Antimicrobial Resistance in Staphylococci Special Emphasis on Methicillin Resistance among Companion Livestock and Its Impact on Human Health in Rural India

Sweta Jangra, Sandhya Khunger and Debasish Chattopadhya

Abstract

Antimicrobial resistance (AMR) is a global threat worldwide. Inappropriate and irrational use of antibiotics are the responsible causes for the development of AMR in the pathogenic microorganisms. In the developing countries like India the data encountered a higher burden of resistance in the rural communities. In such scenario the AMR may lead to difficulty in treatment of various ailments among human as well as companion livestock. In India cows and buffalo are considered as companion livestock. However the definition of companion livestock is slightly different in the developed countries. Most of the rural population in India is dependent on the livestock for their livelihood as the dairy farming in the rural community may contribute in the financial status of the rural population. Staphylococcus aureus (S. aureus) is one of the foremost causative agent of skin and soft tissues infections among humans as well as in companion livestock. The situation is further complicated by methicillin resistance in S. aureus. The carriage of MRSA by humans and companion livestock may lead to further AMR spread to the community. In the civic health point of view, it is important to initiate appropriate interventions to tackle the problem at the rural population.

Keywords: Companion livestock, Antimicrobial resistance, Staphylococcus aureus, Methicillin resistant S. aureus, Rural India, LA-MRSA

1. Introduction

Antimicrobial resistance (AMR) is a global threat and is of a major public health concern globally [1]. AMR is defined as a state when microbes including bacteria, virus, fungi and parasites no longer respond to the drugs thereby increasing their risk of disease spread, causing severe illness and death (Figure 1) [2].

AMR can spread through ‘horizontally’ by different transformation method in which bacteria transfer a part of their genetic material with another bacteria, or the
spread may be ‘vertically’ where AMR genes are continuously transferred from one generation to the next and so on [3].

Although inappropriate and irrational use of antimicrobial agents in animals has been considered to be responsible for the emergence of drug-resistant pathogens [4].

Making the treatment of infectious disease with antimicrobial agents challenging contributing to the community with respect to infectious disease burden. World Health Organization (WHO) declared AMR as one of the top 10 public threats as a result this may lead to high disease load in India which is considered as maximum in the world [2]. The current situation is reflected by high rate of AMR against several infectious diseases including urinary tract infections (UTIs), soft tissue infections, diarrhea and sepsis. In addition the rapid spread of penicillin-resistant bacteria (Methicillin resistant Staphylococcus aureus (MRSA) superbugs are also alarming.

Many sustainable development goals framework in the rural India have included “AMR indicator” that monitors the frequency of bloodstream infections caused due to antimicrobial resistant organisms including S. aureus (S. aureus). S. aureus is a part of human skin flora and a common infection causing agent implicated in acute food poisoning episodes, scalded skin syndrome, impetigo, cellulitis, folliculitis toxic shock syndrome, and furuncles [5]. Reports in the literature suggest that patients with MRSA infections are 64% more likely to die due to unresponsiveness of beta-lactam antibiotics and vancomycin which are the drug of choice for treating various ailments produced by Staphylococcus [6].

Notably S. aureus infections have raised concerns these days due to increasing antimicrobial resistance (MRSA). In rural India the antibiotic usage in humans and in the livestock is high with no regulation on the usage of antibiotics which may be a leading cause of antimicrobial resistance [7]. Indian Network for surveillance of Antimicrobial Resistance (INSAR) along with WHO monitors AMR and its magnitude in India. Their major goal is to focus on AMR patterns of various antimicrobial resistant microorganisms including S. aureus.
Rural community of India is dependent on companion livestock for their livelihood as livestock sector is major part in developing their socio-economic status. Livestock sector found to be responsible for about 6% to the gross domestic product (GDP) and 25% to the agricultural GDP of India [7, 8].

The dairy farming is a common practice which have a positive impact on the rural system [9]. Thus, the rural population is much exposed to acquisition of AMR from livestock. Most reports on AMR in human associated with companion livestock have been confined to enteric organisms. However, staphylococcal infections in livestock is palpably common in India which include staphylococcal infections viz. Bovine mastitis, wound infections and udder impetigo ultimately affecting the public health and economy [10].

The present report attempts to review the problem of AMR in Staphylococci in livestock animals and their possible transmission to human.

2. Antimicrobial resistance

AMR occurs when pathogens change genetically over time so as to become resistant to antimicrobials. As a result, the antimicrobials become ineffective against microorganisms and the infections remain persistent in the body. Antimicrobials including antibiotics, antivirals, antifungals and antiparasitic are the form of drugs that used to prevent and treat respective infections in humans and animals. Microorganisms that develop AMR are sometimes referred to as “superbugs” [2].

AMR has developed as one of the foremost community well-being issue of the 21st century that threaten the health care system due to ineffective prevention and treatment measures against wide range of infections. The problem of AMR in bacteria is of great concern. Over several decades, bacteria are involved in common or severe infections along with resistance towards variety of antimicrobials used against variety of ailments caused by bacteria. It is quite difficult to underestimate the impact of AMR in terms of death rate and community health. Thus, a much-needed action plan is required to estimate such developing global issue in health care settings as well as in the community.

In natural environment, antibiotic resistance occurs in antibiotic-exposed microorganisms over time. Susceptible bacteria are killed or inhibited under the bactericidal effect of antibiotics. However, microorganisms that have acquired antibiotic-resistant genes due to overuse, misuse and unsuitable (inadequate dosing inappropriate choices and weak acceptance of updated treatment guidelines) of antibiotics have a greater chance to survive and proliferate. This is how the antimicrobial resistance is facilitated. In a developing country like India, the excessive prescription by general practitioners due to similarity of clinical presentations in viral or bacterial etiology can be seen. In addition the diagnostic uncertainty, self-medication and easy availability of antimicrobial drugs without a proper prescription is also have significant root cause in the inappropriate use of antibiotics [11].

2.1 Methicillin resistance S. aureus in human

*S. aureus* has been reported as a significant pathogen of human subjects. Sir Alexander Ogston in 1880 firstly reported *S. aureus* as a major cause of wound suppuration. Skinner and Keefer provided the first evidence of *S. aureus* virulence in 1941 and reported 82% mortality rate due to *S. aureus* associated bacteremia. In 1960s, the introduction of β-lactam antibiotic revolutionized the clinical care system and decreased the mortality rate associated with *S. aureus* bacteremia markedly to 27% with its widespread usage [12, 13].
**S. aureus** is one of the most studied troublesome resident and notorious pathogen in the human skin. **S. aureus** is a member of genus Staphylococcus that consist of fifteen different strains with differential molecular data. The status of **S. aureus** as a commensal is highly controversial. Several reports suggest that at around 30% of the nasal cavity flora of humans carries **S. aureus** or coagulase positive **S. aureus** (CoPS) species [14, 15]. Asymptomatic healthy humans and animals could harbor multiple species and strains of staphylococci [16].

Methicillin was the first semisynthetic penicillinase-resistant penicillin introduced in 1961 for treatment of Staphylococcal infections. Soon after its introduction in clinical practice, reports of methicillin-resistant isolates encountered [17].

The dissemination of MRSA have a great impact on both rural society as well as on hospital settings [18]. with all evidences centers for diseases control (CDC) declared methicillin resistant as a consequential issue to public wellness [19]. Thus, knowledge regarding the mechanisms of methicillin resistance in **S.aureus** has great clinical and epidemiological importance.

Based on the antimicrobial susceptibility, MRSA exists in three forms i.e., community associated MRSA (CA MRSA); health care-associated MRSA (HA-MRSA) and livestock associated MRSA (LA-MRSA). The difference among all the three forms lies with their clinical features, molecular biology, antibiotic susceptibility pattern and treatment measures. CA-MRSA and HA-MRSA are the major form of infections. MRSA infections are endemic in India with an incidence rate of 25% in Western regions and 50% in South regions of India. However in India, CA-MRSA and LA-MRSA are more prevalent as compared to HA-MRSA. The major concern arises when the isolation rate of CA MRSA enhanced as these species lead to replace HA-MRSA among hospitality settings which in turn build infection preventive and control measures slighter effective and significant for reducing the isolation rates of MRSA in healthcare settings [20].

### 2.2 LA- MRSA

The problem of methicillin resistant **S. aureus** associated with livestock is long recognized as LA-MRSA. A-MRSA is entirely different from the other two forms (Hospital acquired, and community acquired). However LA-MRSA is not associated with health-related concerns in animals, but it also affects human health if they are in contact with them. In India most of the population is dependent on livestock for their livelihood. Transmission of the methicillin resistant strains from animals to humans or vice versa and may lead to any infection.

The MRSA carriers (animals/humans) are considered as colonized. Harbored animals may pretend as MRSA pools. Persons who lives and comes in direct interaction with MRSA colonized livestock are at high risk of being harbored/colonized by LA-MRSA. This could be a leading cause of transmission of LA-MRSA to further subjects subsequently transmitting the disease in the community at very high extent [21].

LA-MRSA is grouped under zoonoses which is described as the naturally spread infections among “animals and humans” as per the definition by WHO expert committee, 1951. Based on the prevalent direction of transmission between humans and other vertebrates, ‘zoonosis’ is also considered as ‘Anthropozoonosis’ which is suggestive for the transmission of humans to animals. Colonization with LA-MRSA may result into various ailments among human as well as in animals.

MRSA is commonly associated with bovine mastitis and the first evidence of mastitis was recorded in dairy cattle in 1972. Since then, MRSA colonization has been reported in the domestic animals namely cows, dogs, horses, sheep, cats and pigs [22, 23]. Mastitis with **S. aureus** features the genotypes of hugely deviating
mecA gene, termed as mecC in a type XI SCCmec or ST398 MRSA with SCCmec types IV and V. The appearance of LS MRSA (MRSAmecc and CC398) carrying SCCmec types (IV and V) and mecC were isolated firstly from pigs afterwards in cattle, pet animals, lineal calves, chickens, horses, fauna and human subjects in adjacent vicinity in those tame livestock’s [24]. The clone type ST-398 of LA-MRSA, is commonly detected in European and North American countries whereas ST-9 primarily in the Asian region. The SCCmec type IV and V have to be found as co-resistant towards tetracycline and lincosamide, which are moderated by tet and erm genes successively [25]. A special attention is needed to be given for the patients with SARS-CoV requiring ventilation support as this pandemic may result into markedly rise in MRSA infection [26].

Due to highest milk production yield in India in the world and involved in dairy production results in high prevalence of LA-MRSA. The zoonotic potential of many bacterial strains among humans and animals are increasingly being isolated in Europe with much of the industrialized world [27, 28]. Most of the cattle’s in India shared same residential premises with humans hence are more prone to transfer MRSA to the humans who are in close contact with them. The detection of MRSA special emphasis to cattle with sub/clinical mastitis is highly concerned from public health sentiments as the cattle looks all right even if they are colonized with reservoirs with MRSA [27, 28]. However the situation is something different in India as livestock’s are considered as a family members due to their same residential premises sharing.

In addition to the above Jully G Tiwari from Assam showed that all the family members of the dairy farm worker were suffering from an identical type of cutaneous disease as of the bovine infection. The antibiotic susceptibility pattern (AST) of all biotype A strains from animals’ origin were found alike to that of the biotype A strains isolated from the humans associated with the day care activities with the animals. In addition to the previous findings the rate of resistance towards commonly used antimicrobial agents in different ailments were also found markedly higher among the biotype C strains originated from human subjects than the biotype C strains from the animal origin. In addition many strains from animals and human origins revealed similar antimicrobial susceptibility testing patterns against various tested antimicrobial agents. [29]

The prevalence of Staphylococcus species was found in the mastitis cases of dairy animals as 45% (95% CI, 39–50%) based on the previous meta-analysis in India reported by Krishnamoorthy et al. [30].

2.3 Rural/urban areas and associated risk of MRSA in India

As per Census of India 2011, the definition and criteria for characterization of urban and rural area was as follows;

i. Minimum population of 5,000;

ii. A minimum of 75 percentile male population should be enrolled in non-agricultural tasks;

iii. Population weightage of at least 400 people per sq. km.

If an area justify all the above requirements, that will be classified as “Urban” however an area is considered as ‘Rural’ if it is not qualified the criteria of ‘Urban’ as per the above definition. In the rural communities of India, majority of human subjects are involved in agricultural pursuits and hence agriculture is their major
profession. Thus, this population is at high risk of developing/acquiring MRSA. The acquisition of drug resistant bacteria like MRSA due to contact with colonized animals is a common method for the spread of LA-MRSA. This may be a significant way for acquisition of LA-MRSA by the human population in India.

In developed countries i.e., US, the defining criteria of companion livestock’s is different according to that dogs and cats are majorly treated as companion animals whereas in developing countries including India, the livestock’s definition is slightly different as buffaloes and cattle’s are considered as companion animals in rural population on the basis of sharing of similar residential premises. Livestock’s have a significant potential to improvement towards food & nutritional status, agricultural enhancement, reduction in rural poverty and alleviating farm households in India [31–33].

Livestock’s fostering is found to be an important concept of the rural financial status, significantly at the family circle extent. However not much data is available on the impartation of animal fostering sector towards the family incomes. In India, livestock raising are mainly emerged as a part of mixed agricultural organizations as they contribute 25–30% of farming GDP outputs. It is estimated that just about 3/4th of the manpower required in livestock’s production is significantly donated by women [34]. However the significance of women in livestock building is hugely applauded but the issues related to their authority over the financial inputs from livestock’s activities and its probable effects on children's wellness, nutritional status and schooling have not gained further attraction among the empirical writings [35]. According to two assessment surveys that were conducted in 2003 and 2013, by the National Sample Survey Organization (NSSO) that was situational based they reported that livestock cover only farmer households [36].

3. Antibiotic resistance among companion livestock

MRSA was identified for very first time in 1972, from mastitis-affected cows and then MRSA from human origin was isolated from dairy cows [37]. MRSA has been found in almost all tame animals since its first observation. Major associative factor for MRSA found to be wound infections and post-operative skin infections, especially in dogs, cats, horses, and rabbits [38, 39]. In one of the study of milk-producing bovines in Mathura reported that MRSA in India was shown to be $S. \text{aureus}$ was found in 33.75% of subclinical mastitis and clinical mastitis cases among cattle than buffaloes [40]. Tiwari et al. (2015) published $S. \text{aureus}$ among different specimens from pigs, buffalo, dogs, goats, sheep, camels, and horses with different skin disorders of all companion livestock’s [41]. $S. \text{aureus}$ isolates from healthy cow milk samples were found to be resistant to erythromycin (75%), penicillin (100%), and amoxicillin (100%), but susceptible to cloxacillin (100%), neomycin (100%) oxacillin (100%), and ciprofloxacin (83.33%) [42]. MRSA study by Kumar et al. (2017) was shown to be penicillin and oxytetracycline resistant (88% each), cefoxitin resistant (75%), cotrimoxazole resistant (62%), and amoxyclav resistant (62%) in antimicrobial susceptibility screening conducted in study on 136 skin and nasal samples collected from cows and buffaloes. Vancomycin resistance was discovered in 3 (16.7%) MRSA isolates from buffalo isolates [43].

3.1 Transmission of antimicrobial resistance from livestock to humans

Livestock’s colonization with antimicrobial resistance organisms and human infections due to drug resistant organisms are appearing as a potential threat worldwide. MRSA is now regarded as an emerging zoonotic agent. Over the last
two decades, MRSA has been noticed in the population. Novel MRSA strain known as livestock-associated MRSA (LA-MRSA) has been discovered in farmers and fodder producing animals [44, 45]. In previously literature, MRSA sequence form was known as non-typable MRSA (NT-MRSA) lacking property of typed using pulsed field gel electrophoresis (PFGE) with SmaI. ST398 isolated as a prevalent sequence type in the agricultural animals, especially pigs and veal calves, as well as persons who worked with these animals [46]. Carriers of MRSA are at risk of developing an MRSA (wound) infection following skin damage (scarification) or surgery. The mode of MRSA transmission from animal to human is frequently inferred from parallel genetic observations including isolates obtained from in-vitro experiments [47, 48]. Another study revealed that incorporation of mecA gene encoding penicillin-binding protein 2a into the Staphylococcal cassette chromosome mec (SCCmec), are considered as factors in the drug resistance of S. aureus strains. There is evidence that methicillin-sensitive S. aureus strains inherited the SCC mec factor from coagulase-negative staphylococcal strains and subsequently became methicillin-resistant [49].

Reports on the carriage rate of pigs and the farmers associated with those pigs in Netherland divulge a high isolation of MRSA ST398 whereas the same sequence lineage has been observed in the dirt samples from the pig propagation space and eatable samples in Austria. In China, LA MRSA ailment is considered as an professional pitfall for farm workers, LAMRSA in the animal handlers may ranges from region to region i.e., 19.2% in Taiwan, 5.5% from Malaysia and 15% in China [50, 51]. Globally, MRSA percentage increased by 20% in all WHO sectors while 80% increase in few countries [52].

Factors - The emergence and spread of LA-MRSA is attributed to antimicrobial resistance upsurge. However hygiene along with under-described or poorly investigated factors i.e., farm dimensions, cultivation system, use of bioinoculants, and in-feed microelements also contributing the emergence of AMR [53]. Other than S. aureus some species of Coagulase negative staphylococci (CoNS) may also be transferred from animals to humans in contact with them, evidence found from a study (Jangra et al. 2018) that revealed some pathogenic strains of Coagulase negative staphylococci (Staphylococcus warneri and Staphylococcus scuiri) that are announced as a particular pathogen linked with animal origin however their isolation from the human subjects associated with them were also be detected. These results further strengthening the probability for the transmission of such pathogenic species from the domesticated animals [54].

4. Conclusion

We can conclude from the above literature that methicillin resistance MRSA freight among humans and animals seems a great concern towards effectiveness of antibiotic treatment. AMR may spread due to indiscriminate use of antibiotics without prescription, supervision and guidance of general practitioner in the developing countries including India. However in the rural India antimicrobials use in dairy animals for growth promotion and food producing animals for the cure of any ailments are probably major contribution towards the altogether issues of the resistance. Policies governing prescriptions of antibiotics should be strictly followed in animal farming to avoid AMR and associated infections. Clinicians and healthcare institutions should be encouraged to espouse appropriate guidelines about the use of antimicrobials regarding MRSA affected patient treatments in command to containment of community acquired staphylococcal infections. Farmers should be made aware about the dosage, length and
administration of the treatment and withdrawal period of antibiotics prescribed by the clinicians in order to cure any infection.

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**Conflict of interest**

“The authors declare no conflict of interest.

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