

## **AIRBORNE TRANSMISSION OF ANTIMICROBIAL-RESISTANT BACTERIA: A REVIEW**

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### **ABSTRACT**

Antimicrobial substances have multifaceted applications, primarily discovered and introduced for the treatments of infection diseases but now a day's it uses as a preservative, sanitizer, cosmetics, and growth promoters is rampant. The irrational and unwarranted application of antimicrobial substance affects the environments causing antibiotics pollution. Presence of antimicrobial substances in environment and pre-existing microorganisms containing pools of antimicrobial genes, synergistically guiding the development of newer resistance microorganisms become a major global health concern, as it can be transmitted from one environment to even via air. The aim of this work was to compile the studies on generation, dissemination, and prevalence of the bio aerosols containing antimicrobial resistance traits from artificial or natural environment including their probable effect on their surrounding communities, the measures so far been taken by various authorities, and the recommendation made by the scholars, which were carried out in recent past. Literature search was conducted mainly by using the Google scholar, Google search engine, MEDLINE and PubMed databases, including articles published until February 2016.

**Keywords:** Airborne, Antimicrobial Resistance, Antibiotics, Environment, Soil, Water, Resistance Genes

### **INTRODUCTION**

For the management of pathogens, antimicrobial substances are the only option available to the clinicians, but the emergence of resistance towards most potent antibiotics jeopardizes the current management protocols in practices (ECDC, 2015). Resistance toward antibiotics in microorganism is not a new phenomenon; it existed in the microbial world, much before even the discoveries of the antimicrobial substances. Previously thought that resistance traits in microorganism were developed due to the selection pressure or drug pressure exerted by the misuse and mismanagement of antibiotics, also known as antibiotics pollution, however, the recent findings are suggestive of antimicrobial resistance (AMR) is a natural phenomenon as evident by the releases of antimicrobial bioactive molecules in response to quorum or other organism, exhibiting hormesis, are also responsible for the augmentation, selection, and transmission of antibiotic resistance genes in environment naturally (Baltz, 2005; Marti *et al.*, 2013; D'Costa *et al.*, 2011; Hall and Barlow, 2004, Davies *et al.*, 2006; Calabrese & Baldwin, 2002; Ryan and Dow, 2008; Linares *et al.*, 2006; Allen *et al.*, 2010; Sauer, 2003; Martinez, 2009; Igbiosa and Oviasogie, 2014; Whitman *et al.*, 1998). Thus, the study of AMR required multifaceted and multidimensional approaches, as it includes all the factors (biotic and abiotic) guiding the AMR acquisition and its sources (Cantas *et al.*, 2013; Chee-Sanford *et al.*, 2009; Davies and Davies, 2010; Huijbers *et al.*, 2015).

Segawa *et al.*, (2013) while studying the regional geographical distribution of resistance genes believed that the most plausible modes of transmission of resistance genes are through airborne bacteria and migrating birds from distant regions where these genes exist either in form of resistome or subsistome. Antibiotic wastes and antibiotics excreted through urine or faeces may remain in environment for a longer duration, before degradation (Pei *et al.*, 2006; Dolliver and Gupta, 2008). These remained antibiotics put forth a selection pressure on environmental pathogenic or saprophytic bacteria, accountable for the emergence of more resistant strains either by mutation or acquiring the genes or both (Boxall *et al.*, 2004; Chander *et al.*, 2005).

World health organization in its policy paper "Worldwide country situation analysis: response to antimicrobial resistance" accepted that the antimicrobial resistance is a natural phenomenon, there is an urgent need of comprehensive national plans, based on a multi sectoral approach and with sustainable

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financing to fight antimicrobial resistance globally (WHO, 2011; 2015). However, this surveillance based on the recognition of antibiotic patterns of microorganisms and identifies trends and outbreaks in clinical setup; it did not include the study on resistome or subsistome of the regions in questions. Therefore, to fight the menace of AMR, all the sources like, clinical, agriculture, waste, engineering, or natural environments and the means of transmission like anthropogenic, soil, water, and air must be included in the policies.

The sources of airborne microorganisms are diverse includes both artificial and natural environments. The transmission of airborne microorganisms through air is familiar to all. Aero-microbial flora of any environment is highly specific, based on sources, aerosolization, anthropogenic, climatic, and spatial-temporal factors (Clauß, 2015). These aeromicroflora containing diverse microorganism having AMR traits descended to the diverse environments that also includes those inhabited by human, is one of the biggest threat to communities. This review examines those studies, so far been conducted to assess the generation and transmission of microbes carrying AMR traits aerosolized from diverse environments and their threats impact on surroundings. The main objectives of the present review has been to analyses the generation and dissemination of microorganism containing antibiotic resistance genes and to consider whether, these bio-aerosols containing resistant microorganism poses some real threat to their surroundings are not.

## MATERIALS AND METHODS

The literature reviewed in MEDLINE and PubMed databases, Google scholar, Google search engine and others, including articles published until February 2016. The keywords used for the search included: Aerobiology and/or bioaerosols and/or airborne microorganism and/or airborne bacteria with resistance, aero-bio-pollutants, air sampling, antibiotic, or antimicrobial resistance, aerobiological pathways, and cultivation. The meta-analysis was conducted to collect the recent researches performed in the area of emergences of AMR microorganism and AMR containing bio-aerosols in particular, which yielded plethora of references, out of which 100 references were included for analysis, without publication bias. In addition, the citations in each study found during the main search were reviewed for potential relevance. Finally, standard textbooks on aerobiology, medical and veterinary microbiology, and aerosol science were examined for information.

### Transmission of Resistant Bacteria

Antimicrobial resistance traits among microorganisms are a global problem, first recognised the Paul Ehrlich, and followed by many scholars (Ehrlich, 1909; Neuschlosz, 1919; Ross, 1939; Abraham & Chain, 1940, Rammelkamp & Maxon, 1942; Kirby, 1944). The practices of misuse and mishandling of antibiotics in various residential and occupational environments are widespread (Heuer *et al.*, 2009; Marshall *et al.*, 1990; Roe and Pillai, 2003; Sharma *et al.*, 2008, Stockwell and Duffy, 2012; Thiele-Bruhn, 2003), leads to the transmission of microorganism carrying AMR traits to newer places through the both biotic and abiotic modes like food chain, water, direct contact and others, poses a serious threat to public health (Arya and Agarwal, 2011; Marshall and Levy, 2011; Segura *et al.*, 2009; Shah *et al.*, 2012, Walsh *et al.*, 2011). In this review the menace of AMR and its transmission through aerial routes were extensively discuss based on available literatures till date.

### Clinical Environment

Airborne transmissions of pathogens are indicated in more than 2 millions community associated and nosocomial infections. Fernstrom and Goldblatt (2013) after reviewing the scholarly article concluded that, of all the hospital acquired infections the air routes accounted for 10-35%. The average monthly concentrations of airborne bacteria ranged from  $3.0-8.7 \times 10^3$  cfu/m<sup>3</sup> in dental practices and 257.1–6,223 cfu/m<sup>3</sup> in hospital and those contributed from its occupants in a word could be as high as 336 cfu/m<sup>3</sup> (Augustowska and Dutkiewicz, 2006; Bennett *et al.*, 2000; Frączek and Górny, 2011; Igbiosa and Oviasogie, 2014).

According to Lynch (2001), the *Enterobacter* are the most common causes of hospital-acquired pneumonia. Humphreys *et al.*, (1994) reported higher rate of emission of *Burkholderia* (*Pseudomonas*)

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*cepacia* in air by the cystic fibrosis patients in an enclosed hospital ward area. Huang *et al.*, (2013) reiterated that finding by adding that *P. aeruginosa* represented the most frequently detected and abundant bacterium in the air samples and was the only bacterium exhibiting a positive correlation of the mean counts between air and surface samples, which is intrinsically resistance towards many antibiotics (Chopra and Roberts, 2001; Huang *et al.*, 2006). The Extended-spectrum  $\beta$ -lactamases were reported in the species belonging to the genera of *Enterobacter* and *Klebsiella* isolated from the air of hospital associated environment (Pathak, 2011).

Fifteen month aerobiological surveys were undertaken by Greene *et al.*, (1962) in various ward and area of two general hospitals. They have reported the Gram-positive cocci as a predominant airborne microbial flora followed by Gram-positive rods, Gram-negative rods, molds, actinomycetes, yeasts, and the diphtheroids and coccobacillary types, representing both human and environmental origins, Mirzaii *et al.*, (2012), reported the contribution of airborne Gram-positive cocci in hospital environment is up to 84.2%. Messi *et al.*, (2015) also reported Gram-positive cocci as a dominant microbial flora of nosocomial environment; he further added that more than 95% of isolates were resistant toward multiple drugs (MDR). However, Gandara *et al.*, (2006) reported, low concentration (13.96%) MDR *S. aureus* from the houses of a residential area, as compare to nosocomial environment showing that presence of drug pressure is responsible for higher prevalence of MDR in nosocomial environment. Therefore, relatively higher concentration or the "cloud" phenomenon of *S. aureus* in air make it the most prevalent cause of hospital- and community-acquired bloodstream, skin and soft tissue, and lower respiratory infection (Beggs, 2003; Cooper *et al.*, 2004; Cotterill *et al.*, 1996; Diekema *et al.*, 2001; Li and Hou, 2003; Roberts *et al.*, 2006; Tambekar *et al.*, 2005; Wagenvoort *et al.*, 1993).

Matthias *et al.*, (2000) reported coagulase negative *Staphylococci* (30%) and *Pseudomonas aeruginosa* (24.4%) in a secondary care hospital and while measuring the indoor and outdoor air contamination of various sections in hospital, he also reported that various places of hospital act as a reservoirs of multi-resistant nosocomial pathogens, where labour room was recorded as most contaminated site, followed by the dressing room and the operation theatre. The increased rate of methicillin-resistant *Staphylococcus aureus* (Dürmaz *et al.*, 2005; Saadoun *et al.*, 2015) followed by vancomycin-resistant enterococci (VRE) or extended-spectrum  $\beta$ -lactamase-resistant microorganism transmission associated with a prior occupant's carriage is suggestive of some odd routes for the transmission of pathogen in intensive care unit (ICU) and other ward area of a nosocomial environment. Shiomori *et al.*, (2001, 2002) reported that the diseased pre-occupants bed making procedure generate airborne methicillin-resistant *Staphylococcus aureus* (MRSA) could be responsible for nosocomial infection; he further added that sources of MRSA in wards include both animate and inanimate objects (Dürmaz *et al.*, 2005). Wilson *et al.*, (2004) reported a correlation between the resistance patterns and diseased patients admitted in wards; whereas, Messi *et al.*, (2015) correlated it with the environmental source of MDR bacterial isolates. Kumar *et al.*, (2013) reviewed various studies conducted in India pertaining to the menace of antibiotic resistance, recommended for more effective action for the introduction and enforcement of appropriate regulations and allocation of appropriate resources for education and surveillance in India.

## Agriculture Environment

Hamscher *et al.*, (2003) analyses the soil sample taken from piggery, detected higher concentration of five different antibiotics, including tylosin, tetracyclines, sulfamethazine, and chloramphenicol; according to them the dust containing antibiotics, microorganisms, endotoxins, and allergens not only hazardous to the communities but also it exert a selection pressure on microorganism to be evolved into more resistant strains. Dahm *et al.*, (2014) from the meta-analysis reported the high prevalence up to 88.0% of methicillin- or multi resistant *Staphylococcus aureus* (MRSA), Extended spectrum beta-lactamases (ESBL), Vancomycin-resistant enterococci (VRE) and Methicillin-resistant coagulase-negative staphylococci (MR-CoNS) in human and animals in Europe, recommended more Interdisciplinary research between human and veterinary medicine.

In agriculture environments it was assumed that the transmission of antibiotics and resistant bacteria were anthropogenic (Gilchrist *et al.*, 2007), however other mode of transmission including airborne

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transmission is thoroughly studied by the scholars (Griffin, 2007; McEachran *et al.*, 2015). According to Seedorf *et al.*, (1998) resistant microorganisms released into the environment via the aerial route may contribute to the development of antibiotic resistance in wild-type strains of other microorganisms, in which, concentrated animal feeding operation may play as a reservoir for multiple drug resistance microorganism (Sapkota *et al.*, 2006). The bacterial concentrations with multiple antibiotic resistances reported from the sites even after antibiotics were discontinued, might be a threat to the workers and its nearby inhabitants (Gibbs *et al.*, 2006).

From an animal feeding operation, the aerobiological pathways of antibiotic resistance microorganism were evaluated by Gibbs *et al.*, (2006), recorded antibiotic-resistant *S. aureus* decreased with increasing distances from the facility, and the percentage of resistant group 'A' streptococci, faecal coliform and total coliform increased within the facility compared with upwind values for antibiotics tested, these bioaerosols containing antibiotic resistance genes could travel up to two km. from its sources of origins (Ling *et al.*, 2013).

According to Friese *et al.*, (2012), the airborne transmission of MRSA within pig herds indicative of potential contamination of the barns environment. Ling *et al.*, (2013) positively correlates the concentrations of aerosolized bacteria with the concentrations of airborne resistance genes, also noted higher frequency of resistance genes for some specific classes (Kumari and Choi, 2014). Resistant towards oxacillin and kanamycin were reported higher among the *Proteobacteria* followed by *Actinobacteria*, *Firmicutes*, *Bacteroidetes* in airborne bacterial communities of Hog Farm and Spray Field, by Arfken *et al.*, (2014), towards Chloramphenicol and Gentamicin among the members of the genus *Staphylococcus*, by Heo *et al.*, (2010) and rifampicin, erythromycin, and penicillin in *Escherichia coli* by Yao *et al.*, (2007), isolated from the air of various agro-environments.

## Other Environment

In order to investigate the occurrence of multidrug-resistant hospital strains in residence air, Lis *et al.*, (2009) reported the presence of methicillin resistance of airborne coagulase-negative staphylococci in homes of people having contact with a hospital environment. Furthermore, Gandara *et al.*, (2006), reported higher concentrations of airborne multidrug-resistant *Staphylococcus aureus* from inside of residential homes compared to the extramural environment, these findings were reiterated by Messi *et al.*, (2015), while analyzing four types of environments in Modena (Italy) that includes indoor environments (both residential and public), dental clinics, operating rooms of hospitals and area associated with solid waste management.

Odeyemi (2012) reported high level of resistance among the airborne isolates of the members of the family Enterobacteriaceae during an aerobiological survey conducted at municipal refuse dump in Ado-Ekiti, Nigeria.

More than a million times as many soil microorganisms on our planet than stars in the universe (Nesme *et al.*, 2016); in which, the members of the family Streptomycetaceae are predominant. The *Streptomyces* is the type genus of family Streptomycetaceae are the major source of antibiotics, contributing more than 50 antibiotics available till dates and based on discovery trends, may contain more than one lakh (294,300) antimicrobial compounds (Watve *et al.*, 2001), that may actively released in its vicinity. D'Costa *et al.*, (2006) while studying streptomyces from soil concluded that the antibiotic resistome are much more extensive in soil than as previously thought that were due to the presence of pre-existing genes that confers resistance towards these antibiotics, and hence, this is an ecological problem rather than regulatory (Singer *et al.*, 2006).

Allen *et al.*, (2010) has concluded from the meta-analysis that many factors like translocation of wildlife into suburban areas owing to game release, habitat destruction, pollution, and changes to water storage, irrigation, or the climate, ecotourism, hunting and camping, exotic foods, wet markets, bush meat and game farms, exotic pets and the long-distance transport of live animals, zoos, aquaria, wildlife safari parks and circuses, and trapping or rearing of Fur-bearing animals, were responsible for dissemination of preexisting resistance microorganism and inappropriate uses of antibiotics, other anthropogenic activities and natural physical and biological factors were acted it's as selectors.



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### Conclusion

The higher number of resistance airborne bacteria reported by many workers in various environments previously, thus, it is essential to rectify present approaches to fight the menace of evolution, transportation, and incidence of AMR microorganism.

Since, the rate of development of new antimicrobial agents is much lower than the incidence of resistance developments towards existing drugs; moreover the emergence of pandrug-resistant alarmed the world to resolve this problem with iron hands (WHO, 2015).

WHO (2014) surveyed for the magnitude of AMR and the current state of surveillance has reported the significant gaps in surveillance, lack of standards for methodology, data sharing and coordination among all its stakeholders.

Antimicrobial Resistance Technical Working Group of WHO has introduces a six points policy package to combat the menace of AMR, these includes: conception and implementation of antimicrobial resistance policies, strengthening surveillance and laboratory capacity, ensured availability of essential medicines timely pro- and metaphylaxis measures with its rational uses, and finally, to foster innovations, research and development for new tools by all its stakeholders (Leung *et al.*, 2011).

Keeping in the mind the ubiquity of AMR microorganism, Singer *et al.*, (2006) and Cantas *et al.*, (2013) recommends for the uses of more advance study design, tools and techniques to accurately measuring the diversity of selection pressures, and routes of transmission that are influencing the evolution, dissemination and persistence of antimicrobial resistance traits/genes in microorganisms. Probably these kinds of integrative approaches for the containment of AMR acquisition and spread may reduce the rapid emergence of resistance organism specifically for those against newer drugs.

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