Antibiotic Use and Resistance in Food Animals

Current Policy and Recommendations

CDDEP CENTER FOR Disease Dynamics, Economics & Policy
WASHINGTON DC • NEW DELHI

Global Antibiotic Resistance Partnership

CENTER FOR DISEASE DYNAMICS, ECONOMICS & POLICY
1400 Eye Street, NW
Suite 500
Washington, DC 20005
USA

For more information, please contact:

Ramanan Laxminarayan, Director: ramanan@cddep.org
Hellen Gelband, Associate Director: gelband@cddep.org
Jordan Levinson, Senior Research Analyst: levinson@cddep.org
Molly Miller-Petrie, Senior Research Analyst, millerpetrie@cddep.org

Antibiotic Use and Resistance in Food Animals

Current Policy and Recommendations

ACKNOWLEDGEMENTS

Chand Wattal, *Sir Ganga Ram Hospital*

D. Agarwal, *Consultancy Development Centre*

Elizabeth Rogawski, *Public Health Foundation of India*

JPS Gill, *Guru Angad Dev Veterinary and Animal Sciences University*

Jyoti Misri, *Indian Council of Agricultural Research*

K. Vijayakumar, *Ministry of Agriculture*

Manish Kakkar, *Public Health Foundation of India*

Nadeem Fairoze, *Karnataka Veterinary, Animal and Fisheries Sciences University*

Papiya Ghosh, *Council of Scientific and Industrial Research*

Samir Brahmachari, *Council of Scientific and Industrial Research*

Sarala Balachandran, *Council of Scientific and Industrial Research*

Sarita Bhalla, *Ministry of Agricultural Research*

Shah Hossain, *National Centre for Disease Control*

Shipa Vijaivargia, *Consultancy Development Centre*

V.I. George, *Marine Products Exports Development Authority*

Table of contents

Executive Summary

Increasing antibiotic use is driving an increase in antibiotic resistance, in both humans and animals. Because resistant bacteria can be transmitted between humans and animals through contact, food products and the environment, the use of antibiotics in animals plays a role in human health. More antibiotics are used in agriculture than in humans, more often to promote growth or prevent disease than to treat sick animals. Many of the agents commonly given to animals are the same antibiotics relied upon to treat human infections, raising concerns about depleting the effectiveness of these agents at the expense of human health.

The limited information available indicates that antibiotic resistance is a major problem in India, and that the use of antibiotics in agriculture is widespread. Reducing the amount of antibiotics used in agriculture and phasing out the non-therapeutic use of antibiotics in animals is possible without jeopardizing animal health and will contribute to reducing the burden of antibiotic-resistant infections.

Antibiotic Use and Resistance

Rising incomes and a growing population are driving an increased demand for animal products in India, as is the case in other low- and middle-income countries. This transition is causing a shift into intensive farming, and in order to stay competitive producers often rely on antibiotics as a stopgap in place of improving hygiene and sanitation in large-scale operations. Livestock is responsible for over a fourth of India's total agricultural output, and 4 percent of the gross domestic product (GDP). India is one of the top consumers of agricultural antibiotics worldwide, accounting for 3 percent of global consumption. By 2030, this use is estimated to double.

Resistant bacteria and antibiotic residues have been detected in living bovines, chickens, and fish in India as well as in related food products. In many cases, the same strains of resistant bacteria are found in animal, human, and environmental sources within the same community. All relevant studies are discussed in chapter 2 and summarized in annex 3. Resistant strains of coagulase-negative staphylococci, *Escherichia coli* and *Staphylococcus aureus*, including strains carrying extended spectrum beta-lactamase (ESBL) and New Delhi metallo-beta-lactamase (NDM-1) genes, have been detected in cattle. In poultry, resistance has been detected in *E. coli, S. aureus,* enterococci*, Pasteurella multocida, Campylobacter jejuni* and *Salmonella,* including ESBL-producing strains. Resistant bacteria have also been detected in pigs, horses, donkeys and mules; and in aquatic animals, including fish and shellfish.

Current Regulation

Currently, few laws in India govern antibiotic use in food animals, and most pertain only to animal products for export. General Statutory Rule (GSR) 28(E) mandates a withdrawal period for use of antibiotics in food producing animals from the time of administration until the production of foodstuffs. GSR 588 (E) specifies that all drugs in the H1 category, including many antibiotics, require a prescription, and requires separate pharmacy documentation of those prescriptions that are subject to review. Statutory Order (SO) 722(E) restricts some antibiotic use in aquatic animals for export, and the Export Inspection Council monitors for antibiotic residues in eggs, honey, milk and poultry for export.

In the European Union (EU), the use of antibiotics for growth promotion has been banned since 2006, resulting in some decreases in antibiotic use and resistant bacteria. In the United States, voluntary recommendations from the Food and Drug Administration encourage drug companies to remove growth promotion as an approved use, and to require prescriptions. Opposition to such bans often arises from concern over the economic impact of removing antibiotics from agriculture, but

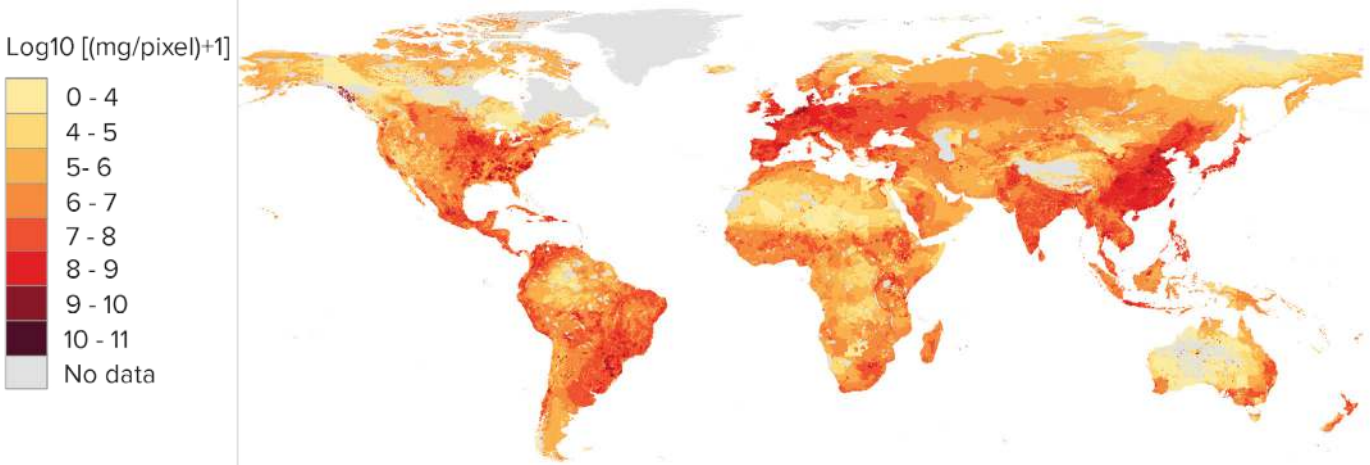

FIGURE 1: Global antibiotic consumption in livestock (milligrams per 10 km² pixels) 2010

Source: Van Boeckel et al. 2015

recent research indicates that the impact is not substantial when other optimization practices, such as improved hygiene, are put in place first.

Recommendations

This report suggests a series of options to reduce veterinary antibiotic use and the spread of antibiotic resistance in humans and animals:

1) Track rates of veterinary antibiotic use, resistance, and residues through a nationwide surveillance and monitoring system

Too little is known about antibiotic use and resistance patterns in India; the establishment of a nationwide surveillance system is required to inform policymaking.

2) Change incentives to discourage unnecessary antibiotic use in animals

Subsidies and alternatives to antibiotics are necessary to offer incentives for farmers to decrease antibiotic use without causing economic harm.

3) Educate farmers, veterinarians, and consumers on the dangers of antibiotic resistance

Veterinarians, farmers, and consumers should be educated on appropriate use of antibiotics and the benefits of antibiotic-free meat.

4) Phase out the sub-therapeutic use of antibiotics in animals

A gradual and monitored phaseout of the sub-therapeutic use of antibiotics, delivered in premixed feeds for disease prevention and growth promotion, is the most important intervention available to reduce antibiotic use in agriculture.

Surveillance, incentives, education, and appropriate laws and regulation, along with the enforcement of current laws, have the potential to reduce antibiotic use in India, lowering the resistance burden in humans and animals.

CHAPTER 1

Antibiotic Use and Resistance

A little more than seventy years ago, the first human infection was cured by penicillin. In the ensuing decades, antibiotics have tamed many once-deadly illnesses. However, their role has expanded far beyond the treatment of serious infections. Today antibiotics are used medically to prevent infections in surgical patients and in patients with weakened immune systems from disease or treatment for serious diseases, such as cancer. They also are used to promote growth in food animals, an application that does not promote health or cure disease. As a result, once easy-to-treat infections are becoming difficult or impossible to cure, with a stark global increase in both patient mortality and medical costs (CDDEP 2015).

Resistant bacteria are increasingly more prevalent, more virulent, and more diverse. Their rise is a direct result of antibiotic use, regardless of its form or necessity. These antibiotic-resistant bacteria can infect both humans and animals, sometimes traveling from one to the other, both within and across national borders. The chances of antibiotic-resistant bacteria prevailing in the race for survival are in direct proportion to the volume of antibiotics used (CDDEP 2015), a principle which makes it all the more critical to examine current habits and encourage rational and conservative use.

Antibiotic Resistance and its Spread

The development of bacterial resistance arises in two ways: (i) intrinsic resistance, which occurs when the bacterial species is able to innately resist the activity of an antibacterial agent (by preventing either the entry or binding of the antibacterial agent); and (ii) acquired resistance, which occurs when once-susceptible bacterial species mutate or obtain genes from other bacteria, to acquire resistance (Figure 1). The speed at which bacteria multiply, as well as their exposure to a continuously changing environment, results in the development of naturally occurring mutations that reduce their sensitivity to antibiotics. Bacteria are also able to adapt to their environment by acquiring genetic material through plasmids and transposable elements from other species of bacteria. This is known as horizontal gene transfer (Serrano 2005).

The use of antibiotics leads directly to the development and spread of resistance. Selection pressure on a bacterial population, such as that from antibiotics, can result in few surviving members who carry resistant genes (Figure 2). These bacteria then multiply, contributing to a growing population of bacteria with antibiotic-resistant genes. Bacteria resistant to one type of antibiotic may exhibit resistance to related antibiotics. If robust enough, these bacteria can spread through a human population (Laxminarayan et al. 2007). 'Antibiotic resistance cannot be prevented. Every time antibiotics are used, whether they save a life or are used to no effect (to treat viral rather than bacterial infections, for example), the effective lifespan of that antibiotic and perhaps related drugs is shortened' (Laxminarayan et al. 2007).

Patterns of antibiotic resistance—species, mechanisms, transmission pathways and concentrations—differ significantly within and between countries, though ultimately the issue is borderless. In general, resistant bacteria are increasing in both incidence and virulence, meaning multi-drug-resistant and extensively-drug-resistant strains are increasingly common in the environment.

In general, there are a few categories of pathogen that are responsible for a large portion of resistant infections in humans. The New Delhi metallo-ß-lactamase-1 (NDM-1) gene confers broad resistance to most antibiotics, including carbapenems, and can be transferred to a wide variety of bacterial species (Deshpande et al. 2010). Since its discovery, NDM-1 has been found around the world, including major cities in India (Ganguly 2012).

Other resistant Gram-negative bacteria carry extended-spectrum beta-lactamase enzymes, (ESBLs), which can confer high levels of resistance to some of the most commonly prescribed antibiotics. ESBL is increasingly found in *Escherichia coli* and *Klebsiella pneumoniae* isolates worldwide, especially in Asia—over 80 percent of *E. coli* isolates in India are ESBL producers (CDDEP 2015).

Carbapenem-resistant *Enterobacteriaceae* (CRE) are of top concern as well. Carbapenems are considered 'last-resort' antibiotics, often used to treat infections that are resistant to all other known agents. India has the highest incidence of carbapenem-resistant *K. pneumoniae* of nearly anywhere in the world (CDDEP 2015).

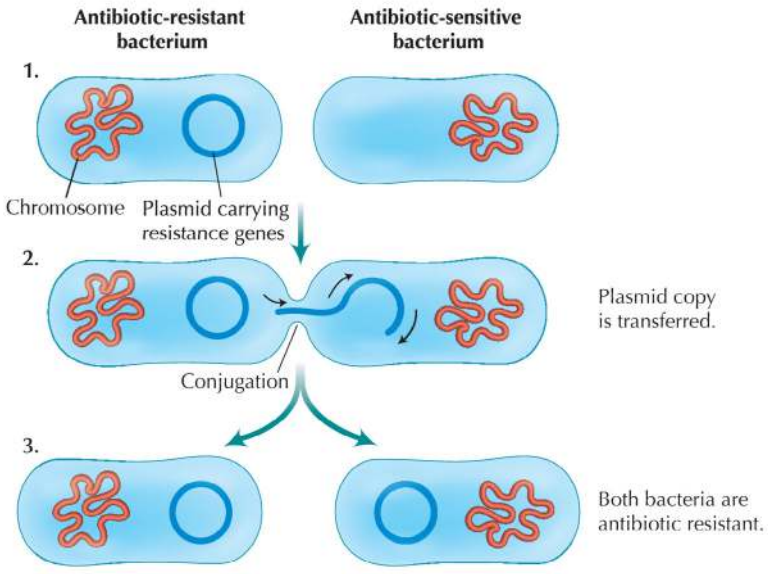

FIGURE 2: The Transfer of Antibiotic Resistant Plasmids between Bacteria (Barton et al. 2007)

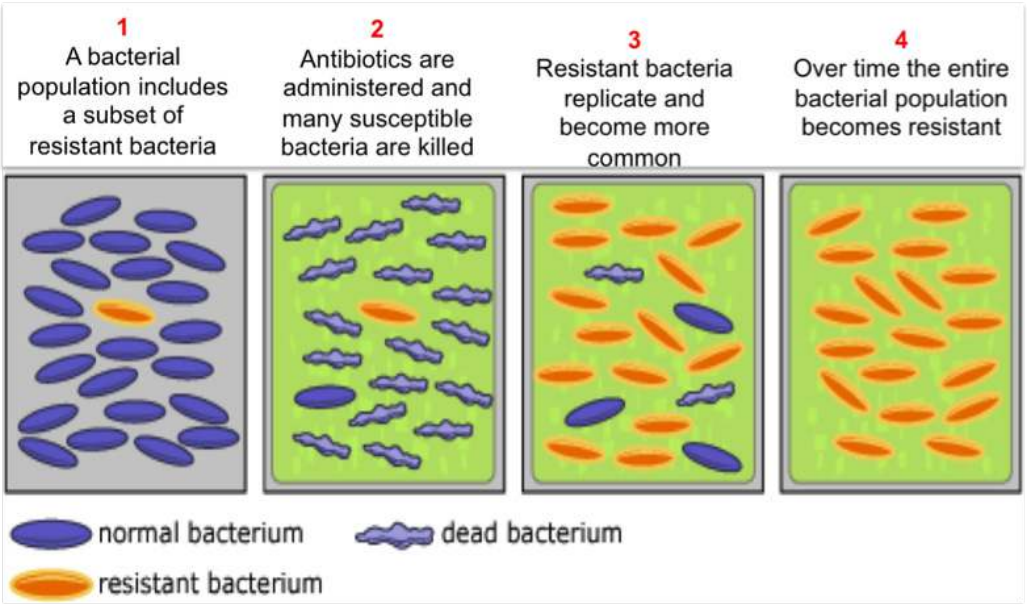

FIGURE 3: How Antibiotics Contribute to Resistance. (Figure adapted from an image courtesy of the University of California Museum of Paleontology Understanding Science website, www.evolution.berkeley.edu

Certain animal pathogens are of particular concern because they are easily transferred between species and can cause serious infections in humans. Methicillin-resistant *Staphylococcus aureus* (MRSA) is resistant to all ß-lactam antibiotics, including the penicillin and cephalosporin classes (Dancer 2001). Livestock are known to harbor MRSA, and these bacteria move easily to humans in close contact with infected or colonized animals. As animals infected by MRSA are often asymptomatic, the transfer of Livestock-Associated MRSA (LA-MRSA) to humans can go unnoticed (Köck et al. 2011).

E. coli infections are at once some of the most common zoonotic infections and, depending on the strain, some of the most complicated to treat. The plasmid-mediated colistin resistance mechanism MCR-1 is a recent addition to the list of documented threats. MCR-1 was first reported in China from farmed pigs' guts, raw meat, and *E. coli*-infected humans in the same community and has now been detected in stored samples from around the world. Colistin, an older and therefore relatively inexpensive antibiotic from the class known as polymixins, is widely used as a growth promoter in Chinese agriculture. At least one of the top 10 producers of colistin for agricultural use is in India, and these drugs are increasingly common 'last resorts' used to treat domestic cases of multi-drug resistant (MDR) *Pseudomonas aeruginosa* and *Acinetobacter baumannii* (Liu et al. 2015; Gupta et al. 2009). India, especially New Delhi, also has high levels of ciprofloxacin resistance among community-acquired *E. coli* isolates, meaning there is likely a large reservoir of resistance genes among healthy *E. coli* carriers in the community (CDDEP 2009).

Resistant *Salmonella* and *Campylobacter* species are commonly found in animal products and pose significant risks to human health, especially in India. A joint report from the Food and Agriculture Organization (FAO), World Organization for Animal Health (OIE), and World Health Organization (WHO) identified these three foodborne pathogens as priorities for research and risk assessment (Elliott 2015). Ciprofloxacin-resistant *Salmonella enterica* serovar Typhi and ciprofloxacin resistance among *Salmonella* species are on the rise in India, mostly sourced from poultry (T. Kumar et al. 2013). *Campylobacter jejeuni* are among the most common origins of enteric diarrhea worldwide, and have shown resistance to macrolides and fluoroquinolones since the 1980s (Mukherjee et al. 2013).

Widespread resistance to antibiotics means that infections that were once easily treatable can become deadly. For example, just over 30 percent of neonatal sepsis deaths in India—some 58,000 per year—are attributable to antibiotic resistance (CDDEP 2012). The implications of resistant infections are of special concern to highly populous low- and middle-income countries (LMICs) such as India, where the burden of infectious diseases is high and health care capacity is low (Ganguly 2011). In addition to causing increased morbidity and mortality, resistant infections are more expensive to treat than sensitive ones, often requiring longer hospital stays and pricier drugs (Michigan State University 2011).

Transmission of Resistance Between Animals, Humans and the Environment

A growing body of evidence supports the concept that the amount of antibiotics used in animals has an impact on the levels of resistant bacteria in humans, though the exact health impacts are poorly understood (Elliot 2015). Many of the antibiotics used in farming are the same as those we rely on for human health, raising fears regarding the speed at which we are 'using up' the effectiveness of these agents by nonessential use in animals. Annex 2 outlines the WHO's hierarchy of antibiotic agents in terms of their importance to human health, as well as the livestock-related usage of the same drugs.

Nine of 14 classes of drugs labeled 'critically important' to human health are also commonly used in animals (Annex 2, table 1). In 2009, macrolides ($600 million), penicillins ($600 million), and tetracyclines ($500 million) all of which are categorized as critically important in human medicine, were the top grossing antibiotics in livestock-related sales (CDDEP 2015). FAO, OIE and WHO cite some of the same agents--quinolones, 3rd and 4th generation cephalosporins, and macrolides—as top priorities for risk assessment in animal use (Elliott 2015).

Identical resistant strains of bacteria have been detected in animals and the farmers working with them, a finding reinforced through genetic testing (CDDEP 2015). The use of antibiotics as growth promoters has been shown to increase the load of resistant bacteria in farmers' guts, compared to farmers not using them for growth, and compared to the general population (Price et al. 2007).

Resistant bacteria transmitted through animal products have led to large epidemics, such as multi-drug resistant *Salmonella* in the United States (Tacket et al. 1985). Outside epidemics, resistant bacteria have been detected in animal food products throughout the world, including in Denmark and Italy (Normanno et al. 2007). In some countries, decreases in the use of certain antibiotics in animals has led to a decrease in bacteria resistant to those antibiotics in humans (Dutil et al. 2010).

Resistant bacteria, as well as resistance genes and antibiotic residues, have also been detected in water, soil and other environmental sites. Environmental reservoirs include water, soil and wildlife (Wellington et al. 2013). Resistant bacteria can also be transmitted through human and animal waste, spread through manure and sewage treatment into soils and surface and ground waters, where new strains of resistant bacteria can be created through gene transfer.

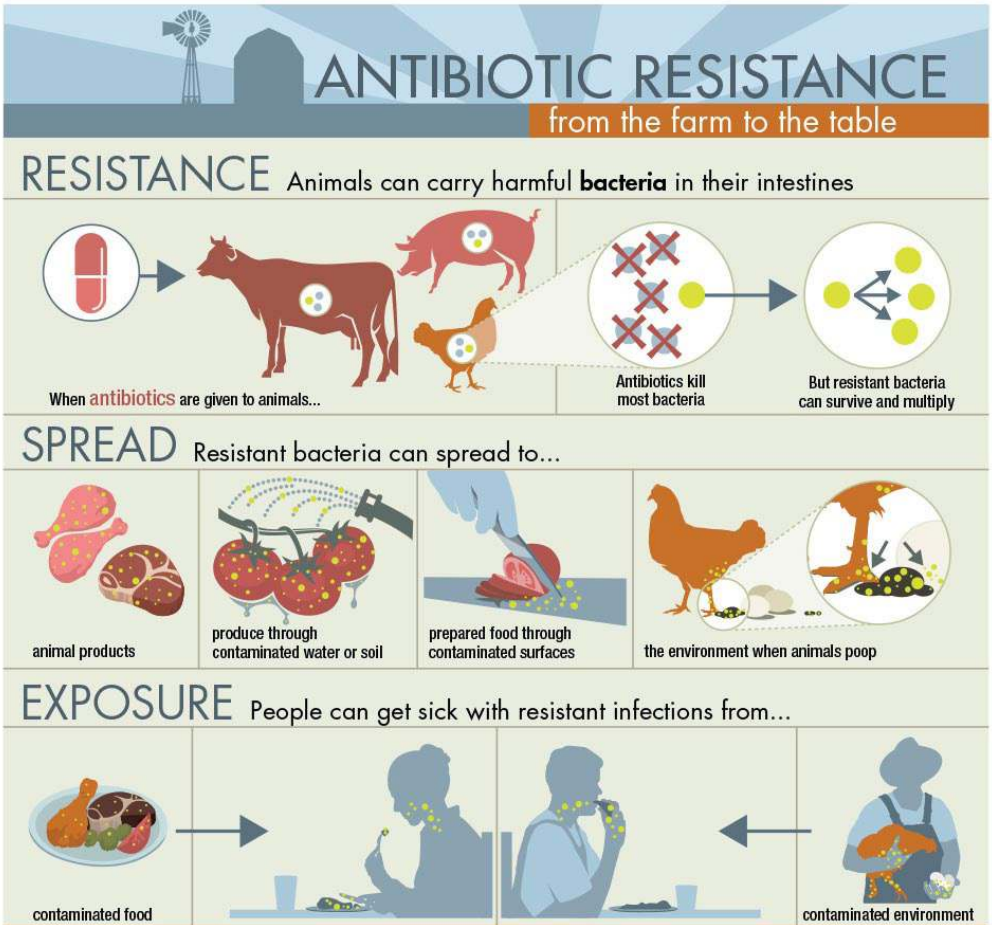

FIGURE 4: Antibiotic Resistance from Farm to Table (Figure adapted courtesy of the Center for Disease Control and Prevention, Foodborne Outbreak Tracking and Reporting, http://www.cdc.gov/foodsafety/from-farm-to-table.html)

Resistant bacteria have been detected in soil and surface water on farms, around wastewater treatment plants and in drinking water samples (Meena et al. 2015; Walsh et al. 2011). In turn, resistant bacteria in the environment can spread to humans and animals through contact and contaminated foods and water. Some environmental sites are hotspots for resistant bacteria, including wastewater treatment plants, hospitals and food animal production sites (Berendonk et al. 2015). A lack of access to clean water and sanitation increases human exposure to and transmission of resistant bacteria.

Antibiotic residues are also released into the environment through human waste and disposal, animal feeds and waste and particularly around the sites of antibiotic production, and have been detected in ground and surface waters and soil (Daghrir and Drogui 2013; Halling-Sørensen 1998). Animals can excrete up to 75 percent of an antibiotic dose in feces and up to 90 percent in urine (Sarmah, Meyer, and Boxall 2006). In India, some of the highest levels of residues ever detected in surface waters were found in lakes and wells surrounding a wastewater processing plant that serves close to 100 pharmaceutical manufacturing plants around Hyderabad (Fick et al. 2009).

In a recent example of zoonotic transmission of resistance, an emerging strain of MRSA (clonal complex 398) originated in humans, was transmitted to pigs (where resistance emerged), and then transferred back to humans who were in close contact with the animals (Price et al. 2012). Other cases in which farmers have acquired strains of bacteria resistant to the antibiotics used in their animals are reviewed by van den Bogaard and Stobberingh (Van den Bogaard and Stobberingh 2000).

The buildup of resistance due to animal use can be quite rapid. In an early study by Tufts University, poultry were supplemented with tetracycline, and nearly all of the birds' intestinal flora showed resistance to the drug within one week. Within a few months, one-third of the fecal samples of the humans on the same farm had much higher levels of tetracycline-resistant bacteria than their counterparts nearby (Elliott 2015).

However, the effects of such transference do not seem to be permanent. After a study showing a strong correlation between antibiotic use in hatcheries and local incidence of drug-resistant *Salmonella*, Quebec hatcheries voluntarily stopped injecting eggs with a cephalosporin related to an important human drug.

The prevalence of resistant salmonella in broiler meat dropped from 60 percent to 10 percent in the first year after the ban, and from 40 percent to nearly zero in humans. The incidence of drug resistant infections also dropped (Elliott 2015).

The Use of Antibiotics in Food Animals

Van Boeckel et al. estimate that annually, 45 m/kg–1, 148 m/kg–1, and 172 mg/kg–1 are consumed to produce each kilogram of cattle, chicken, and pigs, respectively. They report that the global consumption of antimicrobials will increase by 67 percent from 2010 levels by 2030, from 63,151 ± 1,560 tons to 105,596 ± 3,605 tons (Van Boeckel et al. 2015).

That small doses of antibiotics could increase the rate of weight gain and 'feed efficiency' of animals was first noted in the 1940s, and though the exact mechanism is not well understood, the practice gained widespread use soon after (Dibner and Richards 2005; Cogliani, Goossens, and Greko 2011). Today, more antibiotics are used worldwide in poultry, swine, and cattle production than in the entire human population (CDDEP 2015). In the United States, approximately 80 percent of all antibiotics consumed are used in the livestock sector (Food and Drug Administration 2010). The amount of antibiotics given to animals for nontherapeutic reasons, including prophylaxis (also referred to as 'metaphylaxis') and growth promotion (AGPs), far outstrips the volume used to treat disease, though exact figures are lacking.

The European Union has banned the use of antibiotics for growth promotion, and forces in the United States are pushing toward this goal, though neither has restricted antibiotic use for disease prevention. AGP use is on the rise in much of the developing world as producers scramble to keep pace with the growing global population and increased demand for animal products. The numbers are even more staggering in light of the prediction that the global consumption of animal products may double over 2006 rates by 2050 (FAO 2006).

Disease outbreaks can occur quickly and ravage animal herds and flocks, and crowded, dirty conditions exacerbate the problem, hence the widespread reliance on prophylactic antibiotic treatment. Besides being administered at regular intervals—and sometimes unknowingly, by farmers who have bought any of the common commercial feeds pre-mixed with antibiotics—doses are also given pre- and post-surgery, prior to transportation, and at other times when animals are under stress. In aquaculture, antibiotics are used therapeutically and prophylactically—often in high concentrations due to the ease with which bacteria travel in water—but not for growth promotion (Food and Drug Administration, Center for Veterinary Medicine 2011). While it does prevent many disease outbreaks, the consistent dosing with small concentrations of antibiotics confers a selective advantage to the most virulent bacteria, which means that disease events that do occur are often more difficult, if not impossible, to treat.

The intensification of animal production also plays a significant role in the spread of resistance, as the pressure on operations to produce more animals more cheaply in less space creates all the incentive in the world to compromise animal health and hygiene and instead rely on the quick fix of regular antibiotic dosing.

CHAPTER 2

A Review of the Literature on Antibiotic Use and Antibiotic-Resistant Bacteria in Food Animals

Estimates of global antibiotic use in poultry, swine and cattle in 2010 indicate that India accounts for 3 percent of global consumption and is among the top consumers worldwide, along with China, the United States, Brazil and Germany (Van Boeckel et al. 2015). In India, hotspots for consumption include the south coast, Mumbai and Delhi. Projections for 2030 estimate an overall increase of about two thirds in animal antibiotic consumption worldwide. In the BRICS countries (Brazil, Russia, India, China and South Africa) antibiotic use in animals is expected to double. Use of antibiotics in chickens, in particular, is expected to triple in India by 2030 (Van Boeckel et al. 2015).

The published reports of antibiotic use and bacterial resistance in agriculture in India are summarized in this chapter. The literature covers a number of settings, antibiotics, and bacterial species, but the body of evidence is small compared with the size of the agricultural enterprise in India, and in light of the seriousness of the resistance problem. From our review, however, the sum of the evidence suggests high and increasing levels of bacterial resistance in all veterinary sectors. Basic information from all the studies included in this review can be found in annex 3; tables 1 and 2.

Antibiotic Use

While a number of studies have examined the resistance profiles of bacteria isolated from livestock, poultry, and aquaculture, the frequency of antibiotic use and reasons for use during animal rearing are poorly represented in the published literature. There are also few qualitative studies of farmers' knowledge and intent regarding antibiotic use in their operations. Several researchers have measured antibiotic residues in animals or animal products as a proxy for the level of antibiotic usage, but scant large-scale data are available. In India, the Ministry of Agriculture's early implementation of programs such as Assistance to the States for Control of Animal Diseases (ASCAD) the National Animal Disease Reporting System (NADRS), and the National Livestock censuses, all discussed later in this report, indicates that the capacity for widespread data collection is in place, and more extensive data collection on antibiotic use in farming may be possible in the coming years.

Poultry

In many countries, antibiotics are commonly added to commercial feed for growth promotion in chickens. Often the amount of antibiotics given is not under the direct control of the farmers, due to premixed antibiotics contained in the feed they purchase. Dr. Mohamed Nadeem Fairoze, of the Veterinary College of KVAFS University, estimates that in Karnataka, 70 percent of antibiotics used in poultry are for growth promotion, while the remaining 30 percent are for therapeutic use (Fairoze 2012). However, there is limited documentation of the level of antibiotic use in the poultry sector, either for growth promotion, prophylaxis, or treatment.

Many poultry farmers purchase commercially manufactured feeds, none of which are produced without AGPs in India, according to a recent fact sheet published by the Delhi-based Center for Science and the Environment (CSE) (Center for Science and Environment 2014). Mixed supplements and AGPs are also available to add to home-mixed feed. Antibiotic residues in commercial poultry are high: a recent study by CSE found antibiotics in 40 percent of samples taken in the Delhi-National Capital Region; 17 percent tested positive for multiple antibiotics (Sahu and Saxena 2014). Data compiled by CSE states that, of fifteen common agents used as AGPs in Indian chicken feed, 11 are considered by WHO to be important, highly important, or critically important for human health, and all are banned for agricultural use in the EU (Center for Science and Environment 2014).

Dairy

In an early study (1985), Ramakrishna and Singh tested raw milk samples in markets in Haryana for streptomycin, which was found in approximately 6 percent of samples (Ramakrishna and Singh 1985). One decade later, dairy farmers in Hyderabad, Secunderabad, and surrounding villages were surveyed on antibiotic use practices. Among 38 dairy farmers, about half used oxytetracycline to treat diseases such as mastitis and fever. Oxytetracycline residues were found in samples from markets (9 percent) and individual animals (73 percent), while no residues were found in government dairy samples. From interviews with 155 urban and rural farmers, Sudershan and Bhat found that antibiotic use was lower among farmers in rural areas (20 percent) compared to those in urban areas (55 percent). In addition, these interviews revealed that 87 percent of urban and 38 percent of rural farmers treated their animals without consulting a veterinarian (Sudershan and Bhat 1995).

A survey completed by the National Dairy Research Institute near Bangalore in 2000 reported that tetracyclines, gentamycin, ampicillin, amoxicillin, cloxacillin, and penicillin were commonly used to treat dairy animals. Mastitis was treated with beta-lactams or streptomycin (Unnikrishnan et al. 2005). None of the above studies mentioned antibiotic use for the purpose of growth promotion in dairy farming.

The prevalence of antibiotic residues in milk samples has been reported to be higher in silo and tanker samples than in market and commercial pasteurized milk samples (Unnikrishnan et al. 2005). Two of the five pooled milk samples collected from public

milk booths in Assam contained antibiotic residues at high levels (at least 5 µg/ml equivalent of penicillin) (G. Dutta et al. 2001), and two to six percent of milk samples collected from individual cows, tankers, and organized and unorganized farms in southern states were reported to contain antibiotics (Ram, Bhavadasan, and Vijya 2003).

In 2010, 11 percent of raw milk samples collected from Delhi and villages surrounding Delhi contained beta-lactams, and 2 percent contained streptomycin. Other antibiotics, including gentamicin, tetracycline, and erythromycin were not detected (National Dairy Research Institute 2011). The presence of antibiotic residues in milk is evidence that antibiotics are used in dairy animals from these regions, though details of the frequency, duration, and reasons for use are unknown.

Fisheries

The aquaculture situation is slightly different from that in livestock. An extensive ban on pharmaceuticals in aquaculture was put in place by the Food Safety and Standards Authority in India. The ban includes a hard limit on residues of tetracycline, oxytetracycline, trimethoprim, and oxolinic acid, all below 0.1 mg/kg (Gazette, 2011). In general, feed for aquaculture is not manufactured with antibiotics, but antibiotics may be added to feed by the farmers themselves.

A survey of freshwater fish hatcheries in West Bengal in 2006–2007 reported that oxytetracycline, althrocin, ampicillin, sparfloxacin, and enrofloxacin were used commonly in fish farms both for prophylaxis and treatment. The aquaculturists also reported using ciprofloxacin, enrofloxacin, and other drugs in a few hatcheries to improve larval survival. The authors report that responsible use of antibiotics in the hatcheries is lacking and suggest that the observed usage patterns may contribute to the development of drug resistance (Bharathkumar and Abraham 2011).

Antibiotic Resistance

There are few surveillance systems for antibiotic resistance in animals, but what data are available indicate that high levels of resistant bacteria are present in animals around the world. In Europe, *Salmonella* bacteria from poultry and swine showed resistance levels reaching over 80 percent to tetracyclines, sulfonamides and ampicillin (EFSA and ECDC 2015), while in the United States *Salmonella* resistance to the same classes reached over 10 percent in poultry, cattle and swine, and was highest to the tetracyclines at over 30 percent (NARMS 2011). Similar rates of resistance have been detected in smaller studies conducted in several low- and middle-income countries (CDDEP 2015).

In India, a number of researchers have isolated bacteria from animals or seafood and tested them for resistance to common antibiotics. The levels of resistance reported are consistently high in food animals including livestock, poultry, fish, and shellfish. For instance, resistance has been detected in *Staphylococcus, Pasteurella multocida* and other bacteria in poultry, reaching 100 percent resistance to some drugs (Shivachandra et al. 2004; Dhanarani et al. 2009).

Poultry

The level of resistance in Indian poultry is reported to be high for many antibiotics; however, resistance to chloramphenicol remains low.

In 1981, a study of fowl from the area around Ludhiana reported that almost all *E. coli* strains from apparently healthy fowl and about 80 percent from diseased fowl were resistant to chlortetracycline, tetracycline, oxytetracycline, and triple sulfas (Sarma et al. 1981). In 1995, isolates of *Enterococcus* from State Duck Farms in Assam showed total resistance to oxytetracycline, chlortetracycline, erythromycin, oleandomycin, lincomycin, and clindamycin. Some strains were also resistant to streptomycin and nitrofurantoin, and high sensitivity remained only for chloramphenicol (Saikia et al. 1995).

Similarly, all 123 strains of *Pasteurella multocida* isolated from chicken and other birds (duck, quail, turkey, and goose) from 11 states across India were resistant to sulfadiazine. A majority of isolates were also resistant to amikacin, carbenicillin, erythromycin, and penicillin, with sensitivity to chloramphenicol at 74 percent (Shivachandra et al. 2004). In contrast, only a minority of *Campylobacter jejuni* strains isolated from healthy chickens in northern India showed resistance to ampicillin and tetracycline (7 percent and 13 percent respectively) (Prasad et al. 1994).

In 2009, several species of bacteria in poultry litter from a farm in Tamil Nadu were screened for resistance to a variety of antibiotics. A majority of isolates were resistant to at least one antibiotic, and resistance was highest to streptomycin (75 percent) and erythromycin (57 percent). Resistance was also greater than 40 percent for kanamycin, ampicillin, tobramycin, and rifampicin. The authors speculate that the high levels of resistance may be due to antibiotic use for growth promotion (Dhanarani et al. 2009).

A study of *Salmonella* from eggs in South India reported that all strains isolated were resistant to ampicillin, neomycin, polymyxin-B and tetracycline. Lower levels of resistance were recorded for ciprofloxacin, kanamycin, nalidixic acid, and sulfamethoxazole (Suresh et al. 2006). Multidrug resistance was also reported in *Salmonella* isolated from poultry in Haryana (T. Kumar et al. 2012).

Saravanan et al. found that 21 of 1215 samples collected at 154 different farms in Southern India were positive for non-typhoidal *Salmonella*. 16 were classified as *S.* Typhimurium and 5 as *S.* Enteritidis, both strains highly associated with human disease. All 21 isolates were resistant to oxytetracycline, a routine poultry feed additive (Saravanan et al. 2015).

A 2014 survey of backyard layers in West Bengal isolated *Salmonella* in cloacal swabs, feed samples, drinking water samples, and eggs. The isolates were found to be resistant to chloramphenicol, ciprofloxacin, gentamicin, levofloxacin, norfloxacin, and oxytetracycline, though none were ESBL producing (Samanta et al. 2014).

Mir and colleagues found 32 of 504 samples containing *Salmonella enterica* that were resistant to a variety of antibiotic agents: 100 percent were resistant to oxacillin, penicillin and clindamycin, 69 percent to ampicillin, 66 percent to tetracycline,

56 percent to nalidixic acid and 47 percent to colistin (Mir, Kashyap, and Maherchandani 2015).

A small study of meat shops in Bikaner found that 96 percent of chicken samples contained *S. aureus* (n=48). All of the samples were sensitive to ciprofloxacin, doxycycline and gentamycin, however all were resistant to ampicillin and cloxacillin, and most were resistant to tetracycline (Hemlata and et al. 2015).

The first systematic study of multi-drug-resistant ESBL-producing *E. coli* in Indian poultry and cattle found 18 of 316 *E. coli* isolates sampled in Odisha were ESBL producers. All ESBL-producing strains emerged as a single lineage through phylogenetic analysis and were resistant to oxyimino cephalosporins and monobactam, as well as a host of other antibiotics (Kar et al. 2015).

A broader study sampled twelve random locations in Hyderabad found drug-resistant *E. coli* incidence in a variety of settings, from raw chicken (23 percent prevalence), vegetable salad (20 percent), raw meat (13 percent), raw egg surface (10 percent), and unpasteurized milk (7 percent). Overall prevalence of *E. coli* was 14.7 percent, and 4 percent of isolates were ESBL producers, two each from vegetable salads and raw chicken, one each from raw egg-surface and raw meat (Rasheed et al. 2014).

A recent study conducted by members of the Global Antibiotic Resistance Partnership found significant differences in the resistance profiles of broiler farms vs. layer farms in the Punjab region of northern India, with drug resistance being far more common in broiler operations. Broiler farms ranged from twice as likely to more than twenty times as likely to harbor resistant *E. coli*, and prevalence of multi-drug resistance was much higher (94 percent in broiler farms vs. 60 percent in layers). ESBL prevalence in broiler farms was also higher at 87 percent vs. 42 percent among layers. Independent broiler operations had overall higher rates of resistant *E. coli*, while contracted layer farms (not independent) had higher prevalence of ESBL producers (Brower et al., manuscript in preparation).

Bovines

Several studies have reported resistance profiles of bacteria isolated from sick cattle and buffalo. In 2003, *E. coli* O157 was isolated from stool samples collected from adult cattle after slaughter and from diarrhoeic calves in West Bengal. Of the 14 strains isolated, resistance was found most frequently against antibiotics commonly used in the region, such as nitrofurantoin (57 percent), co-trimoxazole (29 percent), tetracycline (21 percent), and ampicillin (21 percent). Nearly three-quarters of the isolates were resistant to at least one antibiotic, and more than half were multidrug resistant (Manna et al. 2006).

Similarly, a high level of antimicrobial resistance was reported from shiga toxin-producing *E. coli* isolated from calves with diarrhoea in Gujarat and the Kashmir Valley (Arya et al. 2008; Kawoosa et al. 2007). All of the strains from Gujarat were resistant to at least three antibiotics, and almost half were resistant to eight or more of the 11 antibiotics tested. Resistance was ubiquitous for kanamycin and cephalexin and was above 50 percent for seven of the antibiotics (Arya et al. 2008).

Isolates of *S. aureus* from milk samples of cows with mastitis were also resistant to a variety of antibiotics (T.K. Dutta et al. 2007; R. Kumar et al. 2011; V. Kumar et al. 2012). Between 20 percent and 30 percent of isolates from mastitic buffalo were resistant to tetracycline, gentamicin, erythromycin, and lincomycin (R. Kumar et al. 2011). Similarly, *S. aureus* isolates from milk samples of mastitic Sahiwal cattle were resistant to streptomycin (36 percent), oxytetracycline (34 percent), and gentamicin (30 percent). Thirteen percent were methicillin-resistant, and these MRSA isolates were significantly more resistant to other antibiotics than methicillin-susceptible isolates. All isolates from the mastitic Sahiwal cattle remained susceptible to vancomycin (V. Kumar et al. 2011). Another study on mastitic cattle found that resistance to ampicillin, carbenicillin, and oxacillin was near 100 percent for all bacteria tested (T.K. Dutta, Kumar, and Kotwal, 2007). Analysis of milk samples and milk products from shops in Mizoram showed similar resistance patterns, with complete resistance against ampicillin as well as high resistance to penicillin (87 percent) and cefotaxime (59 percent) (Tiwari et al. 2011).

A 2015 study of mastitis in dairy buffalo in South India found high concentrations of coagulase-negative staphylococci (64.8 percent) bacteria, as well as streptococci (18.1 percent), *E. coli* (9.8 percent) and *S. aureus* (7.3 percent). The majority of pathogens were resistant to multiple antibiotics, especially beta-lactams (Preethirani et al. 2015)

A similar study by Ghatak et al. in 2013 found 1 of 8 *E. coli* samples from mastitic cow's milk carrying multi-drug resistant New Delhi metallo-beta-lactamase and another carrying an ESBL gene (Ghatak et al. 2013).

A study of 160 raw milk samples from Rajasthan showed high percentages of resistant bacteria. 81 percent of *E. coli* isolates were resistant to ampicillin and 77 percent were resistant to penicillin; they were also moderately resistant to nirtofurantoin (42.11 percent) and oxacillin (38.60 percent). 86 percent of *S. aureus* were resistant to penicillin-G, and also showed high levels of resistance to cefotaxime (84.62 percent), nirtofurantoin (81.54 percent), ampicillin (73.85 percent) chloramphenicol (69.23 percent) and tetracycline (64.62 percent) (Sharma et al. 2014).

Studies Including Other Livestock

Resistance patterns in *Salmonella* isolated from livestock have been reported in India since the 1970s, when resistance to streptomycin and tetracycline was substantial, but sensitivity to ampicillin, chloramphenicol, erythromycin, and nitrofurans remained high (Sethi et al. 1976; Tiwary and Prasad 1972). In the years since, more studies have investigated the levels of resistance in livestock across the country. A quarter of the *E. coli* strains isolated from livestock near Lucknow in 1984–1986 were resistant to at least one antibiotic among the nine that were tested, and almost half of these isolates were multidrug resistant. Resistance was most frequent in isolates from sheep and goat diarrhea (82 percent and 100 percent respectively) (M. Singh et al. 1992a). Similarly, a majority of *E. coli* strains isolated from bovines, sheep, and poultry in 1992 at the Veterinary Hospital in Lucknow were resistant to one or more of the seven antibiotics tested (M. Singh et al. 1992b). Two recent studies of bacteria

from pigs in northeast India reported a high prevalence of resistance to many antibiotics in *Pasteurella* and *E. coli* isolates (T. K. Dutta et al. 2011; T. K. Dutta et al. 2009).

B. R. Singh and colleagues have published several papers reporting drug resistance patterns in *Salmonella* and *Enterococcus* isolated from equines (hoofed mammals such as horses). Almost all *Salmonella* isolates from horses, donkeys, and mules kept by low-income individuals and from equine farms were resistant to three or more antibiotics. The highest frequencies of resistance were to sulfamethoxazole (91 percent), tetracycline (71 percent), doxycycline (68 percent), furazolidone (66 percent) and colistin (55 percent) (B. R. Singh et al. 2007). Widespread resistance was found in *Salmonella* isolates from equids in Izatnagar: 100 percent were resistant to at least one antibiotic and 89 percent were resistant to more than one. Resistance was highest to furazolidone (87 percent), sulfamethoxazole (82 percent), and tetracycline (43 percent) (B. R. Singh et al. 2009). Finally, Singh showed that resistance levels of *Enterococci* isolates from equids were higher in North India than have been seen in the United States and many countries in the EU. Eighty percent of the isolates from the equids studied were resistant to vancomycin, and over 99 percent were resistant to at least five of the 19 antibiotics for which resistance was tested. Resistance was highest to cefdinir (97 percent), oxacillin (91 percent), cefotaxime (89 percent), ampicillin (88 percent), cloxacillin (88 percent), cotrimazine (87 percent), and vancomycin (80 percent) (B. R. Singh 2009).

Seafood

Antibiotic resistance in the marine sector has been closely studied in India in comparison with other agriculture sectors. Several studies of *Salmonella* isolates from fish and other seafood have been conducted. One study from Tamil Nadu found that over 90 percent of *Salmonella* isolates from fish and crustacean samples from retail outlets were resistant to bacitracin, penicillin, and novobiocin. Many of the antibiotic-resistant isolates originated from poultry, livestock, and humans, suggesting transmission of antibiotic-resistant bacteria (Hatha and Lakshmanaperumalsamy 1995).

In a study conducted in Cochin from 2003 to 2007, half of the *Salmonella* isolates from seafood were resistant to sulfamethizole. Resistance to carbenicillin and oxytetracycline was also prevalent. Multidrug resistance was detected in two-thirds of isolates, with four out of 256 samples resistant to five drugs (R. Kumar et al. 2009).

In 2012, *Salmonella* isolates from fish and shellfish from markets and fish landing centers in Mangalore were tested for nine antibiotics. Two-thirds were resistant to at least two antibiotics, and a quarter of the isolates were resistant to three drugs or more (Deekshit et al. 2012). A study of *Salmonella* isolates from fresh water prawns and cuttlefish found no resistance to the 16 antibiotics tested (Shashidhar et al. 2005).

Examinations of *Vibrio* species isolated from seafood have also revealed high levels of antibiotic resistance (P. A. Kumar et al. 2009; Sathiyamurthy et al. 1997; Shanthini et al. 2004). In 1988–1989 *V. cholerae* isolates from finfish, shellfish, and crustaceans in southeast India were resistant to 10 of the 13 antibiotics tested. Among the antibiotics tested, the highest levels of resistance were found against tetracycline (50 percent) and sulfadiazine (43 percent) (Sathiyamurthy et al. 1997).

More recently, *V. cholerae* isolated from seafood in the same region have showed higher levels of resistance. In a study completed in 2009, resistance to ampicillin, penicillin, streptomycin, and bacitracin was 88 percent, 84 percent, 85 percent, and 64 percent respectively, while resistance to other antibiotics was present at lower levels (P. A. Kumar et al. 2009).

Similarly, *V. parahaemolyticus* isolated from finfish in Cochin showed a high level of resistance to ampicillin (89 percent) and streptomycin (89 percent). More than half were also resistant to carbenicillin, cefpodoxime, cephalothin, colistin, and amoxycillin. Most isolates remained susceptible to tetracycline, nalidixic acid, and tetracycline (Sudha et al. 2012).

Finally, a study of *Aeromonas, Pseudomonas,* and other bacteria isolated from freshwater fish hatcheries in West Bengal showed high prevalence of resistance to oxytetracycline, nitrofurantoin, and co-trimoxazole. Resistance to multiple antibiotics was observed in 90 percent of the bacteria isolated from catfish hatcheries and 30 percent of the bacteria present in carp hatcheries (Bharathkumar and Abraham 2011).

Resistance was widespread in farmed shrimp from the east coast of India between 1999 and 2002. All *Vibrio* and *Aeromonas* isolates were resistant to ampicillin, and a large proportion were also resistant to chlortetracycline (66 percent) and erythromycin (53 percent) (Vaseeharan et al. 2005). Similarly, *E. coli* O157:H7 isolates from shrimp collected from retail markets in Cochin were resistant to bacitracin and polymyxin-B (A. Surendraraj et al. 2010).

Several other studies of antibiotic resistance in bacteria isolated from the marine sector are similar to the studies summarized here (Kishore et al. 2012; P. A. Kumar et al. 2011; R. Kumar and Surendran 2005; Sahoo and Mukherjee 1997; Sasmal et al. 2004; Shome and Shome 1999; Sunder et al. 2006; A. Surendraraj et al. 2005).

Though not yet well studied, antibiotic use in farmed fish may impact the greater marine ecosystem, and wild-caught fish are not exempt from the effects. A study of commercial catch operations in West Bengal found significant levels of resistance to ampicillin in the gills and intestines of fish sampled, indicating that wild-caught fish may also act as reservoirs of resistant bacteria (Ghosh and Mandal 2010).

CHAPTER 3

Production and Regulation in India

Animal Husbandry

Scale of Food Animal Farming

India's livestock sector is one of the largest in the world. India is home to 57 percent of the world's buffaloes, 12 percent of the world's cattle, 1.5 percent of pigs and 3.1 percent of poultry. Output of meat and animal products was an estimated 2075 billion Indian rupees (Rs.) in 2011 (2004-5 prices) (Government of India 2012). The 'nutritional transition' common to fast-developing LMICs—growing populations and incomes leading to a dramatic increase in demand for animal products—means that India in particular is shifting to a highly intensified, vertically-integrated style of livestock production. Small operations are giving way to large, industrial operations, especially in poultry farming. Currently, farms with fewer than 5,000 birds are a rarity, and broiler (meat) farms producing up to 50,000 chickens per weekly cycle are the norm. In layer farms, flock sizes frequently range from 10-50,000 birds (FAO 2003).

The Indian Department of Animal Husbandry, Dairying and Fisheries (DAHD) estimates that in 2012, India was home to 729.2 million fowl, a 12.4 percent increase since 2007. Cattle, buffalo, and total dairy cow populations dropped slightly in the same period, but still numbered 190 million, 109 million, and 300 million, respectively. The female milk (milch) cow population was up more than 30 percent in 2012 (DAHD 2012), indicating selective breeding and further intensification of the dairy industry, though herd sizes remain small (Kahn and Cottle 2014).

India is the world's 5th largest meat producer, with an estimated 6.3 million tonnes output per year, 77 percent of which is red meat (APEDA 2015). Milk production was 115 million tons in 2011, making India the largest producer of milk in the world. India is the third largest producer of eggs with production of 5980 crore eggs per year. India produces 34 lakh tonnes of broiler meat, almost all of which is consumed domestically (GOI 2012). Fish production has almost doubled in the last 10 years, and India is now the second largest producer of fish, producing 96 lakh tonnes of fish per year (DAHD 2015).

Economically, livestock alone contributes 26 percent of the agricultural output of India and 4 percent of total GDP. The total export earnings from livestock and poultry products were Rs. 19,036 crore in 2011 (DAHD 2012). Marine products contributed to Rs. 16,597 crore of exports in 2011–2012 (Marine Products Export Development Authority 2012).

Livestock employs 8.8 percent of the agricultural work force, which in turn employs 57 percent of the total working population of India. Variation is high, however: high livestock-reliant states like Punjab and Haryana can see 40-48 percent of agricultural labor devoted to animals, whereas in the Northeastern states this figure is about 3 percent (Government of India 2012).

Animal Health and Government Initiatives

Bacterial infections make up a significant proportion of animal illnesses. The reported number of bacterial infections in Indian livestock is summarized in the 2010–2011 report by the Department of Animal Husbandry, Dairying, and Fisheries. In 2009, 120,923 Indian livestock animals had salmonellosis (7,129 died), 26,333 were affected by mastitis, 3,729 suffered from haemorrhagic septicaemia (1,595 died), 1,109 were affected by black quarter (481 died), and 94 fell ill from brucellosis. In addition, enterotoxemia caused by *Clostridium perfringens* killed 533 animals and affected 2,167. These numbers may be underestimated, as reporting levels are unknown. (Ministry of Agriculture Department of Animal Husbandry, Dairying, and Fisheries, 2011) (DAHD 2011).

To mitigate farmers' losses resulting from disease outbreak, the government has taken several initiatives. In 2008, it began offering livestock insurance in 300 districts to compensate for animal deaths. In addition, the government set up six quarantine centers. Imported animals found to be diseased are moved to one of six quarantine stations, located in New Delhi, Chennai, Mumbai, Kolkatta, and airports in Hyderabad and Bangalore.

In 2010, the government expanded the Centrally Sponsored Scheme to involve:

(a) Assistance to States for Control of Animal Diseases (ASCAD)—an organization responsible for immunizations, strengthening existing state-run biological production units and diagnostic laboratories, and providing training to veterinarians and para-veterinarians. The organization is also responsible for reporting incidence rates of livestock and poultry diseases to the OIE twice a year.

(b) National Project on Rinderpest Eradication (NPRE)

(c) Professional Efficiency Development (PED), a regulatory organization for veterinary practitioners

(d) Foot and Mouth Disease Control Programme (FMD-CP)

(e) National Animal Disease Reporting System (NADRS)—a new computerized reporting system

(f) National Control Programme on Peste des Petits Ruminants (NCPPPR)

(g) National Control Programme on Brucellosis (NCPB)—mass vaccination program completely funded by the government

(h) Establishment and Strengthening of Veterinary Hospitals and Dispensaries (ESVHD) (responsible for improving the current infrastructure of veterinary clinics and hospitals)

(Department of Animal Husbandry, Dairying, and Fisheries, 2011)

Many components of the scheme are still undergoing implementation. ASCAD, NADRS, ESVHD have seen heavy investment as of 2013-14, in addition to the completion of the 19th Livestock Census, which falls under the same scheme (DAHD 2014). The ASCAD program far exceeded its target for animal vaccine coverage in 2013-14, providing 360 million vaccines compared to a projection of 250 million. Another 227 million were provided in 2014 (DAHD 2015).

Most vaccines are manufactured within India, with 21 public veterinary vaccine production units and seven private producers. The government has recently given the responsibility for ensuring vaccine quality to the Choudhary Charan Singh National Institute of Animal Health. In addition, 250 disease diagnostic laboratories are currently in place for microbiological testing. The 2013-14 period of DAHD activities saw scaling up of NADRS and implementation of the Central Project Monitoring Unit, a scheme to streamline and centralize data collection on animal disease reporting, vaccination coverage, and other useful veterinary data (DAHD 2015).

Lack of veterinary capacity is a major concern in India. Only 34,500 veterinarians are employed for field services against the required 67,000, based on animal population and geographic coverage. Only 3,050 veterinary scientists are available for teaching and research, compared to proposed requirement of 7, 500. The biggest dearth is in the realm of veterinary technicians and support staff, where the 52,000 actively employed meets less than 20 percent of the need (Planning Commission of India 2013).

In order to improve veterinary and diagnostic capacity, the DAHD is providing shared funding on 75 percent/25 percent basis to states looking to open new veterinary hospitals and dispensaries or update existing ones. In the Northeastern states, a priority area for animal health, the Department is providing 90 percent funding (DAHD 2015).

National and Regional Policies

In 2011, the Ministry of Health and Family Welfare released the *National Policy for Containment of Antimicrobial Resistance*. This policy encourages the development of regulations for antibiotic use in food animals, appropriate food labeling, and banning nontherapeutic uses of antibiotics in animals. The development of an inter-sectorial committee and the creation of this report were also recommended. Directorate General of Health Services Ministry of Health and Family Welfare 2011.

The 2012 *Chennai Declaration—A Roadmap to Tackle the Challenge of Antimicrobial Resistance*, was developed at the annual conference of the Clinical Infectious Disease Society and outlined the following needs (Ghafur et al. 2013):

1) to evaluate the extent of antibiotic usage in the veterinary practice and the indications of use (prophylaxis, treatment, or growth promoter)

2) to regulate antibiotic usage in the veterinary practice

3) to ascertain and monitor the prevalence of resistant bacteria, especially important zoonotic food-borne bacteria in animals and food of animal origin to quantify the rate of transfer of medically relevant resistance genes and resistant bacteria from animals to humans.

4) to regulate monitoring of residues of antibiotics in food of animal origin and study the role of antibiotic residues in food towards development of resistance

5) to formulate/implement proper regulations for observance of withholding or withdrawal periods between the use of antibiotics and animal slaughter or milking to avoid residues of antibiotics in milk and meat.

An international effort by the Global Antibiotic Resistance Partnership made through the *New Delhi Call to Action on Preserving the Power of Antibiotics* in 2011 was signed by the governments of Ghana, Kenya, Mozambique, South Africa, and Vietnam. It emphasized the need for a multi-sectorial approach to (Global Antibiotic Resistance Partnership 2011a):

1) prevent bacterial infections and their spread

2) ensure access to appropriate drug prescribing, dispensing, and use

3) strengthen and enforce regulation to ensure drug quality

4) implement surveillance for resistant bacteria and for antibiotic use patterns

5) stimulate R&D for new antibiotics

6) discourage subtherapeutic use of antibiotics in animal feed for growth promotion.

The Global Antibiotic Resistance Partnership draft report by the Center for Disease Dynamics, Economics & Policy (CDDEP) describes government agencies responsible for antibiotic use in India:

> Within the Ministry of Agriculture, the Directorate of Marketing & Inspection runs the Agricultural Marketing Information Network (AGMARK). This organisation certifies manufacturers of selected products, including eggs and chilled or frozen raw meat. In the early 2000s, AGMARK began upgrading some of its laboratories to measure antibiotic residues in animal products (AGMARKNET 2003; AGMARKNET 2006). However, limits on antibiotic residues in animal products are not yet widely established as a part of AGMARK certification (Johnson, Jadon et al. 2010).

The Ministry of Health and the Drug Controller General of India have responsibility for enforcing regulations related to food safety and the quality and use of antibiotics for both humans and animals in India. State Drug Controllers also have some responsibilities (Srivastava, R.C. et al. 2011). However, the absence of uniform regulations for dairy and poultry farming in India poses a serious challenge to the enforcement of rational use of antibiotics. Anecdotal evidence also suggests a general lack of awareness in India about regulations for antibiotic use and an absence of routine testing, making it likely that consumers are receiving products with more than the maximum permissible level of antibiotic residues (Ganguly 2012).

Laws and Regulation for Antibiotic Use in Animals

Laws aim to limit the amount of antibiotic residue ingested by consumers and to reduce antibiotic use with the aim of slowing the evolution and spread of antibiotic-resistant bacteria in animals and humans. In the EU, a critical step in this process was the banning of antibiotic use for growth promotion. India has no such ban, and at least eight antibiotics deemed 'highly' or 'critically' important for human health that are banned for growth promotion purposes in the EU are used for such purposes in India (Center for Science and Environment 2014).

There has been opposition to banning the use of antibiotics as growth promoters in many countries due to the potential negative economic impact. A recent assessment (Laxminarayan et al. 2015) estimates that the impact would be marginal in countries where farm production systems are already optimized, and more significant in countries with non-optimized systems. In India, projected production losses were estimated at about 1 to 3 percent of annual meat production, or $1,110 to 2,599 million USD. Commercial poultry farmers account for one half to three quarters of total production in India, and would face the greatest impact (Center for Science and Environment 2014) (Sasidhar and Suvedi 2015).

In addition to laws, the *Codex Alimentarius,* developed by FAO and the WHO, specifies a series of recommendations to 'ensure safety and quality in international food trade'. The *Maximum Residue Limits for Veterinary Drugs in Foods*, updated in July 2015, recommends maximum residue limits (MRLs) for commonly used veterinary drugs, including antibiotics (Codex Alimentarius Commission 2015). It includes detailed recommendations for MRLs in specific types of animal tissue. These are designed to assist countries as they consider adopting national MRLs.

The World Organization for Animal Health (OIE) has three major texts that deal with antibiotic resistance: the *Terrestrial Animal Health Code, the Aquatic Animals Health Code* and the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (OIE 2015b; OIE 2015a; OIE 2008). These include guidelines for testing antimicrobial susceptibility, creating surveillance systems for use and resistance, promoting rational antibiotic use and conducting risk analyses.

Laws in India

ndia has few regulations on antibiotic use in food animals. Most existing laws are concerned with exports and aquaculture. Recommendations have been made by various bodies to regulate the non-therapeutic use of antibiotics in animals, including by the National Centre for Disease Control, the Central Drugs Standard Control Organization and the Directorate General of Health Services, Ministry of Health & Family Welfare (G. Singh 2014; Directorate General of Health Services Ministry of Health and Family Welfare 2011). A poultry feed specification from the Bureau of Indian Standards recommended that antibiotics with systemic action not be used as growth promoters, and phase out of antibiotics that act in the gut in five years (the recommendations were issued in 2007).

To date, none of these recommendations have been formalized as regulations or laws.

The Indian Central Drugs Standard Control Organization issued a widely-lauded directive in mid-2014 to recommend the cessation of antibiotics in animal feeds as well as stricter enforcement of a 2012 law outlined below (Singh 2014).

Laws that Apply to Animal Products Consumed within the Country

There are two laws that regulate antibiotics in food animals within India. In January 2012, G.S.R. 28(E) required that medicine for treatment of animals state a withdrawal period[1] in the labeling (Ministry of Health and Family Welfare, Department of Health 2012). For medicines with no defined withdrawal period, withdrawal periods in meat/poultry and marine products should be 28 days and 500 degree-days,[2] respectively.

In addition to veterinary-specific regulations on antibiotic use, the Second Amendment of the Drugs and Cosmetics Rules (2006) contains a list of 536 drugs that fall under Schedule H. These drugs, which include antibiotics, require by law a prescription for their use (Ministry of Health and Family Welfare, Department of Health 2006). In 2013, a new category of H1 drugs was added in a Fourth Amendment to the Drugs and Cosmetics Rules (GSR 588 (E)).

[1]Withdrawal time is calculated for any particular drug from the day the drug is administered until the residues of that drug fall below the MRL, so at which point animals may be slaughtered for subsequent processing and consumption.

[2]A degree-day is calculated based on the temperature of the medium in which the food animals are raised/cultured. For example, if the temperature of the water in which the fish is cultured is 25˚C, the withdrawal time is calculated by dividing 500 by 25 (500 ÷ 25 = 20 days). 500 degree-days is thus calculated as 20 days for a culture environment with temperature of 25˚C.The withdrawal time/period therefore depends on environmental conditions (Dr. V.I. George, 2013).

Use of these drugs[3] now requires a prescription, pharmacists must provide separate prescription documentation subject to review, and non-compliance with the regulations can incur penalties (Department of Health and Family Welfare 2013). A 2015 amendment (GSR 289 (E)) further prohibited the advertisement of drugs in Schedule H, H1 or X without prior government approval.

Laws that Apply to Exported Animal Products

In 2002, S.O. 722(E) amended an order from 1995 to include restrictions for antibiotics in fresh, frozen, and processed fish and fishery products intended for export (see Annex 4). The amendment includes maximum residue limits for tetracycline oxytetracycline, trimethoprim, and oxolinic acid, and it prohibits the use of certain antibiotics (Table 1) in units processing all types of seafood (Ministry of Commerce and Industry, Department of Commerce 2002).

A residue monitoring plan, implemented by the Export Inspection Council, monitors antibiotic residues in eggs, honey, milk and poultry meat.

TABLE 1: Prohibited Antibiotics for Use in Seafood as per S.O. 722(E) dated July 10, 2002.

All nitrofurans (including furaltadone, furazolidone, furylfuramide, nifuratel, nifuroxime, nifurprazine, nitrofurnatoin and nitrofurazone)
Chloramphenicol
Neomycin
Nalidixic Acid
Sulfamethoxazole
Dapsone
Dimetridazole
Metronidazole
Ronidazole
Ipronidazole
Other nitroimidazoles
Sulfonamide drugs (except approved sulfadimethoxine, sulfabromomethazine, and sulfaethoxypyidazine)
Fluoroquinolones
Glycopeptides

In 2003, order S.O. 1227(E) prohibited the use of 'antibacterial substances, including quinolones' from the culture of, or in any hatchery for producing the juveniles or larvae or nauplii of, or any unit manufacturing feed for, or in any stage of the production and growth of shrimps, prawns or any other variety of fish and fishery products without authorization from qualified veterinary surgeons or fishery scientists (Gazette, 2003b).

[3]H1 drugs: alprazolam, balofloxacin, buprenorphine, capreomycin, cefdinir, cefditoren, cefepime, cefetamet, cefexime, cefoperazone, cefotaxime, cefpirome, cefpodoxime, ceftazidime, ceftibuten, ceftizoxime, ceftriaxone, chlordiazepoxide, clofazimine, codeine, cycloserine, diazepam, diphenoxylate, doripenem, ertapenem, etambutol hcl, ethinamide, feropenem, gemifloxacin, imipenem, isoniazid, levofloxacin, meropenem, midazolam, moxifloxacin, nitrazepam, pentazocine, prulifloxacin, pyrazinamide, ribabutin, rafampicin, sodium para-aminosalicylate,

In addition to laws restricting antibiotic use in aquaculture for export, the Export Inspection Council of India regulates establishments that process fish and fishery products meant for export. Procedures for testing for antibiotic residues are one such regulation. (Export Inspection Council of India 2005).

In 2003, order S.O. 1037(E) amended a 1997 law regulating antibiotic residues in eggs and egg products. MRLs for antibiotics in food products consider an acceptable daily intake, based on an assumed average daily intake, with a margin of safety. The amendment lists the following MRLs for the indicated antibiotics in egg powder for export (Table 2) (Gazette, 2003a).

TABLE 2: The MRLs in Exported Egg Products as of September 9, 2003 (S.O. 1037(E))

Antibiotic	Maximum Residue Limit
Erythromycin	150 µg/kg
Tylosin	200 µg/kg
Lincomycin	50 µg/kg
Neomycin	500 µg/kg
Colistin	300 µg/kg
Chlortetracycline	200 µg/kg
Tetracycline	200 µg/kg
Spectinomycin	200 µg/kg
Tiamulin	100 µg/kg
Josamycin	200 µg/kg
Oxolinic Acid	50 µg/kg

In addition, this order bans the following antibiotics from feed, treatment, or use in any stage of production of egg powder for export: chloramphenicol, dimetridazole, metronidazole, nitrofurans, including metabolites of furazolidone and nitrofurazone.

Tables 1 and 2 in annex 5 show the list of antibiotics prohibited for use in food animals. The minimum required performance limit (MRPL) of the laboratory testing equipment for these antimicrobials is also indicated. India has adopted EU MRLs for antimicrobials in food animal products for export.

The European Commission Decision 2002/657/EC describes detailed rules for method validation within the framework of residue monitoring programs for countries exporting to the EU. National analytical surveillance testing to meet regulatory standards for export is undertaken in public sector laboratories and institutions that export products to the EU (MPEDA 2012).

Laws in the European Union

In 2006, the EU banned all antibiotic growth promoters. Since the ban of avilamycin, erythromycin, vancomycin, and virginiamycin as antibiotic growth promoters in Denmark, antibiotic resistance levels in humans have decreased, suggesting that the agriculture ban has had the desired

effect. For example, following the ban on virginiamycin as a growth promoter in 1998, virginiamycin resistance decreased by one-third by 2000 (Aarestrup et al. 2001). In Great Britain the percent of *S. typhimurium* isolates from calves resistant to tetracycline dropped from 60 percent to 8 percent in the seven years after banning tetracycline for growth promotion (Cherubin 1984).

Based on the council regulation established in 1990, (EEC) No. 2377/90, the commission regulation (EU) 37/2010 outlines maximum levels of antibiotics in foodstuffs of animal origin. This commission regulation also includes a list of several antimicrobials that are banned from use in food products because safe levels have not been determined. They are chloramphenicol, dapsone, dimetridazole, metronidazole, nitrofurans (including furazolidone), and ronidazole (European Commission 2010).

In November 2011, the EU put forward a five-year plan to fight against antimicrobial resistance. The plan included 12 recommendations to restrict veterinary use of antibiotics, both new antibiotics and antibiotics that are considered critically important to humans. Other recommendations focused on the 'promotion of appropriate use of antimicrobials' and the strengthening of 'regulatory frameworks on veterinary medicines'. In addition, the commission suggested a new animal health law pertaining to good farming practices to avoid infections and the reduction of antimicrobials in aquaculture, to be implemented shortly (European Commission 2011).

The World Health Organization Regional Office for Europe also released a strategic action plan on antibiotic resistance in 2011 (World Health Organization Regional Office for Europe 2011). Strategic objectives include the prevention and control of the development and spread of antibiotic resistance in the veterinary and agricultural sectors.

The EU collects data on antimicrobial use and resistance in animals through the European Medicines Agency's European Surveillance of Veterinary Antimicrobial Consumption (ESVAC), the European Food Safety Authority (EFSA) and the European Centre for Disease Prevention and Control (ECDC). Audits on the implementation of relevant legislation are conducted by the Food and Veterinary Office.

Laws in the United States

In the United States, the Food and Drug Administration (FDA) has considered imposing limits on antibiotic use in growth promotion since the 1970s. In 2014, the FDA passed voluntary guidance for industry (GFI) 209 and 213. These guidelines target pharmaceutical companies that sell veterinary antibiotics, recommending that they voluntarily increase veterinary oversight of antibiotics (by changing their drug indications to require a prescription) and change the labels on their drugs so that their use for 'production', or growth promotion, is no longer allowed. Companies have three years (until 2018) to comply with the guidance (Food and Drug Administraton 2013).

The U.S. Food and Drug Aministration (FDA) prohibits the extra-label (off-label) use of certain antibiotics in food-producing animals (Table 3). Extra-label use in livestock includes using the drug at unapproved dosage levels, as a growth promoter or for disease prevention, and using drugs meant for one species on another (for example, using cephalosporins meant to treat humans on chickens). The use of chloramphenicol for any reason is prohibited (FDA 2012).

TABLE 3: Antibiotics Prohibited for Extra-label Use in Food Animals by the FDA as of April 1, 2015.

Chloramphenicol
Clenbuterol
Diethylstilbestrol (DES)
Dimetridazole
Ipronidazole
Other Nitroimidazoles
Furazolidone
Nitrofurazone
Sulfonamide drugs in lactating dairy cows (except approved use of sulfadimethoxine, sulfabromomethazine, and sulfaethoxypyridazine)
Fluoroquinolones
Glycopeptides (e.g., vancomycin)
Phenylbutazone in female dairy cattle 20 months of age or older
Cephalosporin (excluding cephapirin) in cattle, swine, chickens, or turkeys

CHAPTER 4

Recommendations

The use of antibiotics in animals for any reason leads to declining antibiotic effectiveness against infections in animals and eventually in humans. Some uses in animals, such as for the treatment of bacterial infections, are appropriate. However, use of antibiotics purely as growth promoters and for some prophylactic purposes is unnecessary and avoidable. These recommendations are aimed at reducing the inappropriate use of antibiotics to decrease the total amount used in livestock without causing harm to human or animal health. The following recommendations are similar to those that the OIE presented to member countries in May 2015 (see Annex 6).

In order to conserve antibiotic effectiveness in humans and animals, we recommend the following:

1) Track rates of veterinary antibiotic use, resistance, and residues through a nationwide surveillance and monitoring system

2) Change incentives to discourage unnecessary antibiotic use in animals

3) Educate farmers, veterinarians, and consumers on the dangers of antibiotic resistance

4) Phase out the sub-therapeutic use of antibiotics in animals

1) Track rates of veterinary antibiotic use, resistance, and residues through a nationwide surveillance and monitoring system

Veterinary antibiotic use, residues, and resistance have not been tracked systematically in India. To fill this knowledge gap, a sentinel surveillance system should be initiated, collecting qualitative (i.e., patterns of use) and quantitative information to track patterns of use and resistance levels over time. The system could be designed and overseen by a working group that includes veterinary scientists, representatives from the ministry, and surveillance experts. Preliminary steps would include determining implementation partners and the microorganisms and antibiotics that would be a part of the surveillance program. Partners could include veterinary colleges and the Indian Council of Agricultural Research (ICAR).

2) Change incentives to discourage unnecessary antibiotic use in animals

There is a need to develop incentives that will reduce antibiotic use without jeopardizing animal or human health. Randomized intervention trials can provide further insight into the types of incentives that might successfully reduce use. For instance, trials might explore the impact of subsidizing microbiological tests for bacterial infections in animals; introducing national certificates for antibiotic-free animal food products sold for human consumption; or the implementation of alternative methods for disease control.

3) Educate farmers, veterinarians, and consumeres on the dangers of antibiotic resistance

Worldwide, there is still a lack of awareness about antibiotic resistance. Education and awareness raising among farmers, veterinarians and the public can play a role in reducing antibiotic use in animals. A national strategy would ensure that all segments are covered and that the messages delivered to this diverse set of audiences are consistent. Farmers could be targeted at market days and fairs, through extension education conducted by veterinary and agricultural universities, and by radio, television and print campaigns. Veterinarians can be educated by modifying college curricula to include antibiotic resistance content. Awareness raising among the general public, through regular and social media, may be able to generate increased demand for antibiotic-free products.

4) Phase out the sub-therapeutic use of antibiotics in animals

Elimination of the sub-therapeutic use of antibiotics has the potential to greatly reduce overall antibiotic use and resistance. This use should be phased out over time, with monitoring to ensure that the phase-out does not have unintended negative consequences for animal health and that overall antibiotic use does decrease. The approach to the phase-out will vary between animals, depending on how sub-therapeutic antibiotics are administered. The total amounts of antibiotics used and total production costs should be monitored. The adoption of alternatives to antibiotics in conjunction with other incentives as recommended above may help encourage the gradual phase-out of sub-therapeutic uses of antibiotics while maintaining animal health.

References

Aarestrup, F.M., Seyfarth, A.M., Pedersen, K., Hendriksen, R.S. and Emborg H. 2001. "Effect of Abolishment of the Use of Antimicrobial Agents for Growth Promotion on Occurrence of Antimicrobial Resistance in Fecal Enterococci from Food Animals in Denmark Effect of Abolishment of the Use of Antimicrobial Agents for Growth Promotion on Occu." doi:10.1128/AAC.45.7.2054.

APEDA. 2015. "Red Meat Manual." Agricultural and Processed Food Products Export Development Authority. http://apeda.gov.in/apedawebsite/six_head_product/animal.htm.

Arya, G., Roy, A., Choudhary, V., Yadav, M.M. and Joshi, C.G. 2008. "Serogroups, Atypical Biochemical Characters, Colicinogeny and Antibiotic Resistance Pattern of Shiga Toxin-Producing Escherichia Coli Isolated from Diarrhoeic Calves in Gujarat, India." *Zoonoses and Public Health* 55 (2): 89–98. doi:10.1111/j.1863-2378.2007.01093.x.

Barton, N. H., Brigg, D.E.G., Eisen, J.A., Goldstein, D.B., and Patel, N.H. 2007. *Evolution*. Cold Spring Harbor, New York: Cold Spring Harbour Laboratory Press.

Berendonk, T.U., Manaia, C.M., Merlin, C., Fatta-Kassinos, D., Cytryn, E., Walsh, F., Bürgmann, H. et al. 2015. "Tackling Antibiotic Resistance: The Environmental Framework." *Nature Reviews Microbiology* advance on (March).

Bharathkumar, G, and Abraham, T.J. 2011. "Antibiotic Susceptibility of Gram-Negative Bacteria Isolated from Freshwater Fish Hatcheries of West Bengal, India." *Indian J. Fish*. 58 (3): 135–38.

Brower, C.H., Mandal, S., Hayer, S., Sran, M., Zehra, A., Patel, S., Kaur, R. et al. "Widespread prevalence of ESBL-producing multidrug resistant *Escherichia coli* in poultry chickens modulated by farming practices in Punjab, India." Manuscript in Preparation.

Center for Disease Dynamics, Economics & Policy (CDDEP). 2009. "Community-Level E. Coli Resistance to Ciprofloxacin Is High in India, Particularly in Delhi." Washington, D.C.: CDDEP. http://www.cddep.org/tool/community_level_e_coli_resistance_ciprofloxacin_high_india_particularly_delhi#sthash.gdjnftjN.dpbs.

———. 2012. "The Burden of Antibiotic Resistance in Indian Neonates." http://www.cddep.org/tools/burden_antibiotic_resistance_indian_neonates.

———. 2015. "State of the World's Antibiotics, 2015."

Center for Science and Environment (CSE). 2014. "Factsheet 03: Use of Antibiotics in Animals." New Delhi: Center for Science and Environment.

———. 2014. "Feed with Antibiotic Growth Promoters." New Delhi: Center for Science and Environment. http://www.cseindia.org/userfiles/factsheets/factesheet%206.pdf.

Chand, R., Bhavadasan, M.K., and Vijya, G.V. 2003. "Antimicrobial Drugs in Milk from Southern India." *Indian Dairyman* 55 (3): 154.

Cherubin, C.E. 1984. "Epidemiological Assessments of Antibiotic Resistance in Salmonella." In *CRC Handbook Series in Zoonoses*, edited by JH Steel and GW en Baran, 173–200. Boca Raton, FL, USA: CRC Press.

Codex Alimentarius Commission. 2015. "Maximum Residue Limits for Veterinary Drugs in Foods." http://www.codexalimentarius.org/standards/veterinary-drugs-mrls/en/

Cogliani, C., Goossens, H. and Greko, C. 2011. "Restricting Antimicrobial Use in Food Animals: Lessons from Europe" 6 (6): 274–79.

Daghrir, R., and Drogui, P. 2013. "Tetracycline Antibiotics in the Environment: A Review." *Environmental Chemistry Letters* 11 (3): 209–27.

DAHD. 2011. "Annual Report, 2010-11." Government of India Department of Animal Husbandry, Dairying & Fisheries.

———. 2012. "19th Indian Livestock Census." Indian Department of Animal Husbandry, Dairying and Fisheries. http://dahd.nic.in/dahd/statistics/livestock-census/19th-indian-livestock-census.aspx.

———. 2014. "A Background Note on the Implementation of 100% Centrally Sponsored Schemes of Government of India Ministry of Agriculture, Department of Animal Husbandry, Dairying & Fisheries (DADF) New Delhi." Government of India Department of Animal Husbandry, Dairying & Fisheries. http://chdanimalhusbandry.gov.in/background%20note.pdf.

———. 2015. "Annual Report 2014-15." Government of India Department of Animal Husbandry, Dairying & Fisheries. http://dahd.nic.in/sites/default/files/Animal%20Husbandry%20English%202014-15%20%201.pdf.

Dancer, S. J. 2001. "The Problem with Cephalosporins." *Journal of Antimicrobial Chemotherapy* 48 (4): 463–78. doi:10.1093/jac/48.4.463.

Deekshit, V.K., Kumar, B.K., Rai, P., Srikumar, S., and Karunasagar, I. 2012. "Detection of Class 1 Integrons in Salmonella Weltevreden and Silent Antibiotic Resistance Genes in Some Seafood-Associated Nontyphoidal Isolates of Salmonella in South-West Coast of India." *Journal of Applied Microbiology* 112 (6): 1113–22. doi:10.1111/j.1365-2672.2012.05290.x.

Deshpande, P., Rodrigues, C., Shetty, A., Farhad, K., Hedge, A., and Soman, R. 2010. "New Delhi Metallo-B Lactamase (NDM-1) in Enterobacteriaceae: Treatment Options with Carbapenems Compromised." *Journal of Association of Physicians of India* 58: 147–49.

Dhanarani, T.S., Shankar C., Park, J., Dexilin, M., Kumar, R.R. and Thamaraiselvi, K. 2009. "Study on Acquisition of Bacterial Antibiotic Resistance Determinants in Poultry Litter." *Poult Sci* 88 (7): 1381–87. doi:10.3382/ps.2008-00327.

Dibner, J.J., and Richards, J.D. 2005. "Antibiotic Growth Promoters in Agriculture: History and Mode of Action." *Poultry Science* 84 (4): 634–43.

Directorate General of Health Services, Ministry of Health and Family Welfare. 2011. "National Policy for Containment of Antimicrobial Resistance." New Delhi: MHFW

Dutil, L., Irwin, R., Finley, R., Lai King, N., Avery, B., Boerlin, P., Bourgault, A.M. et al. 2010. "Ceftiofur Resistance in Salmonella Enterica Serovar Heidelberg from Chicken Meat and Humans, Canada." *Emerging Infectious Diseases* 16 (1): 48–54. doi:10.3201/eid1601.090729.

Dutta, G.N., Dutta, R., Jyoti, B., and. Milli, D.C. 2001. "Antibiotic Residues in Milk after Treatment of Mastitis." *Indian Journal of Dairy Science* 54: 322–25.

Dutta, T.K., Kumar, V.S. and Kotwal, S.K. 2007. "Prevalence and Antibiotic Resistance Pattern of Bacteria from Clinical and Subclinical Cases of Bovine Mastitis in Jammu Region." *The Indian Journal of Animal Sciences*; 77 (6).

Dutta, T. K., Roychoudhury, P., Bandyopadhyay, S., and Chandra, R. 2011. "Detection and Characterization of Shiga Toxigenic Escherichia Coli from Piglets with or without Diarrhoea in Mizoram." *The Indian Journal of Animal Sciences* 81 (9).

Dutta, T.K., Roychoudhury, P. and Banik, S. 2009. "Antimicrobial Drug Resistance of Pasteurella Multocida Isolated from Pigs in North Eastern Hilly Region of India." *The Indian Journal of Animal Sciences* 79 (11).

EFSA and ECDC. 2015. "EU Summary Report on Antimicrobial Resistance in Zoonotic and Indicator Bacteria from Humans, Animals and Food in 2013." Stockholm: EFSA and ECDC

Elliott, K. 2015. "Antibiotics on the Farm: Agriculture's Role in Drug Resistance." Policy Paper 059. Washington, D.C.: Center for Global Development.

European Commission. 2011. "Communication from the Commission to the European Parliament and the Council: Action Plan against the Rising Threats from Antimicrobial Resistance." Brussels: European Commission

———. 2010. "Commission Regulation (EU) No 37/2010." Official Journal of the European Union, no. 2377. Brussels: European Commission

Export Inspection Council of India. 2005. "Scheme for Approval and Monitoring of Establishments/Factory Vessels/ Freezer Vessels Processing/Storing Fish & Fishery Products for Export with Amendments No. 1, 2 & 3." New Delhi: Export Inspection Council

Fairoze, M.N. 2012. *Personal Communication with Dr. Mohamed Nadeem Fairoze, Professor and Head of Dept. of Livestock Products Technology at Veterinary College, KVAFS University.*

FAO. 2003. "Project on Livestock Industrialization, Trade and Social-Health-Environment Impacts in Developing Countries. Policy, Technical, and Environmental Determinants and Implications of the Scaling-Up of Livestock Production in Four Fast-Growing Developing Countries: A Synthesis." Food and Agriculture Organization of the United Nations (FAO). http://www.fao.org/documents/card/en/c/a8743e1c-ea2e-5007-a3e4-8e75864539cc/.

———. 2006. "Livestock's Long Shadow: Environmental Issues and Options." Food and Agriculture Organization of the United Nations (FAO). http://www.fao.org/docrep/010/a0701e/a0701e00.HTM.

FDA. 2012. "Part 530: Extralabel Drug Use in Animals." *Code of Federal Regulations, Title 21,* Volume 6. www.fda.gov/downloads/AnimalVeterinary/ResourcesforYou/AnimalHealthLiteracy/ucm109808.pdf.

Fick, J., Soderstrom, H., Lindberg, R.H., Phan, C., Tysklind, M., and Larsson, J.D.G. 2009. "Contamination of Surface, Ground, and Drinking Water From Pharmaceutical Production." *Environmental Toxicology and Chemistry* 28 (12): 2522–27.

Finley, R.L., Collignon, P., Larsson, J.D.G., McEwen, S., Li, X., Gaze, W.H., Reid-Smith, R., Timinouni, M., Graham, D.W., and Topp, E. 2013. "The Scourge of Antibiotic Resistance: The Important Role of the Environment." Clinical Infectious Diseases, June, 1–7. doi:10.1093/cid/cit355.

Food and Drug Administration (FDA). 2015. "Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals." Washington D.C.: FDA. http://www.fda.gov/downloads/ForIndustry/UserFees/AnimalDrugUserFeeActADUFA/UCM476258.pdf.

———. 2013. “The Judicious Use of Medically Important Antimicrobial Drugs in Food-Producing Animals.” Washington D.C.: FDA.

———. 2012. “Part 530: Extralabel Drug Use in Animals.” Code of Federal Regulations, Title 21, Volume 6. Washington, D.C.: FDA

———. 2010. “2009 Summary Report on Antimicrobials Sold or Distributed for Use in Food-Producing Animals.” Washington D.C.: FDA.

http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=530&showFR=1.

FDA Center for Veterinary Medicine. 2011. “A Quick Reference Guide to: Approved Drugs for Use in Aquaculture.” Washington, D.C.: FDA

Ganguly, N. K. 2011. “Situation Analysis: Antibiotic Use and Resistance in India.” New Delhi: Global Antibiotic Resistance Partnership.

Gazette of India. 2013. “Gazette Notification G.S.R. 588.” New Delhi: Gazette of India.

———. 2012. “Gazette Notification G.S.R. 28 (E).” New Delhi: Gazette of India.

———. 2006. “Drugs and Cosmetics Rules (2nd Amendment) G.S.R. 160(E).” New Delhi: Gazette of India.

———. 2003a. “Gazette Notification, S.O. 1037 (E).” New Delhi: Gazette of India.

———. 2003b. “Gazette Notification S.O. 1227(E).” New Delhi: Gazette of India.

———. 2002. “Gazette Notification S.O. 722 (E).” New Delhi: Gazette of India.

Ghafur, A., Gill, J.P.S., Gopalakrishnan, R., Hegde, B.M., Huilgol, A., Jayalal, J.A., Kant, R. et al. 2013. “‘The Chennai Declaration’ Recommendations of ‘A Roadmap-to Tackle the Challenge of Antimicrobial Resistance’ - A Joint Meeting of Medical Societies of India.” *Indian Journal of Cance*r. doi:10.4103/0019-509X.104065.

Ghatak, S., Singha, A., Sen, A., Guha, C. Ahuja, A. Bhattacharjee, U., Das, S. et al. 2013. “Detection of New Delhi Metallo-Beta-Lactamase and Extended-Spectrum Beta-Lactamase Genes in Escherichia Coli Isolated from Mastitic Milk Samples.” *Transboundary and Emerging Diseases* 60 (5): 385–89. doi:10.1111/tbed.12119.

Ghosh, K., and Mandal, S. 2010. “Antibiotic Resistant Bacteria in Consumable Fishes from Digha Coast, West Bengal, India.” *Proceedings of the Zoological Society* 63 (1): 13–20. doi:10.1007/s12595-010-0002-8.

Global Antibiotic Resistance Partnership. 2011a. “New Delhi: Call to Action on Preserving the Power of Antibiotcs.”

———. 2011b. “Rationalizing Antibiotic Use to Limit Antibiotic Resistance in India.” The Indian Journal of Medical Research 134 (3): 281–94.

Government of India. 2012. “Report of the Working Group Animal Husbandry and Dairying, 12th 5-Year Plan (2012-2017).” New Delhi: Government of India Planning Commission. https://www.google.co.in/webhp?sourceid=chrome-instant&ion=1&espv=2&ie=UTF-8#q=india+16%25+of+world+cattle+population+57%25+buffaloes+.

Gupta, S., Govil, D. Kakar, P.N., Prakash, O., Arora, D., Das, S., Govil, P. and Malhotra, A. 2009. “Colistin and Polymyxin B: A Re-Emergence.” *Indian Journal of Critical Care Medicine : Peer-Reviewed, Official Publication of Indian Society of Critical Care Medicine* 13 (2): 49–53. doi:10.4103/0972-5229.56048.

Halling-Sørensen, B., Nors Nielsen, S., Lanzky, P.F., Ingerslev, F., Lützhøft, H.C., and Jørgensen, S.E. 1998. “Occurrence, Fate and Effects of Pharmaceutical Substances in the Environment- A Review.” *Chemosphere* 36 (2): 357–93.

Hemlata et al. 2015. “Enumeration and Antibiotic Resistance Pattern of Staphylococcus Aureus from Raw Chicken Meat Sold in Bikaner City.” *Journal of Pure and Applied Microbiology* 9 (2).

Kahn, L., and Cottle, D. 2014. *Beef Cattle Production and Trade*. CSIRO PUBLISHING. https://books.google.co.in/books?id=suFZAwAAQBAJ.

Kar, D., Bandyopadhyay, S., Bhattacharyya, D., Samanta, I., Mahanti, A., Nanda, P.K., Mondal, B. et al. 2015. “Molecular and Phylogenetic Characterization of Multidrug Resistant Extended Spectrum Beta-Lactamase Producing Escherichia Coli Isolated from Poultry and Cattle in Odisha, India.” *Infection, Genetics and Evolution : Journal of Molecular Epidemiology and Evolutionary Genetics in Infectious Diseases* 29 (January): 82–90. doi:10.1016/j.meegid.2014.11.003.

Kawoosa, S.S., Samanta, I., and Wani, S.A. 2007. “In Vitro Drug Sensitivity Profile Of Positive Escherichia Coli from Diarrhoeic Calves in Kashmir Valley.” *The Indian Journal of Animal Sciences* 77 (7).

Kishore, P., Lalitha, K.V., Joseph, T.C., and Thampuran, N. 2012. “Biotyping and Antibiotic Resistance Profile of Yersinia Enterocolitica Associated with Seafoods from South-West Coast of India.” *Fishery Technology* 49: 64–71.

Köck, R., Mellmann, A., Schaumburg, F., Friedrich, A.W., Kipp, F. and Becker, K. 2011. “The Epidemiology of Methicillin-Resistant Staphylococcus Aureus (MRSA) in Germany.” *Deutsches Ärzteblatt International* 108 (45): 761–67. doi:10.3238/arztebl.2011.0761.

Kumar, P.A., Joseph, B., and Patterson, J. 2011. "Antibiotic and Heavy Metal Resistance Profile of Pathogens Isolated from Infected Fish in Tuticorin, South-East Coast of India." Indian J. Fish. 58 (2): 121–25.

Kumar, P.A., Patterson, J., and Karpagam, P. 2009. "Multiple Antibiotic Resistance Profiles of Vibrio Cholerae Non-O1 and Non-O139." *Japanese Journal of Infectious Diseases* 62: 230–32.

Kumar, R., and Surendran, P.K. 2005. "Phenotypic Characterization and Antibiotic Resistance of Pseudomonas Spp. from Seafood and Aquaculture Farm Environments." *Fishery Technology* 42 (2): 203–8.

Kumar, R., Surendran, P.K. and Thampuran, N. 2009. "Analysis of Antimicrobial Resistance and Plasmid Profiles in Salmonella Serovars Associated with Tropical Seafood of India." *Foodborne Pathogens and Disease* 6 (5): 621–25. doi:10.1089/fpd.2008.0252.

Kumar, R., Yadav, B.R., Anand, S.K. and Singh, R.S. 2011. "Molecular Surveillance of Putative Virulence Factors and Antibiotic Resistance in Staphylococcus Aureus Isolates Recovered from Intra-Mammary Infections of River Buffaloes." *Microbial Pathogenesis* 51 (1-2): 31–38. doi:10.1016/j.micpath.2011.03.006.

Kumar, R., Yadav, B.R., and Singh, R.S. 2011. "Antibiotic Resistance and Pathogenicity Factors in Staphylococcus Aureus Isolated from Mastitic Sahiwal Cattle." *Journal of Biosciences* 36 (1): 175–88.

Kumar, S.G., Adithan, C., Harish, B.N., Sujatha, S., Roy, G. and Malini, A. 2013. "Antimicrobial Resistance in India: A Review." *Journal of Natural Science, Biology, and Medicine* 4 (2): 286–91. doi:10.4103/0976-9668.116970.

Kumar, T., Mahajan, N.K. and Rakha, N.K. 2012. "Isolation and Prevalence of Salmonella Serovars from Poultry in Different Parts of Haryana, India*." *The Indian Journal of Animal Sciences* 82 (6).

Kumar, V., Das, S.C., Guin, S., and Malik, S.V.S. 2012. "Virulence, Enterotoxigenicity and Antibiotic Profile of Staphylococcus Aureus from Buffalo Clinical Mastitis." *The Indian Journal of Animal Sciences* 81 (1).

Laxminarayan, R., Malani, A., Howard, D., and Smith, D.L. 2007. "Extending the Cure: Policy Responses to the Growing Threat of Antibiotic Resistance." Washington, DC. Resources for the Future.

Laxminarayan, R., VanBoeckel, T., and Teillant, A. 2015. "The Economic Costs of Withdrawing Antimicrobial Growth Promoters from the Livestock Sector," *OECD Food, Agriculture and Fisheries Papers* no. 78.

Liu, Y.Y., Wang, Y., Walsh, T.R., Yi, L.X., Zhang, R., Spencer, J., Doi, Y. et al. 2015. "Emergence of Plasmid-Mediated Colistin Resistance Mechanism MCR-1 in Animals and Human Beings in China: A Microbiological and Molecular Biological Study." *The Lancet Infectious Diseases*, November. doi:10.1016/S1473-3099(15)00424-7.

Manna, S.K., Brahmane, M.P, Manna, C., Batabyal, K. and Das, R. 2006. "Occurrence, Virulence Characteristics and Antimicrobial Resistance of Escherichia Coli O157 in Slaughtered Cattle and Diarrhoeic Calves in West Bengal, India." *Letters in Applied Microbiology* 43 (4): 405–9. doi:10.1111/j.1472-765X.2006.01975.x.

Marine Products Export Development Authority. 2012. "Marine Products Exports Crossed 3.5 Billion Marks in 2011-12." Kochi: Marine Products Export Development Authority

Marshall, B.M, and Levy, S.B. 2011. "Food Animals and Antimicrobials: Impacts on Human Health." Clinical Microbiology Reviews 24 (4): 718–33. doi:10.1128/CMR.00002-11.

Meena, V.D., Dotaniya, M.L., Saha, J.K, and Patra, A.K.. 2015. "Antibiotics and Antibiotic Resistant Bacteria in Wastewater : Impact on Environment , Soil Microbial Activity and Human Health" 9.

Michigan State University. 2011. "Veterinary Public Health." *Michigan State University Antimicrobial Learning Site.* http://amrls.cvm.msu.edu/veterinary-public-health-module/veterinary-public-health-module.

Mir, I. A., Kashyap, S.K., and Maherchandani, S. 2015. "Isolation, Serotype Diversity and Antibiogram of Salmonella Enterica Isolated from Different Species of Poultry in India." *Asian Pacific Journal of Tropical Biomedicine* 5 (7): 561–67. doi:10.1016/j.apjtb.2015.03.010.

MOHFW. 2011. "FOOD SAFETY AND STANDARDS (CONTAMINANTS, TOXINS AND RESIDUES) REGULATIONS, 2011." Government of India Ministry of Health and Family Welfare. http://www.fssai.gov.in/Portals/0/Pdf/Food%20safety%20and%20standards%20(contaminats,%20toxins%20and%20residues)%20regulation,%202011.pdf.

MPEDA. 2012. "Development of Regulations on Usage of Antimicrobials in Aquaculture." 2012.

Mukherjee, P., Ramamurthy, T. Bhattacharya, M.K., Rajendran, K. and Mukhopadhyay, A. K. 2013. "Campylobacter Jejuni in Hospitalized Patients with Diarrhea, Kolkata, India." *Emerging Infectious Diseases* 19 (7): 1155–56. doi:10.3201/eid1907.121278.

NARMS. 2011. "Annual Animal Report." Washington, D.C.:NARMS

National Dairy Research Institute. 2011. "Annual Report 2010-2011." Karnal: NDRI

Normanno, G., Corrente, M., La Salandra, G., Dambrosio, N.C., Quaglia, Parisi, A., Greco, G., Bellacicco, L., Virgilio, S., and Celano, G.V. 2007. "Methicillin-Resistant Staphylococcus Aureus (MRSA) in Foods of Animal Origin Product in Italy." *International Journal of Food Microbiology* 117 (2): 219–22. doi:10.1016/j.ijfoodmicro.2007.04.006.

OIE. 2015a. "Aquatic Animal Health Code (2015)." Paris: World Organization for Animal Health. http://www.oie.int/en/international-standard-setting/aquatic-code/access-online/.

———. 2015b. "Terrestrial Animal Health Code (2015)." Paris: World Organization for Animal Health. http://www.oie.int/international-standard-setting/terrestrial-code/access-online/.

———. 2008. "Manual of Diagnostic Tests and Vaccines for Terrestrial Animals." World Organization for Animal Health. http://www.oie.int/manual-of-diagnostic-tests-and-vaccines-for-terrestrial-animals/. Paris: World Organization for Animal Health

Planning Commission of India. 2013. "12th Five-Year Plan (2012-2017), Social Sectors, Volume III." New Delhi: Government of India

Prasad, K.N., Mathur, S.K., Dhole, T.N. and Ayyagari, A. 1994. "Antimicrobial Susceptibility and Plasmid Analysis of Campylobacter Jejuni Isolated from Diarrhoeal Patients and Healthy Chickens in Northern India." *Journal of Diarrhoeal Diseases Research* 12 (4): 270–73.

Preethirani, P. L., Isloor, S., Sundareshan, S., Nuthanalakshmi, V., Deepthikiran, K., Sinha, A.Y., Rathnamma, D. et al. 2015. "Isolation, Biochemical and Molecular Identification, and In-Vitro Antimicrobial Resistance Patterns of Bacteria Isolated from Bubaline Subclinical Mastitis in South India." *PloS One* 10 (11): e0142717. doi:10.1371/journal.pone.0142717.

Price, L.B., Graham, J.P., Lackey, L.G., Roess, A., Vailes, R., and Silbergeld, E. 2007. "Elevated Risk of Carrying Gentamicin-Resistant Escherichia Coli among U.S. Poultry Workers." *Environ Health Perspect* 115 (12): 1738–42. doi:10.1289/ehp.10191.

Price, L.B., Stegger, M., Hasman, H., and Aziz, M. 2012. "Staphylococcus Aureus CC398 : Host Adaptation and Emergence of Methicillin Resistance in Livestock." MBio 3 (1). doi:10.1128/mBio.00305-11.Editor.

Ramakrishna, Y., and Singh, R.S.. 1985. "Residual Streptomycin in Milk. A Survey." *Indian Journal of Dairy Science* 38: 148–49.

Rasheed, Uddin, M., Thajuddin, N., Ahamed, P., Teklemariam, Z., and Jamil, K. 2014. "Antimicrobial Drug Resistance in Strains of Escherichia Coli Isolated from Food Sources." *Revista Do Instituto de Medicina Tropical de Sao Paulo* 56 (4): 341–46.

Sahoo, P.K., and Mukherjee, S.C. 1997. "In-Vitro Susceptibility of Three Bacterial Pathogens of Catfish to 23 Antimicrobial Agents." *Indian Journal of Fisheries* 44 (4): 393–97.

Sahu, R., and Saxena, P. 2014. "Antibiotics in Chicken Meat." New Delhi, India.

Saikia, P.K., Dutta, G.N., Devriese, L.A., and Kalita, C.C. 1995. "Characterisation and Antimicrobial Susceptibility of Enterococcus Species from the Intestines of Ducks in Assam." *Research in Veterinary Science* 58 (3): 288–89.

Samanta, I., Joardar, S.N., Das, P.K., Sar, T.K., Bandyopadhyay, S. and Dutta, T.K. 2014. "Prevalence and Antibiotic Resistance Profiles of Salmonella Serotypes Isolated from Backyard Poultry Flocks in West Bengal, India." *Journal of Applied Poultry Research* 23 (3): 536–45.

Saravanan, S., Purushothaman, V., Murthy, T.R., Sukumar, K., Srinivasan, P., Gowthaman, V., Balusamy, M., Atterbury, R., Kuchipudi, S.V. 2015. "Molecular Epidemiology of Nontyphoidal Salmonella in Poultry and Poultry Products in India: Implications for Human Health." *Indian Journal of Microbiology* 55 (3): 319–26. doi:10.1007/s12088-015-0530-z.

Sarma, D.K., Sambyal, D.S. and Baxi, K.K. 1981. "Drug Susceptibility of Escherichia Coli from Domestic Fowl." *Zentralblatt Für Veterinärmedizin. Reihe B. Journal of Veterinary Medicine.* Series B 28 (4): 333–35.

Sarmah, A.K, Meyer, M.T., and Boxall, A.B. 2006. "A Global Perspective on the Use, Sales, Exposure Pathways, Occurrence, Fate and Effects of Veterinary Antibiotics (VAs) in the Environment." C*hemosphere* 65 (5): 725–59. doi:10.1016/j.chemosphere.2006.03.026.

Sasidhar, P.V.K. and Suvedi, M. 2015. "Integrated Contract Broiler Farming: An Evaluation Case Study in India." Washington D.C.: Feed the Future. https://agrilinks.org/library/integrated-contract-broiler-farming-evaluation-case-study-india-long.

Sasmal, D., Banerjee, T., Bandyopadhyay, S. and Abraham, T.J. 2004. "Antibiotic Sensitivity of Bacterial Flora Associated with Ornamental Fish." *Indian J. Fish.* 51 (2): 245–49.

Sathiyamurthy, K., Purushothaman, A. and Ramaiyan, V. 1997. "Antibiotic-Resistant Vibrio Cholerae in Parangipettai Coastal Environs, South East India." *Microbial Drug Resistance* 3 (3): 267–70.

Serrano, P.H. 2005. "Responsible Use of Antibiotics in Aquaculture." Food and Agriculture Organization of the United Nations (FAO). http://www.fao.org/3/a-a0282e.pdf.

Sethi, S.K., Anand, S., Singh, A. and Vadehra, D.V. 1976. "Resistance of Salmonella Serotypes to Chloramphenicol." *Bulletin of the World Health Organization* 54 (3): 353–54.

Shanthini, C., Felicia, P., Kumar, A. and Patterson, J. 2004. "Incidence and Antibiotic Susceptibility of Vibrio Parahaemolyticus from Sea Foods of Tuticorin." Indian *Journal of Fisheries* 51 (1): 43–47.

Shashidhar, R., Jajoo, S., Karani, M., Warrier, S.B. and Bandekar, J.R. 2005. "Studies on Salmonella Isolates from Fishery Products." *Fishery Technology* 42 (2): 217–24.

Shivachandra, S.B., Kumar, A., Biswas, A., Ramakrishnan, M., Singh, V.P. and Srivastava S.K. 2004 "Antibiotic Sensitivity Patterns among Indian Strains of Avian Pasteurella Multocida." *Tropical Animal Health and Production* 36 (8): 743–50.

Shome, R. and Shome, B.R. 1999. "Antibiotic Resistance Pattern of Fish Bacteria from Freshwater and Marine Sources in Andamans." *Indian Journal of Fisheries* 46 (1): 49–56.

Singh, B.R. 2009a. "Prevalence of Vancomycin Resistance and Multiple Drug Resistance in Enterococci in Equids in North India." *The Journal of Infection in Developing Countries* 3 (07). doi:10.3855/jidc.467.

Singh, B.R., Jyoti, J., Chandra, M., Babu, N. and Sharma, G. 2009b. "Drug Resistance Patterns of Salmonella Isolates of Equine Origin from India." *The Journal of Infection in Developing Countries* 3 (02). doi:10.3855/jidc.61.

Singh, B.R., Babu, H., Jyoti, J., Shankar, H., Vijo, T.V., Agrawal, R.K., Chandra, M., Kumar, D., Teewari, A., and Babu, N. 2007. "Prevalence of Multi-Drug-Resistant Salmonella in Equids Maintained by Low Income Individuals and on Designated Equine Farms in India." *Journal of Equine Veterinary Science* 27 (6): 266–76. doi:10.1016/j.jevs.2007.04.011.

Singh, G.N. 2014. "Use of Antibiotics for Treatment of Food Producing Animals and in Animal Feeding." India: Central Drugs Standard Control Organization. http://www.cdsco.nic.in/writereaddata/Meneka%20Sanjay%20Gandhi.pdf.

Singh, M., Chaudhry, M.A., Yadava, J.N. and Sanyal, S.C. 1992. "The Spectrum of Antibiotic Resistance in Human and Veterinary Isolates of Escherichia Coli Collected from 1984-86 in Northern India." The Journal of Antimicrobial Chemotherapy 29 (2): 159–68.

Singh, M., Sanyal, S.C. and Yadav, J.N. 1992. "Enterotoxigenic Drug Resistant Plasmids in Animal Isolates of Escherichia Coli and Their Zoonotic Importance." *The Journal of Tropical Medicine and Hygiene* 95 (5): 316–21.

Sudershan, R.V. and Bhat, R.V. 1995. "A Survey on Veterinary Drug Use and Residues in Milk in Hyderabad." *Food Additives and Contaminants* 12 (5): 645–50. doi:10.1080/02652039509374353.

Sudha, S., Divya, P.S., Francis, B. and Hatha A.A.M. 2012. "Prevalence and Distribution of Vibrio Parahaemolyticus in Finfish from Cochin (south India)." V*eterinaria Italiana* 48 (3): 269–81.

Sunder, J., Jeyakumar, S., Ahlawat, S.P.S., Rai, R.B., Kundu, A., Senani, S., Chatterjee, R.N., Saha, S.K. and Yadav, S. 2006. "Antibiotic Resistance Pattern of Bacterial Isolates from Fishes of Andaman and Nicobar Islands." *Indian Journal of Fisheries* 53 (2): 231–35.

Surendraraj, A., Thampuran, N. and Joseph, T.C. 2010. "Molecular Screening, Isolation, and Characterization of Enterohemorrhagic Escherichia Coli O157:H7 from Retail Shrimp." *Journal of Food Protection* 73 (1): 97–103.

Surendraraj, A., Thampuran, N. and Surendran, P.K. 2005. "Level of Escherichia Coli in Seafood in Domestic Trade and Their Antibiotic Resistance Pattern." *Fishery Technology* 42 (2): 209–16.

Suresh, T., Hatha, A.A.M., Sreenivasan, D., Sangeetha, N. and Lashmanaperumalsamy, P. 2006. "Prevalence and Antimicrobial Resistance of Salmonella Enteritidis and Other Salmonellas in the Eggs and Egg-Storing Trays from Retails Markets of Coimbatore, South India." *Food Microbiology* 23 (3): 294–99. doi:10.1016/j.fm.2005.04.001.

Tacket, C.O., Dominguez, L.B., Fisher, H.J. and Cohen, M.L. 1985. "An Outbreak of Multiple-Drug-Resistant Salmonella Enteritis from Raw Milk." *JAMA : The Journal of the American Medical Association* 253 (14): 2058–60. doi:10.1001/jama.253.14.2058.

Tiwari, J.G., Chaudhary, S.P., Tiwari, H.K., Dutta, T.K., Saikia, P. and Hazarika, P. 2011. "Microbial Evaluation of Market Milk and Milk-Products of Mizoram, India with Special Reference to Staphylococcus Aureus." *The Indian Journal of Animal Sciences* 81 (4).

Tiwary, B.K. and Prasad, L.B.M. 1972. "Enteric Infection in Livestock and Poultry Caused by Salmonellae and Shigellae." *The Veterinary Record* 91: 510–13.

Unnikrishnan, V., Bhavadassan, M.K., Nath, B.S. and Ram, C. 2005. "Chemical Residues and Contaminants in Milk: A Review." *The Indian Journal of Animal Sciences* 75 (5).

Van Boeckel, T.P., Brower, C., Gilbert, M., Grenfell, B.T., Levin, S., Robinson, T.P., Teillant, A. and Laxminarayan, R. 2015. "Global Trends in Antimicrobial Use in Food Animals." *Proceedings of the National Academy of Sciences*, no. 16: 201503141–201503141. doi:10.1073/pnas.1503141112.

Van den Bogaard, A.E. and Stobberingh, E.E. 2000. "Epidemiology of Resistance to Antibiotics. Links between Animals and Humans." *International Journal of Antimicrobial Agents* 14 (4): 327–35.

Vaseeharan, B., Ramasamy, P., Murugan, T., and Chen J.C. 2005. "In Vitro Susceptibility of Antibiotics against Vibrio Spp. and Aeromonas Spp. Isolated from Penaeus Monodon Hatcheries and Ponds." *International Journal of Antimicrobial Agents* 26 (4): 285–91. doi:10.1016/j.ijantimicag.2005.07.005.

Walsh, T.R., Weeks, J., Livermore, D.M. and Toleman, M. 2011. "Dissemination of NDM-1 Positive Bacteria in the New Delhi Environment and Its Implications for Human Health: An Environmental Point Prevalence Study." *The Lancet Infectious Diseases* 11 (5): 355–62. doi:10.1016/S1473-3099(11)70059-7.

Wellington, E.M.H., Boxall, A.B., Cross, P., Feil, E.J., Gaze, W.H., Hawkey, P.M., Johnson-Rollings, A.S. et al. 2013. "The Role of the Natural Environment in the Emergence of Antibiotic Resistance in Gram-Negative Bacteria." *The Lancet Infectious Diseases* 13 (2): 155–65.

World Health Organization Regional Office for Europe. 2011. "European Strategic Action Plan on Antibiotic Resistance." In EUR/RC61/14. Baku, Azerbaijan: WHO. http://www.euro.who.int/__data/assets/pdf_file/0008/147734/wd14E_AntibioticResistance_111380.pdf?ua=1.

ANNEX 1

Acronyms

AGP	Antibiotic growth promoter
ASCAD	Assistance to States for Control of Animal Diseases
AGMARK	Agricultural Marketing Information Network
BRICS	Brazil, Russia, India, China, and South Africa
CRE	Carbapenem-Resistant Enterobacteriaceae
CSE	Center for Science and the Environment
DAHD	Indian Department of Animal Husbandry, Dairying and Fisheries
ECDC	European Centre for Disease Prevention and Control
ESBL	Extended-spectrum beta-lactamase
ESVAC	European Medicines Agency's European Surveillance of Veterinary Antimicrobial Consumption
ESVHD	Establishment and Strengthening of Veterinary Hospitals and Dispensaries
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FDA	Food and Drug Administration (United States)
FMD-CP	Foot and Mouth Disease Control Programme
GDP	Global Domestic Product
GFI	Guidance for Industry
GSR	General Statutory Rule
ICAR	Indian Council of Agriculture Research
LA-MRSA	Livestock-Associated Methicillin-resistant *Staphylococcus aureus*
LMICs	Low- and middle-income countries
MCR-1	Plasmid-Mediated Colistin Resistance
MDR	Multi-drug Resistant
MRL	Maximum Residue Limit
MRPL	Minimum Required Performance Limit
MRSA	Methicillin-resistant *Staphylococcus aureus*
NADRS	National Animal Disease Reporting System
NARMS	National Antimicrobial Resistance Monitoring System (CDC)
NCPB	National Control Programme on Brucellosis
NCPPPR	National Control Programme on Peste des Petits Ruminants
NDM-1	New Delhi metallo-beta-lactamase-1
NPRE	National Project on Rinderpest Eradication
OIE	World Organization for Animal Health
PED	Professional Efficiency Development
SO	Statutory Order
VLSP	Village-based Livestock Service Provider
WHO	World Health Organization

ANNEX 2

World Health Organization's Antibiotic Classification for Usefulness in Humans

TABLE 1: Antibiotics Classified by the World Health Organization as Critically Important for Humans

		Poultry			Livestock			
Drug name	Species	Disease treatment	Disease prevention	Growth promotion	Disease treatment	Disease prevention	Growth promotion	Humans
Aminocyclitols: spectinomycin	None	No	No	No	No	No	No	Not in India
Cyclic polypeptides: bacitracin	Poultry	Yes	Yes	Yes	No	Yes	Yes	Yes
Nitrofurantoins: furazolidone, nitrofurantoin, nifurtoinol, nitrofural	Poultry, pigs	Yes	Yes	Yes	Yes	No	No	Yes
Nitroimidazoles: metronidazole, tinidazole, ornidazole	Poultry, pigs	Yes	No	No	Yes	No	No	Yes

TABLE 2: Antibiotics Classified by the World Health Organization as Highly Important for Humans

Drug name	Species	Poultry			Livestock			Humans
		Disease treatment	Disease prevention	Growth promotion	Disease treatment	Disease prevention	Growth promotion	
Amidinopenicillins: mecillinam, pivmecillinam	None	No	No	No	Yes	No	No	Not used in India
Amphenicols: chloramphenicol, thiamphenicol Veterinary use only: florfenicol	Poultry, Large animals	Reserved drug, used sparingly	No	No	yes	No	No	Yes
Cephalosporins (1st and 2nd generation): cefaclor, cefacetrile, cefadroxil, cefaloridine, cefalexin, cefalotin, cefamandole, cefapirin, cefatrizine, cefazedone, cefazolin, cefbuperazone, cefmetazole, cefminox, cefonicid, ceforanide, cefotetan, cefotiam, cefoxitin, cefprozil, cefradine, cefroxadine, ceftezole, cefuroxime, flomoxef, loracarbef Veterinary use only: cefalonium	Cephalexin/ cephalothin used in small and large animals	Yes	No	No	Yes	No	No	Yes
Lincosamides: clindamycin, lincomycin Veterinary use only: pirlimycin	Poultry	No	No	Yes	Yes	No	No	Yes
Penicillins (antistaphylococcal): cloxacillin, dicloxacillin, flucloxacillin, oxacillin, nafcillin	Cloxacillin used in combination with others in small and large animals	Yes	No	No	Yes	No	No	Yes
Pleuromutilins: retapamulin	None	No	No	No	No	No	No	No
Pseudomonic acids: mupirocin	None	No	No	No	No	No	No	Yes
Riminofenazines: clofazimine	None	No	No	No	No	No	No	Yes
Steroid antibacterials: fusidic acid	None	No	No	No	No	No	No	Yes
Streptogramins: quinupristin/dalfopristin, pristinamycin Veterinary use only: virginiamycin	None	No	No	No	No	No	No	Yes
Sulfonamides, DHFR inhibitors, and combinations: brodimoprim, iclaprim, pyrimethamine, sulfadiazine, sulfadimethoxine, sulfadimidine, sulfafurazole, sulfaisodimidine, sulfalene, sulfamazone, sulfamerazine, sulfamethizole, sulfamethoxazole, sulfamethoxypyridazine, sulfametomidine, sulfametoxydiazine, sulfametrole, sulfamoxole, sulfanilamide, sulfaperin, sulfaphenazole, sulfapyridine, sulfathiazole, sulfathiourea, tetroxoprim, trimethoprim Vetrinary use: ormosulfathiazole, phthalylsulfathiazole	Poultry, ruminants	Yes	No	No	Yes	Yes	No	Yes
Sulfones: dapsone, aldesulfone	None	No	No	No	No	No	Yes	Yes
Tetracyclines: chlortetracycline, clomocycline, demeclocycline, doxycycline, lymecycline, metacycline, minocycline, penimepicycline, rolitetracycline, oxytetracycline, tetracycline	Poultry, large animals	Yes	Yes	Yes	Yes	Yes	Yes	Yes

TABLE 3: Antibiotics Classified by the World Health Organization as Critically Important for Humans

Drug name	Species	Poultry			Livestock			Humans
		Disease treatment	Disease prevention	Growth promotion	Disease treatment	Disease prevention	Growth promotion	
Aminoglycosides: amikacin, arbekacin, bekanamycin, dibekacin, dihydrostreptomycin, gentamicin, isepamicin, kanamycin, neomycin, netilmicin, ribostamycin, sisomicin, streptoduocin, streptomycin, tobramycin Veterinary use only: apramycin, framycetin	All species	Yes	No	No	Yes	No	No	Yes
Carbenems and other penems: biapenem, doripenem, ertapenem, faropenem, imipenem, meropenem, panipenem	None	No	No	No	No	No	No	Yes
Cephalosporins (3rd and 4th generation): cefcapene, cefdinir, cefditoren, cefepime, cefetamet, cefixime, cefmenoxime, cefodizime, cefoperazone/sulbactam, cefoselis, cefotaxime, cefozoporin,cefpiramide, cefpirome, cefpodoxime, cefsulodin, ceftaroline, ceftazidime, ceftizoxime, ceftobiprole, ceftibuten, ceftriaxone, latamoxef Veterinary use only: cefovecin, cefquinome, ceftiofur	All species	Yes	No	No	Yes	No	No	Yes
Cyclic ethers: fosfomycin	None	No	No	No	No	No	No	Yes
Fluoro- and other quinolones: cinoxacin, ciprofloxacin, enoxacin, fleroxacin, flumequine, garenoxacin, gatifloxacin, gemifloxacin, grepafloxacin, levofloxacin, lomefloxacin, moxifloxacin, nalidixic acid, norfloxacin, ofloxacin, oxolinic acid, pazufloxacin, pefloxacin, pipemidic acid, piromidic acid, prulifloxacin, rosoxacin, rufloxacin, sitafloxacin, sparfloxacin, temafloxacin, trovafloxacin Veterinary use only: danofloxacin, difloxacin, enrofloxacin, ibafloxacin, marbofloxacin, orbifloxacin	All species	Yes	Yes	No	Yes	No	No	Yes
Glycopeptides: dalbavancin, oritavancin, teicoplanin, telavancin, vancomycin Veterinary use only: avoparcin	Poultry	No	No	No	No	Yes	Yes	Yes
Glycylcyclines: tigecycline	No	No	No	No	No	No	No	Yes
Lipopetides: daptomycin	No	No	No	No	No	No	No	Yes
Macrolides and ketolides: azithromycin, clarithromycin, erythromycin, dirithromycin, flurithromycin, josamycin, midecamycin,miocamycin, oleandomycin, rokitamycin, roxithromycin, spiramycin, telithromycin, troleandomycin Vetrinary use only: gamithromycin, kitasamycin, tilmicosin, tulathromycin, tylosin, tylvalosin	All species	Yes	No	No	Yes	Yes	No	Yes
Monobactams: aztreonam, carumonam	None	No	No	No	No	No	No	Yes
Oxazolidinones: linezolid	All species	No	No	No	No	No	No	Yes
Penicillins (natural, aminopencillins and antipseudomonal): amoxicillin, amipicillin, azidocillin, azlocillin, bacampicillin, carbenicillin, carindacillin, clometocillin, epicillin, hetacillin, metampicillin, meticillin, mezlocillin, penamecillin, penicillin G and V, pheneticillin, piperacillin, pivampicillin, propicillin, sulbenicillin, sultamcillin, talampicillin, temocillin, ticarcillin	All species	Yes	No	No	Yes	Yes	Yes	Yes
Polymyxins: colistin, polymyxin-B, polymyxin-A13	Poultry	Yes	Yes	Yes	Yes	No	No	Yes
Rifamycins: rifabutin, rifampicin, rifaximin, rifapentine, rifamycin	Large animals	No	No	No	Yes	No	No	Yes
Drugs used solely to treat TB or other mycobacterial diseases: calcium aminosalicylate, capreomycin, cycloserine, ethambutol, ethionamide, isoniazid, morinamide, para-aminosalicylic acid, protionamide, pyrazinamide, sodium aminosalicylate, terizidone, tiocarlide	Dogs	No	No	No	Yes	No	No	Yes

ANNEX 3

Summary of Published Literature on Antibiotic Use and Resistance in India

TABLE 1: Summary of Published Antibiotic Use Studies in India (Dairy and Fisheries)

Study	Population	Main Findings
Ramakrishna and Singh, 1985*	203 raw milk samples from markets (152) and the National Dairy Research Institute (51) in Haryana	5.9 percent of the samples from the market and 3.9 percent of the samples from the national dairy research instituted contained 10–20 µg/ml of streptomycin.
Sudershan and Bhat, 1995*	205 milk samples from dairy farms in Hyderabad and Secunderbad and 12 surrounding suburban villages	Interviews with 155 dairy farmers (38 urban and 117 rural) found that use of oxytetracyline was 55 percent and 20 percent in urban and rural farms respectively. 205 milk samples (97 from individual buffalos, 101 from the market, and 7 from government organized dairies) were analyzed for oxytetracycline residues. 73 percent of animal samples, 9 percent of market samples, and none of the government dairy samples contained these residues. No information was provided on the sampling structure or the details of the markets from which samples were collected.
Unnikrishnan, Bhavadassan, Nath, and Ram, 2005* Study Date: 2000	Survey of farms in Bangalore and surrounding areas	Tetracycline, gentamicin, ampicillin, amoxicillin, cloxacillin, and penicillin were commonly used for treatment of dairy animals. Common treatment for mastitis was found to be beta-lactams or beta-lactams in combination with streptomycin. No other details were provided.
G. Dutta, R. Dutta, Buragohain, and Mili, 2001*	Five pooled milk samples from public milk booths in Guwahati, Assam	Two of the samples contained high levels of antibiotics (the equivalent of 5 µg/ml of penicillin), while 3 of the samples did not contain any antibiotics
Ram, Bhavadasan, and Vijya, 2003*	Milk from individual animals (125 cow and 87 buffalo), farms (93 organized and 89 unorganized), tankers (385), and pasteurized-branded samples (650) were collected from southern India.	Beta-lactam and tetracycline were found in 2.4 percent of the individual cow samples. None of the individual buffalo samples contained antibiotics. Of the samples collected from farms, 5.4 percent of the organized samples and 2.2 percent of the unorganized samples contained beta-lactam and tetracycline residues. 3.9 percent of the tanker milk supplies had beta-lactam residues; tetracycline, streptomycin, and gentamicin were not detected. 0.61 percent of the pasteurized milk samples contained beta-lactam antibiotic drugs, and no other antibiotic drugs were detected. 3.9 percent of tanker milk samples received at six commercial dairies in southern India contained antibiotic residues.
National Dairy Research Institute, 2011* Data collected: 2010	44 raw milk samples from Delhi and surrounding villages	11 percent contained beta-lactams 2 percent contained streptomycin Overall antibiotic incidence rate was 14 percent. No gentamicin, tetracycline, or erythromycin detected. .
Bharathkumar and Abraham, 2011** Data collected: 2006–2007	74 Auromonas, Pseudomonas, and other bacteria isolates from fisheries in west Bengal	oxytetracycline, althrocin, ampicillin, sparfloxacin, and enrofloxacin, commonly used in fish farms for both prophylactic and treatment purposes Use of ciprofloxacin, enrofloxacin, and other drugs in a few hatcheries to improve larval survival. Responsible use of antibiotics in the hatcheries was lacking.

*Dairy study
**Fisheries study

TABLE 2.1: Summary of Published Antibiotic Resistance Studies in India (Bovines)

Study	Population	Main Findings
Manna, Brahmane, Manna, Batabyal, and Das, 2006 Data collected: 2003	14 *E. coli* O157 strain isolates from stool samples of adult cattle and diarrhoetic calves in West Bengal	Resistance was most frequent against antibiotics commonly used in the region, such as nitrofurantoin (57 percent), co-trimoxazole (29 percent), tetracycline (21 percent), and ampicillin (21 percent). 71 percent of the strains were resistant to at least one antibiotic, and over half were multi-drug resistant.
Arya, Roy, Choudhary, Yadav, and Joshi, 2008 Data collected: 2004–2005	41 Shiga-like toxin producing *E. coli* (STEC) isolates from diarrhoetic calves in Gujarat	All strains resistant to at least 3 of the 11 antibiotics tested. 100 percent resistance to kanamycin and cephalexin >50 percent resistance to cephaloridine (95 percent), enrofloxacin (85 percent), amikacin (80 percent), ampicillin (73 percent), tetracycline (63 percent) 49 percent resistant to ≥8 of the 11 antibiotics tested
Kawoosa, Samanta, and Wani, 2007	44 STEC isolates from diarrhoetic calves in Kashmir valley	≥ 50 percent resistant to oxytetracycline (51 percent) and nalidixic acid (51 percent). High resistance also to co-trimoxazole (42 percent), oflaxacin (21 percent), enrofloxacin (18 percent), and chloramphenicol (18 percent) Four of the isolates showed resistance to six of the nine antimicrobials used in the study. 45 percent were resistant to more than one antibacterial tested.
Ravinder Kumar, Yadav, Anand, et al., 2011	111 *S. aureus* isolates from milk samples of bovines suffering from mastisis	20 percent–30 percent of samples resistant to tetracycline, gentamicin, erythromycin and lincomycin
Ravinder Kumar, Yadav, and Singh, 2011	117 *S. aureus* isolates from milk samples of mastitic cattle in North Western India	Resistant to streptomycin (36 percent), oxytetracycline (34 percent), and gentamicin (30 percent). 13 percent of the isolates were MRSA, and these were more resistant to other antibiotics than methicillin-susceptible isolates. All isolates from the mastitic Sahiwal cattle remained susceptible to vancomycin.
Tiwari et al., 2011 Study dates: 2008-2009	*S. aureus* isolates from milk samples (105) and milk products (100) in Mizoram	High resistance to ampicillin 100 percent, penicillin (87 percent), and cefotaxime (59 percent) 100 percent of the strains were sensitive to cloxacillin, co-trimoxazole, and gentamicin
Dutta, Kumar, and Kotwal, 2007	215 isolates of *S. aureus* and other bacteria agents from clinical and subclinical mastitic milk samples in the Jammu region	Resistance to ampicillin, carbenicillin, and oxacillin was near 100 percent for all bacterial agents Gentamicin was the most effective antibiotic.
V. Kumar, Das, Guin, and Malik, 2012	70 *S. aureus* isolates from buffalo with clinical mastitis	Highest resistance to penicillin (84 percent), cefotaxime (78 percent). and cloxacillin (59 percent)
Preethirani et al., 2015	48.4 percent positive clinical mastitis samples, out of 190 milk samples from 57 buffaloes	64.8 percent of samples contained isolates of coagulase-negative staphylococci, as well as streptococci (18.1 percent), *Escherichia coli* (9.8 percent) and *Staphylococcus aureus* (7.3 percent). The majority were resistant to multiple antibiotics, especially beta-lactams.
Ghatak et al., 2013	8 *E. coli* samples from mastitic cows	1 sample carried multi-drug resistant New Delhi metallo-beta-lactamase and another was an ESBL producer.
Sharma et al., 2015	160 raw milk samples from Rajasthan	81 percent of *E. coli* isolates were resistant to Ampicillin and 77 percent were resistant to Penicillin; samples also showed high levels of resistance to Cefotaxime (84.62 percent), Nirtofurantoin (81.54), Ampicillin (73.85 percent) Chloramphenicol (69.23 percent) and Tetracycline (64.62 percent)._+_

TABLE 2.2: Summary of Published Antibiotic Resistance Studies in India (Poultry)

Study	Population	Main Findings
Sarma, Sambyal, and Baxi, 1981	*E. coli* isolated from healthy and diseased fowl in Ludhiana	All isolates from apparently healthy fowl and about 80 percent from diseased fowl were resistant to chlortetracycline, tetracycline, oxytetracycline, and triple sulfas.
Saikia, Dutta, Devriese, and Kalita, 1995	35 *Enterococcus* isolates from ducks in Assam	Complete resistance to oxytetracycline, chlortetracycline, erythromycin, oleandomycin, lincomycin, and clindamycin High sensitivity remained only for chloramphenicol.
Shivachandra et al., 2004	123 *Pasteurella multocida* isolates from chickens and other birds in 11 states across India	100 percent resistance to sulfadiazine Majority of isolates were also resistant to amikacin, carbenicillin, erythromycin, and penicillin. Sensitivity remained to chloramphenicol (74 percent).
Prasad, Mathur, Dhole, and Ayyagari, 1994	30 *Campylobacter jejuni* isolates from healthy chickens in northern India	Only a minority of isolates showed resistance to ampicillin (7 percent) and tetracycline (13 percent). One strain (1.3 percent) was resistant to 3 or more drugs (multidrug resistant (MDR)).
Dhanarani et al., 2009	120 *Staphylococcus* and other bacteria isolates from poultry litter in Salem, Tamil Nadu	Highest resistance to streptomycin (75 percent), erythromycin (57 percent), tobramycin (54 percent), ampicillin (50 percent), rifampicin (46 percent), and kanamycin (40 percent)
Suresh, Hatha, Sreenivasan, angeetha, and Lashmanaperu-malsamy, 2006	*Salmonella* in eggs and egg-storing trays from a residential area of Coimbatore	All strains resistant to ampicillin, neomycin, polymyxin-B and tetracycline. No resistance to chloramphenicol and gentamicin.
Saravanan et al., 2015	21 non-typhoidal *Salmonella* isolates found in 1215 samples from 154 different farms in Southern India	All isolates resistant to oxytetracycline.
Samanta et al., 2014	*Salmonella* isolated in cloacal swabs, feed samples, drinking water samples, and eggs.	All isolates resistant to chloramphenicol, ciprofloxacin, gentamicin, levofloxacin, norfloxacin, and oxytetracycline.
Mir et al., 2015	32/504 samples containing *Salmonella enterica*	64.8 percent of samples contained isolates of coagulase-negative staphylococci, as well as streptococci (18.1 percent), *Escherichia coli* (9.8 percent) and *Staphylococcus aureus* (7.3 percent). The majority were resistant to multiple antibiotics, especially beta-lactams.
Hemlata et al., 2015	96 percent of 48 samples contained *S. aureus*	All were resistant to ampicillin and cloxacillin, and most were resistant to tetracycline.
Kar et al., 2015	18 of 316 *E. coli* isolates sampled in Odisha confirmed to be ESBL producers through PCR analysis	All were resistant to oxyimino cephalosporins and monobactam and multiple other antibiotics.
Rasheed et al., 2014	Broad sampling of *E. coli* isolates in twelve random locations in Hyderabad	23 percent of raw chicken, 20 percent of vegetable salads, 13 percent of raw meat, 10 percent of raw egg surface, and 7 percent of unpasteurized milk. Overall prevalence of *E. coli* was 14.7 percent, and 4 percent of isolates were ESBL producers.
Brower et al., manuscript in preparation	1556 *E. coli* isolates from 530 birds at 18 poultry farms (9 layers and 9 broilers) from the region surrounding Ludhiana, Punjab	ESBL-producing strains 87 percent in broilers and 42 percent in layers Resistance to tetracycline, nalidixic acid and ciprofloxacin were observed in broiler farms MDR prevalence was 94 percent in broilers and 60 percent in layers

TABLE 2.3: Summary of Published Antibiotic Resistance Studies in India (Studies including other livestock)

Study	Population	Main Findings
Sethi, Anand, Singh, and Vadehra, 1976	704 *Salmonella* isolates from various sources and locations in India	Resistance to chloramphenicol tested; none of the animal isolates were resistant.
M. Singh, Chaudhry, Yadava, and Sanyal, 1992 Data collected: 1984-1986	154 *E. coli* isolates from poultry, bovine, sheep, and equine species near Lucknow	25 percent resistant to at least one antibiotic among the nine that were tested Almost 50 percent of the resistant isolates were MDR. Resistance was most frequent in isolates from sheep and goat diarrhoea (82 percent and 100 percent respectively).
M. Singh, Sanyal, and Yadav, 1992	31 *E. coli* isolates from bovines, sheep, and poultry in a veterinary hospital in Lucknow	The majority of the strains were resistant to one or more of the seven antibiotics tested.
T. K. Dutta, Roychoudhury, Bandyopadhyay, and Chandra, 2011 Data collected: 2007–2008	774 *E. coli* isolates from piglets with or without diarrhoea, districts of Mizoram	> 80 percent resistance to ampicillin, cefixime, erythromycin, lincomycin, nalidixic acid, oxytetracycline, roxythromycin, sulfadiazine, and penicillin Most sensitivity was found to amoxicillin.
T. K. Dutta, Roychoudhury, and Banik, 2009	72 *Pasteurella multocida* isolates from swines in the Northeast Hill region	>70 percent resistant to amikacin, streptomycin, penicillin-G, and vancoymcin
B. R. Singh et al., 2007	65 *Salmonella* isolates from equids in around India	63 out of 65 isolates were MDR. highest resistance to sulfamethoxazole (91 percent), tetracycline (71 percent), doxycycline (68 percent), furazolidone (66 percent), and colistin (55 percent)
B. R. Singh, Jyoti, Chandra, Babu, and Sharma, 2009 Data collected: 1982–1996	111 *Salmonella* isolates from equids in Izatnagar	100 percent were resistant to at least one antibiotic. 89 percent were resistant to more than one. 76 percent were MDR. Resistance was highest to furazolidone (87 percent), sulfamethoxazole (82 percent), and tetracycline (43 percent).
B. R. Singh, 2009	267 *Enterococcus* isolates from healthy and diseased equines from North India	80 percent of the isolates were resistant to vancomycin. >99 percent were resistant to at least five antibiotics. Highest resistance was to cefdinir (97 percent), oxacillin (91 percent), cefotaxime (89 percent), ampicillin (88 percent), cloxacillin (88 percent), cotrimazine (87 percent), and vancomycin (80 percent).

TABLE 2.3: Summary of Published Antibiotic Resistance Studies in India (Seafood)

Study	Population	Main Findings
Hatha and Lakshmana-perumalsamy, 1995	240 *Salmonella* isolates from fish and crustacean samples in Tamil Nadu	>90 percent of the isolates were resistant to bacitracin, penicillin, and novobiocin. The least resistance was observed to chloramphenicol (6.7 percent) and nalidixic acid (12 percent).
Rakesh Kumar, Surendran, and Thampuran, 2009 Data collected: 2003–2007	256 *Salmonella*, isolates from seafood in Cochin	50 percent resistant to sulfamethizol High resistance to sulfamethizole and carbenicillin Moderate resistance to nalidixic acid and oxytetracycline Susceptibility to ampicillin, ciproflaxin, chloramphenicol, gentamicin, kanamycin MDR in 2/3 of isolates; 4/256 samples resistant to 5 drugs. 39 percent resistant to carbenicillin and 14 percent resistant to oxytetracycline
Deekshit et al., 2012	40 *Salmonella* isolates from seafood taken from market and fish landing centers in Mangalore	67.5 percent were resistant to at least two antibiotics. 25 percent were MDR
Shashidhar, Jajoo, Karani, Warrier, & Bandekar, 2005	34 Salmonella isolates from fresh water prawns and cuttle fish	None of the bacteria were resistant to the 16 antibiotics tested.
Sathiyamurthy, Purushothaman, and Ramaiyan, 1997 Data collected: 1988-1989	770 *Vibrio cholerae* non-O1 isolates from seafood samples in the Parangipettai costal environs	Highest levels of resistance were found against tetracycline (50 percent) and sulfadiazine (43 percent) Some level of resistance to 10 of the 13 antibiotics tested (> 25 percent) also see to oxytetracycline, streptomycin, sulfadiazine, tetracycline, and to streptomycin
P. A. Kumar, Patterson, and Karpagam, 2009	730 *Vibrio cholerae* non-O1 and non-O139 species isolates from seafood in Southeast India	Highest resistance to ampicillin (88 percent), penicillin (84 percent), streptomycin (85 percent), and bacitracin (64 percent) 10–20 percent of species showed a 3–5 MDR pattern.
Shanthini, Kumar, and Patterson, 2004	42 *Vibrio parahaemolyticus* isolates from seafoods from landing centres of Tuticorin	98 percent of the strains showed resistance to bacitracin and vancomycin. 57 percent resistance to oxytetracycline and penicillin 81 percent of the strains were found to be sensitive to chloramphenicol.
Sudha, Divya, Francis, and Hatha, 2012 Data collected: 2009–2010	82 *Vibrio parahaemolyticus* isolates collected from finfish samples from four retail fish outlets in and around Cochin	High resistance to ampicillin (89 percent), streptomycin (89 percent), carbenicillin (83 percent), cefpodoxime (80 percent), cephalothin (80 percent), colistin (77 percent), and amoxicillin (63 percent) 100 percent of isolates remained susceptible to nalidixic acid and tetracycline.
Bharathkumar and Abraham, 2011 Data collected: 2006–2007	74 *A. Pseudomonas* and other bacteria isolates from freshwater fish hatcheries in West Bengal	High prevalence of resistance to oxytetracycline, nitrofurantoin, and co-trimoxazole. Low resistance to chloramphenicol in strains of *A. hydrophila* (15 percent), A caviae (9 percent), and *Pseudomonas* spp. (25 percent) Resistance to at least two broad spectrum antibiotics found in 30 percent of gram-negative bacteria of carp and 90 percent of gram-negative bacteria in catfish. 57 percent of all strains were resistant to oxytetracycline. Least resistance was to gentamicin.
Vaseeharan, Ramasamy, Murugan, and Chen, 2005 Data collected: 1999–2002	97 *Vibrio* and *Aeromonas* isolates from shrimp hatcheries and ponds on the east coast	Overall: 100 percent resistant to ampicillin, 66 percent resistant to chlortetracycline, 53 percent resistant to erythromycin *Aeromonas* spp. 100 percent resistance to ampicillin, streptomycin, kanamycin and furazolidone Isolates from hatcheries were more resistant than isolates from ponds.
Alagarsamy Surendraraj, Thampuran, and Joseph, 2010	*E. Coli* O157:H7 isolates from fish and shrimp samples from retail markets in Cochin	Resistant to bacitracin and polymyxin-B

ANNEX 4

Laws in India (in order of date)

MINISTRY OF COMMERCE AND INDUSTRY
(Department of Commerce)

ORDER
New Delhi, 21st August 1995

S.O. 729(E). :- Whereas for the development of the export trade of India, certain proposals for subjecting Fresh, Frozen and Processed Fish & Fishery Products to quality control inspection prior to export, were published a required by sub-rule (2) of rule II of the Export (Quality Control and Inspection) Rules, 1964 in the Gazette of India, Part II, Section 3, Sub-section (ii) dated 1st November, 1994 under the Order of the Government of India in the Ministry of Commerce No S.O. 785 (E) dated the 1-11-1994;

2. And, whereas, the objections and suggestions were invited from all persons likely to be affected thereby within a period of forty five days of the date of publication of the said order in the official gazette;
3. And, whereas, the coppies of the said Gazette were made available to the public on 1-11-1994;
4. And, whereas, the objections and suggestions received from the public on the said draft have been considered by the Central Government;
5. And, whereas, it is necessary to maintain the highest quality standards as per the health requirements of the importing countries that would encompass the standards like unified directive on 91/493/EEC dated the 22 July, 1991 of the European Community, the proposed HACCP of United States of America, Quality Assurance Standards of Japan.
6. And, whereas, fish and fishery products freshly caught are in principle free of contamination with micro-organizm;
7. And, whereas, however, contamination and subsequent decomposition may occur when handled and treated unhygienically;
8. And, whereas, therefore, the essential requirements should be laid down for correct hygienic handling of Fresh, Frozen and Processed Fish and Fishery Products at all stages of production and during storage and transport;
9. And whereas, it is responsibility primarily of the fisheries industry to ensure that fishery products meet the health requirements laid down in this notification;
10. And whereas, it is expedient that these control measures should be introduced to guarantee the uniform application and to ensure smooth operation of the provisions of the notification and that the measures apply in an identical manner;
11. And whereas, provisions should, therefore, be made for procedure for monitoring to ensure the above conditions of equivalence with reference to the requirements of importing countries;
12. And whereas, the Government nominated competent authority should ensure the effective compliance of the quality standards in the country;
13. Now, therefore, in exercise of the powers conferred by section 6 of the Export (Quality Control and Inspection) Act, 1963 (22 of 1963) and in super cession of the
Notification in the Ministry of Commerce No. S. O. 1153 dated the 9th April, 1988 relating to Frozen Fish and Fishery Products, S.O. 952 dated 30-3-1987 relating to Frozen Claim Meat and S.O. 862 dated 12-2-1983 elating to Canned Fish & Fishery products, the Central Government, after consulting the Export Inspection Council, being of the opinion that it is necessary are expedient to do so for the development of the export trade of India, hereby :-

(i) notifies that Fresh, Frozen and Processed Fish and Fishery products shall be subject to quality control, inspection and monitoring prior to export.

(ii) Specifies that the type of quality control, inspection and monitoring shall be in accordance with the export of Fresh Frozen and processed Fish and Fishery Products (Quality Control, Inspection and Monitoring) Rules, 1995 as the type of quality control, inspection and monitoring which shall be applied to such Fresh, Frozen and processed Fish & Fishery products prior to their export.

(iii) recognises the specifications as set out in Schedule I appended to this Order as the standard specifications for Fresh, Frozen and Processed Fish and Fishery Products.

(iv) Prohibits the export of Fresh, Frozen and Processed Fish & Fishery Products by a unit in the course of international trade unless it conforms to the standard specifications applicable to it, and is accompanied by a certificate starting that such unit is approved and monitored by the Export Inspection Agencies established under Section 7(1) of the Export (Quality Control & Inspection) Act, 1963 (the competent authority).

14. In this Order, Fresh Frozen and Processed Fish & Fishery Products means:-

all sea water and fresh water animals or part thereof, including their roes, in fresh, chilled, frozen or processed from, but excluding Frogs.

[F. No. 6/2694-EI&EP]
A. DIDAR SINGH, Jt. Secy.

Foot Note: The principal notifications were published vide
No. S.O. 1153 dated 9-4-88, S.O. No. 862
dated 12-2-83 and 952 dated 30-3-87.

MINISTRY OF COMMERCE AND INDUSTRY
(Department of Commerce)

ORDER

New Delhi, the 10th July, 2002

S. O. 722 (E) : - Whereas, for the development of the export trade of India, certain proposals for amending the Order No. SO 729 (E) dated 21st August, 1995, of erstwhile Ministry of Commerce, Government of India, relating to Fresh, Frozen and Processed Fish and Fishery Products and in suppression of Order No. SO 792 (E) dated 17th August, 2001, Ministry of Commerce and Industry relating to Maximum Residual Limits (MRLs) for antibiotics, pesticides and heavy metals in fish and fishery products were forwarded to Export Inspection Council and published in Part II section 3, sub-section (ii) of the Gazette of India, Extraordinary, dated the 17th May 2002 vide Order of the Government of India in the Ministry of Commerce and Industry (Department of Commerce), number SO 528 (E), as required by sub-rule (2) of rule 11 of the Export (Quality Control and Inspection) Rules, 1964 under Export (Quality Control and Inspection) Act, 1963;

And, whereas, the objections and suggestions were invited from all persons likely to be affected thereby within a period of thirty days from the date the said notification was made available to the public;
And whereas the copies of the said Gazette were made available to the public on17th May 2002 ;
And whereas the objections and suggestions received from the public on the said draft have been considered by the Central Government;
Now, therefore, in exercise of the powers conferred by section 6 of the Export (Quality Control and Inspection) Act, 1963 (22 of 1963), the Central Government after consulting Export Inspection Council, hereby makes the following amendments to the Order No. SO 729 (E) dated 21st August, 1995, of erstwhile Ministry of Commerce, Government of India, relating to Fresh, Frozen and Processed Fish and Fishery Products and in suppression Order No. SO 792 (E) dated 17th August 2001 of Ministry of Commerce and Industry relating to Maximum Residual Limits (MRLs) for antibiotics, pesticides and heavy metals in fish and fishery products, which shall take effect on the date of its publication in the Official Gazette, namely:
In the said Order, in schedule – I, for clause (e), the following shall be inserted, namely:-
a) Maximum Residual Limits (MRLs) for pesticides, heavy metals and antibiotics and other pharmacologically active substances in fish and fishery products shall meet the requirements as given below. However, if the MRLs fixed by the importing countries are more stringent than these prescribed limits, the standards specified by those countries will be complied with.
b) Pesticides:

Pesticides	Max. permissible residual level in ppm
BHC	0.3
Aldrin	0.3
Dieldrin	0.3
Endrin	0.3
DDT	5.0

Heavy Metals:

Heavy Metals	Max. permissible residual level in ppm
Mercury	1.0
Cadmium	3.0
Arsenic	75
Lead	1.5
Tin	250
Nickel	80
Chromium	12

Antibiotics and other Pharmacologically Active Substances

Antibiotics	Max. permissible residual level in ppm
Tetracycline	0.1
Oxytetracycline	0.1
Trimethoprim	0.05
Oxolinic acid	0.3

c) The use of any of the following antibiotics and other pharmacologically active substances shall be prohibited in the culture of; or in any hatchery for producing the juveniles or larvae or nauplii of; or in any unit manufacturing feed for or in any unit pre-processing or processing shrimp, prawns or any other variety of fish and fishery products:
d)All Nitrofurans including

- Furaltadone
- Furazolidone
- Furylfuramide
- Nifuratel
- Nifuroxime
- Nifurprazine
- Nitrofurantoin
- Nitrofurazone

1. Chloramphenicol
2. Neomycin
3. Nalidixic acid
4. Sulfamethoxazole
5. Aristolochia spp and preparations thereof
6. Chloroform
7. Chlorpromazine
8. Colchicine
9. Dapsone
10. Dimetridazole
11. Metronidazole
12. Ronidazole
13. Ipronidazole
14. Other nitroimidazoles
15. Clenbuterol
16. Diethylstilbestrol (DES)
17. Sulfonamide drugs
18. (except approved Sulfadimethoxine, Sulfabromomethazine & Sulfaethoxypyridazine)
19. Fluoroquinolones
20. Glycopeptides
21. Glycopeptides

Ministry of Commerce and Industry
(Department of Commerce)
Order
New Delhi, the 9th of September, 2003

S.O. 1037(E) – Whereas, in exercise of the power conferred by section 6 of the Export (Quality Control and Inspection) Act, 1963 (22 of 1963), the Central Government has formulated certain proposals for amending the Order No. SO 2077 sated 4th August, 1998, of the erstwhile Ministry of Commerce, Government of India, relating to Egg Products in the manner specified below for the development of eport trade of India and has forwarded the same to the Export Inspection Coucil as required by sub-rule (2) or rule 11 of the Export (Quality Control and Inspection) Rules, 1964;

Now, therefore, in pursuance of the said sub-rule, the Central Government hereby publishes the said draft proposals for the information of the public likely to be affected thereby;

Notice is herby given that any person desiring to forward any objection or suggestion with respect to the said proposal, may forward the same within thirty days of the date of publication of this Order in the Official Gazette, to the Export Inspection Council, 3rd Floor, New Delhi YMCA Cultural Center Building, 1, Jai Singh Road, New Delhi – 110001.

Proposal

In exercise of the powers conferred by section 6 of the Export (Quality Control and Inspection) Act, 1963 (22 or 1963) the Central Government after consulting the Export Inspection Council, herby makes the following amendment to the Order of the Government of India in the erstwhile Ministry of Commerce, SO 2077 dated 4th August, 1997, which shall take effect o the date of the publication of the final proposals in the Official Gazette, namely: -
2566 GI/03-2

1. In the said Order, after clause (d), the following shall be inserted, namely: -
'(e) specifies the maximum residual limits (MRLs) for antibiotics, organochlorine compounds and pyrethroids in egg powder as given below, namely: -
(1) Antibiotics

Antibiotics	Maximum residue limits
Erythromycin	150
Tylosin	200
Lincomycin	50
Neomycin	500
Colistin	300
Chlortetracycline	200
Oxytetracycline	200
Tetracycline	200
Spectinomycin	200
Tiamulin	1000
Josamycin	200
Oxolinic Acid	50

(2) Anti-parasitic agents Piperazine derivatives

Piperazine	2000
Flubendazole	400
Amprolium	1000

(f) The use of the following antibiotics and other pharmacological active substances shall be prohibited in manufacture of feed, medication of chicken and poultry, or at any stage of production of egg powder:

Chloramphenicol
Dimetridazole
Metronidazone
Nitrofurans Metabolites Furazolidone (AOZ) and Nitrofurazone (SEM)

(1) Organocholorine Compounds

Compounds	MRL in mg/kg
Aldrin,,Dieldrin	0.02 (Combined limit)
Chrorthalonil	0.01

DDT (all isomers) 0.05 (Combined limit)
Dicofol 0.05
Dieldrin 0.02
a-Endosulfanb 0.1
Endosulfansulfat 0.005
Endrin 0.005
HCH(all isomers) 0.03 (Combined limit) A 0.02 0.1

Lindane (-HCH) 0.01
Methoxychlor 0.01
PCB 0.01

(2) Pyrethroids
Cypermethrin 0.05
Deltamethrin 0.05
Permethrin 0.05
-cypermethrin 0.05

Provided that if the MRLs fixed by the importing countries are more stringent than the limits herein specific, the MRLs specified by the importing countries shall be complied with.

2. Type of quality control shall be in accordance with the proposed notification on the Export of Egg products (Quality Control, Inspection and Monitoring) (Amendment) Rules, 2003 as set out in the Annexure to this order'

[F. No6/1/95-EI&EP]
M. V. P. C. SASTRY, Jt Secy

Note:- The principal Order was published vide S.O. 2077 dated 4th August 1997 in the Gazette of India, Part II, Section 3, sub-section (ii) dated 23.08.1997

Annexure

New Delhi, the 9th September, 2003
S.O – (E) In exercise of the powers conferred by section 17 of the Export (Quality Control and Inspection) Act, 1963(22 of 1963), the Central Government herby makes the following rules to amend the Export of Egg Products (Quality Control, Inspection and Monitoring) Rules, 1997, namely: -

1. (1) These rules may be called the Export of Egg Products (Quality Control, Inspection and Monitoring) (Amendment) Rules, 2003.
(2) They shall come into force from the date of their publication in the Official Gazette.
2. In Part I of the Export of Egg Products (Quality Control Inspection and Monitoring) Rules, 1997(hereafter referred to as the principal rules)-,
(i) in the rule 2, after sub rule (o), the following sub-rule shall be inserted, namely:-
'(p) 'Director' means, the director (Inspection and Quality Control) appointed by the Central Government under section 4 of the Act.';
(ii) in rule 4, after Sub-rule 4.21, the following sub-rule shall be inserted, namely:-
'4.22 the Director may take the assistance of the Agricultural and Processed Food Productes Export Development Authority (APEDA) or any other suitable organization for residue monitoring.';
3. In Part-II of the principal rules,-
(i) in rule 2, after sub rule (w), the following sub-rule shall be inserted, namely:-
'(x) 'Director' means, the Director (Inspection and Quality Control) appointed by the Central Government under section 5 of the Act.':
(ii) rule 4, after sub-rule 4.7, the following shall be inserted:-
'4.8 Director may take the assistance of the Agricultural and Processed Food Products Export Development Authority (APEDA) or any other suitable organization for residue monitoring.'
Note: The principal notification was published vide S.O.2078 dated the 4th August 1997 in the Gazette of India, Part II, section 3, sub-section(ii) dated 23.08.1997

Ministry of Commerce and Industry
(Department of Commerce)
ORDER
New Delhi, the 23rd of October, 2003

S.O. 1227 (E). – Whereas, for the development of the export trade of India, certain proposals for amending the order No. S.O. 729 (E) dated 21st August 1995, of the erstwhile Ministry of Commerce, Government of India for prohibiting the use of substances having anabolic effect and unauthorized substances, veterinary drugs and contaminants, other substances and environmental contaminants in fish and fishery products were published in part II, sub-section (ii) of section 3 of the Gazette of India, Extraordinary, vide Order of the Government of India in the Ministry of Commerce and Industry, Department of Commerce, under S.O. 1035 (E) dated the 9th September, 2003, as required under sub-rule (2) of rule 11 of the Export (Quality Control and Inspection) Rules, 1964 made under the Export (Quality Control and Inspection) Act, 1963;

And, whereas, the objections and suggestions were invited from all the persons likely to be affected thereby within a period of thirty days from the date of publication of the said Order in the Official Gazette;

And, whereas, the objections and suggestions received from the public on the said proposals have been considered by the Central Government;

Now, therefore, in exercise of the powers conferred by section 6 of the Export (Quality Control and Inspection) Act, 1963 (22 of 1963), the Central Government, after consulting the Export Inspection Council, hereby makes the following amendments in the said Order No. S.O. 729 (E) dated 21st August, 1955 relating to Fresh, Frozen and Processed Fish and Fishery Products which shall take effect on the date of its publication in the Official Gazette, namely: -

1. In the said Order, in Schedule I after clause (g), the following shall be inserted, namely: -

'(h) the use of any of the following substances having anabolic effect and unauthorized substances, veterinary drugs and contaminants and other substances and other environmental contaminants shall be prohibited in the culture of, or in any hatchery for producing the juveniles or larvae or nauplii of, or any unit manufacturing feed for, or in any unit pre-processing or processing, shrimps, prawns or any other variety of fish and fishery products, namely: -

(i) substances having anabolic effect and unauthorized substances, namely: -
(a) stilbenes, stilbene derivatives and their salts and esters;
(b) steroids.

(ii) Veterinary drugs and contaminants, namely: -
(a) antibacterial substances, including quinolones;
(b) anthelmintics.

(iii) Other substances and environmental contaminants namely: -
(a) organochlorone compounds including PcBs;
(b) mycotoxinsl
(c) dyes.

Provided that the use of items at sl. No. (i)(b), (ii)(a) and (b) for therapeutic or zoo-technical purposes may be authorized by qualified Veterinary surgeons or Fishery Scientists.'

[F.No. 6/2/2001 – EI & EP]
M.V.P.C. SASTRY, Jt. Secy.

Note: - The principal order was published in the Gazette of India vide S.O. 729(E) dated 21st August, 1995 and subsequently amended vide S.O. 729(E) dated 17th August, 2001, S.O. 722 (E) dated 10th July, 2002 and S.O. 464(E) dated 24th April, 2003.

DRUGS AND COSMETICS (2ND AMENDMENT) RULES, 2006

MINISTRY OF HEALTH AND FAMILY WELFARE

(Department of Health)

NOTIFICATION

New Delhi, the 16th March, 2006 G.S.R. 160(E).– Whereas a draft of certain rules further to amend the Drugs and Cosmetics Rules, 1945 was published, as required by Sections 12 and 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), in the Gazette of India, Extraordinary, Part II, Section 3, Sub-section (i), dated the 24th February, 2005, under the notification of the Government of India in the Ministry of Health and Family Welfare (Department of Health), number G.S.R. 105(E), dated the 24th February, 2005, inviting objections and suggestions from all persons likely to be affected thereby, before the expiry of a period of forty five days from the date on which copies of the Official Gazette containing the said notification were made available to the public; And whereas copies of the said Gazette were made available to the public on 25th February, 2005; And whereas, objections and suggestions received from the public on the said draft rules have been considered by the Central Government. Now, therefore, in exercise of the powers conferred by Sections 12 and 33 of the said Act, the Central Government, after consultation with the Drugs Technical Advisory Board, hereby makes the following rules further to amend the Drugs and Cosmetics Rules, 1945, namely:–

1. (1) These rules may be called the Drugs and Cosmetics (2nd Amendment) Rules, 2006.

*Published in the Gazette of India (extraordinary) Part-II, section 3, sub-section (i) vide G.S.R. 160(E), dated 16th March, 2006.

(2) They shall come into force on the date of their publication in the Official Gazette.

2. In the Drugs and Cosmetics Rules, 1945, for Schedule H, the following Schedule shall be substituted, namely:-

SCHEDULE-H

(See Rules 65 and 97)

PRESCRIPTION DRUGS

1. ABACAVIR
2. ABCIXIMAB
3. ACAMPROSATE CALCIUM
4. ACEBUTOL HYDROCHLORIDE
5. ACLARUBICIN
6. ALBENDAZOLE
7. ALCLOMETASONE DIPROPIONATE
8. ACTILYSE
9. ACYCLOVIR
10. ADENOSINE
11. ADRENOCORTICOTROPHIC HORMONE (ACTH)
12. ALENDRONATE SODIUM
13. ALLOPURINOL
14. ALPHACHYMOTRYPSIN
15. ALPRAZOLAM
16. ALPROSTADIL
17. AMANTADINE HYDROCHLORIDE
18. AMIFOSTINE
19. AMIKACIN SULPHATE
20. AMILORIDE HYDROCHLORIDE
21. AMINEPTINE
22. AMINOGLUTETHIMIDE
23. AMINOSALICYLIC ACID
24. AMIODARONE HYDROCHLORIDE
25. AMITRIPTYLINE
26. AMLODIPINE BESYLATE
27. AMOSCANATE
28. AMOXOPINE
29. AMRINONE LACTATE
30. ANALGIN
31. ANDROGENIC ANABOLIC, OESTROGENIC & PROGESTATIONAL SUBSTANCES
32. ANTIBIOTICS
33. APRACLONIDINE
34. APROTININ
35. ORGANIC COMPOUND OF ARSENIC
36. ARTEETHER
37. ARTEMETHER
38. ARTESUNATE
39. ARTICAINE HYDROCHLORIDE
40. ATENOLOL
41. ATRACURIUM BESYLATE INJECTION
42. ATORVASTATIN
43. AURANOFIN
44. AZATHIOPRINE
45. AZTREONAM
46. BACAMPICILLIN
47. BACLOFEN
48. BALSALAZIDE
49. BAMBUTEROL
50. BARBITURIC ACID
51. BASILIXIMAB
52. BENAZEPRIL HYDROCHLORIDE
53. BENIDIPINE HYDROCHLORIDE
54. BENSERAZIDE HYDROCHLORIDE
55. BETAHISTINE DIHYDROCHLORIDE
56. BETHANIDINE SULPHATE
57. BEZAFIBRATE
58. BICALUTAMIDE
59. BICLOTYMOL
60. BIFONAZOLE
61. BIMATOPROST
62. BIPERIDEN HYDROCHLORIDE
63. BIPHENYL ACETIC ACID
64. BITOSCANATE
65. BLEOMYCIN
66. PRIMONIDINE TARTRATE
67. BROMHEXINE HYDROCLORIDE
68. BROMOCRIPTINE MESYLATE
69. BUDESONIDE
70. BULAQUINE
71. BUPIVA CAINE HYDROCHLORIDE
72. BUPROPION
73. BUSPIRONE
74. BUTENAFINE HYDROCHLORIDE
75. BUTORPHANOL TARTRATE
76. CABERGOLINE
77. CALCIUM DOBESILATE
78. CANDESARTAN

79. CAPECITABINE
80. CAPTOPRIL
81. CARBIDOPA
82. CARBOCISTEINE
83. CARBOPLATIN
84. CARBOQUONE
85. CARISOPRODOL
86. L-CARNITINE
87. CARTEOLOL HYDROCHLORIDE
88. CARVEDILOL
89. CEFADROXYL
90. CEFATOXIME SODIUM
91. CEFAZOLIN SODIUM
92. CEFDINIR
93. CEFEPIME HYDROCHLORIDE
94. CEFETAMET PIVOXIL
95. CEFPIROME
96. CEFPODOXIME POXETIL
97. CEFTAZIDIME PENTAHYDRATE
98. CEFTIZOXIME SODIUM
99. CEFUROXIME
100. CELECOXIB
101. CENTCHROMAN
102. CENTBUTINDOLE
103. CENTPROPAZINE
104. CETIRIZINE HYDROCHLORIDE
105. CHLORDIAZEPOXIDE
106. CHLORMEZANONE
107. Omitted vide GSR 790 (E) dtd 29.10.2009
108. CHLORPROMAZINE
109. CHLORZOXAZONE
110. CICLOPIROX OLAMINE
111. CIMETIDINE
112. CINNARIZINE
113. CIPROFLOXACIN HYDROCHLORIDE MONOHYDRATE / LACTATE
114. CISPLATIN
115. CITALOPRAM HYDROBROMIDE
116. CLARITHROMYCIN
117. CLAVULANIC ACID
118. CLIDINIUM BROMIDE
119. CLINDAMYCIN
120. CLOBAZAM
121. CLOBETASOL PROPENATE
122. CLOBETASONE 17-BUTYRATE
123. CLOFAZIMINE
124. CLOFIBRATE
125. CLONAZEPAM
126. CLONIDINE HYDROCHLORIDE
127. CLOPAMIDE
128. CLOPIDOGREL BISULPHATE
129. CLOSTEBOL ACETATE
130. CLOTRIMAZOLE
131. CLOZAPINE
132. CODEINE
133. COLCHICINE
134. CORTICOSTEROIDS
135. COTRIMOXAZOLE
136. CYCLANDELATE
137. CYCLOSPORINS
138. DACLIZUMAB
139. DANAZOLE
140. DAPSONE
141. DESLORATADINE
142. DESOGESTROL
143. DEXRAZOXANE
144. DEXTRANOMER
145. Omitted vide GSR 790 (E) dtd 29.10.2009
146. DEXTROPROPOXYPHENE
147. DIAZAPAM
148. DIAZOXIDE
149. DICLOFENAC SODIUM/POTASSIUM/ACID
150. DICYCLOMIN HYDROCHLORIDE
151. DIDANOSINE
152. DIGOXINE
153. DILAZEP HYDROCHLORIDE
154. DILTIAZEM
155. DINOPROSTONE
156. DIPHENOXYLATE, ITS SALTS
157. DIPIVEFRIN HYDROCHLORIDE
158. DI-SODIUM PAMIDRONATE
159. DISOPYRAMIDE
160. DOCETAXEL
161. DOMPERIDONE
162. DONEPEZIL HYDROCHLORIDE
163. DOPAMINE HYDROCHLORIDE
164. DOTHIEPIN HYDROCHLORIDE
165. DOXAPRAM HYDROCHLORIDE
166. DOXAZOSIN MESYLATE
167. DOXEPIN HYDROCHLORIDE
168. DOXORUBICIN HYDROCHLORIDE
169. DROTRECOGIN-ALPHA
170. EBASTINE
171. ECONOZOLE
172. EFAVIRENZ
173. ENALAPRIL MELEATE
174. ENFENAMIC ACID
175. EPINEPHRINE
176. EPIRUBICINE
177. EPTIFIBATIDE
178. ERGOT, ALKALOIDS OF WHETHER HYDROGENATED OR NOT, THEIR HOMOLOGOUES, SALTS
179. ESOMEPRAZOLE
180. ESTRADIOL SUCCINATE
181. ESTRAMUSTINE PHOSPHATE
182. ETANERCEPT
183. ETHACRIDINE LACTATE
184. ETHAMBUTOL HYDROCHLORIDE
185. ETHAMSYLATE
186. ETHINYLOESTRADIOL
187. ETHIONAMIDE
188. ETIDRONATE DISODIUM
189. ETODOLAC
190. ETOMIDATE
191. ETOPOSIDE
192. EXEMESTANE
193. FAMCICLOVIR
194. FAMOTIDINE
195. FENBENDAZOLE
196. FENOFIBRATE
197. FEXOFENADINE
198. FINASTERIDE
199. FLAVOXATE HYDROCHLORIDE
200. 5-FLUOROURACIL
201. FLUDARABINE
202. FLUFENAMIC ACIDS
203. FLUNARIZINE HDROCHLORIDE

204. FLUOXETINE HYDROCHLORIDE
205. FLUPENTHIXOL
206. FLUPHENAZINE ENANTHATE AND DECANOATE
207. FLURAZEPAM
208. FLURBIPROFEN
209. FLUTAMIDE
210. FLUTICASONE PROPIONATE
211. FLUVOXAMINE MALEATE
212. FORMESTANE
213. FOSFESTRIL SODIUM
214. FOSINOPRIL SODIUM
215. FOSSPHENYTOIN SODIUM
216. FOTEMUSTINE
217. GABAPENTIN
218. GALANTHAMINE HYDROBROMIDE
219. GALLAMINE, ITS SALTS, ITS QUATERNARY COMPOUND
220. GANCYCLOVIR
221. GANIRELIX
222. GATIFLOXACIN
223. GEMCITABINE
224. GEMFIBROZIL
225. GEMTUZUMAB
226. GENODEOXYCHOLIC ACID
227. GLICLAZIDE
228. GLIMEPIRIDE
229. GLUCAGON
230. GLYCOPYRROLATE
231. GLYDIAZINAMIDE
232. GOSERELIN ACETATE
233. GRANISETRON
234. GUANETHIDINE
235. GUGULIPID
236. HALOGENATED HYDROXYQUINOLINES
237. HALOPERIDOL
238. HEPARIN
239. HEPATITIS B. VACCINE
240. HYALURONIDASE
241. HYDROCORISONE 17-BUTYRATE
242. HYDROTALCITE
243. HYDROXIZINE
244. IBUPROFEN
245. IDEBENONE
246. IINDAPAMIDE
247. IMIPRAMINE
248. INDINAVIR SULPHATE
249. INDOMETHACIN
250. INSULIN HUMAN
251. INTERFERON
252. INTRAVENOUS FAT EMULSION
253. IOBITRIDOL
254. IOHEXOL
255. IOPAMIDOL
256. IOMEPROL
257. IOPROMIDE
258. IRBESARTAN
259. IRINOTECAN HYDROCHLORIDE
260. IRON PREPARATION FOR PARENTERAL USE
261. ISEPAMICINE
262. ISOCARBOXSIDE
263. ISOFLURANE
264. ISONICOTNIC ACID HYDRAZINE AND OTHER-HYDRAGINE DERIVATIVES OF ISONICOTINIC ACID
265. ISOSORBIDE DINITRATE/ MONONITRATE
266. ISOTRETINOIN
267. ISOXSUPRINE
268. ITOPRIDE
269. KETAMINE HYDROCHLORIDE
270. KETOCONAZOLE
271. KETOPROFEN
272. KETOROLAC TROMETHAMINE
273. LABETALOL HYDROCHLORIDE
274. LACIDIPINE
275. LAMIVUDINE
276. LAMOTRIGINE
277. LATANOPROST
278. LEFUNOMIDE
279. LERCANIDIPINE HYDROCHLORIDE
280. LETROZOLE
281. LEUPROLIDE ACETATE
282. LEVAMESOLE
283. LEVARTERENOL
284. LEVOBUNOLOL
285. LEVOCETIRIZINE
286. LEVODOPA
287. LEVOFLOXACIN
288. LEVOVIST
289. LIDOFLAZINE
290. LINEZPLID
291. LITHIUM CARBONATE
292. LOFEPRAMINE DECANOATE
293. LOPERAMIDE
294. LORAZEPAM
295. LOSARTAN POTASSIUM
296. LOTEPREDNOL
297. LOVASTATIN
298. LOXAPINE
299. MEBENDAZOLE
300. MEBEVERINE HYDROCHLORIDE
301. MEDROXY PROGESTERONE ACETATE
302. MEFENAMIC ACID
303. MEFLOQUINE HYDROCHLORIDE
304. MEGESTROL ACETATE
305. MEGLUMINE IOCARMATE
306. MELAGENINA
307. MELITRACEN HYDROCHLORIDE
308. MELOXICAM
309. MEPHENESIN, ITS ESTERS
310. MEPHENTERMINE
311. MEROPENAM
312. MESTEROLONE
313. METAXALONE
314. METHICILLIN SODIUM
315. METHOCARBAMOL
316. METHOTRAXATE
317. METOCLOPRAMIDE
318. METOPROLOL TARTRATE
319. METRIZAMIDE
320. METRONIDAZOLE
321. MEXILETINE HYDROCHLORIDE
322. MIANSERIN HYDROCHLORIDE
323. MICONAZOLE
324. MIDAZOLAM

325. MIFEPRISTONE
326. MILRINONE LACTATE
327. MILTEFOSINE
328. MINOCYCLINE
329. MINOXIDIL
330. MIRTAZAPINE
331. MISOPROSTOL
332. MITOXANTRONE HYDROCHLORIDE
333. MIZOLASTINE
334. MOCLOBEMIDE
335. MOMETASONE FUROATE
336. MONTELUKAST SODIUM
337. MORPHAZINAMIDE HYDROCHLORIDE
338. MOSAPRIDE
339. MOXIFLOXACIN
340. MYCOPHENOLATE MOFETIL
341. NADIFLOXACIN
342. NADOLOL
343. NAFARELIN ACETATE
344. NALIDIXIC ACID
345. NAPROXEN
346. NARCOTICS DRUGS LISTED IN NARCOTIC DRUGS & PSYCHOTROPIC SUBSTANCES ACT, 1985
347. NATAMYCIN
348. NATEGLINIDE
349. N-BUTYL-2-CYANOACRYLATE
350. NEBIVOLOL
351. NEBUMETONE
352. NELFINAVIR MESILATE
353. NETILMICIN SULPHATE
354. NEVIRAPINE
355. NICERGOLINE
356. NICORANDIL
357. NIFEDIPINE
358. NIMESULIDE
359. NIMUSTINE HYDROCHLORIDE
360. NITRAZEPAM
361. NITROGLYCERIN
362. NORETH ISTERONE ENANTHATE
363. NORFLOXACIN
364. OCTYLONIUM BROMIDE
365. OFLOXACIN
366. OLANZAPINE
367. OMEPRAZOLE
368. ORNIDAZOLE
369. ORPHENADRINE
370. ORTHOCLONE STERILE
371. OXAZEPAM
372. OXAZOLIDINE
373. OXCARBAZEPINE
374. OXETHAZAINE HYDROCHLORIDE
375. OXICONAZOLE
376. OXOLINIC ACID
377. OXPRENOLOL HYDROCHLORIDE
378. OXYBUTYNIN CHLORIDE
379. OXYFEDRINE
380. OXYMETAZOLINE
381. OXYPHENBUTAZONE
382. OXYTOCIN
383. OZOTHINE
384. PACLITAXEL
385. PANCURONIUM BROMIDE
386. PANTOPRAZOLE
387. PARA-AMINO BENZENE SULPHONAMIDE, ITS SALTS & DERIVATIVES
388. PARP-AMINO SALICYLIC ACID, ITS SALTS, ITS DERIVATIVES
389. PARECOXIB
390. PAROXETINE HYDROCHLORIDE
391. D-PENICILLAMINE
392. PENTAZOCINE
393. PENTOXIFYLLINE
394. PEPLEOMYCIN
395. PHENELZINEH SULPHATE
396. PHENOBARBITAL
397. PHENOTHIAZINE, DERIVATIVES OF AND SALTS OF ITS DERIVATIVES
398. PHENYLBUTAZINE
399. PIMOZIDE
400. PINDOLOL
401. PIOGLITAZONE HYDROCHLORIDE
402. PIRACETAM
403. PIROXICAM
404. PITUITORY GLAND, ACTIVE PRINCIPLES OF, NOT OTHERWISE SPECIFIED IN THIS SCHEDULE AND THEIR SALTS
405. POLIDOCANOL
406. POLYESTRADIOL PHOSPHATE
407. PORACTANT ALFA
408. PRAZIQUANTEL
409. PREDNIMUSTINE
410. PREDNISOLONE STEAROYLGLYCOLATE
411. PRENOXDIAZIN HYDROCHLORIDE
412. PROMAZINE HYDROCHLORIDE
413. PROMEGESTONE
414. PROPAFENON HYDROCHLORIDE
415. PROPANOLOL HYDROCHLORIDE
416. PROPOFOL
417. PROTRISTYLINE HYDROCHLORIDE
418. PYRAZINAMIDE
419. PYRVINIUM
420. QUETIAPINE FUMERATE
421. QUINAPRIL
422. QUINIDINE SULPHATE
423. RABEPRAZOLE
424. RACECADOTRIL
425. RALOXIFENE HYDROCHLORIDE
426. RAMIPRIL HYDROCHLORIDE
427. RANITIDINE
428. RAUWOLFIA, ALKALOIDS OF, THEIR SALTS, DERIVATIVES OF THE ALKALOIDS OR RAUWOLFIA
429. REBOXETINE
430. REPAGLINIDE
431. REPROTEROL HYDROCHLORIDE
432. RILMENIDINE
433. RILUZONE
434. RISPERIDONE
435. RITONAVIR
436. RITODRINE HYDROCHLORIDE
437. RITUXIMAB
438. RIVASTIGMINE
439. ROCURONIUM BROMIDE
440. ROPINIROLE
441. ROSOXACIN

442. ROSIGLITAZONE MELEATE
443. SALBUTAMOL SULPHATE
444. SALICYL-AZO-SULPHAPYRIDINE
445. SALMON CALCITONIN
446. SAQUINAVIR
447. SATRANIDAZOLE
448. SECNIDAZOLE
449. SEPTOPAL BEADS & CHAINS
450. SERRATIOPEPTIDASE
451. SERTRALINE HYDROCHLORIDE
452. SIBUTRAMINE HYDROCHLORIDE
453. SILDENAFIL CITRATE
454. SIMVASTATIN
455. SIROLIMUS
456. SISOMICIN SULPHATE
457. S-NEOMINOPHAGEN
458. SODIUM PICOSULPHATE
459. SODIUM CROMOGLYCATE
460. SODIUM HYALURONATE
461. SODIUM VALPROATE
462. SODIUM AND MAGLUMINE IOTHALAMATES
463. SOMATOSTATIN
464. SOMATOTROPIN
465. SOTALOL
466. SPARFLOXACIN
467. SPECTINOMYCIN HYDROCHLORIDE
468. SPIRONOLACTONE
469. STAVUDINE
470. SUCRALFATE
471. SULPHADOXINE
472. SULPHAMETHOXINE
473. SULPHAMETHOXYPYRIDAZINE
474. SULPHAPHENAZOLE
475. SULPIRIDE
476. SULPROSTONE HYDROCHLORIDE
477. SUMATRIPTAN
478. TACRINE HYDROCHLORIDE
479. TAMSULOSIN HYDROCHLORIDE
480. TRAPIDIL
481. TEGASEROD MALEATE
482. TEICOPLANIN
483. TELMISARTAN
484. TEMOZOLAMIDE
485. TERAZOSIN
486. TERBUTALINE SULPHATE
487. TERFENADINE
488. TERIZIDONE
489. TERLIPRESSIN
490. TESTOSTERONE UNDECOANOATE
491. TERATOLOL HYDROCHLORIDE
492. THALIDOMIDE
493. THIACETAZONE
494. THIOCOLCHICOSIDE
495. THIOPROPAZATE, ITS SALTS
496. THYMOGENE
497. THYMOSIN-ALPHA 1
498. TIAPROFENIC ACID
499. TIBOLONE
500. TIMOLOL MALEATE
501. TINIDAZOLE
502. TIZANIDINE
503. TABRAMYCIN
504. TOLFENAMIC ACID
505. TOPIRAMATE
506. TOPOTECAN HYDROCHLORIDE
507. TRAMADOL HYDROCHLORIDE
508. TRANEXAMIC ACID
509. TRANYLCYPROMINE, ITS SALTS
510. TRAZODONE
511. TRETINOIN
512. TRIFLUPERAZINE
513. TRIFLUPERIDOL HYDROCHLORIDE
514. TRIFLUSAL
515. TRIMETAZIDINE DIHYDROCHLORIDE
516. TRIMIPRAMINE
517. TRIPOTASSIUM DICITRATE BISMUTHATE
518. TROMANTADINE HYDROCHLORIDE
519. UROKINASE
520. VALSARTAN
521. VASOPRESSIN
522. VECURONIUM BROMIDE
523. VENLAFAXINE HYDROCHLORIDE
524. VERAPAMIL HYDROCHLORIDE
525. VERTEPORFIN
526. VINCRISTINE SULPHATE
527. VINBLASTINE SULPHATE
528. VINDESINE SULPHATE
529. VINORELBINE TATRATE
530. XIPAMIDE
531. ZIDOVUDINE HYDROCHLORIDE
532. ZIPRASIDONE HYDROCHLORIDE
533. ZOLEDRONIC ACID
534. ZOLPIDEM
535. ZOPICLONE
536. ZUCLOPENTHIXOL

Note:- 1. Preparations exempted under proviso to para 2 of Note to Schedule X shall also be covered by this Schedule.
2. The salts, esters, derivatives and preparations containing the above substances excluding those intended for topical or external use (except ophthalmic and ear / nose preparations containing antibiotics and/ or steroids) are also covered by this Schedule.
3. The inclusion of a substance in this Schedule does not imply or convey that the substance is exempted from the provisions of Rule 122A/122B.'

[No. X-11014/3/2004-DMS & PFA]
RITA TEOTIA, Jt. Secy.

Foot Note- The Principal Rules were published in the Official Gazette vide notification No. F. 28-10/45-H(1) dated 21.12.1945 and last amended vide No. G.S.R. 790 (E) dated 29.10.2009.

Ministry of Health and Family Welfare (Department of Health)
NOTIFICATION
New Delhi, the 17th of January, 2012

G.S.R. 28 (E). – Whereas a draft of certain rules further to amend the Drugs and Cosmetics Rules, 1945, was published, as required by Sections 12 and 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), vide notification of the Government of India, Ministry of Health and Family Welfare (Department of Health), number G.S. R. 911 (E), dated 12th November, 2010, in the Gazette of India, Extraordinary, Part II, Section 3, Sub-section (i), dated the 12th of November, 2010, inviting objections and suggestions from all persons likely to be affected thereby before the expiry of a period of forty five days from the date on which the copies of the Official Gazette in which this notification is published are made available to the public;

And whereas copies of the Gazette were made available to the public on the 15th day of November, 2010;

And whereas, objections and suggestions received from the public on the said rules have been considered by the Central Government;

Now, therefore, in exercise of the powers conferred by Sections 12 and 33 of the Drugs and Cosmetics Act 1940 (23 of 1940), the Central Government, after consultation with the Drugs Technical Advisory Board, hereby makes the following rules, further to amend the Drugs and Cosmetics Rules, 1945, namely : -

1. (1) These rules may be called the Drugs and Cosmetics (1st Amendment) Rules, 2012.

(2) They shall come into force on the date of their publication in the Official Gazette.

2. In the Drugs and Cosmetics Rules, 1945, in rule 97, after sub-rule (3) the following shall be inserted, namely: -

'(3A) The container of a medicine for treatment of food producing animals shall be labeled with the withdrawal period of the drug for the species on which it is intended to be used:

Provided that if the specific withdrawal period has not been validated, the withdrawal period shall not be less than seven days for eggs or milk, twenty eight days for meat from poultry and mammals including fat and offal, five hundred degree days for fish meat.

Explanation – For the purpose of this rule the withdrawal period is the period of interval between the last administration of a veterinary medicine to animals under the normal conditions of use and the production of food stuff from such animals to ensure that food stuffs do not contain residues in quantities in excess of the maximum residue limits laid down.'

[F.No. X – 110014/1/2010 – DFQC]

ARUN K. PANDA, Jt. Secy

Note: - The principal rules were published in the Official Gazette vide notification No. F. 28-10/45-H (1), dated 21st December, 1945 and last amended vide notification number G.S.R. 899(E), dated the 27th December, 2011.

MINISTRY OF HEALTH AND FAMILY WELFARE
(Department of Health and Family Welfare)
NOTIFICATION
New Delhi, the 30th August, 2013

G.S.R. 588(E).-Whereas certain draft rules further to amend the Drugs and Cosmetics Rules, 1945-;-werepublished, as required by sections 12 and 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), without consulting the Drugs Technical Advisory Board vide notmcation of the Government of India, Ministry of Health and Family Welfare (Department of Healthand Family Welfare), number G.S.R. 228(E), dated the zo" March, 20121 published in the G~zette of India, Extraordinary, Part II, Section 3, Sub-section (i), dated the zo" March, 2012, in~iting objections and suggestions from all persons likely to be.affected thereby before the expiry of a period of forty-five days from the date on which the cdpies of the Official Gazette containinq the said notification were made available to the public;

And whereas the copies of the Gazette in which the said notification was published were made available to the public on the zo" March, 20'12;

And whereas, the Drugs Technical Advisory Board has been consulted in thematter,

And whereas, objections and suggestions received in respect of the said draft rules
have been considered by the Central Government;

I ·i:ftlT II---"&1T.S 3(i)J 5

Now, therefore, in exercise of the powers conferred by sections 12· and 33 of the Drugs and Cosmetics Act, 1940 (23 of 1940), the Central Government, after consultation with the Drugs Technical Advisory Board, hereby makes the following rules further to amend the Drugs and Cosmetics Rules, 1945, namely:- - -

1. (1) These rules may be called the Drugs and Cosmetics (FourthAmendment)
Rules, 2013.

(2) They shall come into force after six months of their publication in the Official
Gazette.

2. In the Drugs and Cosmetics Rules, 1945 (hereinafter referred to as said rules),•

(i) in rule 65,-

(a) in condition (3), in clause (1),-

(A) in sub-clause (f) and in item (ii) of the third proviso to sub-clause (g), for the words and letter 'Schedule H', the words and letters "Schedule H and Schedule H1",shall respectively be substituted;

(B) after clause (g) and the provisos thereof, the following shall be inserted, namely:- "(h) the supply of a drug specified in Schedule H1 shall be recorded in a separate register at the time of the supply giving the name and address of the prescriber, the name of the patient, the name of the drug and the quantity supplied and such records shall be maintained for three years and be open for inspection.

(b) in condition (9), in clauses (a) and (b), for the words and letter 'Schedule H', the words and letters "Schedule H and Schedule H1" shall respectively be substituted;

(c) in condition (11), for the words and letter 'Schedule H', the words and letters "Schedule Hand Schedule H1" shall be substituted;

(d) in condition (11A), for the words and letter 'Schedule H', the words and letters "Schedule Hand Schedule H1" shall be substituted;

(ii).in rule 97, in sub rule (1), after clause (d), the following shall be inserted, namely,-

'(e) if it contains a drug substance specified in Schedule H1, the drug formulation shall be labelled with the symbol Rx which shall be in red and conspicuously displayed on the left top corner of the label, and shall also be labelled with the following words)n a box with a red border:

6 THE GAZE1TE OF INDIA : EXTRAORDINARY jPAJ\: 11- S1.c. 3(i)J

"SCHEDULE H 1 DRUG - WARNING:

-It is dangerous to take this preparation except in
accordance with the medical advice.

-Not to be sold by retail without the prescription of a!
Registered Medical Practitioner."';

3. In the said rules, in Schedule H, the following entries shall be omitted, namely:•

" 1. Alprazolam
2. Cefdinir .
3. Cefepime Hydrochloride
4. Cefetamet Pivoxil
5. Cefpirome
6. Cefpodoxime Poxetil
7. Ceftazidime Pentahydrate
8. Ceftizoxime Sodium
9. Chlordiazepoxide
10. Clofazimine
11. Codeine
12. Diazepam

13. Diphenoxylate and its salts
14. Ethambutol Hydrochloride
15. Ethionamide
16. Levofloxacin
17. Meropenam
18. Midazolam
19. Moxifloxacin
20. Nitrazepam
21. Pentazocine
22. Pyrazinamide
23. Sparfloxacin
24. Thiacetazone
25. Tramadol hydrochloride
26. Zolpidem";

4. In the said rules, after Schedule H, the following Schedule shall be inserted,
namely:-
1. Alprazolam
2. Balofloxacin
3. Buprenorphine
4. Capreomycin
5. Cefdinir
6. Cefditoren
7. Cefepime
8. Cefetamet
9. Cefixime
1 O. Cefoperazone
11. Cefotaxime
12. Cefpirome
13. Cefpodoxime
14. Ceftazidime
15. Ceftibuten
16. Ceftizoxime
17. Ceftriaxone
"ScheduleH1
(See rules 65 and 97)
18. Chlordiazepoxide
19. Clofazimine
20.Codeine
21. Cycloserine
22. Diazepam
23. Diphenoxylate
24. Doripenem
25. Ertapenem
26. Ethambutol Hydrochloride
27. Ethionamide
28. Feropenem
29. Gemifloxacin
THE GAZEITE OF INDIA : EXTRAORDINARY
30. Imipenem
31. Isoniazid
32. Levofloxacin
33. Meropenem
34. Midazolam
35. Moxifloxacin
36. Nitrazepam
37. Pentazocine
38. Prulifloxacin
39. Pyrazinamide
40. Rifabutin
41. Rifampicih
42. Sodium Para-aminosalicylate
43. Sparfloxacin
44. Thiacetazone
45.Tramadol
46. Zolpidem
Note.- Preparations containing the above drug substances and their salts excluding those intended for topical or external use (except ophthalmic and ear or nose preparations) containing above substances are also covered by this Schedule.".

[F. No. X-11014/6/2010-DFQC]
ARUN K. PANDA, Jt. Secy
Foot note : The principal rules were published in the Official Gazette vide
notification No. F.28-10/45-H (1), dated 21st December, 1945 and last amended
vide notification number G.S.R. 72 (E), dated the ath February, 2013.
---------- -.--
Printed by the Manager, Government of India Press, Ring Road,

ANNEX 5

Minimum Required Performance Limits (MRPLs) and Maximum Residual Limits (MRLs) for Substances in Aquaculture Products and Food Animals for Export

The below MRPLs and MRLs follow EU Regulation no. 37/2010, dated 22nd December 2009.

TABLE 1: Substances Prohibited for Use in Aquaculture

Active substance	Species/Matrix	MRPL	Comments
Nitrofuran Metabolites	Muscle/Products of all Aquaculture species	1 µg/kg	MRPL determined
Chloramphenicol	Muscle/Products of all Aquaculture species	0.3 µg/kg	MRPL determined
Nitroimidazoles	Muscle/Products of all Aquaculture species	3 µg/kg	Working limit determined
Malachite Green & Leuco-malachite green	Muscle/Products of all Aquaculture species	2 µg/kg	Working MRPL

TABLE 2: Substances with prescribed residue limits (MRL) in case of use in food animals

Active substance	Species/Matrix	MRPL	Comments
Amoxicillin	All food producing species (Muscle/Fat/Liver/Kidney/ Milk)	100 µg/kg	For finfish the muscle MRL relates to 'muscle and skin in natural proportions'. MRLs for fat, liver and kidney do not apply to finfish. For porcine and poultry species the fat MRL relates to 'skin and fat in natural proportions'. Not for use in animals from which eggs are produced for human consumption.
Sulfonamides	All food-producing species	100 µg/kg	MRPL determined
Sarafloxacin	Chicken	10 µg/kg	Working limit determined
	(skin and far/liver	100 µg/kg	
Tetracycline	All species/Muscle	100 µg/kg	This MRL refers to the total of the parent drug and its 4 epimers
Oxyetracycline	All species/Muscle	100 µg/kg	This MRL refers to the total of the parent drug and its 4 epimers
Oxolinic acid	All species/Muscle	100 µg/kg	In case of fish, MRL for muscle means muscle and skin in natural proportion
Chlortetracycline	All food-producing species/ muscle	100 µg/kg	In case of fish, MRL for muscle means muscle and skin in natural proportion
Enamectin B1a	Fin fish/muscle	100 µg/kg	In case of fish, MRL for muscle means muscle and skin in natural proportion
Flumequine	Fin fish/muscle	600 µg/kg	In case of fish, MRL for muscle means muscle and skin in natural proportion
Deltamethrin	Fin fish	10 µg/kg	In case of fish, MRL for muscle means muscle and skin in natural proportion
Enrofloxacin (sum of enrofloxacin and ciprofloxacin)	Fin fish/muscle	100 µg/kg	In case of fish, MRL for muscle means muscle and skin in natural proportion

Erythromycin A	Fin fish/muscle	100 µg/kg	In case of fish, MRL for muscle means muscle and skin in natural proportion
Florfenicol (sum of florfenicol and its metabolites measured as florfenicol-amine)	Fin fish/muscle	1000 µg/kg	In case of fish, MRL for muscle means muscle and skin in natural proportion
Paramomycin	Fin fish/muscle	500 µg/kg	In case of fish, MRL for muscle means muscle and skin in natural proportion
Thiamphenicol	Fin fish/muscle	50 µg/kg	In case of fish, MRL for muscle means muscle and skin in natural proportion
Tilmicosin	Fin fish/muscle	50 µg/kg	In case of fish, MRL for muscle means muscle and skin in natural proportion
Trimethroprim	Fin fish/muscle	50 µg/kg	In case of fish, MRL for muscle means muscle and skin in natural proportion
Tylosin A	Fin fish/muscle	100 µg/kg	In case of fish, MRL for muscle means muscle and skin in natural proportion

ANNEX 6

Recommendations by the OIE on Combating Antimicrobial Resistance and the Responsible and Prudent Use of Antimicrobial Agents in Animals

RESOLUTION No. 26
Combating Antimicrobial Resistance and Promoting the Prudent Use of Antimicrobial Agents in Animals

CONSIDERING

1. That antimicrobial agents are essential tools for protecting animal health and welfare and also contribute to meeting the increasing global demand for safe meat, milk, fish and eggs, and other products of animal origin,
2. That antimicrobial resistance (AMR) is a significant global animal and human health threat that is influenced by the use of antimicrobial agents in some conditions,
3. That during the 77th General Session 2009, the World Assembly of Delegates (the Assembly) adopted Resolution No. 25 on Veterinary Products, which considered previous Resolutions on harmonisation of registration requirements for veterinary drugs, their responsible and prudent use and monitoring of resistance,
4. The recommendations of the OIE Global Conference on the responsible and prudent use of antimicrobial agents in animals, held in March 2013 in Paris, France, including recommendation No.7 to collect harmonised quantitative data on the use of antimicrobial agents in animals with the view to establishing a global database,
5. The recent update and development of OIE standards and guidelines related to antimicrobial resistance, which include references to the relevant standards developed by Code Alimentarius,
6. The tripartite agreement between FAO, OIE and WHO to address as a priority antimicrobial resistance and the important contribution of the OIE to the development and achievement of the WHO global action plan on antimicrobial resistance,
7. The network of OIE National Focal Points for Veterinary Products and its role in supporting the global implementation of the OIE standards regarding veterinary products,
8. The importance of the PVS pathway in supporting compliance of national veterinary services with OIE standards including legislation, as a prerequisite to ensuring good governance covering production, registration, distribution and use of antimicrobial agents at the national level,
9. The importance of appropriate Veterinary Education and Veterinary Statutory Bodies in the promotion of veterinary oversight to ensure responsible use of antimicrobial agents in animals,

THE ASSEMBLY RECOMMENDS THAT

1. The OIE continue to develop and update standards and guidelines related to antimicrobial resistance and the prudent use of antimicrobial agents including updating regularly the OIE List of Antimicrobial Agents of Veterinary Importance.
2. The OIE, with support from relevant organisations and donors, work with Member Countries to support them to implement OIE standards and guidelines using the PVS pathway and other relevant OIE capacity building mechanisms, including twinning and regional seminars.
3. The OIE develop a procedure and standards for data quality for collecting data annually from OIE Member Countries on the use of antimicrobial agents in food-producing animals with the aim of creating an OIE global database to be managed in parallel with the World Animal Health Information System (WAHIS).
4. OIE Member Countries set up an official harmonised national system, based on OIE standards, for the surveillance of antimicrobial resistance and the collection of data on the use of antimicrobial agents in food-producing animals, and actively participate in the development of the OIE global database.
5. The participation of OIE Member Countries in the VICH Outreach Forum be facilitated with the aim of adopting and utilising harmonised international guidelines related to the technical requirements for registration of veterinary medicinal products.
6. OIE Member Countries improve veterinary legislation and education, where necessary, in order to facilitate implementation of OIE and Codex Alimentarius standards and guidelines related to antimicrobial resistance and veterinary oversight of the use of antimicrobial agents.
7. The OIE and OIE Member Countries encourage Veterinary Statutory Bodies and the veterinary profession as a whole to develop, implement and ensure compliance with ethics and codes of good veterinary practices, with particular reference to the prescription and delivery of antimicrobial agents by well-trained veterinarians or veterinary para-professionals under their direct oversight.
8. OIE Member Countries follow the guidance of the WHO Global Action Plan on Antimicrobial Resistance, developed with the support of the OIE in the spirit of the “One Health” approach, in particular by developing national action plans, with the support of FAO and WHO where feasible and warranted, in respect of the use of antimicrobial agents in animals and ensuring their close collaboration with public health officials.

9. The OIE continue to seek donor support for the organisation of dedicated regional training seminars for OIE National Focal Points for Veterinary Products with the participation of FAO and WHO within the tripartite collaboration and invite other relevant partners to build capacity at the national and regional levels to enable the implementation of OIE and Codex Alimentarius intergovernmental standards to combat antimicrobial resistance and support the recommendations of the WHO Global Action Plan on Antimicrobial Resistance.
10. The OIE strengthen its collaboration with international organisations, such as the World Customs Organisation and Interpol, and stakeholders to combat counterfeit products with the aim of ensuring access to antimicrobial agents of proven quality.
11. Research be promoted to improve tools for rapid diagnostics for use in animals and to explore alternatives to antimicrobial use in animals, including the development of vaccines and other tools for priority diseases.

_____

(Adopted by the World Assembly of Delegates of the OIE on 26 May 2015
in view of an entry into force on 30 May 2015)

ABOUT THE CENTER FOR DISEASE DYNAMICS, ECONOMICS & POLICY

The Center for Disease Dynamics, Economics & Policy (CDDEP) was founded with the objective of using research to support better decision-making in health policy. CDDEP researchers employ a range of expertise—including economics, epidemiology, disease modeling, risk analysis, and statistics—to conduct actionable, policy-oriented research on malaria, antibiotic resistance, disease control priorities, environmental health, alcohol and tobacco, and other global health priorities.

CDDEP projects are global in scope, spanning Africa, Asia, and North America and include scientific studies and policy engagement. The CDDEP team is experienced in addressing country-specific and regional issues, as well as the local and global aspects of global challenges, such as antibiotic resistance and pandemic influenza. CDDEP research is notable for innovative approaches to design and analysis, which are shared widely through publications, presentations and web-based programs.

CDDEP has offices in Washington, D.C. and New Delhi and relies on a distinguished team of scientists, public health experts and economists around the world.