AMR in Animal Husbandry: The missing link of One Health

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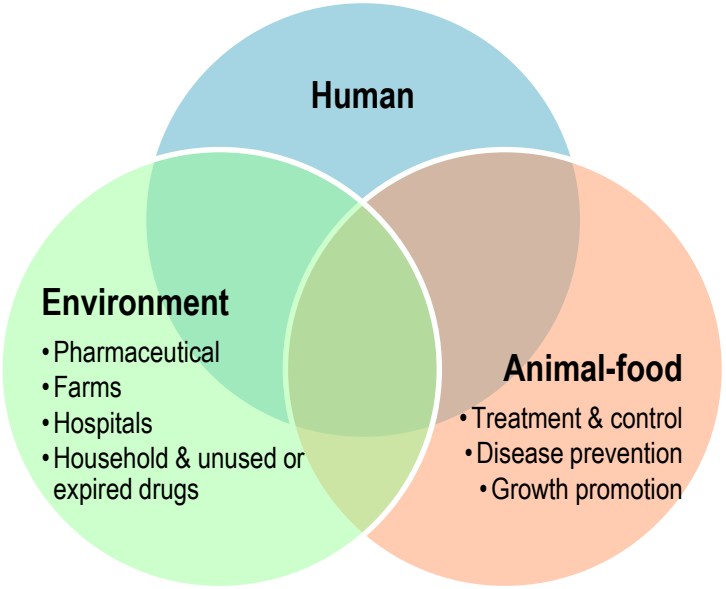
Antimicrobial resistance is a complex issue



Major health, food security, environment & economic threat

Pathogens resistant to #antimicrobials can circulate between animals, humans, and the environment.

Human health and animal health are ***interdependent***, linked closely to the health of the environment they live in.

Drivers for AMR in India

- In India the major driver for AMR should be the antibiotic use for **Human Health** and problems with **sanitation** especially in view of rapid urbanization.
- Poverty compounds the problems, because people do not have access to clean water and hygiene and **malnutrition** and are at an increased risk of acquiring infections coupled with **privatization** of health care.
- **Use of antibiotics in food animals**. We need to particularly take care that antibiotic is not used a cheap production tool to counter poor hygiene in farms.

Patterns of Animal Antibiotic Use

- With respect to consumption of antimicrobials in food animals, the global consumption was estimated to be around 70000 tons;
- India accounts for 3% of the global consumption and is the fourth highest in the world, behind China (23%), the United States (13%) and Brazil (9%).
- The consumption of antimicrobials in the food animals sector in India is expected to double by 2030

AMR and Food Safety

- In Veterinary Medicine, antimicrobials play a critical role in protection of animal health, animal welfare, and food-safety
- Humans and animals are often affected by similar, or even the same, pathogens and many of the antimicrobials used to treat these infectious diseases are similar
- Farm animals are exposed to considerable quantities of antimicrobials and act as an important reservoir of AMR genes, which can be transmitted to humans through the food chain, direct animal contact and the wider environment
- *Good farm management practices, better biosecurity and vaccination can minimise diseases and reduce use of Antibiotics in Animal Health.*

Weak Regulators in India

- There is absence of any stringently framed and implemented regulatory framework to limit the use of antimicrobials in livestock and food animals, especially for non-therapeutic purposes, like growth promotions.

Burden of AMR in Food Animals

- The burden of AMR in livestock and food animals has been poorly documented in India.
- Aside from sporadic, small, localized studies, evidence that can be extrapolated to the national level is lacking.
- Given that there are few regulations against the use of antibiotics for non-therapeutic purposes in India, the emergence of AMR from antibiotic overuse in the animal sector is likely to be an unmeasured burden in India

Industrial Food Animal Production (IFAP)

- The 20th century saw unprecedented transformation in the scale and practices associated with food animal agriculture.
- The resulting industrial model first emerged in US poultry production over the 1930s–1950s, with parallel developments in Europe. Industrial food animal production (IFAP) today is characterized by large-scale, highly specialized, **densely stocked operations designed to maximize output at minimal cost to producers**.
- Production relies heavily on inputs, including specially formulated feeds, pharmaceuticals, and synthetic hormones (in cattle), the use of which has been implicated in the presence of environmental, occupational, and food-borne hazards
- This model has become increasingly globalized, with multinational corporations expanding operations in Southeast Asia, Mexico, Eastern Europe, and other parts of the world

Ways of Antimicrobials use in Food Animals

- The indication for anti microbial treatment is enteric and respiratory disorders in animals and mastitis in dairy cows Therapeutic use can include individual animals, but can also be treatment of a group of diseased animals by injection or orally.
- Preventive use varies from targeted interventions to control the spread of a diagnosed disease to routine treatment of all animals. Preventive use is mostly given via feed or water.
- **In India, infectious diseases in animals has a huge effect on the economy of a local community dependent on small-scale rearing of animals and the spread of resistance could lead to a local food security problem affecting the overall public health**

Antibiotic resistance in Animal Health

- Drug resistant bacteria have been isolated from dairy cattle as early as the 1970s. One of the most common clinical issues encountered in the dairy farms is mastitis, which maybe sub-clinical or overtly symptomatic.
- there is limited evidence available on the exact amount of antibiotic consumed within the poultry industry, and how these medications were prescribed.
- In many cases, since the antibiotic is given as a growth promoter through the premixed feed, which comes with added antibiotics that are not even mentioned on the label
- The existence of legislative provisions to contain the inappropriate and non-therapeutic use of antibiotics in fisheries along with a NRCP helps.
- Hence it is imperative to have a broad based surveillance system in place.

Problems with shortage of Veterinary care

- Treatment by others than the **Registered Veterinary Doctors**–increases this problem manifold.
- Lack of **Veterinary laboratories** with full scale diagnostics facility and veterinary standard treatment protocols
- Lack of awareness among the farmers, pharma retailers and even Industry and no Stewardship models

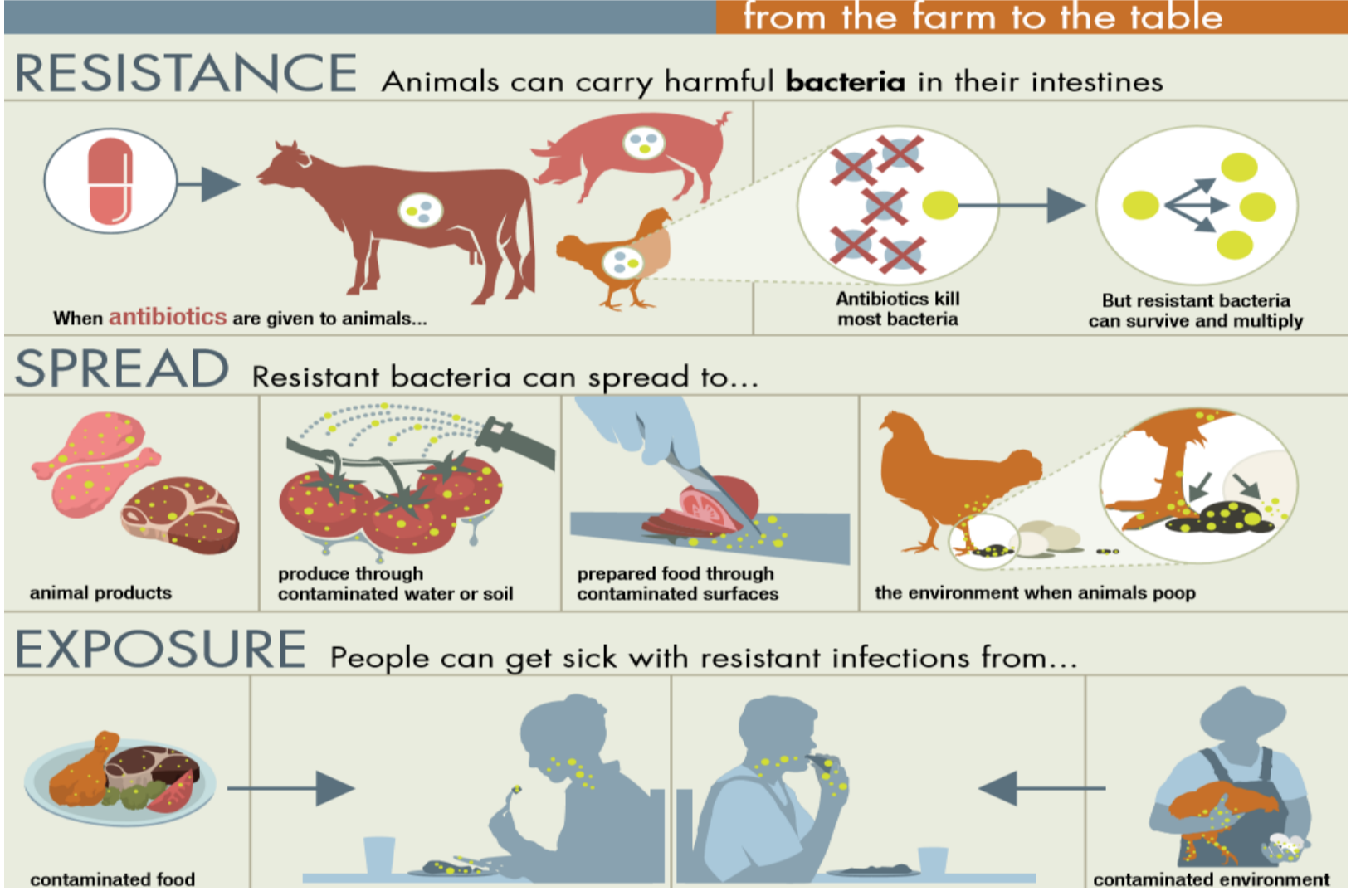
Types of Antimicrobials used in Animal Health

- Feeding sub therapeutic doses of antimicrobials became an integral part of intensive rearing of animals.
- Undoubtedly, these practices supported the intensification of modern food production by increased animal densities, and cheap feed sources.
- Furthermore, suboptimum growth caused by unsanitary conditions is sometimes compensated with addition of antibiotics to feed.
- Worldwide, many substances have been or are used, some of which are not used in human medicine and some from classes that are used in humans

Types of Antimicrobials used in Food Animals

- Overall, *tetracyclines, sulphonamides, penicillins and enrofloxacin* are the main classes sold. However, because the use of antimicrobials varies between animal species and even between production systems, further associations between sales and resistance are hampered by the dearth of sales data by animal species.
- For poultry production it is Bacitracin, tetracycline, tylosin and anticocidials (ionophores) are used as growth promotents.
- However, some newer types of antimicrobials, such as carbapenems are not used for animals reared for food.

Farm to Table



@ from CDC

One-Health approach

- Complex epidemiology of AMR emphasizes the need for highly interdisciplinary research approaches, comprising humans, animals, and the wider environment
- Along with socioeconomical factors, make this the quintessential One Health issue
- Hence reducing the dissemination and transmission of resistant bacteria within and between animal and human populations is central when aiming to fight AMR
- Ability of bacteria to disseminate from one setting to another, over large geographic distances and among the different populations, makes it difficult to explain the origin of resistant bacteria strains
- Therefore, the reservoirs and the transmission pathways of antimicrobial-resistant bacteria, should be investigated through a One-Health approach

Molecular epidemiology & study of resistance genes

- One Health approaches should be backed with molecular epidemiological data
- Strong circumstantial evidence suggests that resistance genes (ARGs) circulate between people, animals, and the environment. Any further increase in prevalence among animals will increase the likelihood of spread
- Resistance genes should be studied not only in human, animal samples but also in the wider farm environment, other livestock species, farm pets, wildlife, manure, fishery and water
- These ecological data can provide the molecular link to characterize reservoirs of resistant bacteria and could support studies on transmission pathways from animals to humans and vice versa
- Molecular epidemiology data will shed light on how much of the resistance reservoir is attributed to the spread of resistant bacteria or de novo emergence due to antibiotic use selection pressure in animal health

Constraints in Laboratory Testing for AMR

- The scarcity of quality-assured microbiology laboratories and lack of priority given to sustained bacterial surveillance. And Lack of One Health Approach and Integrated surveillance of AMR in Foods and Food Animals.
- culture-based assays have remained the gold standard for identification of pathogens and susceptibility testing. However, these methods are slow and are of limited value and resistance genes should be studied not only in human, animal samples but also in the wider farm environment.
- laboratory studies are lacking in understanding the molecular mechanisms of resistance, to provide insight into the factors that promote the survival and spread of AMR genes and resistant organisms through animal and environmental routes, such studies may require international colloborations

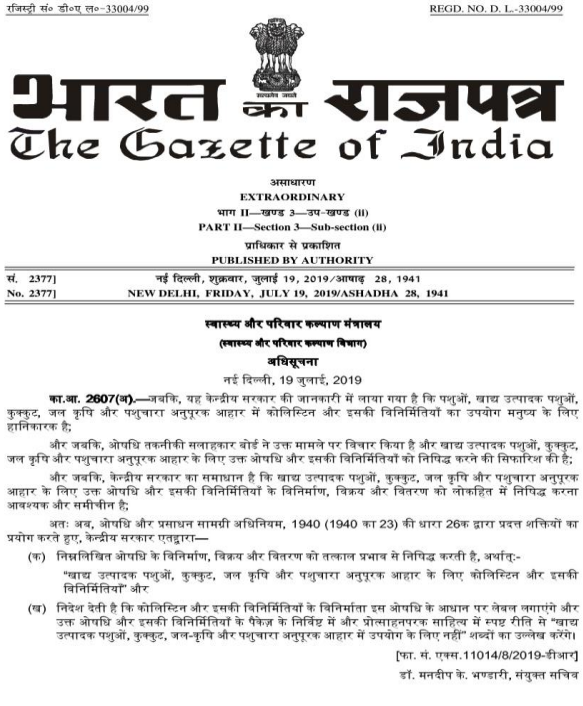
Constraints in Laboratory Testing for Antibiotic Residues in Food

- Antibiotics are of many categories and various formulations.
- Residue testing done at **parts per billion levels**. Quantification at ppb levels (MRLs) can only be achieved with High End Equipment which require very well trained Lab Staff with adequate supervision.
- Lengthy sample preparation for each type of Antibiotic, analysis, using high purity chemicals and consumables hence only can be done in specialised labs.
- Residue Control plans are usually not implemented due to inadequate traceability in animal foods and lack of suitable Lab support. Even the existing labs are not accredited to ISO 17025.

Entry of Antibiotic Residue contaminated food into Market

- This is our major challenge in India, as we prefer to eat animal foods fresh and there is only a select market for frozen/processed foods.
- So by the time official sampling and analysis is completed, the food might have already been consumed.
- The need for a targeted systemic Antibiotic Residue Monitoring Program including drawing of official samples and Lab Analysis followed by action on violations will go a long way to ensure Safe Food
- But, There are no food traceability systems as this is not a regulatory requirement

The Colistin Ban



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का.आ. 2607(अ).—जबकि, यह केन्द्रीय सरकार की जानकारी में लाया गया है कि पशुओं, खाद्य उत्पादक पशुओं, कुक्कुट, जल कृषि और पशुचारा अनुपूरक आहार में कोलिस्टिन और इसकी विनिर्मितियों का उपयोग मनुष्य के लिए हानिकारक है;

और जबकि, ओषधि तकनीकी सलाहकार बोर्ड ने उक्त मामले पर विचार किया है और खाद्य उत्पादक पशुओं, कुक्कुट, जल कृषि और पशुचारा अनुपूरक आहार के लिए उक्त ओषधि और इसकी विनिर्मितियों को निषिद्ध करने की सिफारिश की है;

और जबकि, केन्द्रीय सरकार का समाधान है कि खाद्य उत्पादक पशुओं, कुक्कुट, जल कृषि और पशुचारा अनुपूरक आहार के लिए उक्त ओषधि और इसकी विनिर्मितियों के विनिर्माण, विक्रय और वितरण को लोकहित में निषिद्ध करना आवश्यक और समीचीन है;

अतः अब, ओषधि और प्रसाधन सामग्री अधिनियम, 1940 (1940 का 23) की धारा 26क द्वारा प्रदत्त शक्तियों का प्रयोग करते हुए, केन्द्रीय सरकार एतद्द्वारा—

(क) निम्नलिखित ओषधि के विनिर्माण, विक्रय और वितरण को तत्काल प्रभाव से निषिद्ध करती है, अर्थात्:-

"खाद्य उत्पादक पशुओं, कुक्कुट, जल कृषि और पशुचारा अनुपूरक आहार के लिए कोलिस्टिन और इसकी विनिर्मितियाँ" और

(ख) निदेश देती है कि कोलिस्टिन और इसकी विनिर्मितियों के विनिर्माता इस ओषधि के आधान पर लेबल लगाएंगे और उक्त ओषधि और इसकी विनिर्मितियों के पैकेज़ के निर्विष्ट में और प्रोत्साहनपरक साहित्य में स्पष्ट रीति से "खाद्य उत्पादक पशुओं, कुक्कुट, जल-कृषि और पशुचारा अनुपूरक आहार में उपयोग के लिए नहीं" शब्दों का उल्लेख करेंगे।

[फा. सं. एक्स.11014/8/2019-डीआर]

डॉ. मनदीप के. भण्डारी, संयुक्त सचिव

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- Gram negative bacteria containing a gene known as mcr-1 – which confers resistance to this antibiotic, had spread around the world at an alarming rate since its original discovery few years earlier. In many LMICs, it was estimated that a quarter of hospital have bacteria that now carry this gene.

Colistin is now known as the "antibiotic of last resort" and in many parts of the world, hospitals have turned to its use because pan-drug-resistant (PDR) *Klebsiella* were no longer responding last available category of human antimicrobial agent carbapenems, and this comparatively toxic veterinary antibiotic was the only last hope

Standards and guideline on AMR-OIE

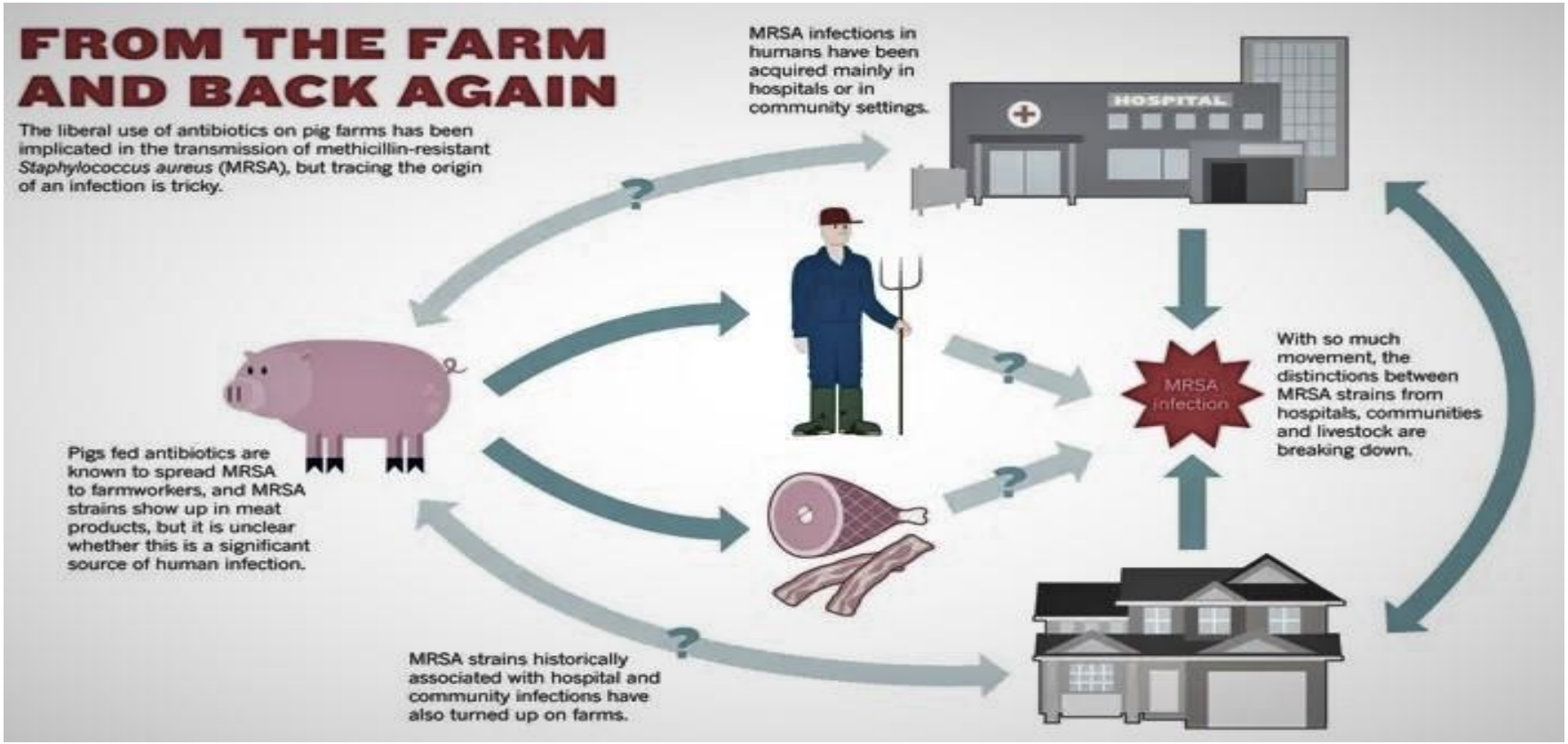
Recommendations Among the Veterinary Critically Important Antimicrobial Agents, some are also of critical importance for human health (third and fourth generation Cephalosporins, and Fluoroquinolones):

- Not to be used as preventive treatment in feed or water or in absence of clinical signs.
- Not to be used as first line, unless justified and bacteriological test.
- Extra-label/off label use should be limited and reserved for instances no alternatives are available.

The Blame Game

- General guidance spanning regulatory needs and prudent use of antimicrobials in Food Animals is provided by all international organisations: the OIE, WHO, and the UN Food and Agriculture Organization (FAO).
- Implementation of prudent use is in the domain of farmers, consumer groups as veterinarians in regulators are non existent in India. And Legitimate conflict of interests; eg-production practice and the ethical obligation to care for diseased animals.
- **In view of the polarised debate, veterinarians feel that they and livestock farmers are blamed by the consumers/regulators for a problem that is essentially generated by medical doctors.**

MRSA-from Human to Animals & Back



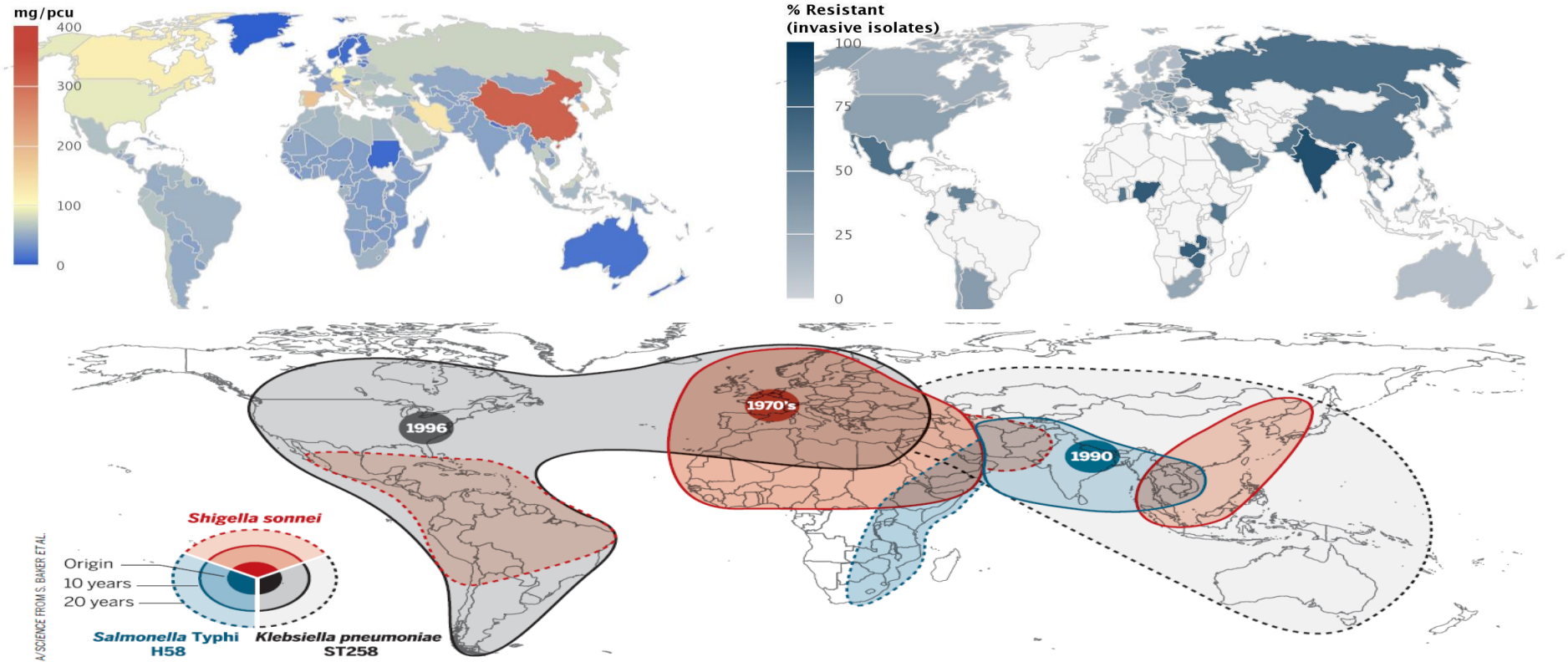


Fig. 2. Origin and blast radius for the clonal expansion for three multidrug-resistant Gram-negative bacteria clones. The map summarizes data for the global dissemination of: dysentery causing *Shigella sonnei* clone lineage III-global, with a chromosomal insertion of a mobile genetic element encoding resistance to streptomycin, trimethoprim-sulfamethoxazole, and tetracycline (red); the typhoid fever pathogen *Salmonella* Typhi, clone H58, with a plasmid encoding resistance to chloramphenicol, ampicillin, trimethoprim-sulfamethoxazole, streptomycin, and tetracycline (blue); health care–associated *Klebsiella pneumoniae* clone ST258, carrying the KPC carbapenemase encoding resistance to all β-lactam antimicrobials, including carbapenems and third-generation cephalosporins (gray).

Genomic insights into the emergence, maintenance and spread of AMR pathogens

- Although AMR organisms arise continuously, national- and international-level WGS snapshots show that most AMR infections are attributable to a few clones within the broad population of the specific pathogen.
- Thus, only a small fraction of emergent AMR variants is sufficiently fit for broader dissemination. Investigations of Gram-negative opportunistic pathogens clonal spread that begins as localized expansions, rapidly progressing to intercontinental spread (within years) and even global dissemination (within decades).
- Ex. resistant clones K. pneumoniae KPC ST258 **which carries the plasmid-borne K. pneumoniae carbapenemase gene KPC**, E. coli ST131, and A. baumannii GC1 all also display extensive surface antigen diversifications, so a major health care challenge, complicating alternative strategies, such as vaccines and targeted immunotherapies.

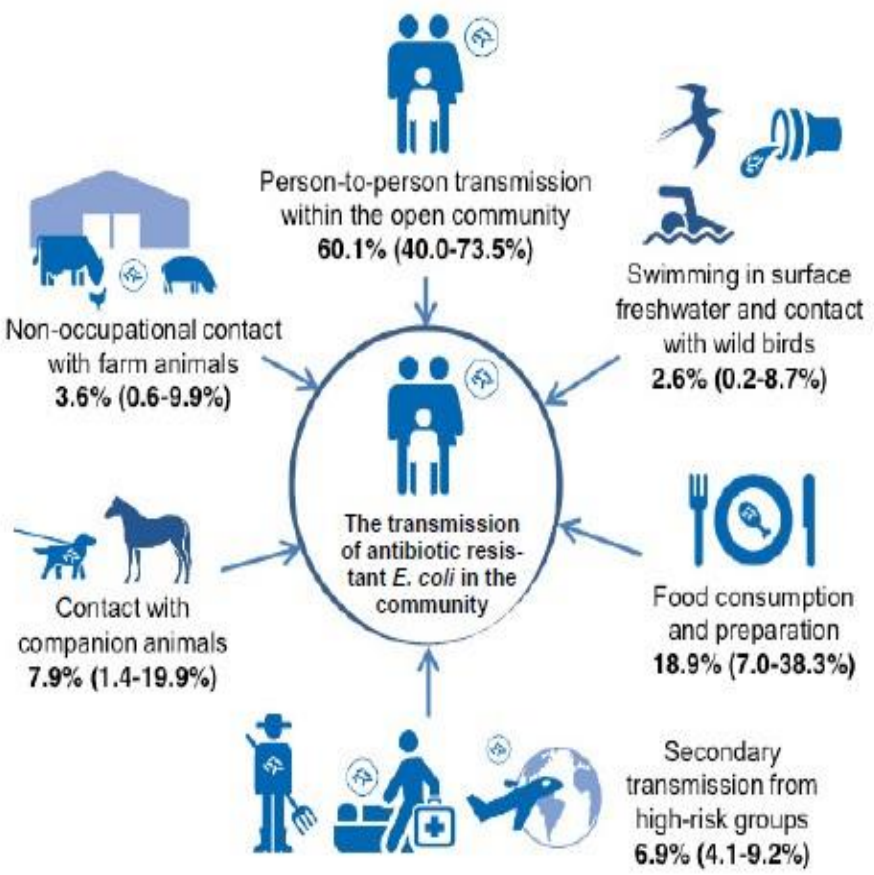


Diagram: Potential routes of transmission of antibiotic resistant E. coli in the community.

One Health European Joint Programme (One Health EJP)

RaDAR-Risk and Disease burden of Antimicrobial Resistance

Study shows that humans, rather than animals and food is the primary source of direct ESBL resistance

MedVetKlebs- Klebsiella pneumoniae: from ecology to source attribution and transmission control

This organism represents a significant threat to public health when associated with multi-drug resistance. K. pneumoniae is present in the gastrointestinal tracts of both humans and animals, yet the main reservoirs and routes of transmission between humans and animals remain undefined. This is mainly due to the lack of optimised protocols to detect and identify K. pneumoniae. These important gaps are addressed by the MedVetKlebs project

GAP-AMR

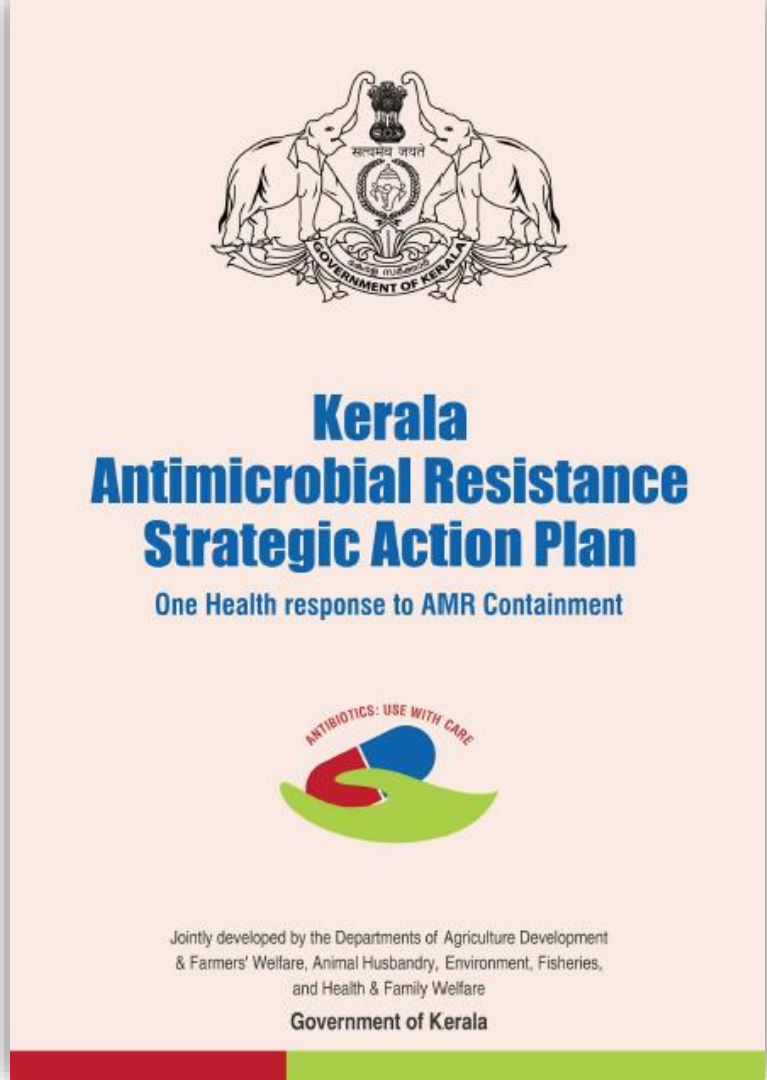
- 2015

NAP-AMR

- 2017

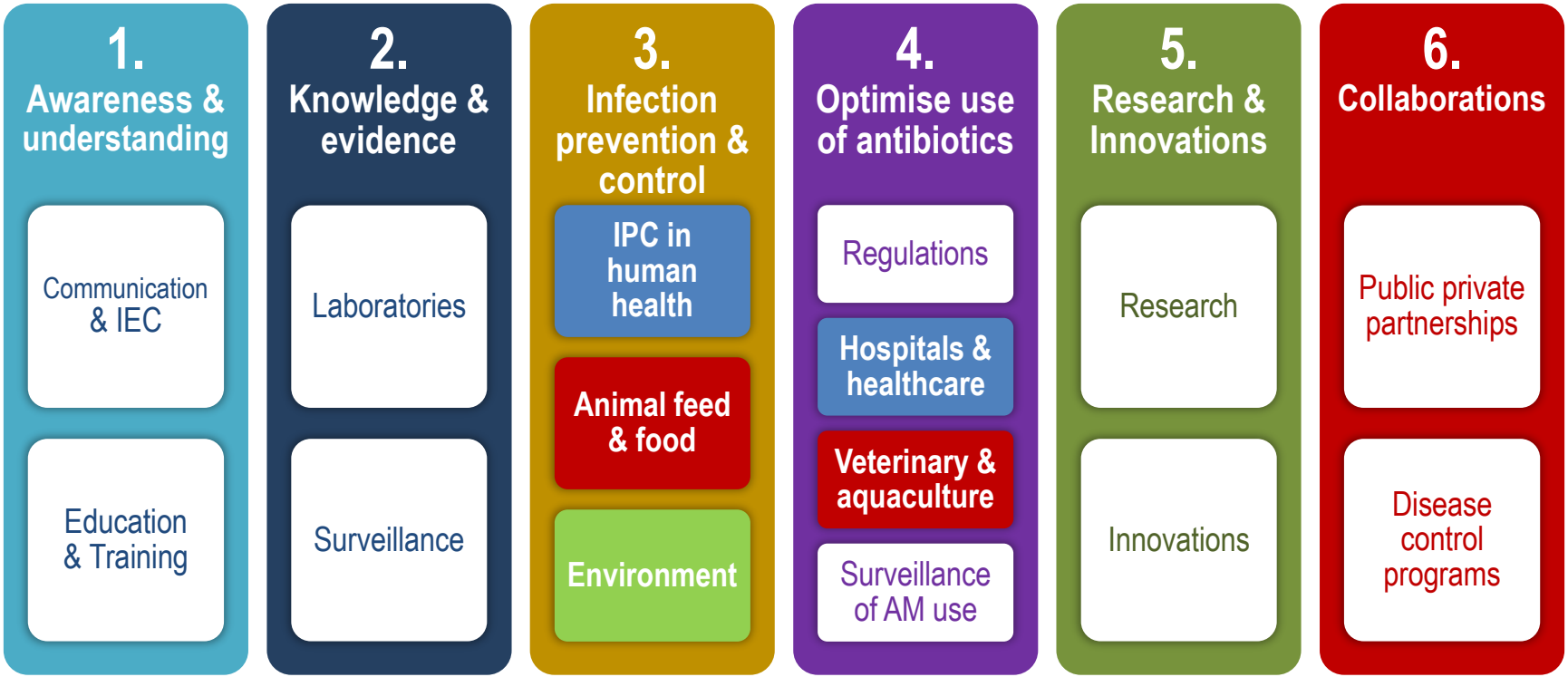
KARSAP

- 2018



KARSAP-One Health-Release by Hon. CM, Kerala

KARSAP strategic priorities & focus areas



Major drivers of AMR in Kerala

- Use, misuse and abuse of antibiotics
- Kerala is a consumer state for pharmaceuticals
- Uncontrolled use of antibiotics for growth promotion & for disease prevention in animals and fisheries
- Inadequate treatment of effluents containing antibiotic residue from pharmaceutical industry, farms & **HC facilities**

Kerala specific AMR challenges

Activities undertaken by Animal Health sector under the framework of KARSAP

- (1) Monitoring of Antibiotic Residues in Kerala (Meat, Milk, Poultry)
- (2) AntiMicrobial Resistance in Food and Food Animals (Meat, Milk, Poultry)
- (3) Detection of Oxytetracycline & Penicillins in Milk in by screening by Immuno chromatography & Quantification of Oxytetracycline by HPLC by SIAD
- (4) AST in avian species by ADDL
- (4) Awareness programs for Farmers/Vets
- (5) Distribution of antibiotic sensitivity kits to Veterinary Dispensaries/Hospitals/Polyclinics under AHD by IH & VB, Palode (Aprox 5000 nos)
- (6) AHD dept. manual revised and reissued, this has recommended antibiotics for select disease & AMR expert committee of AHD constituted
- (7) World Organization for Animal Health-OIE Performance of Veterinary Services-assessment of AHD Kerala.

AMR related Projects at SLMAP

Completed Projects (2017-18)

- Residue Monitoring for Antibiotics in Kerala

Surveillance Projects (2018-19)

- Residue Monitoring for Antibiotics in Broiler Chicken (New Districts)
- Antimicrobial Resistance (AMR) In Food and Food Animals: An Integrated Surveillance Program For Kerala (Meat, Milk, Poultry)
- Molecular Identification and Resistance Study of Bacteria isolated from Milk, Meat and Eggs

SAMPLE COLLECTION (72 farms) from Across Kerala

- **Poultry meat and liver samples-** ***Collected 144 samples from 5 major broiler chicken producing districts viz. Though Departments local Veterinary Hospitals,***

DISTRICTS	No of Farm SAMPLES COLLECTED	No of Meat samples showing presence of above 100 ppb
Ernakulam	30	1-tetra+sulfa
Kozhikode	40	1-tetra+sulfa;1-sulfa, 1-enro
Malappuram	36	1-sulfa, 1 tetra
Kollam	20	-
Thiruvanthapuram	18	-

Residue Monitoring for Antibiotics in Kerala

Broiler Meat/Liver Screened for 10 Antibiotics (3 groups)

- ***TETRACYCLINES***
- Oxytetracycline
- Chlortetracycline
- Tetracycline
- Doxycyline
- ***FLUROQUINOLONES***
- Enrofloxacin
- Ciprofloxacin

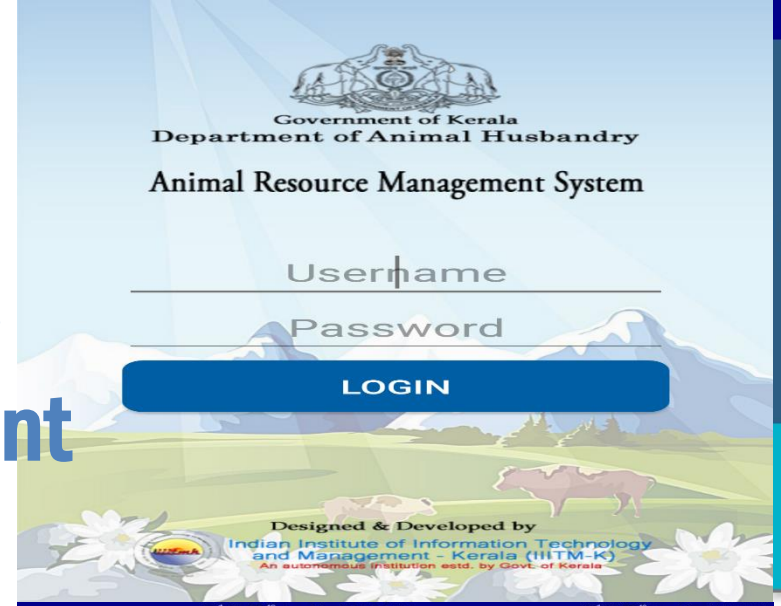
- ***SULFONAMIDES***
- Sulfadiazine
- Sulfadimidine
- Sulfathiazole
- Sulfadimetrazole

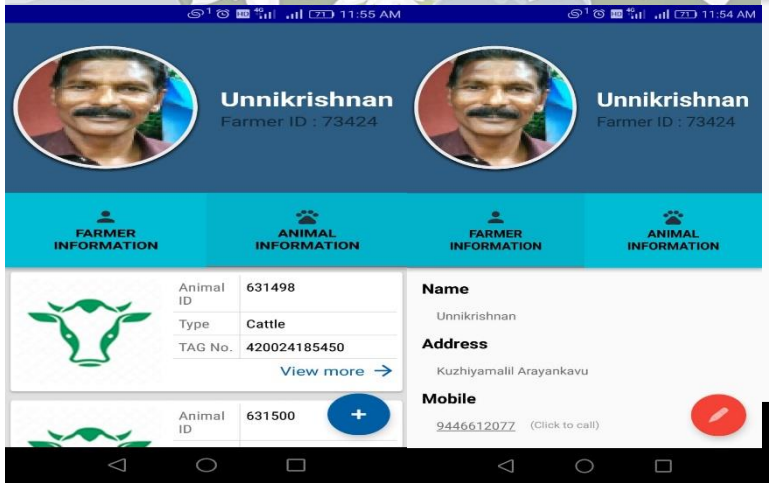
AMR in IN FOOD AND FOOD ANIMALS ; AN INTEGRATED VETERINARY SURVELLIANCE PROGRAME FOR KERALA

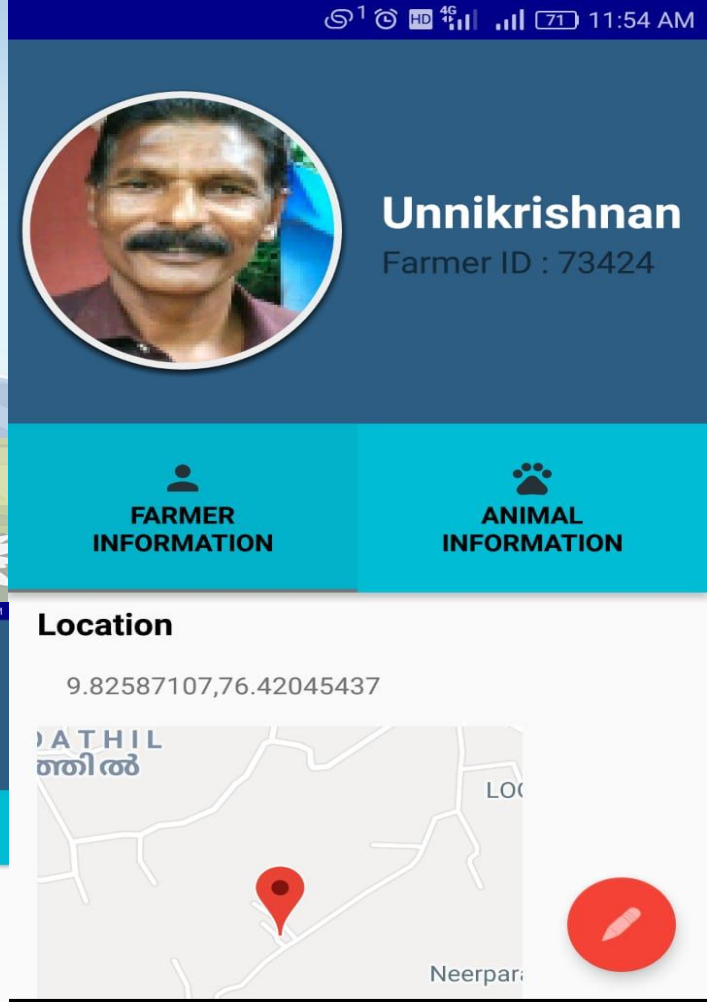
Sample	Sample description	Name of Bacteria	Level of sampling
Clinical Sample	*Mastitis Milk*	*Staph. aureus*	*Veterinary Hospitals*
		E. coli	
Food Sample	*Poultry Meat*	*Salmonella*	*Farms/Retail Markets*
		E. coli	
	Beef	*Salmonella*	*Retail Markets*
		E. coli	
	Milk (Unpasteurised)	*Staph. aureus*	*Farms/Milk societies*
		E. coli	
	Fish	*Vibrio*	*Farms/Retail Markets*

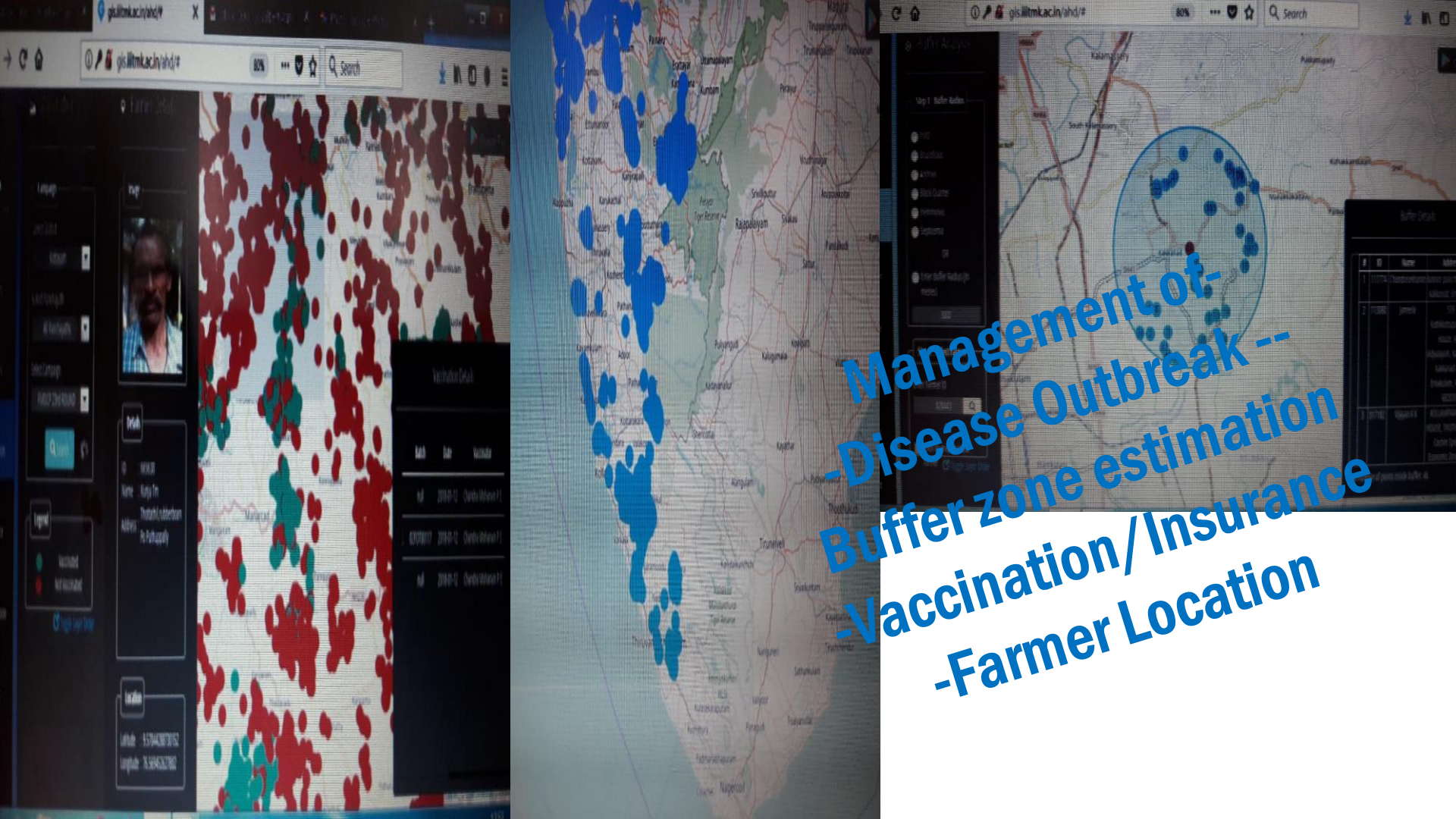
Animal Resource Management System

FARM IDENTI FICATION








Management of-
-Disease Outbreak --
Buffer zone estimation
-Vaccination/Insurance
-Farmer Location

The way forward

- A way forward would be to acknowledge that human health, animal health, and the environment are all interlinked, and that the responsibility for dealing with the problems of resistance is shared by all stakeholders.
- Strong local and global partnerships are needed in which policy makers, academia, consumers and professionals from all sectors work together to improve present system.
- Good national/sub national action plans are need with adequate lab support, with **The common goal is to preserve the effectiveness of antimicrobials for future generations of human beings, and also for animals**

Thank You