Status of Chemical Antibiotics Against Bacterial Zoonosis

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ABSTRACT

Bacterial zoonoses are a major threat to the world even if we try to control and eradicate them. This happens when we use a lot of antibiotics which can make the bacteria resistant. These diseases like bubonic plague, bovine tuberculosis, and glanders caused a large loss a long time ago. Chances to get these diseases through close contact with farm animals, treating pets like a family, and some jobs. These diseases still affect us. We diagnose these diseases through better testing techniques. In this study, we talk about relationship of bacterial diseases and resistant. We explain how diseases like anthrax, salmonellosis, bovine tuberculosis, lyme disease, brucellosis, and plague are treated with antibiotics. People with weak immune systems are at high risk. These diseases are treated by using chemical antibiotics like ciprofloxacin, levofloxacin, doxycycline and others but they are not working as well because of resistance. This section looks at global importance of antibiotics, how they work, how bacteria become resistant. Animals can carry resistant genes of bacteria and transfer to the people. This chapter explains bacterial zoonosis, how diseases spread and role of animals. We look at specific germs like Pasteurella, salmonella, brucella, campylobacter, Coxiella burnetti, laptospira, and Bordetella bronchiseptica, discussing about how they resist antibiotics and what we can done. We also discuss other ways to treat these diseases, like using phytochemicals, nanoparticals, chemothrepies and vaccines. We highlight the problems with these methods and say that still need more search and new ideas to treat these diseases and solution of antibiotic resistance.

Keywords: bacterial zoonoses, antibiotic resistance, chemical antibodies, phytochemicals, nanoparticals

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1. INTRODUCTION

Bacterial zoonoses are one of the major zoonotic diseases which could relapse meanwhile we are considering them to be eradicated or under control. The main concern behind this is the excessive or repeated control of antibiotics which leads to the culminating antimicrobial resistance and results in a lot of health problems (Paho 2001). About a century ago when there were no vaccines and a severe lack of hygiene, some bacterial zoonotic diseases caused millions of deaths and irreparable loss to farmers. Such mentionable diseases are bubonic plague, bovine tuberculosis, and glanders. Inflicted by heavy losses due to bacterial zoonotic diseases in the past, such countries are paying special heed to the issue and investing huge resources in the better screening of animal products to maintain good preventive health (Blancou et al. 2005). Surveillance programs and improved diagnostics have detected various bacterial zoonotic diseases. Very close contact with the food animals and the modern lifestyle in which the pets are treated as family members have escalated bacterial zoonotic diseases. (Glaser et al. 1994; Tauxe 1997). People such as veterinarians, abattoir workers, farmers, butchers, and lab workers are at a high risk of acquiring bacterial zoonotic diseases. Immunosuppressed people are also highly susceptible such as temporary immunosuppression in case of infancy and pregnancy while long-term immunosuppression includes chronic diseases (AIDS), diabetes, organ transplant, etc. A typical example is the bubonic plague that hit Surat, India in 1994 and it caused a huge loss of about 2 billion dollars (Marsh 2011).

Zoonotic pathogens are carriers of AMR (antimicrobial resistance). ARBs (Antibiotic-resistant bacteria) are the most common zoonotic pathogens. The emergence of ARB is directly proportional to the excessive use of antibiotics in farm animals. Such zoonotic pathogens after reaching the human gut, transfer the ARG (antibiotic-resistant gene) to the human gut's microbiome. Thus rendering the use of antibiotics useless (Hathroubi et al. 2018). Important bacterial zoonotic diseases are anthrax, salmonellosis, bovine tuberculosis, Lyme disease, brucellosis, and plague (Chomel 2009). Keeping in view the AMR, however, here we will shortly discuss the role of chemical antibiotics in treating bacterial zoonotic diseases. In the case of anthrax, the standard antibiotics used are ciprofloxacin, levofloxacin, or doxycycline. Treatment is effective if started at the initial stage of onset of the disease (Wilson 2020). For treating Salmonellosis, anti-diarrheal like Loperamide are used which reduce the pain due to cramping in diarrhea. Antibiotics are usually not prescribed in this case because they prolong the course of infection which may result in the spread to others (Hohmann 2021).

Mycobacterium Bovis which is the causative agent of bovine tuberculosis is usually resistant to Pyrazinamide but it is treated with a combination of antibiotics. First-line chemotherapies for the treatment of Bovine tuberculosis include rifampin, pyrazinamide, isoniazid, Streptomycin, and Ethambutol. While Capreomycin(CAP), Thioacetazone, and cycloserine are second-line drugs (Waters et al. 2015). For Lyme disease, antimicrobial therapy is useful if administered early after the detection of erythema multiform lesions (Asch et al. 1994). But it would be less effective after the disease has progressed, hence the treatment course should be extended (Shadick et al. 1994; Moody et al. 1994). The treatment course is 2-3 weeks in case of early diagnosis is Amoxicillin or doxycycline administered provided that the patient has no neurological abnormality (Wormser et al. 2006). The patient responds but it may be slow or incomplete (Wormser et al. 2000). The most widely studied treatment for brucellosis is the combination of doxycycline and aminoglycosides. To obtain a high therapeutic rate and less rate of relapse, this treatment duration should be eight weeks (Solís Garcia Del Pozo and Solera 2012; Hasanjani et al. 2006; Hashemi et al.2012; Solera et al. 1995; Bayindir et al. 2003; Roushan et al. 2010; Ersoy et al. 2005).

2. OVERVIEW OF BACTERIAL ZOONOSIS

The term "Zoonoses" is a combination of two Greek words, i.e. "Zoon" means "Animal" and "noses" means "illness". Bacterial diseases that are naturally transmitted from Vertebrate animals to humans with

or without vectors are called bacterial zoonotic diseases (Taylor et al. 2001). According to the older system, zoonoses are classified as Anthropozoonoses, Zooanthroponoses, Amphizoonoses, and Euzoonoses. Here, the discussion is on the bacterial diseases transferred from animals to humans known as Anthropozoonoses (Hubálek 2003). Gram-positive as well as Gram-negative bacteria can induce zoonoses 42% are bacterial pathogens among the zoonotic pathogens arising from bovine origin (Bae and Son 2011). Pathogens from animals can be transmitted to humans directly or indirectly. Direct zoonoses include diseases transmitted directly from animals to humans through any media, such as air. There is a vital role of domestic animals in the transmission of zoonotic diseases to humans. These pathogens are derived from wild animals; domestic animals then amplify these pathogens or serve as reservoir hosts (Morand et al. 2014). These animals include cattle, horses, sheep, goats, dogs, cats, and pigs (Samad 2011). More than half of humans' infectious diseases are induced from vertebrate animals (Taylor et al. 2001). The possible means of transmission are direct contact, biting, abraded skin or mucous membrane, inhalation, ingestion, and conjunctiva (Klous et al. 2016).

Animal bites and scratches induce the most commonly suffered bacterial zoonoses in humans (MMWR 1997-48). There are hundreds of pathogenic bacteria, including Pasteurella species, in the oral cavity of dogs and cats (Goldstein and Richwald 1987). A deep bite near bones and joints may result in osteomyelitis and septic arthritis. Cat scratch disease has been reported to people since a century ago. It is a clinical syndrome with the etiological agent *Bartonella henselae* transmitted through scratches and bites of cats (Stechenberg 2011). Once a person gets infected with cat scratch disease, the clinical signs appear in the form of pustules, papules, and abscessations. If not treated, it may develop into osteomyelitis, encephalopathy, and granulomatous conjunctivitis.

Infectious diarrhea in pets has also been reported to be transmitted in humans via the fecal-oral route. It is caused by salmonella species, campylobacter species, shigella species, and E.coli (Lahuerta et al. 2011). Enteropathogens induce gastrointestinal disturbances such as vomiting, diarrhea, headache, depression, and dehydration in severe cases may lead to death. Pet birds(songbirds such as parrots, finches, and sparrows) contain a smaller proportion of pets. They may have harmful impacts on human health by transmitting zoonotic diseases, which include psittacosis (chlamydophilosis), salmonellosis, and campylobacteriosis (Vanrompay et al. 2007; Wedderkopp et al. 2003; Carlson et al. 2011). *Chlamydia psittaci* is an intracellular pathogen in the respiratory tract of songbirds; it is the causative agent of Chlamydophilosis(Psittacosis) transmitted to humans by aero solar means dust, dander, and nasal secretion of birds (Circella et al. 2011; Dorrestein 2009). Flu-like illness develops which may be mild to severe. It may be misdiagnosed as influenza.

Anthrax is of significant importance in public health. Its causative agent is *Bacillus anthracis* which is a soil-borne bacteria and can produce spores. It may be transmitted by direct contact with infected animals such as cattle, goats, or their products for example meat, wool, dairy products, and bones (Goel 2015). Malignant pustules, pneumonitis, and gastroenteritis may develop in anthrax. If systemic lesions appear, death may occur. One of the most important zoonotic diseases is Bovine Tuberculosis. Its etiological agent is *Mycobacterium Bovis*. Mostly humans are infected while milking or handling unpasteurized milk products, also by inhaling the cough droplets of infected animals (Moda et al. 1996). Respiratory organs and bone marrow are severely affected.

One of the commonest bacterial zoonotic diseases is Brucellosis which is acquired by the consumption of unpasteurized milk or milk products (Corbel et al. 2006). The zoonotic species of Brucella are *Brucella melitensis*, *Brucella ovis* and *Brucella abortus*. It causes influenza-like clinical signs in humans which include pneumonia also it results in meningitis, endocarditis, headache, septicemia, fever, myalgia, and sleep hyperhidrosis (Bae and Son 2011; Rahman et al. 2006). Zoonotic diseases (bacterial zoonotic diseases discussed here) not only affect animals' health and performance but are also very harmful to

humans. Mostly they are originated from wild animals and then undergo a sylvatic or urban cycle. As far as their treatment is concerned, AMR is the burning issue.

3. IMPORTANCE OF ANTIBIOTICS

All over the world, zoonoses are a major problem. Through one health approach control the antibacterial resistance rises by zoonotic pathogens. The discovery of antibiotics during the early 1900s brought about a profound transformation in human health, saving countless lives. Antibiotics are intricate compounds that impede the growth of microorganisms through various mechanisms. These mechanisms include altering cell membranes, inhibiting cell wall synthesis, exerting antimetabolite activity, blocking nucleic acid synthesis, suppressing protein synthesis, and engaging in competitive antagonism. In addition to their crucial role in human medicine, antibiotics are also utilized in animal husbandry and livestock to safeguard against infectious diseases, thereby increasing the production of dairy products and meat. They are further employed on a large scale to promote animal growth and weight. While antibiotics offer significant benefits, their uncontrolled usage and dissemination into the environment raise serious concerns (Parmar et al. 2018).

4. MECHANISM OF ACTION OF ANTIBIOTICS

There are five mechanisms of action of antibiotics: 1) inhibit the bacterial protein synthesis; 2) inhibit the bacterial nucleic acid synthesis; 3) stop the cell wall synthesis; 4) interfere with the cell membrane function and 5) inhibition of metabolic pathway of bacteria as mentioned in Table 1 (Kapoor et al. 2017).

Table 1: Mechanism of action of different antibiotics

Mechanism of action	Drugs	Target	References
Inhibition of protein synthesis	Aminoglycosides and tetracyclines Macrolides and chloramphenicol	30S subunit of the ribosome 50S subunit of the ribosome	Krause et al. 2016
Inhibiting cell wall synthesis	Beta-lactams and glycopeptides	Block the last stage of peptidoglycan synthesis and attach to the D-Ala-D-Ala terminal, respectively	Page 2012, Wang et al. 2018
Inhibition of nucleic acid synthesis	Fluoroquinolones and rifamycin	Inhibit DNA gyrase and topoisomerase IV and DNA-dependent RNA polymerase respectively	Bhattacharjee 2016; Saito et al. 2017, Nainu et al. 2021
Inhibition of metabolic pathways	Sulfonamides and trimethoprim	Inhibits the enzymatic conversion of pteridine and PABA to dihydropteroic acid and dihydrofolate reductase respectively	Fernández-Villa et al. 2019 Akter et al. 2020 , Wróbel et al. 2020
Inhibition of cell membrane function	Polymyxins	Destroy the cell membrane by interfering with the lipopolysaccharide portion	Poirel et al. 2017; Reygaert 2018

4.1. EMERGENCE AND SPREAD OF ANTIBIOTICS RESISTANCE BACTERIA

Bacteria adapt themselves over time for replication, and survival, and spread as quickly as possible. In this way, microbes kept their existence in the environment by adjusting themselves according to surrounding conditions (MacGowan and Macnaughtan 2017). If antibiotics stop the growth of bacteria, they modify their genetic material and guarantee their survival by making them immune to drugs (Munita and Arias

2016). Bacteria have a natural process to make themselves drug-resistant but many other factors contribute to the development of resistance. For example, overuse of antibiotics, use of antibiotics without any prescription from a qualified doctor, poor medication environment, self-medication, poor hygienic conditions, and not completing medication course, etc (Chokshi 2019; Mahmoud et al. 2018; Sreeja et al. 2017). Alteration within the bacteria is the main reason for the development of bacterial resistance (Ventola 2015). During replication, one or few amino acids of the target site are replaced which introduces new base pairs in the bacterial and makes them a new resistant strain. Mostly antibiotic-resistant genes are present in the plasmid. This plasmid shares these resistance genes with other non-resistant bacteria and these genes become a part of non-resistant bacterial DNA and make them antibiotic-resistant bacteria (Von Wintersdorff et al. 2016). when we treated the bacteria with antibiotics, if they survive, they replicate and develop new resistant strains and occupy the population as a dominant form as quickly as possible (Zhao et al. 2018). In the Asia region, most people use antibiotics without any proper prescription from a professional doctor. These drugs may mask the signs of disease and develop resistance in the bacteria (Nepal and Bhatta 2018).

The entry of drug-resistant pathogens in the gut alters the gut microbiome and the community structure by shifting resistant genes to other pathogens in the gut. The opportunistic pathogens which have resistant genes move from animal to human and vice versa by different methods but the most common methods are direct interaction and vector transmission (Parmar et al. 2018). The World Economic Forum identified in its 2013 Global Risks reports that antibacterial resistance to many antibiotics is one of the major public health issues. Antibiotics used in humans and animals are released in unmetabolized forms due to incomplete metabolism. These unmetabolized antibiotics contaminate drinking water and sewage and are excreted in animal feces. The high level of these residues in the environment creates antibiotic-resistant genes by changing the genetic makeup of the bacteria. As a result, produces many antibiotic-resistant bacteria (Parmar et al. 2017).

5. MECHANISM OF DEVELOPMENT OF BACTERIAL RESISTANCE

There are five mechanisms of the development of bacterial resistance: 1) little amount of antibiotics enter into the bacterium due to a change in the permeability of the bacterial cell wall; 2) change in the target site of antibiotics; 3) inactivation of antimicrobial enzymes; 4) change the pathways of those enzymes which are targeted by antimicrobials and 5) remove the antimicrobials out of bacterium (Fig. 1) (Davies 1997; Levy 1994; Salyers et al. 1997). These five mechanisms have been shown in Figure 1. The antimicrobials used in the veterinary field are inactivated by one of these mechanisms. For instance, beta-lactam resistance is developed due to the presence of beta-lactamase, which cleaves the ring of beta-lactam antibiotics (Bush et al. 1995). The resistance of fluoroquinolones antibiotics are developed due to bacterial mutation in the A subunits of the DNA Gyrase enzyme and this mutation cause active efflux and decreased its accumulation (Everett et al. 1996, Piddock 1995; Gonzalez et al. 1989).

There are mainly two forms of antibiotic resistance natural and acquired antibiotic resistance (Reygaert 2018). In acquired resistance, bacteria change their genetic material by conjugation, translation, transposition, and mutation in their chromosomal DNA (Lerminiaux and Cameron 2019: Culyba 2015). There are two ways to inactivate antibiotics:1) chemical alteration of the drugs and 2) destroying the drugs (Blair 2015). Bacteria produce enzymes that are attached to the chemical groups of different drugs that prevent the attachment of drugs to their target spot in the cell wall. Chemical group transfer is one of the most effective methods of drug inactivation for example adenyl, acetyl, and phosphoryl chemical groups (Lin et al. 2015). One of the best examples of drugs is aminoglycosides. Through phosphorylation and adenylation, aminoglycosides are t argeted by altering the hydroxyl and amino

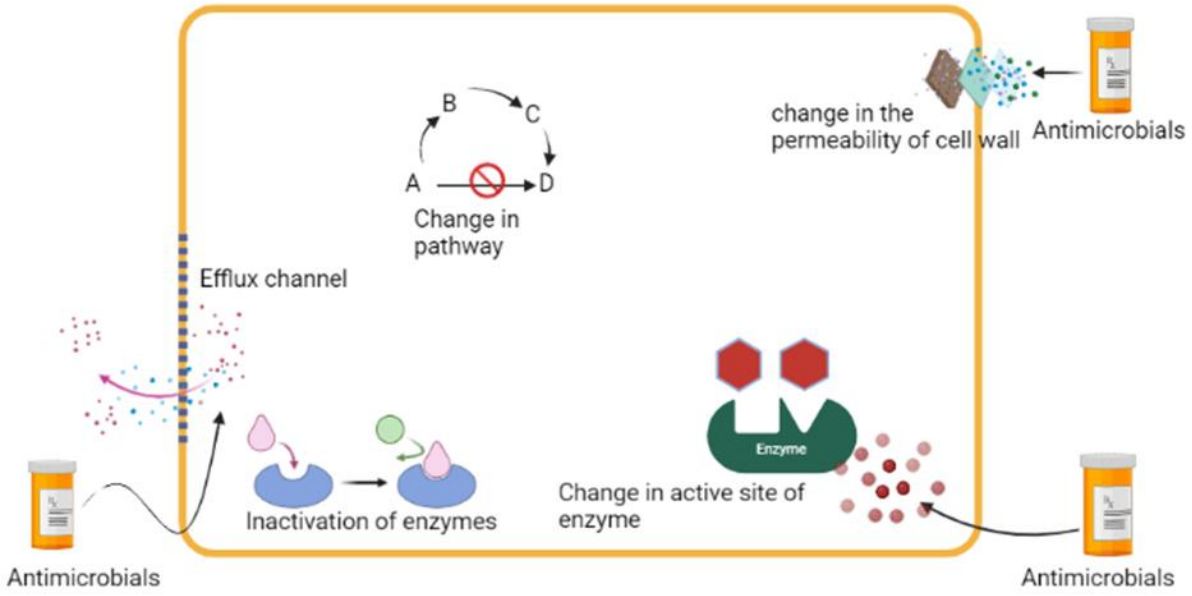

Fig. 1: Mechanisams of antimicrobial resistance

group of it with an aminoglycoside modifying enzyme (AME) and making it inactive (Munita and Arias 2016). The common mechanism of bacterial resistance is the modification of the antibiotics target. The mechanism of resistance towards the beta-lactam drugs is altering the arrangement of the target and changes the amount of penicillin-binding proteins (PBPs). Change in the number of PBPs affects the amount of drugs to attached the target (Bush and Bradford 2016). The other example of target modification against lincosamides, macrolides, and streptomycin is through the erythromycin ribosome methylase (erm) gene family which changes the drug-binding site and methylates the 16S RNA ribosome (Peterson and Kaur 2018).

6. CURRENT STATUS OF CHEMICAL ANTIBIOTICS AGAINST BACTERIAL ZOONOSIS

For treatment purposes, different antibiotics are widely used against different zoonotic bacterial pathogens.

6.1. *PASTEURELLA*

Pasteurella species are gram-negative, anaerobic coccobacillus, which is part of the natural flora in the upper respiratory tract of dogs and cats (Freshwater A 2008; Dolieslagar et al. 2011). *Pasteurella* infection can be transferred to humans through direct or indirect contact such as bites, scratches, or licks (Oehler et al. 2009). A study in Germany shows that *Pasteurella* shows resistance to some antibiotics like tetracycline (11.5% -19.2%), and trimethoprim-sulfamethoxazole (4% -10%) (Kaspar et al. 2007). For the treatment of *Pasteurella*, the first line of antibiotics is Penicillin and potentiated beta-lactams (Roy et al. 2007; Perez Garcia et al. 2009). *Pasteurella* infection can be treated with second and third-generation cephalosporins, macrolides, fluoroquinolones, and cotrimoxazole (Lloret et al. 2013).

6.2. *SALMONELLA*

Salmonella species are anaerobic, gram-negative bacilli found in mammals' large intestines. Investigators recorded resistance patterns in antibiotics like ciprofloxacin (100%), chloramphenicol (91%), ceftriaxone

(91%), and tetracycline (86%) (Adzitey et al. 2020; Casaux et al. 2019). Salmonella spp. could be treated by macrolides, beta-lactams, and fluoroquinolones (Leonard et al. 2011).

6.3. *BRUCELLA*

Brucella is the most widespread bacterial disease which has a very high zoonotic potential. It can be transferred through direct and indirect contact. It is transmitted by the consumption of unpasteurized milk (Saleem et al. 2010; Lucero et al. 2010). The treatment protocol includes a combination therapy of doxycycline plus streptomycin or rifampin for 6 weeks (Pappas et al. 2005).

6.4. *CAMPYLOBACTER*

Campylobacter species are gram-negative bacteria that cause campylobacter enteritis. Campylobacter can be commonly found in the gastrointestinal tract and transmitted directly and indirectly (Janda et al. 2006; Hermans et al. 2012). *Campylobacter* species are resistant to antibiotics like erythromycin, ciprofloxacin, and tetracycline (Harrow et al. 2004). *Campylobacter* can be treated by fluoroquinolones, macrolides, or aminoglycosides successfully (Ternhag et al. 2007).

6.5. *COXIELLA BURNETII*

Coxiella burnetii is an intracellular obligate gram-negative bacteria that causes Q fever in humans. It is mainly transmitted to humans from animals through aerosol or by direct contact (MAURIN et al. 1999). *Coxiella burnetii* can be treated with fluoroquinolones and doxycycline successfully (Patel et al. 2011).

6.6. *LEPTOSPIRA*

Leptospira is aerobic zoonotic bacteria that cause leptospirosis in humans. It can be transferred to humans through environmental sources like soil, urine, and water from infected animals (Moore et al. 2006). *Leptospira* is resistant to antibiotics like gentamycin, kanamycin, Streptomycin, and spectinomycin (Poggi et al. 2010). Many antibiotics like cefotaxime, ceftriaxone, penicillin, amoxicillin, doxycycline, and ampicillin are used for the treatment of leptospirosis (Kobayashi 2001)

6.7. *BORDETELLA BRONCHISEPTICA*

Bordetella bronchiseptica is gram-negative bacteria commonly residing in the upper respiratory tract of cats and dogs and can be transferred to humans via aerosol transmission. It causes kennel cough in humans (Woolfrey and Moody 1991; Ner et al. 2003). *Bordetella bronchiseptica* is resistant to drugs like macrolides and cephalosporins and can be treated by fluoroquinolones and trimethoprim/sulfamethoxazole (Egberink et al. 2009).

So, the zoonotic diseases can be cured with the help of antibiotics. Many antibiotics are widely used in the treatment of bacterial zoonotic diseases such as Penicillin, tetracyclines, macrolides, fluoroquinolones, beta-lactam, cephalosporins, ampicillin, amoxicillin, ceftriaxone, doxycycline, etc (Ghasemzadeh and Namazi 2015).

7. ALTERNATIVE TREATMENT APPROACHES

Antibiotic resistance is increasing day by day and is leading to cause serious problems in the treatment of diseases. So, there is a search for other methods for the treatment of diseases. Some of these methods have been mentioned below:

8. PHYTOCHEMICALS

Bacteria get resistant to excessive use of antibiotics, so need alternative compounds to cope with bacteria. Plant Therapy is the oldest effective experimental treatment used instead of antibiotics (Shin B and Park W 2017). Synthetic medicines are costly and cause toxicity due which causes damage to the intestines while herbal antibacterial compounds are less toxic, least expensive, and environmentally friendly (Newman and Cragg 2012). Phenolic and terpenoids are commonly used phytochemicals (Russel and Duthie 2011). Palmarosa oil extracted from the *Cymbopogon martini* plant has a very good antimicrobial activity against S aureus and E. coli (Lodhia et al. 2009). Carvacrol and Thymol are widely used again pathogens like E. coli, Listeria monocytogenes, and vibrio cholerae (Magi et al. 2015; Hyldgaard et al. 2012). Eugenol and isoeugenol have a synergistic effect with some antibiotics like tetracycline, ampicillin, noro-ofloxacin, rifampicin, and vancomycin (Langeveld et al. 2014).

9. NANO-PARTICLES

Nanotechnology has come up with a bounteous solution for the issue of bacterial antibiotic resistance. Nanoparticles bind to the bacterial surface and rupture the cell wall of the bacteria and cause cell death (Wang et al. 2017). Nanoparticles whose size is <20 nm can penetrate the cell wall and destruct the organelles which leads to cell death (Arakha et al. 2015). Flavonoid caps are naturally present on biogenic nanoparticles which inhibit enzymatic activity and stop the synthesis of nucleic acid (Fayaz et al. 2010). Nanoparticles give damage the cell membrane by generating reactive oxygen species (Li and Webster 2018). The application of nanoparticles is used in the eradication of Methicillin-Resistant Staphylococcus aureus infection (Li et al. 2022; Mohamed et al. 2022). Various nanoparticles like gold, silver, zinc oxide, silica, and bismuth have killing effects on Methicillin-Resistant Staphylococcus aureus (Nunez et al. 2009; Hemeg 2017; Gwon et al. 2021; Kadiyala et al. 2018; Ahmad et al. 2022).

10. PHAGE THERAPY

The most commonly found zoonotic bacterial pathogens related to poultry are Salmonella spp., and E. coli (Wernicki et al. 2017). Resistivity has been shown to antibiotics by these pathogens has been stated in the report by European Food Safety Authority (EFSA) (EFSA 2018). As an alternative approach lytic bacteriophage technique is used to cope with diseases (Fernández et al. 2018). Bacteriophages were discovered by Twort and d'Herelle in UK and France in the 20th Century (Duckworth 1976). Phage therapy has been used to treat Salmonella infection in chickens (El-Gohary et al. 2014).

11. SANITARY PROPHYLAXIS

Sanitary prophylaxis is a method of slaughtering or destroying infected or contaminated animals. This method is proven very efficient in the eradication of bovine tuberculosis, *brucella bovis, and brucella melitensis* in many parts of the world (Blancou et al. 2005).

12. VACCINATION

Due to the increase in antibiotic resistance in the veterinary field, attention has been to edible vaccines for the treatment of many bacterial zoonotic diseases (Sack et al. 2015). Anthrax an emerging bacterial zoonotic disease is controlled by an injectable vaccine obtained from culture filtrate (Koya et al. 2005).

Yersinia pestis a bacterial zoonotic pathogen is controlled by live attenuated and killed vaccines with certain risks (Sinclair et al. 2008). *Tuberculosis* a zoonotic pathogen can be controlled by BCG vaccine, plant-based vaccine, and transgenic modified carrot (Permyakova et al. 2015). *Listeria* is an infectious zoonotic disease that is effectively controlled with the help of a plant-based vaccine (Ohya et al. 2005). There are various limitations to the vaccine, including several booster doses, and temperature maintenance and it's not easy to carry (Shahid and Daniell 2016).

13. CONCLUSION

Zoonotic diseases are transmitted from animals to humans and vice versa. But as a whole everyone is at the risk of disease development from others. Many bacteria have zoonotic significance. The treatment of these infections is possible by antibiotics, but with time most bacteria develop resistance against the antibiotics due to some reasons like lavish use of antibiotics in humans as well as animals and the presence of antibiotics in animals and animals by-products at the sub-therapeutic level that results in an increase in resistance in bacteria.

Nowadays non-antibiotic approaches are widely used on the human and veterinary side to treat bacterial zoonotic diseases. Excessive use of antibiotics without proper knowledge and consultancy causes antibiotic resistance. Due to antibiotic resistance, alternative treatments are used to treat bacterial zoonotic diseases which include phytochemicals, phage therapy, sanitary prophylaxis, and vaccines. But these treatment measures also have some limitations like vaccines also need booster doses, phytochemicals do not act on all bacteria, and phage therapy is limited to some bacteria only. So, we need much more study and research on digging new methods for the treatment of bacterial infections and there is a need for extensive studies on the present alternative methods to overcome the limitations of these methods

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