin but also to a wide range of other antibiotics such as gentamycin, erythromycin, and tetracycline .After the emergence of multidrug resistance in MRSA, the only drug of choice for treating MRSA infections was the glycopeptide vancomycin. It was considered the drug of "last resort" until the unfortunate emergence of another alarming mutated strains of MRSA-Vancomycin-intermediate *Staphylococcus aureus* (VISA), and now recently the biggest threat of all is vancomycin-resistant *Staphylococcus aureus* (VRSA) which has acquired Vancomycin vanA gene from *Enterococcus faecalis*. The emergence of VISA or VRSA isolates alone are the huge threat mankind faces. Thus it has become imperative that analysis of MRSA strains take place and their genetic characteristics may be well understood to fight against the evolution of MRSA into VISA or VRSA.

Keywords: Methicillin-resistant *Staphylococcus aureus*, antibiotic resistance, penicillin, nosocomial infection, vancomycin.

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History

Alexander Fleming in 1928 observed the zone of inhibition that *Penicillium notatum* had produced around staphylococci [1]. Fleming discovered the antibiotic penicillin and in 1940 Florey and Chain isolated and purified it [2]. Penicillin was introduced in 1943, a time when antibiotic resistance in staphylococci was completely unknown and was used extensively in World War II for the treatment of wounded soldiers of the Allied Forces [3]. It was hardly suspected that several years later penicillin resistance would evolve in staphylococci. Resistance to penicillin may have developed as early as 1946 [3].

Mode of Action of the β-Lactam Penicillin

Penicillin belongs to the β-lactam antibiotics which have a bactericidal mode of action and act by inhibiting the peptidoglycan synthesis in bacteria. Gram-positive bacteria have a peptidoglycan layer covering 90% of the cell wall [4]. Because these antibiotics are variants of active site "serine" hydrolases they can bind to the active site of penicillin binding proteins [5]. First an attack on the amide bond on D-Ala-D-Ala on the serine active site takes place. Then acylation occurs after opening of the β-lactam ring and irreversible binding of the open ring to D-Ala-D-Ala on the serine active site. This is the completion of the catalytic reaction which hinders the final peptidoglycan synthesis cross- linking [4].

Emergence of Resistance

In 1961 in the United Kingdom the very first emergence of penicillin-resistant *S. aureus* was observed[6]. It showed resistance against dimethoxyphenecillin, large doses of which were required to treat patients due to its rapid absorption and secretion. [6].

S. aureus first showed resistance to penicillin by the presence of a β-lactamase enzyme penicillinase which hydrolysed the tetrahedral ring (by acquisition of a chromosomal encoded BlaZ gene which encoded the lactamase).

Penicillin showed narrow spectrum activity and proved to be ineffective against evolving strains. Derivatives of penicillin were essential which led to the development of ampicillin now classified as a moderate-spectrum β-lactam antibiotic. It showed better activity than the original penicillins and has been used extensively since 1961. But both ampicillin and amonicillin were ineffective against β-lactamase penicillinase producing bacteria. β-lactamase resistant penicillins were then further developed. Methicillin was developed by Beecham in 1959. Vancomycin was introduced in 1956, Methicillin in 1960, and Ampicillin in 1961. Resistance against methicillin was observed the earliest in 1961 i.e. one year after its introduction, resistance to ampicillin was observed in 1973 and resistance to vancomycin was observed in 1988 [3]. Modifications in the original penicillin molecules Pen G and V gave rise to synthetic antibiotics. In methicillin the unsubstituted aryl groups were replaced with 2, 6 dimethoxy substituents, in oxacillin were replaced by the phenyloxazolyl group. This blocked the β-lactamase active site, making it resistant to hydrolysis. Methicillin shows similar activity like that of all other penicillins. It acts on the peptidoglycan synthesis by acylation and cross linking of the peptidoglycan layer. Methicillin proved to be the answer to penicillin resistant staphylococcus.

The second mode of β-lactam resistance is due to possession of altered penicillin-binding proteins. MRSA possesses a

chwomosomal mecA gene which produce PBP2A or the penicillin binding protein. β-lactams cannot bind as effectively to these altered PBPs, and, as a result, the β-lactams are less effective at disrupting cell wall synthesis [11]. Notable examples of this mode of resistance include 2A which is a cell wall biosynthetic enzyme MRSA. Other methicillin group of antibiotics were then used to treat MRSA. Notably flucloxacillin and dicloxacillin. Altered PBPs do not necessarily rule out all treatment options with β-lactam antibiotics [12].

Multiple Drug Resistance

MRSA shows multiple drug resistance against a variety of different antibiotics erythromycin, tetracycline, and aminoglycosides such as gentamycin [13]. Resistance genes on plasmids have shown resistance to heavy metals such as cadmium acetate, mercuric chloride, resistance to chemicals such as propamidine isoethionate, ethidium bromide [14], and resistance to antibiotics such as chloramphenicol, neomycin, erythromycin, mupirocin, gentamycin, kanamycin, streptomycin, tetracycline, tobramycin, clindamycin, fusidic acid, trimethoprim, ciprofloxacin [14]. Vancomycin was the ideal drug used to treat MRSA infections by 1986. The threat of VISA or even VRSA led to the development of the oxazolidnone linezolid, introduced in 1999 used to treat multidrug resistant staphylococci [3]. As discussed in detail before resistance to antibiotics in *S. aureus* has been mediated through two ways. The first is the presence of the BlaZ lactamase on the chromosome. In MRSA the expression of penicillin –insensitive PBP2a, encoded by the chromosomal mecA gene is responsible for resistance. Resistance genes for other antibiotics include aac6'-aph2", aph (3')-III for gentamycin resistance, ermA, ermB, ermC for erythromycin, tetK tetM encode resistance to tetracycline[14].

Community Acquired MRSA (CA-MRSA)

S. aureus is commonly associated with skin infections [15] and causes infections in various parts of the body including endocardium, long, soft tissues [16]. *S. aureus* is an important hospital pathogen causing various infections and toxinoses including cutaneous abscesses with varying severity and lethal necrotizing fasciitis and life threatening necrotizing pneumonia. [17,18]. With treatment with various β lactams and other modern drugs this dangerous pathogen has evolved into MRSA making the infections even more lethal leaving very limited therapy options [19,20]. *S. aureus* is also responsible for impetigo and staphylococcal scalded skin syndrome causing blisters in children and neonates. Recently it has been observed that from outpatients CA-MRSA has been isolated and found responsible for impetigo which is of serious concern since the CA-MRSA carries resistance genes not only for β-lactams but also for multidrugs [21]. *S. aureus* is a commensal bacterium commonly found in the anterior nares of the human body. It has now been established that the presence of *S. aureus* in the nose has important epidemiological significance especially when there is a widespread multidrug resistant in *S. aureus.* Administration of a wide range of antibiotics to hospitalized patients has been a major risk factor for MRSA infection [22].

The commensal bacteria in the nose undergo modification with the administration of systemic antibiotic drugs [23]. Misuse of penicillin resulting in environmental widespread has been shown to be a significant factor for the colonization and transmission of

penicillin-resistant *S. aureus* in the nose and to other patients. Frequent dosages of tetracycline given to patients with tetracycline-resistant *S. aureus* also facilitated the widespread of tetracycline resistant strains thus antibiotic pressure has been a major factor contributing to the emergence of MRSA [22] which has become a significant threat as MSSA and MRSA strains colonize the human body persistently [15]. In a study conducted in 1998 in Bangladesh it was shown that MRSA was prevalent among diabetic patients; 37.2% among infected hospitalized diabetics and 21.6% among non-hospitalized diabetics in the community [24].

Epidemic MRSA

Methicillin-resistant *Staphylococcus* aureus has been mainly associated with the hospital set up and various other healthcare institutions [28]. There are high there are high risk factors of acquiring MRSA infection during surgery, renal dialysis and by contaminated medical equipment. In hospital environments where MRSA readily causes infection it is often considered as epidemic MRSA or EMRSA. Nursing homes in various parts of the world have been associated with MRSA infections and may be considered as a reservoir. Healthcare institutions MRSA infection has been a major problem causing mortality [27]. In recent years MRSA has been isolated from people in healthy communities who are not at risk of MRSA infection. It is still unclear why some MRSA strains are associated with hospitals and health care centers whereas some strains are present in healthy individuals in the community [29].

Increasing Prevalence of MRSA around the world

First case of Community Acquired-MRSA was reported 1993 in the Aborigines of Western Australia [30]. Following that it appeared in apparently healthy individuals having no risk factors in 1997 and 1999 in the USA and Europe[31]. In children CA-MRSA infection spread through infected skin by contact can be the causative agent of fatal necrotizing pneumonia. An important characteristic of CA-MRSA is the presence of the mec IV the methicillin-resistance locus located on the staphylococcal cassette chromosome SCCmec and a virulent Panton-Valentine leucocidin (PVL) gene. SCCmec elements have been categorized into 5 allelic types out of which throughout the world HA-MRSA carries SCCmec type I, type II, type III. The other two SCCmec elements type IV and type V have been dispersed greatly among CA-MRSA strains. [38]. CA-MRSA has prevalence in the community since the 1990's.

CA- MRSA has emerged in various parts of the world Australia, New Zealand, Canada, the USA, Europe and in Hong Kong. In Hong Kong the strain isolated from a 50 year old man with a good health, showed resistance to 1μg oxacillin disk but it was non-multidrug resistant [32]. A crucial point about CA-MRSA is that there are no specific risk factors which the people in the community are exposed to. In the south Asian region in Bangladesh from the outpatients department of a hospital located in Dhaka community acquired MRSA has been isolated [33]. In Los Angeles it was noted that CA-MRSA was responsible for a surprisingly higher number of infections of necrotizing fasciitis[17] . Studies and data from a MRSA infection in a Lebanese man showed the presence of many toxins and the etA and etD exfoliative toxin genes were described. The resistant genes were the mecA gene and resistance genes for neomycin and streptothricin. Various pathogenicity islands have been

observed in various MRSA strains all around the world. In Japan there are strains carrying etA gene but are rarely found outside of Japan. In the European CA-MRSA etD and edinB containing pathogenicity island is observed [34]. In Michigan in the United States MRSA shows plasmid encoded resistance to aminoglycosides, trimethoprim, disinfectants and β-lactams carrying the resistance genes aacA-aphD, dfrA, qacC and blaZ respectively [35].

In hospitals the criteria for defining a Hospital Acquired-MRSA case includes the above mentioned risk factors showing a history of prolonged stay in a health care facility within a year of the culture date of the MRSA strain, the patient admitted to a hospital and acquiring a MRSA infection after 48 hours and the indwelling percutaneous medical devices (gastrostomy tube) and finally a positive culture for MRSA [36]. Recent surgery and hospitalization, living in health-care institutions e.g. elderly nursing homes, medical devices including catheters, and percutaneous devices and dialysis are all now prominent risk factors leading to MRSA infection [37].

In a multicentre study in Bangladesh there were 510 MRSA isolates out of 3611 samples (14.1%). Incidence of MRSA in four Bangladesh hospitals revealed that the rates of MRSA range from 32.0% and 63.00%. The study conducted in 2005 showed that the incidence of MRSA has greatly increased in Bangladesh over the past 4-5 years in different hospitals of various regions of Bangladesh.[33]. In Japan MRSA has already been found in healthy children. In the analysis of 818 children, 231 children (28.2%) carried methicillin-resistant coagulase-negative staphylococci (MRC-NS), 35 children (4.3%) carried MRSA.

In a study conducted in several Asian countries it was found that out of a total of 1357 MRSA isolates 347 (25.6%) were found to be resistant to 4mg/Litre of vancomycin. Heterointermediate resistance to vancomycin hVISA analysis showed the presence of hVISA in Japan (8.2%), India (6.3%), South Korea (6.1%), the Philippines (3.6%), Vietnam (2.4%), Singapore (2.3%), and Thailand (2.1%). This incidence of hVISA is attributed to the extensive use of glycopeptides in Asian countries [39].
In Pakistan up till now, there has been no case of vancomycin intermediate or resistant S. aureus. In a study conducted in Rawalpindi, the MIC's of vancomycin were calculated for MRSA and it was concluded that up till now there is no presence of VISA or VRSA in Pakistan. [41]

Role of the Glycopeptide Vancomycin and Vancomycin Intermediate and Vancomycin Resistant Staphylococcus aureus (VISA and VRSA)

The treatment of MRSA infections has become problematic due to the acquisition of multiple drug resistance genes. Due to widespread MRSA infections there has been great pressure to use glycopeptides for treatment. The glycopeptide vancomycin has been used to treat patients with MRSA infections [40]. Now through plasmid acquired vancomycin resistance has been acquired by some MRSA strains. Vancomycin resistance was first observed in a strain of *Enterococcus faecalis* in 1988. This high resistance is mediated by a mobile genetic element. The resistance gene was VanA located in a gene cluster. Transference of the mobile genetic element to MRSA creates high level teicoplanin and vancomycin resistance in MRSA. The emergence of vancomycin intermediate and vancomycin resistant Staphylococcus aureus has become a major threat [35].

MRSA infections have been treated with vancomycin since there have been few drugs it is susceptible to. Most MRSA strains showed susceptibility to vancomycin near the value of 1 μg/ml till the late 1990s. In Pakistan [41] as well as Bangladesh [33] MRSA strains show susceptibility to vancomycin MIC < 4 μg/ml. In 1997 in a study in Kuwait MRSA showed MIC values of 0-5-2 mg/L for vancomycin and teicoplanin but from 1999 the strains showed reduced susceptibility to both drugs MIC 3–4 mg/L.[14]. Since the end of 1999 several countries have reported stains with reduced susceptibility to vancomycin and such vancomycin intermediate strains showed MIC values of 8-16 μg/ml. The very first reports of vancomycin resistant *S. aureus* strains was reported in two hospitals in the United States in 2002 showing high resistance MIC of 32 μg/ml [42]. This was a very alarming discovery raising serious concern that the spread of VRSA would make MRSA infection drug therapy very difficult and could even give rise to staphylococcal infections with no chemotherapy or treatment available. [43,44].

The reports of the first strain of *S. aureus* with reduced susceptibility to vancomycin was found in Japan in 1997 named Mu50 showed MIC of 8mg/litre. After this discovery other strains have also been found in United States, Europe and Far East which have been classified as VISA. Now in some parts if the world reports of VRSA have raised serious concern giving rise to the pressure of finding new antibiotics to fight against MRSA and VISA and VRSA [39]. In 1997 a new term was used hVISA to describe MRSA strains showing heterointermediate vancomycin resistance. hVISA stains are generally considered as stains of *S. aureus* in which there are daughter cell subpopulations having intermediate resistance to vancomycin MICs of 1-4mg/litre. Although this is an intermediate susceptibility there is controversy whether hVISA is of medical significance[45].

Future Prospects of Treatment of MRSA infection

In vitro studies showed that copper sulfate has antimicrobial activity against MRSA. Soluble copper silicate has been studied in detail as a possible future treatment for dermatological MRSA infections and nasal decolonization therapy. In phase I studies a topical cream medication containing 0.22% Cu wt/wt was shown to be tolerated by 350 people. It has been shown that MRSA showed an MIC of 175mg Cu/liter. At 2X MIC and 4X MIC bactericidal and post antibiotic effects (in more than 1 hour) were observed. [46].

References

1. Fleming A. On the Antibacterial Action of Cultures of a Penicillium, with Special Reference to Their Use in the Isolation of B. influenzae. Br J Exp Pathol, 1929; 10:226-236.

2. Goldsworthy P, McFarlain AC. Howard Florey, Alexander Fleming and the fairy tale of penicillin. Med J Aust. 2002;176:178-180.

3. Palumbi SR.. Humans as the World's greatest evolutionary force. Science 2001;293, 1786.

4. Walsh, C. Antibiotics. Actions, origins, resistance. ASM Press, Washington, D.C. 2003.

5. Reynolds, PE, and. Brown DF. Penicillin-binding proteins of beta-lactam-resistant strains of Staphylococcus aureus. Effect of growth conditions. FEBS Lett. 1985;192:28–32.

6. Jevons MP. "Celbenin"-resistant staphylococci. Br. Med. J. 1961;124:124–125.

7. Höltje JV. Growth of the stress-bearing and shape-maintaining murein sacculus of Escherichia coli. Microbiol. Mol. Biol. Rev. 1998;62:181-203

8. Schiffer G, and Holtje JV. Cloning and characterization of PBP 1C, a third member of the multimodular class A penicillin-binding proteins of Escherichia coli. J Biol Chem. 1999;274: 32031–32039.

9. AHFS DRUG INFORMATION 2006 (2006 ed.), American Society of Health-System Pharmacists. 2006.

10. Scholar EM, Pratt WB, (Eds). The inhibitors of cell wall synthesis, II. The antimicrobial drugs. Oxford University Press. 2000 New York.

11. Utsui Y, and Yokota T. Role of an altered penicillin-binding protein in methicillin- and cephem-resistant Staphylococcus aureus. Antimicrob. Agents Chemother. 1985;28:397–403.

12. Hartman BJ, and Tomasz A. Low-affinity penicillin-binding protein associated with beta-lactam resistance in Staphylococcus aureus. J. Bacteriol. 1984;158:513–516.

13. Sekiguchi J, Fujino T, Saruta K, Kawano F, Takami J, Miyazaki H, et al. Prevalence of erythromycin-, tetracycline-, and aminoglycoside-resistance genes in methicillin-resistant Staphylococcus aureus in hospitals in Tokyo and Kumamoto. Jpn. J. Infect. Dis. 2004;57, 74-77

14. Udo EE, Al-Sweih N, Mokaddas E, Johny M, Dhar R, Gomaa HH, et al. Antibacterial resistance and their genetic location in MRSA isolated in Kuwait hospitals, 1994–2004. BMC Infect Dis 2006;

15. Lowy FD. Staphylococcus aureus infection. N Engl J Med 1998;339:520-532

16. Kloos WE, Bannerman TL. Staphylococcus and Micrococcus. In: Murray PR, Baron EJ, Pfaller MA, Tenover FC, Yolken RH, editors. Manual of clinical microbiology, 7th Ed. Washington, DC: American Society for Microbiology; 1999. p. 264–82

17. Miller LG, Perdreau-Remington F, Rieg G, Mehdi S, Perlroth J, Bayer AS et al. Necrotizing fasciitis caused by community-associated methicillin-resistant Staphylococcus aureus in Los Angeles. N Engl J Med 2005; 352:1445–53.

18. Gillet Y, Issartel B, Vanhems P, Fourment JC, Lenia G, Bes M, et al. Association between Staphylococcus aureus strains carrying gene for Panton-Valentine leukocidin and highly lethal necrotising pneumonia in young immunocompetent patients. Lancet 2002; 359:753–9.

19. Amyes SGB (2001) Magic bullets, lost horizons, in The Rise and Fall of Antibiotics, Taylor & Francis, London, UK

20. Levy, S. The challenge of antibiotic resistance. Scientific American 1998;278: 3, 32-39.

21. Noguchi N, Nakaminami H, Nishijima S, Kurokawa I, So H,

Sasatsu M. Antimicrobial agent of susceptibilities and antiseptic resistance gene distribution among methicillin-re- sistant Staphylococcus aureus isolates from patients with impetigo and staphylococcal scalded skin syndrome. J Clin Microbiol 2006;44: 2119-2125.

22. Kluytmans, J., A. van Belkum, and H. Verbrugh.. Nasal carriage of Staphylococcus aureus: epidemiology, underlying mechanisms, and associated risks. Clin. Microbiol. Rev. 1997;10:505–520.

23. Aly, R., Maibach H. I., Strauss W. G., and H. R. Shinefield. Effects of systemic antibiotic on nasal bacterial etiology in man. Appl. Microbiol. 1970;20:240–244.

24. Jinnah F, Chowdhury K, Begum J, Sohail M, Rahman MT, Ahmed S, et al. Multi-resistant Staphylococcus aureus isolated from the wound of diabetic patients. J Infect Dis Antimicrob Agents 1998;15:15–8.

25. Ayliffe GAJ. The progressive intercontinental spread of methicillin-resistant Staphylococcus aureus. Clin Infect Dis 1997;24 Suppl 1: S74-S79

26. Grubb WB. Genetics of MRSA. Rev Med Microbiol 1998; 9: 153-162.

27. Von Baum H, Schmidt C, Svoboda D, Bock-Hensley O, Wendt C. Risk factors for methicillin-resistant Staphylococcus aureus carriage in residents of German nursing homes. Infect Control Hosp Epidemiol. 2002;23:511–5

28. Chambers HF: The changing epidemiology of Staphylococcus aureus. Emerg Infect Dis 2001, 7:178-182.

29. Udo EE, Pearman JW, Grubb WB: Genetic analysis of community isolates of methicillin-resistant Staphylococcus aureus in Western Australia. J Hosp Infect 1993, 25:97-108.

30. Riley TV, Pearman JW, Rouse IL. Changing epidemiology of methicillin-resistant Staphylococcus aureus in Western Australia. Med J Aust. 1995 Oct 16;63(8):412-4

31. Yuen KY. CA-MRSA as an emerging Public Health Threat. Medical Bulletin –The Hong Kong Medical Diary 2007 Dec;12 (12):5-6

32. Ho PL, Tse CW, Mak GC, Chow KH, Ng TK. Community-acquired methicillin-resistant Staphylococcus aureus arrives in Hong Kong. J Antimicrob Chemother 2004; 54:845-846.

33. Haq JA, Rahman MM, Asna SMZH, Hossain MA, Ahmed I Haq T, et al. Methcillin-resistant Staphylococcus aureus in Bangladesh: a multicentre study. Int J Antimicrob Agents 2005;25:276-277.

34. Monecke S, Slickers P, Hotzel H, Richter-Huhn G, Pohle M, Weber S. et al. Microarray-based characterisation of a Panton-Valentine leukocidin-positive community-acquired strain of methicillin-resistant Staphylococcus aureus. Clin Microbiol Infect 2006; 12: 718-728.

35. Weigel LM, Clewell DB, Gill SR, Clark NC, McDougal LK, Flannagan SE, et al. Genetic analysis of a high-level vancomycin-resistant isolate of Staphylococcus aureus. Science. 2003;302:1569–71

36. Naimi TS, LeDell KH, Como-Sabetti K, Borchardt SM, Boxrud DJ, Etienne J,et al.. Comparison of community- and health care-associated methicillin-resistant Staphylococcus aureus infection. JAMA 2003;290:2976–2984.

37. Brumfitt W, and Hamilton-Miller J. Methicillin-resistant Staphylococcus aureus. N. Engl. J. Med. 1989;320:1188–1196.

38. Ito T, Okuma K, Ma XX, Yuzawa H, and Hiramatsu K.. Insights on antibiotic resistance of Staphylococcus aureus from its whole genome: genomic island SCC. Drug Resist. Update 2003;6:41–52.

39. Song JH, Hiramatsu K, Suh JY, et al. Emergence in Asian countries of Staphylococcus aureus with reduced susceptibility to vancomycin. Antimicrob Agents Chemother 2004;48:4926-8.

40. Walsh, C. Deconstructing vancomycin. Science 1999;284,442.

41. Mahmood A., Butt T., Usman M.. A study on MRSA isolates to detect reduced susceptibility to vancomycin: a preliminary report. Infect Dis J. Dec 2007;16

42. Centers for Disease Control and Prevention. (2002) Morb. Mortal. Wkly. Rep 51, 565–567,902

43. Chang S, Sievert DM., Hageman JC, Boulton ML, Tenover FC, Pouch-Downes F. Infection with vancomycin-resistant Staphylococcus aureus containing the vanA resistance gene. N. Engl. J. Med. 2003;348, 1342–1347

44. Gonzalez-Zorn B, and Courvalin P. vanA-mediated high level glycopeptide resistance in MRSA. Lancet Infect. Dis. 2003;3, 67–68

45. Carson KC, Bartlett JG, Tan T-J, Riley TV, et al., In vitro susceptibility of methicillin-resistant Staphylococcus aureus and methicillin-susceptible Staphylococcus aureus to a New Antimicrobial, Copper Silicate, Antimicrobial Agents and Chemotherapy. 2007; 4505-4507