Vets Review

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Progressive Veterinary Doctors Association


Dr. Bidhan Chandra Roy

Vets Review

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Editorial Message

Dear Doctor,

It gives me immense pleasure to wish you Subho Bijaya Dashami with Happy Diwali to all our readers/members and veterinary professionals.

The livestock sector in India plays a major contributor to the agricultural economy of our country, not merely in terms of income but also in terms of livelihood and employment. It is usually said that livestock wealth is more equitably distributed than agricultural land. There is an upwards flow of demand for livestock products due to increase in population, growing per capita income and better living standards.

More livestock population means more wealth and more income to the nation and it is one of the major financial supports to the small and marginal farmers in India. 'Vets Review'' has been an instrumental of knowledge dissemination and sharing up to the field label. I think this is an opportunity for us to renew its usefulness and the value that it will try to provides our readers. I therefore encourage you to write to us with suggestions on how to make it better.

On this hopeful note, we were in our happy journey and let us try to convert it a National Journal.

Editors

WEST BENGAL UNIVERSITY OF ANIMAL AND FISHERY SCIENCES

68, Kshudiram Bose Sarani, Belgachia, Kolkata - 700 037,
Phone : 2556 3450, Resi. : (033) 2550 2229, Fax : 91-33-2557-1986
Web : www.wbuafscl.ac.in, E-mail : drpbiswas56@gmail.com / drpbiswas1956@gmail.com

Prof. Purnendu Biswas, Ph.D.
Vice-Chancellor

No. : VCS/WBUAFS/ M-5/69
Date : 11.10.2017

MESSAGE

I am glad to learn that the Progressive Veterinary Doctors' Association, Kolkata is organizing a Scientific Seminar entitled "Present Scenario of sub-clinical mastitis and its prevention and control" and "Role of Veterinarians in Animal Welfare with special reference to Veterinary Jurisprudence' on 15th October, 2017. I am also happy to learn that on that occasion the third edition of the Scientific Magazine "Vets Review" will be published.

I sincerely wish the Scientific Seminar being organized by you will be a grand success and hope that the Scientific Magazine "Vets Review" will be quite informative and serve as a Ready Reference to the practicing Veterinarians.

11/10/17
(Purnendu Biswas)

Dr. Subal Chandra Patra
General Secretary
Progressive Veterinary Doctors' Association
37, Belgachia Road, Kolkata- 700037

B. P. Gopalika, IAS

सत्यमेव जयते

Secretary
Animal Resources Development Department
Government of West Bengal
LB-2, Sector-III, Salt Lake City, Kolkata-700 098
Phone : (033) 2335-1152, Fax : 2335-1128
E-mail : secy.ard-wb@nic.in

Message

I am glad to know that Progressive Veterinary Doctors' Association is going to publish the 3rd edition of their scientific magazine **"Vets Review"** and also organize a seminar.

I convey my best wishes to the Association.

11/10/2017

(B. P. Gopalika)

Dr. Subal Chandra Patra
General Secretary
Progressive Veterinary Doctors' Association

পশ্চিমবঙ্গ সরকার
প্রাণী সম্পদ ও প্রাণী স্বাস্থ্য অধিকার
দূরভাষ ঃ (০৩৩) ২৩৩৫-১১৪৫
মোবাইল ঃ ৯৩৩১২৭৫৫২২
ফ্যাক্স ঃ (০৩৩) ২৩৩৫-১১৮৭
ই-মেল ঃ ডিএএইচভিএস.এআরডি-ডাব্লুবি@এনআইসি.ইন

সত্যমেব জয়তে

Government of West Bengal
Directorate of Animal Resources & Animal Health
Tel : (033) 2335-1145
Mobile : 9331275522
Fax : (033) 2335-1187
E-mail : dahvs.ard-wb@nic.in

No. 138/DAH&VS Dated: Kolkata, the 10th October, 2017

MESSAGE

I am happy to learn that the Progressive Veterinary Doctors' Association is going to bring out the third edition of its Scientific Magazine namely "Vets Review" on 15.10.2017 in a befitting manner.

I believe that the magazine will reflect various scientific advancement, research, new initiatives and techniques in the field of Veterinary Sciences which would help developing Professional efficiency and knowledge of all veterinarians and contribute towards development of Animal resources of our state.

I hope such endeavour will continue over the coming years.

I convey my best wishes for every success of "Vets Review".

10.10.17
[Dr (Capt.) A.G.Bandyopadhyay]

To
Dr. Subal Chandra Patra
General Secretary
Progressive Veterinary Doctors' Association

কার্য্যালয় ঃ প্রাণী সম্পদ ভবন, তৃতীয় তল, এল.বি.-২ ব্লক, সেক্টর-৩, লবণ হ্রদ, কলকাতা-৭০০ ০৯৮
OFFICE : "PRANI SAMPAD BHAWAN", 2nd Floor, LB-2, Sector-III, Salt Lake, Kolkata-700 098

শ্রী স্বপন দেবনাথ
রাষ্ট্রমন্ত্রী
প্রাণীসম্পদ বিকাশ দপ্তর (স্বাধীন দায়িত্বপ্রাপ্ত) এবং
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পশ্চিমবঙ্গ সরকার
টেলি ফ্যাক্স ঃ (০৩৩) ২৩৩৫-১১৩০
দূরভাষ ঃ (০৩৩) ২২১৪-৫৬৬৩ / ১৫৬৪
ফ্যাক্স ঃ (০৩৩) ২২১৪-৫৬৬২
E-mail : wbmosard@gmail.com
mssenard@gmail.com

सत्यमेव जयते

Sri Swapan Debnath
Minister of State
Animal Resources Development Department (Ind. Charge)
And
Micro, Small and Medium Enterprises and
Textiles Department (Textiles & Handloom)
Government of West Bengal
Telefax : (033) 2335-1130
(033) 2214-5663 /1564
Fax : (033) 2214-5662
E-mail : wbmosard@gmail.com
mssenard@gmail.com

D.O No. 828/MOS(IC)/ARD/17.

Date : 09.10.2017.

MESSAGE

It is a great pleasure to me to know that the Progressive Veterinary Doctors' Association is bringing out the third issue of its Scientific Magazine namely "Vets Review" on 15.10.2017 in a befitting manner.

The magazine will serve as a mirror reflecting the various scientific advancement, aspirations and new initiatives in the field of Veterinary Sciences which I believe to be valuable insight for all veterinarians. I am sure that this effort will be repeated over the coming years.

I sincerely appreciate the entire magazine team for making it a reality in releasing the Magazine once again.

I would like to convey my best wishes for every success of "Vets Review".

(Swapan Debnath)

Dr.Subal Chandra Patra
General Secretary
Progressive Veterinary Doctors' Association

West Bengal University of Animal and Fishery Sciences

68, KSHUDIRAM BOSE SARANI, BELGACHIA, KOLKATA - 700 037, PHONE : 2556 3123, MOB. - 09433011956, 9681072250, 9836221622
FAX : 91- 33-2556 3123, web : www.wbuafscl.ac.in, email : ashiskrsamanta@gmail.com, samanta_ashiskr@yahoo com

Prof. Shyam Sundar Dana
Ph. D. (IVRI)
Registrar (Acting)

Message

It is my profuse privilege to convey the message for the **Souvenir and Technical Bulletin *(VETS REVIEW)*,** which is being published by 'Progressive Veterinary Doctors' Association' for giving a comprehensive glimpse of the advanced and latest technical and clinical aspects of animal production and health. This publication, backed by latest reviews on clinical issues, would definitely be a handy resource to veterinary practitioners, doctors, interns and others field level stakeholders for ease of treating animals in light of latest medical innovations in Veterinary Sciences. My best wishes to all the members, whose tireless efforts have made this publication a relevant one.

06.10.2017

S. S. Dana
(Registrar)

Registrar
W. B. University of Animal & Fishery Sciences
68, K. B. Sarani, Kolkata-700 037

PROGRESSIVE VETERINARY DOCTORS' ASSOCIATION

37, Belgachia Road, Kolkata-700 037

(Reg. No. S / 2L / 33080)

PREFACE

This is our great pleasure to inform that scientific wing of PVDA with their utmost endeavour and willingness could finally bring out the 3rd edition of Vets Review.

*Progressive Veterinary Doctors' Association, from the very beginning of its formation, takes pledge to work for the upliftment of Scientific Mindset of our fraternity. Beside work for the professional development, it is the necessity of time to magnify the image of the profession through continuous exchange of knowledge utilizing various platforms. What can be more appropriate than to publish the 3rd edition of ''**Vets Review**'' where the Veterinarians could deliver their work through their well placed articles ?*

*The 3rd edition is going to publish on a day when we are organizing Seminar on "**Present scenario of sub-clinical mastitis and its prevention and control**" and "**Role of Veterinarians in Animal Welfare with special reference to Veterinary Jurisprudence**". We are happy that respectable **Professors Dr. Chancha Guha, Department of Preventive Veterinary Medicine, WBUAFS** and **Dr. Arunashish Goswami, Director of Research, Extension and Farms, WBUAFS** will take part in the seminar as speaker to make it fruitful in every conceivable way.*

I would like to thank our Scientific Magazine Committee who has taken such good effort to publish the 3rd edition of the Scientific Magazine in time so also I am taking the opportunity to thank the Kolkata District committee, PVDA to organize such a time-needed seminar in order to enlight the scientific mind to take up the technical challenges at field level in coming days.

Subal Chandra Patra

(Dr. Subal Chandra Patra)

General Secretary

THE THREAT OF ANTIMICROBIAL RESISTANCE IN DEVELOPING COUNTRIES: CAUSES AND CONTROL STRATEGIES

Dr. Malay Maity & Dr. Sukumar Manna

Institute of Animal Health & Veterinary Biologicals (R&T)

37 Belgachia Road, Kolkata-37

ABSTRACT

The causes of antimicrobial resistance (AMR) in developing countries are complex and may be rooted in practices of health care professionals and patients' behaviour towards the use of antimicrobials as well as supply chains of antimicrobials in the population. Some of these factors may include inappropriate prescription practices, inadequate patient education, limited diagnostic facilities, unauthorized sale of antimicrobials, lack of appropriate functioning drug regulatory mechanisms, and non-human use of antimicrobials such as in animal production. Considering that these factors in developing countries may vary from those in developed countries, intervention efforts in developing countries need to address the context and focus on the root causes specific to this part of the world. Here, we describe these health-seeking behaviours that lead to the threat of AMR and healthcare practices that drive the development of AMR in developing countries and we discuss alternatives for disease prevention as well as other treatment options worth exploring.

INTRODUCTION :

The threat of antimicrobial resistance (AMR) is growing at an alarming rate and the situation is perhaps aggravated in developing countries due to gross abuse in the use of antimicrobials. It is well known that any use of antimicrobials however appropriate and justified, contributes to the development of resistance, but widespread unnecessary and excessive use makes the situation worse. Misuse of antimicrobials is facilitated in developing countries by their availability over the counter, without prescription and through unregulated supply chains. Non-compliance in the use of antimicrobials has many repercussions upon resistance and poverty is a major root factor of antimicrobial misuse in developing countries . On the other hand, even among the rich, some patients miss doses either by mistake or deliberate, especially in cases where signs and symptoms begin to subside after an initial favourable therapeutic response. In other situations, such as in the event of an acute side effect, patients abandon their treatment, only to return to the hospital with a recurring infection by a more virulent and resistant strain of the microbe. These actions result in the exposure of surviving pathogens to sub-therapeutic concentrations of antimicrobials thus increasing the chances of acquiring resistance. Self-medication is a common practice in developing countries where patients often get antimicrobials without prescription and through unregulated supply chains. To make the situation even worst, some patients seek their first-line of treatment from traditional healers who provide them with herbal combinations for the treatment of infections. These substances of unknown composition and potency may enhance pathogen fitness and contribute to the development of resistance. Antimicrobial resistance often occur through the inhibition of specific antimicrobial pathways such as cell wall synthesis, nucleic acid synthesis, ribosome function, protein synthesis, folate metabolism, and cell membrane function (fig. 1) [1–2].

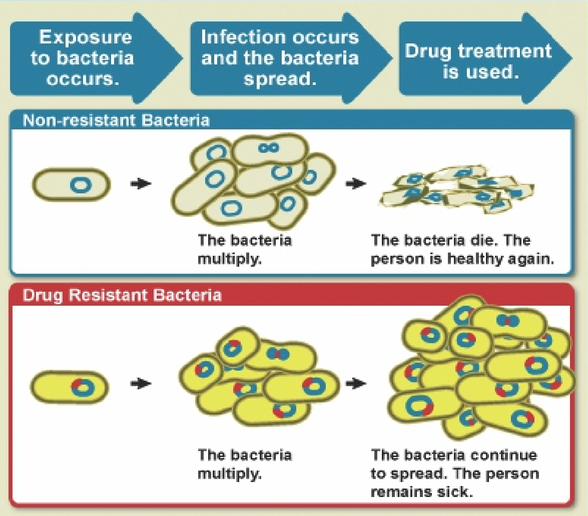
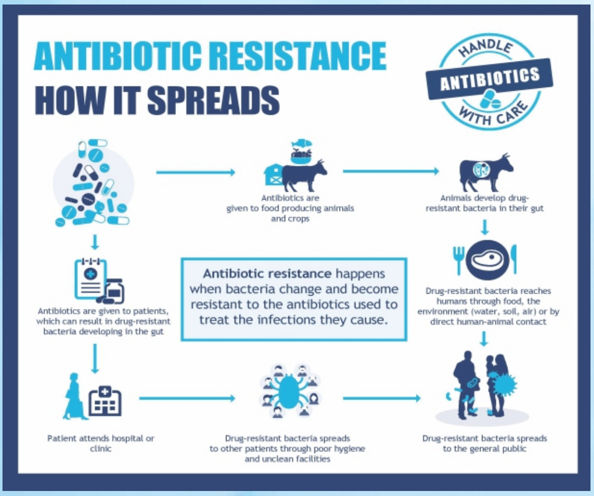


Fig.1

Causes of antimicrobial resistance

To better appreciate the causes of AMR, we need to understand the various sequential steps involved for a drug to get to a patient and the eventual use, which include; production, distribution, prescription, dispensing, and finally consumption of the drug by the patient or use in animal production [3]. Consequently, any imprudent practice along this flow may result in the emergence of resistance (fig. 2).



Drug dispensers and drug quality

The lack of appropriate regulations in the sales of antimicrobials is also a driving factor in the access and misuse of antimicrobials. In most developing countries, antimicrobials can be purchased without medical prescription and are usually dispensed on the streets by untrained persons. These drug vendors will sell medications just to make a sale and accommodate patients' ability to pay. Even pharmacies operating without a license, appear to be more accessible to the public as they have shorter waiting time, do not charge consultation fees and above all are willing to negotiate treatment options to adjust to the financial ability of the patients. Retail pharmacies in developing countries especially in Africa have emerged as the primary level of outpatient care rendering unauthorized services from consultation, diagnosis, prescription and dispensing of medication (fig.2, 3).

It has also been shown that many antimicrobials dispensed in Africa are of questionable pharmacological quality. Adverse climatic conditions such as high ambient temperatures and humidity may affect the overall quality of the antimicrobials during storage. Poor storage also increases the risk of degradation of the drug. Degraded medicines contain less than stated dose, implying that patients consume less than optimal dose of the drug. There is also a problem of outright counterfeit, in which the drug may contain little or no active substance of the antimicrobial or the wrong substance. The influx of counterfeit and sub-standard antimicrobials into the pharmaceutical markets in some regions is a major problem as these preparations of reduced potency also result in pathogens being exposed to sub-therapeutic concentrations of the drug. A study from Cameroon revealed that, out of 284 antimalarial obtained from 132 vendors, 32% of chloroquine, 10% quinine, and 13% sulfadoxine/pyrimethamine were likely to be fake. In addition, some of the quinine contained chloroquine while some chloroquine contained no active ingredient or an amount lower than the expected concentration

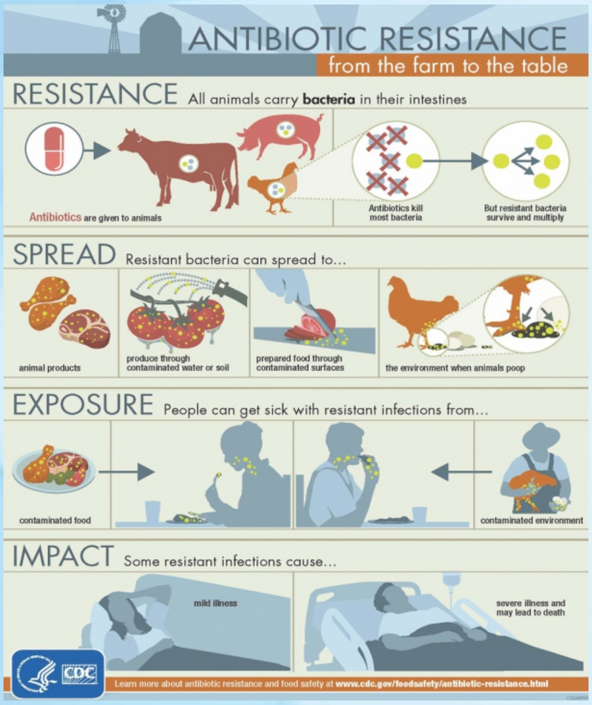


Fig.2

Health professionals

Health care providers play an essential role in the treatment and prevention of diseases, but may jeopardize this if their practices are not evidence-based (Table1). For example, the prescription practices of antimicrobials vary among physicians in most countries. In some cases, the antimicrobial prescriptions are inappropriate (i.e., wrong drug, wrong doses, or antimicrobial not necessary at all) [22]. Due to the high patient-doctor ratio in most developing countries, doctors are over whelmed and there is often inadequate time for meaningful education and communication with the patient on drug adherence guidelines and consequences of poor or non-adherence to these guidelines. Treatment sometimes consists of administering broad-spectrum antibiotics without a definitive diagnosis and indication for antimicrobial treatment. In a Lebanese study, it was shown that in 52% of cases, the prescription dose was inappropriate while 63.7% of physicians prescribed antibiotics with wrong duration of treatment [23].

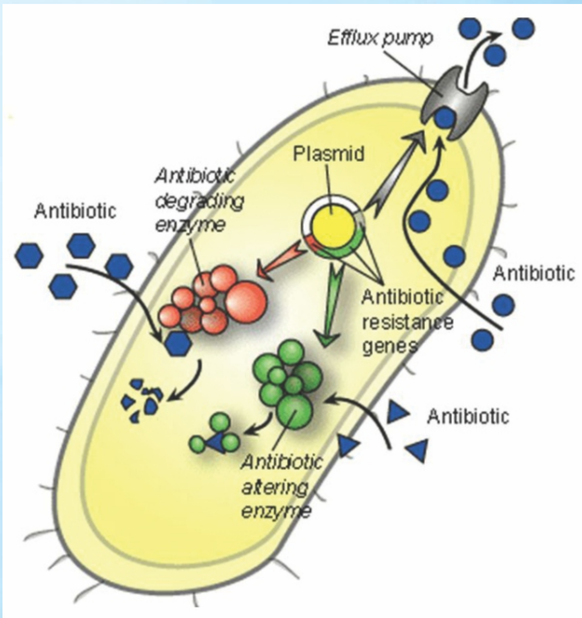


TABLE 1

Factors and stakeholders contributing to the problem of antimicrobial resistance (fig. 4)

Factors	Contribution	Example
Poor drug quality	Sales of counterfeit, adulterated and poor quality antibiotics	These poor quality antibiotics can produce sub-inhibitory concentration in vivo, which increases the selection of resistant strains
Regulators	While most developed countries have developed AMR action plans, this is still lacking in many developing countries especially in Africa	Most countries lack the resources to enforce policies regarding the manufacture and distribution of sub-standard drugs
Prescribers	Excessive clinical use and misuse is partially responsible for increase rate of resistance	Variation in prescription practice among health care provider. Sometimes there is prescription of a wrong drug, wrong doses, or antimicrobial not necessary at all
Dispensers	Drug vendors usually have little or no knowledge of the required dosage regimen, indication, or contraindications	Medications are usually purchased in small aliquots from roadside stall and storage and distribution is usually done under inadequate conditions
Users (patients)	High rate of self- medication and lack of treatment compliance	Patients fail to adhere to dosage regimens and discontinue treatment when symptoms subside before pathogen is eliminated
Animal industry	The use of antimicrobial drugs in agriculture or industrial settings, exerts a selection pressure which can favor the survival of resistant strains (or genes) over susceptible ones, leading to a relative increase in resistant bacteria within microbial communities	Resistant bacteria in animals can be transferred to humans through the consumption of food or through direct contact with food-producing animals or through environmental spread

Due to lack of effective and reliable surveillance systems and poor dissemination of research information, health professionals in developing countries sometimes lack up to date information on the AMR pattern within their populations. In tertiary hospitals with advanced capacities, physicians rely mostly on the resistance or susceptibility pattern of the pathogen isolated from a patient. Health personnel in rural settings without the capacity to do AMR testing have difficulty to decide on the choice of antimicrobial in the absence of an antimicrobial sensitivity test. As a result, health professionals use more and more broad-spectrum antibiotics to treat infections caused by several bacteria species or those for which establishing the etiology is difficult or takes a long time. This practice contributes to the development of resistance [24] as the drug applies selective pressure, not only upon the etiological agent of the disease episode but also upon a large fraction of the patient's microbiota [25]. Some health professionals issue prescriptions that are not evidence-based and rely on a syndromes approach to both infections in the community as well as hospitalized patients. That is treatment is based on easily recognized signs and symptoms (syndromes) as well as to microorganism most commonly responsible for each of these syndromes. This practice is on the rise due to the lack of legal consequences of wrongful prescription of antibiotics. Our preliminary findings in Cameroon revealed that a significant number of physicians are likely to prescribe antibiotics to treat diarrhoea caused by rotavirus, due to the lack of capacity to establish the diagnosis (Unpublished). Due to fear of bad treatment outcomes of critical diseases, some physicians may resort to blind prescription of multiple and broad-spectrum antimicrobials. Meanwhile, because of financial incentives from drug suppliers, some physicians are prone to prescribing multiple antibiotics for the same condition [26].

Patients

As mentioned earlier, compliance is a major contributor to the development of AMR [27]. Patients miss doses, either by mistake or deliberate. Because patients are aware of the adverse impact of drinking alcohol while on antibiotics, some patients may skip doses when invited for a party in favour for the consumption of alcohol (unpublished data). These practices result in exposure of surviving microbes to sub-therapeutic concentrations of the drug and, consequently increase the chances of developing resistance [25]. Because of poverty, many sick individuals in developing countries of Africa often seek their first-line of treatment from traditional healers who provide them with herbal mixtures of unknown efficacy for the treatment of infections. Some combine antibiotics with their herbal mixtures simultaneously while others take antimicrobials and supplement them with herbal mixtures purportedly to improve efficacy [12]. These compounds of unknown potency may enhance pathogen fitness.

Non-human use of antimicrobials

Antimicrobials are used to prevent (prophylaxis in high risk animals) and treat diseases in animals, as well as used as growth promoters in animal breeding [28, 29]. Additionally, they are used as additives in plant agriculture (fruits, vegetables, and orchid, etc.), especially in the spraying of fruit trees for disease prophylaxis and the application of antibiotic-containing manure on farmland and in industrial processes [30]. The use of antimicrobial agents in animals and more importantly food-producing animals has important consequences for both human and animal health as it can lead to the development of resistant bacteria (Table (Table1).1). These resistant bacteria (with resistance genes) in animals can be transferred to humans through the consumption of food or through direct contact with food-producing animals or through environmental spread (e.g. human sewage and runoff water from agricultural sites). The use of antimicrobial drugs in health care, agriculture or industrial settings exerts a selection pressure which can favour the survival of resistant strains (or genes) over susceptible ones, leading to a relative increase in resistant bacteria within microbial communities [31]. It is now known that increased AMR in bacteria affecting humans and animals is primarily influenced by an increase in the use of antimicrobials for a variety of purposes, including therapeutic and non-therapeutic purposes in animal production [32]. A strong association between agricultural use of antimicrobials and the development of resistance has been suggested [33], and it has been shown that the bulk of antimicrobials used worldwide are not consumed by humans but rather are given to animals for the purposes of food production [34].

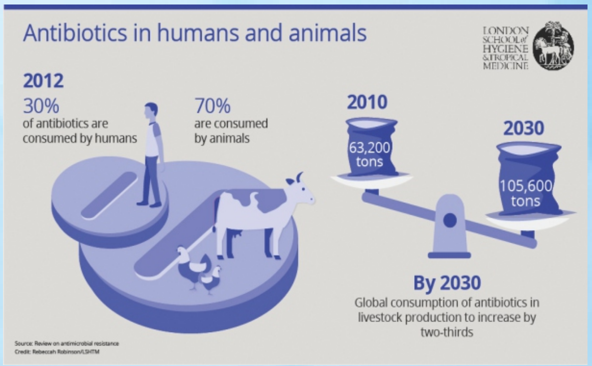


Fig.5

Multidrug resistant bacteria have been detected in both meat and fresh produce [35] and in humans in contact with livestock in many African countries [36–38]. A study in Kenya revealed a high level of antimicrobial drug residues in meat meant for consumption [34]. These findings further demonstrate that food animals are a major reservoir of drug resistant bacteria and present a major risk for dissemination and transmission of antimicrobial resistant bacteria in Africa as well as many developing countries. A large proportion of the population in developing countries live in close proximity with animals, thus increasing the chances of transmission of resistant microorganisms from animals to humans through animal handling [39, 40]. In a recent study in rural Bangladesh animal healthcare providers responded they more often sought animal health care from pharmacies and village doctors, citing the latter two as less costly and more successful based on past performance [41]. In the absence of an effective animal healthcare system, villagers depend on informal healthcare providers for treatment of their animals. This may lead to suboptimal use of antimicrobials in such settings with unhygienic animal husbandry practices. In terms of aquaculture, heavy use of prophylactic antibiotics in aquaculture has been reported in developing countries and is a growing problem for human and animal health and for the environment (fig.5) [42].

Overall, limiting the routine use of in-feed antibiotics will improve human and animal health, by reducing the development and spread of antibiotic-resistant bacteria. Therefore, judicious use of antibiotics in healthcare and agricultural settings is essential to slow the emergence of resistance and extend the useful lifetime of effective antibiotics that are in existence today.

In other to minimize the risk of AMR due to non-human use of antimicrobials especially in animal production, information resources in developing countries need to be strengthened to support health professionals, patients, animal keepers and the public, so that the society can have a better understanding of the value and importance of antimicrobials, especially antibiotics. Taken together, the excessive use of antimicrobials in animals and agriculture and the associated public health consequences justifies the importance of limiting the inappropriate use of antimicrobials in both agriculture and the veterinary sector.

Inadequate surveillance and limited laboratory antimicrobial susceptibility testing

The availability of routine antimicrobial susceptibility testing to provide information on resistance trends, including emerging resistance is very essential for routine clinical practice and for the development of effective policies against AMR. Antimicrobial susceptibility testing is not often performed in most rural laboratories due to lack of capacity. In the absence of patient-specific antimicrobial susceptibility testing, community-based antimicrobial surveillance data may be very useful to health care professionals in particular communities or regions to treat infections with specific susceptible antimicrobials. Such surveillance needs to be conducted regularly and continuously because resistance rates can vary in one region of a country over time.

Antimicrobial resistance control strategies

The problem of AMR is aggravated by the fact that most world pharmaceutical companies consider research for new antimicrobials as being of “low profit” and some speculate that resistance will eventually develop for new antimicrobials anyway. Consequently, they prefer to invest in the development of drugs for chronic diseases (diabetes, hypertension) as well as those used to improve lifestyle (e.g., Cialis, Viagra, etc.) [43]. Therefore, the long-term solution should be focused on methods to prevent the emergence of resistance or the spread of resistant organisms from one person to another.

Hygiene and sanitation

Apart from the irrational use of antimicrobials, unique environmental conditions such as crowding and poor sanitation also contribute in the circulation and spread of resistant microorganisms. Transmission of resistant pathogens is facilitated by person-person contact, through contaminated water, food or by vectors. Improving basic hygiene and sanitation will reduce the spread of resistant organisms (Table 2) [44]. Improving infection prevention and control in hospitals will reduce the nosocomial spread of bacteria with acquired resistance such as Staphylococcus aureus amongst others.

TABLE 2

Strategies to contain and minimize the development of antimicrobial resistance

Control Strategies	Contribution
Hygiene and sanitation	Improving basic hygiene and sanitation will reduce the spread of resistant organisms
Vaccination	Vaccination may reduce severity of disease, provide protection against shedding of pathogens and even raise the threshold load of pathogens required for infection
Alternative therapies	The reluctance of pharmaceutical companies to invest in research and development of novel antimicrobial agents necessitate the exploration of alternative therapies such as bacteriophage, probiotics and Quorum Sensing inhibitors
Education	Health care providers, dispensers and patients need to be educated on how the use and misuse of antimicrobial may contribute to the development of resistance
Infection prevention & control	Proper hospital infection control may prevent the spread of nosocomial pathogens and resistant microbes that may have easily been disseminated to the community if these measure were not in place

Vaccination

While antimicrobials are used for treatment, vaccines are a primary mode of prevention of infectious diseases. Prior vaccination may reduce severity of disease, provide protection against shedding of pathogens and even raise the threshold load of pathogens required for infection [45–47]. Also, indirect population protection of some vaccines as a result of herd immunity in unvaccinated individuals represents additional advantage of vaccination. In most regions of the world, a number of diseases such as smallpox, measles, mumps rubella, diphtheria, hepatitis A, pertussis, and polio have been prevented by vaccination [48]. However, even with the most effective vaccine, the need of antimicrobials or alternative treatment options will still in some cases be solicited. For example, in the case of genetic drift, escape mutants and serotype or strain replacement diseases, vaccination may fail to confer full protection from disease. For bacterial infections, the introduction of conjugate vaccines for example Streptococcus pneumoniae, has reduced the outbreak of respiratory infections in children in developing countries [49].

Alternative therapies

The increase in microbial resistance to traditional antimicrobials and the reluctance of pharmaceutical companies to invest in research and development of novel antimicrobial agents necessitate the exploration of alternative therapies. Future focus of medical therapeutics and research is to look beyond antibiotics [43], and search for alternatives which can regulate the microbial virulence as well as growth inhibition. There are currently a couple of other alternatives approaches at different levels of research and development.

1. The use of bacteriophage is emerging as an alternative treatment option for bacterial infections [50]. Many authors have suggested that bacteriophage therapy is a necessary alternative to conventional antibiotics [51, 52]. Bacteriophages are bacterial viruses with the capacity to invade bacterial cells and induce lysis of the bacteria (lytic cycle). In the present era of multidrug resistant bacteria and reluctance in the development of new antibiotics by pharmaceutical companies, the need to aggressively explore the possibility of phage therapy is unprecedented.

2. Quorum Sensing inhibitors represents an important antimicrobial target that may prevent, suppress, and/or treat infectious diseases. The mechanistic details (including auto-inducers) of Quorum Sensing are different between Gram-negative and Gram-positive bacteria. Gram-negative bacteria utilize N-acyl L-homoserine lactones (AHLs), which are homoserine lactone (HSL) rings with an additional fatty acid side chain while Gram positive bacteria uses oligopeptides [53–55]. While antibiotics kill or slow down the growth of bacteria, quorum sensing inhibitors or quorum quenchers simply attenuate bacterial virulence. A large body of work on Quorum Sensing has been carried out in deadly pathogens like Pseudomonas aeruginosa, Staphylococcus aureus, Vibrio fischeri, Vibrio. harveyi, Escherichia coli and Vibrio. cholerae etc. A number of these studies have succeeded in exploiting the bacterial Quorum Sensing system as potential target for treatment of bacterial infections. The inhibition of Quorum Sensing system is believed to be advantageous over conventional antibiotics, because only the communication mechanism between the bacteria is disrupted without killing the individual cells. Hence, this strategy should generate a lower selective pressure and reduce the rate at which AMR develops during the treatment [55].

3. Probiotics, otherwise referred to as faecal transplant therapy (FTT) is a treatment option that has been employed for decades, albeit with mixed results [56–58]. FTT is the act of using fecal material from pathogen-free healthy donors to repopulate the microbiota of a recipient. Probiotics are considered to be able to destroy pathogenic microorganisms by producing antimicrobial compounds such as bacteriocins and organic acids, improve gastrointestinal microbial environment by adherence to intestinal mucosa thereby preventing attachment of pathogens and competing with pathogens for nutrients, stimulate the intestinal immune responses and improve the digestion and absorption of nutrients. The commonly used probiotics include Bacillus, Lactobacillus, Lactococcus, Streptococcus, Enterococcus, Pediococcus, Bifidobacterium, Bacteroides, Pseudomonas, yeast, Aspergillus, and Trichoderma, etc.

4. This treatment option is an old practice, used many years ago, especially in China and had been successfully used to treat Clostridium difficile infections as well as other enteric diseases [56, 59, 60].
5. Taken together, the application of these alternate therapies is not limited to developing countries and most are still under development or at different stages of clinical trial and their routine availability will require governmental approval and subvention in developing countries.

The role of stakeholders in the control of antimicrobial resistance

The control of AMR cannot be the sole responsibility of medical professionals and scientists. Although continuing education is essential to enable health care providers learn the need in rational prescription practices and the importance of evidence-based prescription [61], the general population and other stakeholders have a central role to play [62]. The government of every country should consider AMR as a public health priority issue. Policies and regulations should be put in place to enforce the prudent access and use of antimicrobials. The population needs to be educated on the threat of AMR and therefore media professionals need to get adequate training on how to convey medical and scientific information in lay language through multiple channels to inform the populations on practices that promote the emergence of AMR organisms [62]. The benefits of an education program for journalists has been successful for the fight against HIV/AIDS in many developing countries and a similar approach for AMR will likely result to an added benefit [63, 64]. A number of initiatives have been taken so far by regulatory agencies and governments in the combat of antimicrobial resistance but most of these initiatives have been done only in developed countries [65–68] and are lacking in resource limited nations [69, 70].

A few African countries have been identified as being involved in the Global Antibiotic Resistance Partnership (GARP), established in 2009 to create a platform for developing actionable policy proposals on antibiotic resistance in low-income and middle-income countries. Unfortunately, to date national GARP working groups are established only in a few African countries [70]. There is therefore need to generate solutions such as to build a strong African laboratory infrastructure to help combat AMR which is a global health threat [71]. A multi-disciplinary approach involving a wide range of partners is therefore needed to limit the risk of AMR and minimize its impact on human and animal health especially in developing countries.

The role of government regulatory agencies

With the new and emergent issue regarding the development of AMR, government agencies globally have engaged in new action plans in order to combat the AMR issue. However, actions toward this has been severely lacking in developing countries especially those in Africa where high quality regulatory agencies are lacking. In May 2015, the WHO endorsed a global action plan to tackle AMR. In September 2014, the US government released a 'National Strategy for Combating

Antibiotic-Resistant Bacteria' that included an executive order signed by the US president [68]. The action plan provided several goals and a roadmap to guide the Nation in rising to this challenge. In 2013, the United Kingdom released the 'UK Five Year Antimicrobial Resistance Strategy (2013 to 2018)' that sets out actions to address the key challenges to AMR [67]. Similarly, in 2015, the government of Canada also released the Federal Action Plan on antimicrobial resistance and use in Canada (Building on the federal framework for action) [66]. While many developed countries have developed such AMR action plans either nationally or at the regional level such as the European Union and Asia-Pacific region, this is still lacking in many developing countries especially in Africa [69]. A few African countries have been identified as being involved in the Global Antibiotic Resistance Partnership (GARP), established in 2009 to create a platform for developing actionable policy proposals on antibiotic resistance in low-income and middle-income countries. However, national GARP working groups are established only in India, Kenya, South Africa, Vietnam, Mozambique, Nepal, Tanzania and Uganda. Moreover, a close look at the national action plans showed that only one African country (Ethiopia), was identified by the WHO as having a national AMR action plan.

What most developing countries especially those in Africa lack is not the legislation prohibiting the manufacture and distribution of sub-standard drugs but resources to enforce these policies and to impose penalties to defaulters. There is also lack of resources to identify counterfeit drugs or verify the quality of locally manufactured or imported drugs. In addition, governments need to address the sale of antimicrobials without prescription and illegalize the dispensing of drugs by unauthorized and unqualified persons. There is also need for the population to be sensitized on the public health risks of AMR. A recent WHO survey revealed that while much activity is underway and many governments are committed to addressing the AMR problem, there are major gaps in actions needed across all 6 WHO regions to prevent the misuse of antibiotics and reduce spread of AMR [69]. Despite these challenges some progress is currently being made in setting up drug regulatory agencies in Africa. The effort is supported by the New Partnership for Africa's Development (NEPAD) of the African Union and the WHO. Through the creation of the African Medicines Regulatory Harmonization (AMRH), it is envisioned that safe, good quality, efficacious and reasonably priced medicines will be available in Africa. Recently, the African Society for Laboratory Medicine (ASLM) has engaged in activities to share research, debate, and generate solutions to build a strong African laboratory infrastructure to help combat common global health threats, like AMR as well as HIV/AIDS, and other medical conditions [71]. Therefore, a multi-disciplinary approach involving a wide range of partners is therefore needed to limit the risk of AMR and minimize its impact on human and animal health especially in developing countries.

Conclusions

The irrational use of antimicrobials is certainly a complex and multifactorial problem in developing countries and a proper under-standing of the problem is necessary for effective control policies. Without effective antimicrobials, diverse medical procedures such as surgery, the care of premature infants, cancer chemotherapy, care of the critically ill, invasive diagnostic and treatment procedures, and transplantation medicine will be severely hampered with a corresponding increase in morbidity and mortality from secondary microbial infections. The challenge of global antimicrobial resistance is comparable to climate change and global warming. Therefore, as we seek to protect the climate for the future generation, it is our responsibility not to pass over to the next generation, microbial population that is resistant to antimicrobial agents that they are supposed to treat as the consequence is likely to be very dangerous.

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ECONOMIC IMPORTANCE OF CONSERVATION OF INDIGENOUS BREED

Arindam Samanta and Subhas Bose***

*Assistant Director, Directorate of AR & AH, ARD Department, Govt. of West Bengal

** Officer on Special Duty, WBUAFS, Kolkata-37,and Ex-Director, Directorate of AR & AH, West Bengal

Overview Of Livestock Sector In India

Animal Husbandry, Dairying and Fisheries activities, along with agriculture, continue to be an integral part of human life since the process of civilization started. These activities have contributed not only to the food basket and draught animal power but also by maintaining ecological balance. Owing to conducive climate and topography, Animal husbandry, Dairying and Fisheries Sectors have played prominent socio-economic role in India. Traditional, cultural and religious beliefs have also contributed in the continuance of these activities. They further also play a significant role in generating gainful employment in the rural sector, particularly among the landless, small and marginal farmers and women, besides providing cheap and nutritious food to millions of people.

Livestock production and agriculture are intrinsically linked, each being dependent on the other, and both crucial for overall food security. According to estimates of the Central Statistics Office (CSO), the value of output livestock sector at current prices was about Rs.5,91,691 crore during 2015-16 which is about 28.5% of the value of output from agricultural and allied sector. At constant prices the value of output from livestock is about 29% of the value of the output from total agriculture and allied sector (Annual Report 2015-16, DADF).

Milk production during 2014-15 and 2015-16 is 146.3 million tonnes and 155.5 million tonnes respectively showing an annual growth of 6.27%. Meat production in the beginning of 12th Plan (2012-13) was 5.95 million tonnes which has been further increased to 7.0 million tonnes in 2015-16. Currently egg production is around 82.93 billion during 2015-16. The poultry meat production is estimated to be 3.26 million tonnes (Annual Report 2015-16, DADF).

India has vast genetic resource of livestock and poultry, which play a vital role in improving the socio-economic conditions of rural masses. There are about 300 million bovines, 65.07 million sheep, 135.2 million goats and about 10.3 million pigs as per 19th Livestock Census in the country (Table:I). India with about 190.9 million cattle (as per 19th Livestock Census 2012) has 14.5% of the world cattle population. Of this, 80% i.e. 151.172 million are indigenous. Other Animal Genetic Resources (AnGR) are also mostly indigenous (Annual Report 2015-16, DADF).

Table: I: Species wise Livestock population as per 19th Livestock Census, 2012 (In million)

Sl	Species	Crossbred	Indigenous	Total	No of Indigenous Breed
1	Cattle	39.731	151.172	190.903	40
2	Buffalo	----	108.702	108.702	13
3	Sheep	3.781	61.288	65.069	42
4	Goat	----	135.173	135.173	26
5	Pig	2.457	7.837	10.294	6
6	Fowl	----	----	692.646	18
7	Duck	----	----	23.539	5

Source: Database maintained at NBAGR, Karnal

Animal Genetic Resources (AnGR) of the country consist of a large number of breeds of domesticated animal and poultry species such as cattle, buffalo, goat, sheep, pig, horse, camel, poultry, etc. Due to loss of a number of breeds over time, conservation and sustainable use of AnGR has become important and urgent. Conservation of genetic diversity between and within domestic animal breeds is an insurance for the future animal agriculture in terms of food production, disease resistance and adaptability to climate changes. They are endowed with qualities of heat tolerance, resistance to diseases and the ability to thrive under extreme climatic stress and less than optimal nutrition. A broad genetic base is crucial to deal with future changes in environment, markets for animal products and animal production systems.

Importance of indigenous breeds:

India ranks 1st in milk production (annual output of 143.3 million tonnes in 2014-15), accounting for 18.5% of the world production.The analysis shows nearly 36% of the milk production is contributed by Indigenous Buffaloes followed by 26% by crossbred cattle. The Indigenous cattle contribute 12% of the total milk production in the country whereas non-descript cattle contribute 9% milk production and non-descript buffaloes contribute 13% milk production (Annual Report 2015-16, DADF).

Cattle not only contribute substantially to milk production but are also used as draught animals for agricultural operations and transport in rural areas. Most of the agricultural operations by small farmers are performed by bullocks.

Indigenous cattle are categorized as Zebu and are suited for draught power because of the presence of a hump. Indigenous cattle are well known for their quality of heat tolerance and ability to withstand extreme climatic conditions. Studies of impact of Climate Change and effect of temperature rise on milk production of dairy animals indicate that temperature rise due to global warming will negatively impact milk production. The annual loss in milk production of cattle and buffaloes due to thermal stress in 2020 will be about 3.2 million tonnes of milk costing more than Rs 5000 Crore at current price rates (DADF,2015-16). The decline in milk production and reproductive efficiency will be highest in crossbred cattle followed by buffaloes. Indigenous Breeds will be least affected by climate change as they are more hardy and robust.

Due to their unique characteristics of heat tolerance, tick and pest resistance, resistance to diseases and the ability to thrive under extreme climatic conditions, these animals have been imported by several countries including USA, Brazil and Australia for development of heat tolerant disease resistant stock.

Most of the Indigenous Breeds possess A2 allele of Beta Casein as compared to Exotic Cattle, known to possess higher frequency of A1 type allele2. Reportedly that A1 milk is possibly associated with some metabolic disorders like diabetes, heart diseases etc. and A2 milk produced by Indigenous Breeds does not have any such association.

Other livestock species which also contribute significantly towards nutritional safety of the country in terms of meat and egg are mainly indigenous type. Indigenous breeds of small ruminants, pigs and poultry are robust and resilient and are particularly suited to the climate and environment of their respective breeding tracts. The potential to enhance the productivity of the indigenous bovine breeds of India through professional farm management and superior nutrition is immense.

Need for Protection and Conservation of Indigenous Breeds:

Economic Potential

Indigenous populations should be conserved for their potential economic use in the future.

Their economic potential may be the production of meat, milk, fibre, skin or draught power. This potential production may be in diverse climatic and environmental conditions. Endangered populations with economic potential may have regional adaptation developed for the country of origin, or adaptations which may be beneficial in other areas of the world where similar or complementary conditions exist.

Economic potential cannot be measured by looking simply at performance. Rare or endangered breeds are often highly adapted and their performance should be measured comparatively, within their own environmental conditions. They should not be compared with other breeds in improved or modified conditions or under intensive management. Furthermore, they should be examined with respect to the products for which they were selected and valued in the conditions under which they evolved (Henson, E.L.,1992)

There are many examples where growth rate, prolificacy, or milk production have been measured and used to illustrate the inferiority of purebred indigenous stock over that of exotic imported breeds or their crosses (Hodges, 1986). However, when survivability of the offspring, fertility and longevity are taken into account the indigenous stock are often found to be very productive overall. For example Black Bengal goat and Garole sheep is famous for its prolificacy though the growth rate or milk production is poor.

The economic success of a breed or agricultural system at any one time is dependent upon many other manmade variables. These variables include the value of land, the cost of oil and other fuels, the international currency markets and exchange rates, the production efficiency of other breeds and populations in this and other regions of the world, the product shelf-life, travel and storage characteristics, health controls, current marketing strategies, consumer preferences and international political objectives. Changes in any one of these features may shift the balance and enhance the economic value of one breed type over another. For example, a shift in oil prices will affect the cost of cereal production, this in turn affects the cost of feeding grains to livestock and may affect the choice of breeds used in human food production towards more forage efficient stocks.

Scientific Use

Indigenous breeds of livestock and poultry should be conserved for their possible scientific use. This includes the use of conservation stocks as control populations, in order to monitor and identify advances and changes in the genetic makeup and production characteristics of selected stocks. They may include basic biological research into physiology, diet, reproduction or climatic tolerance at the physiological and genetic level. It could also help with the identification of specific genes involved in natural disease or parasite control. Some populations may also be used as research models in other species, including man. This is already the case in the use of Ossabaw Island Hogs in the USA. These feral pigs from an isolated island off the east coast of the USA have been shown to have a natural insulin disorder making them a useful research model for human diabetes (Brisbin, 1985).

Cultural Interest

Many populations have played an important role in specific periods of national or regional history. For example, Texas Longhorn cattle in the colonization of the USA, Spanish Merino sheep in the creation of Spain's seventeenth century wealth, or llamas, important as pack animals and fibre producers for the Inca nation of Peru (Henson, E.L.,1992) . There are also breeds which have been associated with social and cultural development; the Navajo-Churro sheep whose wool is essential in the production of the native rugs of the Navajo Indians in the USA, or elephants involved in the religious ceremony of the Perehera in Sri Lanka, or Assel breed of fowl have enormous importance as game fowl to the native people of Jargram and adjacent part of West Bengal.

Government initiatives for conservation of Indigenous breeds of livestock and poultry In India:

A. The National Programme for Bovine Breeding and Dairy Development (NPBBD) has been initiated in February 2014 a) to ensure quality Artificial Insemination services at farmers' doorstep ,b) to bring all breedable females under organised breeding through Artificial Insemination or natural service using germplasm of high genetic merits, c) to conserve, develop and proliferate selected indigenous bovine breeds of high socio-economic importance and d) to provide quality breeding inputs in breeding tracts of important indigenous breeds so as to prevent the breeds from deterioration and extinction.

An allocation of Rs.1200 crore has been made available for implementation of the scheme during 12th Plan. Under the scheme following activities has been implemented throughout the country (Annual Report 2015-16, DADF).

1. Development and conservation of indigenous Breeds:

Indigenous bovine breeds of India are robust and possess the genetic potential to play a crucial role in the national economy. For development and conservation of indigenous cattle and buffalo breeds, the following initiatives have been taken up by the Government:

Rashtriya Gokul Mission has been initiated by the Department of Animal Husbandry, Dairying & Fisheries as a part of National Programme for Bovine Breeding (NPBB) in December 2014 with the objectives of: a) development and conservation of indigenous breed b) breed improvement programme for indigenous cattle breeds to improve their genetic makeup and increase the stock c) enhancement of milk production and productivity d) upgradation of nondescript cattle using elite indigenous breeds like Gir, Sahiwal, Rathi, Deoni, Tharparkar, Red Sindhi and e) distribution of disease free high genetic merit bulls for natural service.

2. National Kamdhenu Breeding Centre:

"National Kamdhenu Breeding Centres" for development, conservation and preservation of Indigenous Breeds are being set up one in north and one in south India, as a Centre of Excellence to develop and conserve Indigenous Breeds in a holistic and scientific manner. A Nucleus Herd of all the Indigenous Bovine Breeds (40 Cattle and 13 Buffaloes), Mithun and Yak will be conserved and developed with the aim of enhancing their productivity and upgrading genetic merit. An allocation of ` 50 crore has been made available under the scheme.

B. National Livestock Mission:

It broadly covers all the activities required to ensure quantitative and qualitative improvement in livestock production systems and capacity building of all stakeholders. The major outcomes of the Mission envisaged are optimal utilization of scarce nutritional resources, conservation and improvement of indigenous breeds particularly small ruminants and pig, higher productivity and production in a sustainable and environment friendly manner, etc. (DADF,2015-16)

Besides, the Department of Animal Husbandry and Dairying (DAHD) through its departmental programmes such as Central Cattle Breeding Farms (CCBFs), Central Frozen Semen Production and Training Institute (CFSP&TI), and Central Herd Registration Scheme (CHRS) are trying to increase the number as well as productivity of indigenous breeds.

State Governments have also initiated different conservation projects and incentive schemes for improving the population of locally available indigenous breeds of livestock and poultry. For example, conservation project on Black Bengal goat and Garole sheep is implemented by Government of West Bengal, incentive schemes has been successfully implemented by the Government of Haryana for increasing the local Hariana breed of Cattle.

Role of National Bureau of Animal Genetic Resources (NBAGR):

Since its inception in 1984, the institute is constantly striving to identify the genetic potentials associated with the Indian farm animal genetic resources and in bringing awareness about the importance of conserving these resources for the prosperity. During this journey this institute have identified and registered 13 buffalo,39 cattle,24 goat, 40 sheep, 6 horses, 9 camel, 16 chicken, 3 pig and 1 donkey breeds so far (Annual Report 2015-16, ABAGR).

Conservation is an important part of this institute mandate under which conservation of Sahiwal and Hariana cattle through Goushalas has been initiated. Under ex-situ conservation programme, the germplasm repository has been strengthen by preserving DNA at National Gene Bank. Epididymal sperm banking has been initiated through cryopre-servation of caprine and ovine epididy-mal sperm. Presently the National Gene Bank at NBAGR stores a total of 1,35,174 frozen semen doses belonging to 44 breeds of 7 species e.g. Cattle, Buffalo, Goat, Sheep, Camel, Equine and Yak (Annual Report 2015-16, NBAGR).

Conclusion

Livestock production systems in India are mostly based on low cost agro-by products and traditional technologies primarily for producing milk, draft power, meat, egg, fiber etc. The land holding is invariably small. Medium to large herds of cattle and buffalo exist in the periphery of large towns and cities mainly for supply of milk. Small ruminants and pigs are reared under extensive and semi-intensive systems of production. Resource-poor small and marginal farmers and landless labourers maintain majority of the livestock. 71% of cattle, 63% of buffaloes, 66% of small ruminants, 70% of pigs and 74% of poultry are owned by marginal and small land holders. In this context, conservation of indigenous breeds of livestock may be the only way for maintaining the food safety, employment generation and sustainable socio-economic development of is country.

The link between climate change and biodiver-sity also cannot be over emphasized, as it is believed that climate change could be a key driver for loss of biodiversity but it is also well understood that biodiversity can reduce the impact of climate change. An ecosystem approach is the need of the hour wherein biodiversity conservation and ecosystem based adaptation can also help in conservation of the ecological, social, economic, cultural values of the resources.

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ZOONOTIC TRANSMISSION OF ANTIMICROBIAL RESISTANCE: IS FRANKENSTEIN'S MONSTER ON THE DINING TABLE ?

Ayan Mukherjee
Veterinary Officer, Additional Block Animal Health Centre,
Raghunathpur-1, Purulia

1. Introduction

The antimicrobial resistance (AMR) is the increasing global incidence of infectious diseases affecting the human and animal population, which are non-responsive to any known antimicrobial agent. Antimicrobials are administered in human and animals for variety of purposes, including, disease treatment, prevention, control, and augmenting growth promotion or feed efficiency. The use of antimicrobials in veterinary practice is very common from early period soon after its use in treatment of human diseases in mid 1940s. Penicillin was used to treat mastitis before world war II.After that antimicrobial are used to relieve the distress of single animal in clinical medicine as well as in large group of animals. Enhanced feed conversion ratio (FCR) was observed in poultry, swine, and beef cattle after using small, subtherapeutic quantities of antibiotics such as procaine penicillin and tetracycline in feed in 1950 (Stokestad& Jukes, 1950). Following that antimicrobial growth promotants (AGPs) were being used in feed. For many years we have evidenced the positive impact of antimicrobial application but overlooked the negative consequences. A huge amount of antimicrobials have been used globally to increase the animal food production and meet the surging demand of fast growing world population. This has given rise to the antimicrobial resistance to several bacterial chemotherapeutic agents and loomed as a global threat to mankind and animal in today's world (Nandivada and Amyes, 1990). Antimicrobial resistance has also become a potential hazard to human as the resilient bacteria may be transmitted through food of animal origin and cause disease in human. Alternatively, the nonpathogenic but resistant bacterial strain can transfer its resistance factor present in the genome to the pathogenic strain through horizontal gene transfer. It is very clear that a risk is present with the antimicrobials used both in animals as well as in human or those antimicrobials showing cross resistance with an antimicrobial used in human medicine. The epidemiology of antimicrobial resistance at human-animal interface is multifaceted and largely unpredictable area. In today's world the concept of 'One Health' strategy has arisen that, instead of studying human or animal disease or environment individually, deals all aspects of healthcare for humans, animals and the environment synergistically. Here we are going to shed light on how antimicrobial resistancedevelops and how it is transmitted zoonotically, evidence of antimicrobial resistance at human-animal interface and controlling measures to stop this menace.

2. Mechanism of antimicrobial resistance development among bacteria

➪ Genetic mechanism of antimicrobial resistance

Antimicobial resistance in bacteria may be inherent i.e., feature of a particularly bacteria (for an example, E. coli has specific resistance for vancomycin) or acquired. Acquired resistance occurs from (i) acquisition of exogenous genes by plasmids (conjugation or transformation), transposons (transposition), and bacteriophages (transduction), (ii) mutation of cellular genes, and (iii) a combination of these mechanisms (Figure 1)

(i) Horizontal gene transfer

A transfer of resistance genes from one bacterium to another is called a horizontal gene transfer (Bennett, 2008). The transfer of resistance gene may be mediated by plasmid (conjugation or transformation), transposon (transposition) or bacteriophage (transduction).

Plasmid mediated

Plasmids are double stranded circular DNA of 2-3 kilobases size.They encode genes that confer resistance tovarious types of antimicrobial agents like cephalosporins, fluoroquinolones, and aminoglycosides (Bennett, 2008), toxic heavy metals like mercury, cadmium, silver), and virulence determinants that help a cell to survive in the environment of lethal antibiotic doses. Fig.1 depicts how antimicrobial resistance is transmitted by bacterial plasmid.

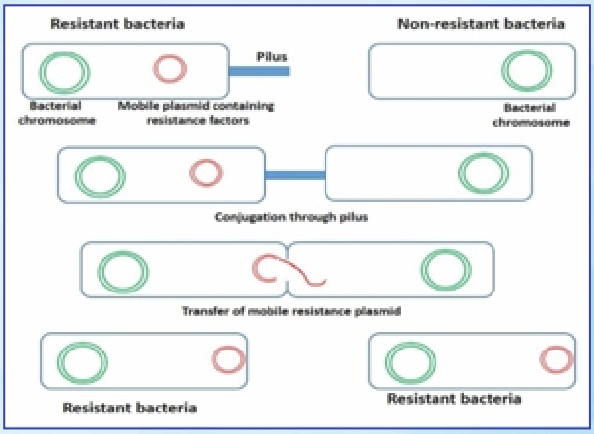


Fig. 1. Mechanism of plasmid mediated transfer of antimicrobial resistance through bacterial conjugation

'Jumping gene' or Transposon mediated

Multiple Drug Resistance (MDR) genes are located in a DNA sequence that is transferred from one plasmid to another or to the genomes, which are called transposons or “jumping gene systems” Transposons are transferred by conjugation, transformation, or transduction (e.g., mecA gene is found in Methicilin Resistant Staphylococcus aureus) and spread quicker than genes in chromosomes.

Bacteriophage mediated

Temperate bacteriophagesact as vehicle of antimicrobial resistance gene transfer in environment. This phenomena is known as transduction (Fig.2). (e.g. Phage ϕC2 Mediates Transduction of Tn6215, encoding Erythromycin resistance, between Clostridium difficile Strains)

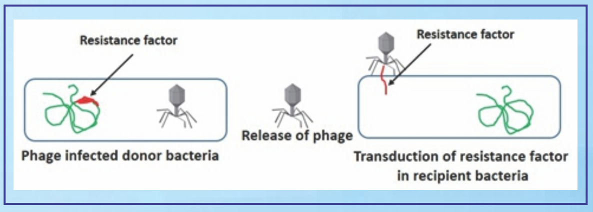


Fig. 2 Bacteriophage mediated transfer of antimicrobial resistance gene (transduction)

(ii) Mutation of cellular genes

Cellular gene mutation is caused spontaneously by erroneous replication procedure or DNA damage response. Resistance to quinolones in E. coli is caused by changes in at least seven amino acids in the gyrAgene or three amino acids in the*par*C gene.

➩ Biochemical mechanism of antimicrobial resistance

Bacteria develop antimicrobial resistance by three main biochemical mechanisms enzymatic modification and its inactivation, target alteration and efflux.

Enzymatic modification and its inactivation

Enzymes like β-lactamases, aminoglycoside-modifying enzymes, and chloramphenicol acetyltransferasesmodify antibacterials and thus, inactivate them. β-Lactamases hydrolyze almost all β-lactams that have ester and amide bond (penicillins, cephalosporins, mono bactams, and carbapenems). Serine β-lactamases-cephalosporinases are found in Enterobacter spp., and Pseudomonas aeruginosa and penicillinases in Staphy lococcus aureus.

3. Zoonotic Transmission of antimicrobial resistance

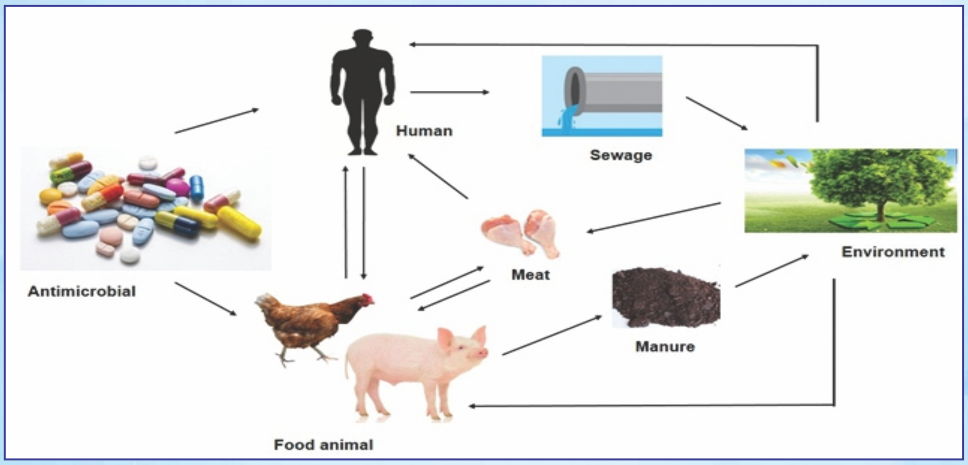
Use of antibiotics will select for drug-resistant bacteria. Antibiotics usage at subtherapeutic dose, prolonged courses of antibiotics among food animals create selective pressures for the propagation of resistant strains. Transmission of antimicrobial resistance may occur by direct contact or indirectly, through food, water, and animal waste application to farm fields. Fig. 3 shows how antimicrobial resistance is transmitted from animal to human via food chain.Here we will show some evidences in support of transmission of antimicrobial resistance from animal to human.

Antimicrobial resistancetransmission through direct contact

Workers in farm and abattoirs, veterinarians, and those in close contact with farm workers are directly at risk of being colonized or infected with resistant bacteria through close contact with colonized or infected animals. Although chance of population level health disaster is very less through this type of transmission, occupational workers and their families provide a channel for the entry of resistance genes into the community and hospital environments, where further spread into pathogens is likely. Levy et al. first reported direct transmission of bacteria from animals to people when he found the same tetracycline-resistant E. coli strains in the gut flora of chicken caretakers as in the chickens receiving tetracycline-laced feed. In another study, apramycin-resitant gene was found to be present in Chinese farm workers in all the farms using apramycin as an antibiotic growth promoter in animal. The same resistance gene, aac(3)-IV, was present in each swine, poultry, and human isolate, with some resistance profiles also matching across species (Zhang et al., 2009).

Antimicrobial resistanceacquistion through food animals

A fistful number of antimicrobial-resistant pathogens have recently been observed in the food-production chain: extended beta-lactamase producing Salmonella and Escherichia coli, transmissible quinolone resistance (qnr) in Salmonella and E. coli and animal-associated methicillin-resistant Staphylococcus aureus (MRSA). All these pathogens have great capability to transmit to, and cause infections in, humans. Emergence of these hazards is associated with the injudicious use of these antimicrobial agents in food animals.(Aarestrup et al., 2010)



4. Antimicrobials and their resistance to microbes-A global perspective

Table 1 shows different antibiotics used in food animal, their mode of action, usage in food animal, development of resistance in human.

Antimicrobial use and ban	Mode of action	Use in food animal	Resistant bacteria	Bad impact on human health	Mechanism of resistance
Avaporicin Used in 1940s-1990s; Banned 1995-2000; Not approved in USA for use in animal.	Targets bacterial cell wall synthesis	As feed additive in food animals	Vancomycin-resistant Enterococci (VRE)	40% of Enterococci infection resistant to Vancomycin in USA	Transfer of vanA & vanM genes through transposition and conjugation
Virginamycin (Streptogramin) (Banned in 1999 in EU)	Blocks transpeptidation during bacterial protein synthesis	To prevent *Clostridium enteritis* infectionand enhancement of growth and feed efficiency in poultry, swine and cattle	Streptogramin-resistant Enterococci (SRE) in US, Canada, Japan	Treatment failure of patients in hospitals with pristinamycin and Synercid (Quinupristin-Dalfopristin) resistant Enterococcus *faeciuminfections.*	Transfer of vat (virginamycin acetyl transferase) gene
Enrofloxacin & Ciprofloxacin (Fluoroquinolones) Use of Enrofloxacin was Banned on Poultry in USA from 2005	Blocks bacterial DNA replication by inhibiting DNA gyrase enzyme	Use to treat bacterial infection in poultry	Fluoroquinolone-resistant *Campylobacter jejuni*	Poultry-borne Campylobacteriosis in USA, Denmark	Mutation in bacterial DNA gyrase enzyme
Tylosin & Tilmicosin (Macrolides)	Blocks bacterial protein synthesis by inhibiting peptidyltransferase	Growth promoters in food animals	Macrolide resistant Campylobacter coli	Treatment failure in Campylobacteriosis in human in US, Canada	Point mutation in target genes of 23S rRNA
Oxytetracycline & Chlortetracycline (EU banned Tetracycline sas growth promotor since 2006)	Prevents bacterial protein synthesis	Treat bacterial infection	Tetracycline-resistant Salmonella *typhimurium*	Human outbreak in USA, Netherland	Enzymatic inactivation of drug
Ceftiofur & Ceftiq uinome (Cephalosporin)	Prevents bacterial cell wall synthesis	Treat bacterial infection	Bacteria carrying extended spectrum ?-lactamase (ESBL)	Less resistance reported so far to Salmonella, E coli.	Not reported

5. Antimicrobial resistance in India-A huge challenge before public health medicos and veterinarians

Antimicrobial resistance has become a direpublic health crisis in India. The mortality rate from crude infectious disease in India today is 416.75 per 100,000 persons (Laxminarayan and Roy Chaudhary, 2016). In India, Escherichia coli isolated from the community showed high overall resistance to ampicillin, nalidixic acid, and co-trimoxazole (75%, 73%, and 59%, respectively) between 2004 and 2007 (Holloway et al., 2009). From 2008 to 2013, E. coli resistance to third generation cephalosporins increased from 70% to 83%, and fluoroquinolone resistance increased from 78% to 85% (Center for Disease Dynamics, Economics & Policy, 2015). Carbapenem resistant E. colihas increased from 10% in 2008 to 13% in 2013 (Center for Disease Dynamics, Economics & Policy, 2015). Resistance to fluoroquinolones among invasive Salmonella typhi isolates in India increased from 8% in 2008 to 28% in 2014 (Datta et al., 2012). Resistance to nalidixic acid in Salmonellatyphi is increasing (resistance is about 20%–30%) because of widespread use of other quinolones.High rates of methicillin-resistant Staphylococcus aureus (MRSA) in clinical isolates from various studiesin India have been documented, with rates as high as 54.8% (ranging between 32% and 80%) recorded (Van Boeckel et al., 2014). Although major reasons behind antimicrobial resistance in India is poor public health infrastructure, over-the-counter sale of antibiotic, inexpensive antibiotic, rising economy etc. indiscriminate use of antimicrobials in food animals plays a significant role to create this ominous burden on the country's public health. With the growing demand of animal protein in India antibiotic use in the animal sector is rising in alarming pace and this results in a greater selection of pathogens. Consumption of chicken in areas of high consumption (30 kg per km2) are expected to grow 312% by 2030 (Van Boeckel et al., 2015). A recent report by Organisation for Economic Co-operation and Development (OECD) showed that the costs of withdrawing antimicrobial growth promoters in India would be roughly US $1.1 billion (Laxminarayan et al., 2015).Unfortunately there are no regulatory provisions for the use of antimicrobials in cattle, chickens, and pigs raised for domestic consumption in India. Although standards for tolerance of antibiotic residues exists for fish and fishery products, seafoods and honey [under the Food Safety and Standards (Contaminants, Toxins, and Residues) Regulations of 2011] there exists no such standards for chicken. Consequently, antibiotic residues have been traced in animal food products in different corners of the country. Antimicrobial resistance producing extended-spectrum β-lactamases (ESBL) producing E. coli has been isolated from chicken meat, chevon meat, raw milk, and human urine and stool samples collected from tribal districts of Chhattisgarh (Bhoomika et al., 2016). Multiple drug resistant Helicobacter pullorum has been isolated from chicken being sold at Hyderabad retail chicken market (Qamar et al., 2016).

6. Controlling measures to prevent antimicrobial resistance in food animals

Abiding by WHO recommendations to prevent antimicrobial resistance

World Health Organization (WHO) has set following guidelines for preventing transmission of antimicrobial resistance through food animals.

1. Require obligatory prescriptions for all antimicrobials used for disease control in food animals.
2. In the absence of a public health safety evaluation, terminate or rapidly phase out the use of antimicrobials for growth promotion if they are also used for treatment of humans.
3. Create national systems to monitor antimicrobial usage in food animals.
4. Introduce pre-licensing safety evaluation of antimicrobials with consideration of potential resistance to human drugs.
5. Monitor resistance to identify emerging health problems and take timely corrective actions to protect human health.
6. Develop guidelines for veterinarians to reduce overuse and misuse of antimicrobials in food animals.
7. Encourage good hygienic practices and farm management to ensure animal health without the use of antimicrobials
8. Require prescriptions for animal antimicrobial use; develop national veterinary guidelines for appropriate antimicrobial prescribing

Development of alternatives to antimicrobials for farm animals

Use of prebiotics and probiotics

There are currently a number of prebiotics and probiotics available, though their efficacy is unclear and likely variable. Mixing the two has also been proposed, so-called 'synbiotics'.

Expanding the range of veterinary vaccines

Although vaccines are already available against many of the major viral diseases of livestock, there is currently limited routine use of vaccines that protect against bacterial infection and disease. Expanding the range of antibacterial vaccines will therefore, minimize the use of antibiotic in food animal and curb the menace.

Use of livestock that are genetically resistant to infection or disease

Genomic manipulation in livestock and development of genetically resistant to infection or disease
will reduce the use of antibiotics in food animal. However, this requires long term research. One example of early progress in this direction comes from the development of transgenic fowl that does not transmit avian influenza (Lyall et al., 2011).

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MANAGEMENT AND TREATMENT OF SARCOPTIC MANGE IN CROSS BREED JERSEY CALVES: A CLINICAL STUDY

Dr. Amal Banerjee

Veterinary Officer, Block Animal Health Centre
Purbasthali-1,PurbaBardhaman,West Bengal.

Abstract

Present study was conducted to evaluate the therapeutic efficacy of ivermectin,gamma Benzene Hexachloride and cetrimide in ten cross breed jersey calves in a local dairy farm. The combined treatment with ivermectin, gamma Benzene Hexachloride and cetrimide gave an excellent result. Complete recovery was performed after six weeks.

Introduction:

Sarcoptic mange is highly contagious disease spread by direct contact between infested and naive animals or by contaminated fomites. Lesions occurred by these burrowing mites at head, neck and shoulder and then can spread all over the body.It will take time six to seven week to spread all body parts. Firstly papules develops in the crust region followed by pruritus will occurred due to secondary bacterial infection. After that, skinwill thickened and form folds. Diagnosis is made by skin scrapping or skin biopsy. It has a zoonotic importance.

Material and method:

Ten cross breed jersey calves aged between 2-4 months with a history of dermatological problem were presented at BAHC,Purbasthali-1,purba barddhaman. These breeds were used for present study. The symptom were severe itching and those areas were excoriated by scratching, grazing and biting.

Alopacia (Fig no-2), red papules(Fig no-3) followed by pruritus were observed in affected areas. Thickening and folding of skin(Fig No-1) were the generalized form of observation. In few part of body, blood were oozing out due to bitting and scratching. Overall body condition were exhausted and pulse rate and temperature were slightly elevated.The white coloured cheesy material was noticed on squeezing of mature nodules.

Skin scrapping were collected from the lesions from different site and were subjected to direct examination with 10% potassium hydroxide solution(Chauhan,R.S. and Agarwal,D.K.,2006). Microscopic examination of the skin scrapping revealed that presence of sarcopticscabieivar .bovis infestation as per soulsby (1986)

Calves were treated with ivermectin @ 0.3 mg/ kg body weight at weekly interval for four week along with animals were given topical application of gamma Benzene Hexachloride and cetrimide lotion throughout the body for half an hour once in a week for four consecutive week. After half an hour animals were cleaned by fresh water. Calves were prevented from liking during the topical application of gamma Benzene Hexachloride and cetrimideby using mouth belt. To prevent secondary bacterial infection, animals were treated by ceftriaxzone @ 10 mg /kg body weight for 5 days. As a supportive therapy, Vitamine A at weekly interval for three weeks and antihistaminic drug (phenaremine maleate) were given to the animals intramuscularly for 5 days.

Recovery in mild form were observed within first weeks and complete improvement from the infestation were seen after six weeks (Fig No-6)

Fig no- 1: Thickening of skin and scab formation

Fig no -2: Aloepacia involved in the entire body

Fig No- 3: Thickening of skin and red papules in affected area of the body.

Fig no-4: Emaciated and anaemic body due to Sarcoptic mange infestation.

Fig No-5: New hair growth in the entire body after 5 weeks of treatment

Fig No-6: Appearance after 6 weeks of treatment

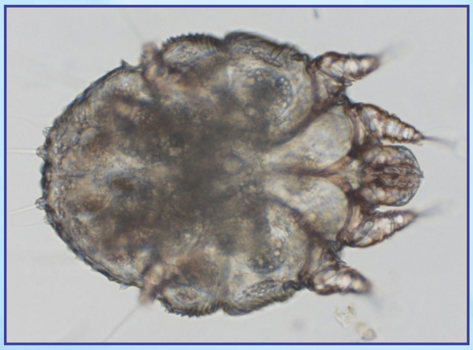

Fig No-7: Sarcopticscabie

Results and discussion:

Sarcoptic mange is highly contagious diseases affecting humans, domestic animals and also wild lives. The disease is caused by sarcoptess cabiei which ruptured the outer layer of skin and form tunnel in the epidermis where they deposits eggs and digestive secretion.

In this present study confirmed the diseases by skin scrapping method of diagnosis in the all animals. And it was observed that local to generalised form of infection of scarcoptic scabei (fig-7) and along with secondary bacterial infection.

Sarcoptic scabei is round or slightly oval shaped like horse shoe with white or yellowish white colouration. It is dorsally convex and ventrally flattened and comprised of multiple cuticularspine. It has 21 days of life cycle and can survive in the host surrounding environment for upto 3 weeks.

The intensity of inflammation was decreased in the first week of treatment but scabes and thickening of skin was still persistent. In the second week, the inflammation and erythema was resolved completely. There was marked improvement after second week. After 3 week no itching were there and all scabes were fallen off. Examination of the skin scrapping after 3 weeks did not show the presence of any mites. But complete healing and normal skin appearance were observed after five to six weeks.

Ivermectin is the drug of choice of many veterinarian and author (Purohit et al, 1997, Ghosh and Nanda , 1997) to control lice, mites and mange infection of domestic animals. Ivermectin binds with high affinity to the glutamated gated chloride channels which occur in the invertebrate nerve and muscle cells causing an increase in the permeability of the cell membrane to the chloride ions with hyper polarisation of the nerve and muscle cells resulting into paralysis and death of the parasites either directly or by causing the worm to starve. Treatment performed in this study was based on these principles and combined treatment with gamma Benzene Hexachloride,cetrimide and ivermectin along with antibiotic, vitamins and anti histaminic gave excellent result. After six weeks skin were glossy and smooth and hair growth were noticed on the entire body(Fig No-6) .

Acknowledgement

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CANINE DEMODICOSIS : AN EMERGING PROBLEM

Dr. Prabir Kumar Santra
Institute of Animal Health & Veterinary Biologicals (R&T)
37 Belgachia Road, Kolkata-37

Canine demodicosis "commonly called Red Mange" infestation caused by Demodex canis . Generally all species of Demodex are named after their hosts except pig and man . Canine demodicosis is one of the most common skin disease in dogs characterized by inflammation with excessive proliferation of commensal mite, which live in the hair follicle and sebaceous glands of host . Though all domestic mammals and human beings are infected with this mange but this form is best documented in the dog (Fig. 01).

Morphology

Under the microscope the mite is shaped like a cigar.It is usually about 0.25 mm long, have a horse shoe–shaped capitulum has clearly visible mandibles, a thorax which bears four pairs of stumpy legs and elongated abdomen which is transversely striated on the dorsal and ventral surfaces (Fig. 02).

Fig. 01: Focal Alopecia and scaling on the back of a dog with demodicosis

Fig.02: Adult D.canis and egg

Transmission

Transmission is occurred from animal to animal through prolonged contact as it is located deep in the dermis . The prolonged contact occurs during suckling and during this time the muzzle , face, periorbital region and forelimbs contact with the body of mother and naturally from the commensal population in the skin of bitch , the puppy get infection.

Pathogenesis and Clinical Symptoms

Demodex canis is a normal member of cutaneous ecology of the dog. But in some situations over population of this mites causes skin diseases. The entire lifecycle is spent on the host , completed 18-24 days . Mites in all stages can be found in a dog's hair follicle and, potentially, the lymphatic system, blood stream and other organs (Scott et al. , 2001) .

Early in the infection ,there is slight loss of hair on the face and fore limbs, followed by thickening of the skin . Most of them resolve spontaneously . This is called localized demodicosis which occurs most commonly at the age of three to nine months. On the other hand , lesions may observed on the whole body due to high ratio of immature to mature mites, is called generalized demodicosis. However there is no uniformly accepted definition regarding localized as well as generalized demodicosis. The term localized was considered when small circumscribed patches limited to 1-2 lesions were present over any part of body where as generalized demodicosis denotes involvement of an entire body with numerous lesions with extensive involvement of the skin (Muller,2004 and Srivastava et al., 2012). Most of generalized cases are observed in dogs 2 to 4 years of age with a history of chronic skin diseases , and often these dogs had a demodicosis as puppies but were undiagnosed (Nash ,2006) . Surprisingly a dog with demodectic mange usually does not itch severely.

The generalized demodicosis may be appeared in two forms: one is squamous demodicosis which is less serious, skin will be dry ,slight reddish but alopecia, desquamation, thickened and wrinkled with a 'mousy' odour. Sometimes face and paws are affected.

The other form *pustular* or follicular *demodicosis,* is severe form and bacterial invasion of the dermis occur. Staphylococcus *intermedius* is the most infecting organism, but secondary infection with gram-negative bacteria, Pseudomonas a*eruginosa* or Proteus mirabilis also found(Scott et al. ,2001).. Extensive dermal infiltrations of *polymorpho* nuclear leucocytes and lymphocytes and plasma cells are seen and pustule or abscess formation, marked inflammation occurs. This form is usually preceded by the squamous forms (Soulsby ,1982) .

In extensive forms of canine demodicosis death results from toxemia or emaciation.

Occurance and severity of demodectic mange depends upon the immune systems. Certain bitches carry some genetically transmitted factor and as a result their off springs are immune deficient which cause susceptible to mite infection (Urquhart et al.,2003) . As the immune system does not mature until one years of age, a dog with demodectic mange sometimes relapses until the age . For juvenile – onset generalized demodicosis other predisposing factors are short hair, poor nutrition, stress, oestrus, endoparasites and debilitating disease, and undue use alkaline soap or shampoo.

The adult- onset generalized demodicosis , can develop in dogs 2 to 4 years old which may have history of undiagnosed demodicosis as puppies. Generally these dogs do not have a genetic predisposition , when immune system is declined or suppressed due to age, poor condition, intercurrent infection(especially virus infection), severe inflammatory bowel disease, diabetes mellitus, hypothyro idism, hyperadrenocorticism, gluco corticoid therapy, neoplasias or chemotherapy the adult –onset may be developed (Mueller et al. , 2004, Nash, 2006).

Diagnosis

The Standard Method to diagnose demodicosis is microscopic evaluation of material obtained by a deep skin scrapping, (Soulsby, 1982). A dulled rounded scalpel blade is generally taken to scrape the skin. The area is selected for scrapping is at the edge of the visible lesions . Deep skin scrapping can be achieved easily by taking a fold of skin then apply a drop of liquid paraffin and blade should be

scrapped back and forth until capillary oozing occurred. Collected debris is then placed on a microscope slide, put a cover slip on it and examine using 10 X microscope objective. Finding a high proportion of immature mites on a skin scrapping is indicative of a more serious infestation than is a predominance of adult mites. More than one mite on a skin scrapping is diagnostic for demodicosis (Mueller, 2012)

If during the initial examination no mite detected , Potassium Hydroxide Centrifugation test is performed. The skin scrapings were taken from the infected areas, the thick scrapings were boiled for few minutes in 10% potassium hydroxide solution to clear the debris. The fluid was then centrifuged at 2000 rpm for five minutes. The supernatant was discarded and the sediments were collected and observed under microscope for recovery of mites.

Treatment

Before going to treatment of canine demodicosis it should be determined whether the pet is affected with localized or generalized infection. Localized demodicosis resolves spontaneously in most patient , do not require generalized therapy.

Where the lesion is mild and localized it may be treated with daily local application of benzoyl peroxide gel or mupirocin ointment rubbed in the direction of the hair growth . A secondary bacterial folliculitis is present in the majority dogs with generalized demodicosis. The generalized form requires more aggressive and long-term treatment using special shampoos and amitraz dips with or without oral medicine (ivermectin). Use of glucocoticoids is contraindicated in pets with demodicosis as it may further suppress the immunity of the patient's.

Amitraz

Amitraz is an acaricide or insecticide of the formamidine family and was the first licensed product use for the treatment of generalized demodicosis. It is a liquid concentrate diluted with water to make a dip solution and applied as a 250-750 ppm solution (0.025%-0.075% of water) to the dog's entire body every week (Kachhawa,2016). To get the optimum result as well as to overcome the hazards clipping the hair coat in medium – and long-haired dogs and bathed with a anti bacterial shampoo like benzoyl peroxide shampoo to remove crust, debris and bacteria

During treatment with amitraz skin scrapping should be performed looking for eggs, larvae or live mites once hair regrowth occurs. If clinical or microscopic improvement is not satisfactory after six treatments , reconsider whether the pet go through any stress or any other problem or change the treatment protocol. During this time high concentration and more frequent application required. Due to higher concentration some adverse effect of amitraz is observed like transient sedation, hyperglycemia, bradycardia, deperession, polydipsia, and polyurea, vomiting and diarrhea. To overcome the adverse effect , bathe the pet with luke warm water with supportive care .In severe cases Yohimbine (0.11 mg/kg) administered slowly intravenously.

Ivermectin

Ivermectin is systemic macrocylic lactones , a fermentation product of Streptomyces avermitilis. Generally, it is used for the treatment of ecto and endoparasite at doses of 200-400 µg/kg weekly. In the mid 1980s it is used for the treatment of generalized demodicosis. In the last three decades several reports evaluated the doses of ivermectin to treat this disease. Number of published data available that ivermectin has given satisfactory result at a dose of 0.3 to 0.6 mg /kg/day PO (Muller and Bettenay, 1999, Rutan, 2006 and Mueller, 2012).

However to avoid neurologic adverse effect of ivermectin in sensitive pet, use it by maintaining the following protocol (Table:01). During this treatment advise to be given to the pet owner to observe whether the treated pet shows any signs of suggesting toxicosis which is discussed later.

If no signs of toxicity, treat the pet for one month after it has received 400 μg/kg PO once daily. For evaluation of treatment further skin scraping is necessary. If the no. of immature or adult mite is lower than the previous one then continue this dose or if more mites observed increase the dosage to 500 to 600 μg/kg PO once daily or every other day (Rutan, 2006).

Toxicities of ivermectin expresses through neurologic adverse effect, it begins with mydriasis

Table 1: Ivermectin Protocol for treatment of Canine Demodicosis (Mueller, 2004)

Day of Treatment	Dosage (μg/kg PO s.i.d)
1	50
2 to 3	100
4 to 6	150
7 to 9	200
10 to 16	300
17 +	400

salivation, depression, anorexia, ataxia, lethargy, tremors, weakness progressing to seizures and coma like states .Ivermectin should not be used in Collies and other herding breeds like Old English Sheepdogs, Australian Shepherds and pets less than 6 weeks or on a daily basis in Pets less than 12 weeks of age.

Milbemycin

Milbemycin oxime is another macrolide is also effective and safe for canine demodicosis at the dose 0.5 -2 mg/kg/day /PO for all breeds including Collies and other breeds that are sensitive to ivermectin or amitraz. Higher doses (1 to 2 mg/kg/day)shows better cure rate. But this is the more costly drug .

Combination Therapy

It is observed in field condition in some cases that oral ivermectin or topically used amitraz alone do not shows satisfactory result in the treatment of canine demodicosis. In this circumstances using this oral as well as tropically used drug combinely which may lead to more success rate.

Herbal preparation

Some herbal preparation containing extracts of Cedrus deodar (Devadaru), Azadirecta indica (Neem)and Embelia ribes (Biranga)may be used successfully as sprayed on tropical lesions of demodicosis. Other indigenous preparation containing Mallotus phillipensis (Kamala), Oleum pinus (Oil of pine) , Oleum terebinth (Oil of Terpentine)and Sulphur sublimitum is also efficacious for the treatment of this disease when applied tropically for 7 days daily twice .

Supportive Therapy

In case of canine demodicosis infected pet with hypothyroidism, hormone therapy is required with usual chemotherapy .

Use of fatty acid supplements helps to rejuvenate the skin's health , can also assist in treatment of canine demdicosis.

Conclusion

To get the best result in canine demodicosis logical diagnosis, prompt treatment with appropriate medicine and owner education is needed specially in long- term treatment. Most of the cases it is very much useful if it is discussed with the owner regarding occurrence of disease , treatment protocol as treatment may require many months for therapy and educate them about drug toxicities as no drug is available for the treatment of the disease without any adverse effect . When the pet is treated with ivermectin, aware them about its extra label usages. Furthermore it is always advisable that the pets with generalized demodicosis or any bitches more prone than others to have susceptible offspring should not be bred for controlling the endemicity of demodicosis .

LASTLY BE POSITIVE AS MOST OF THE CASE HAS A GOOD PROGNOSIS !

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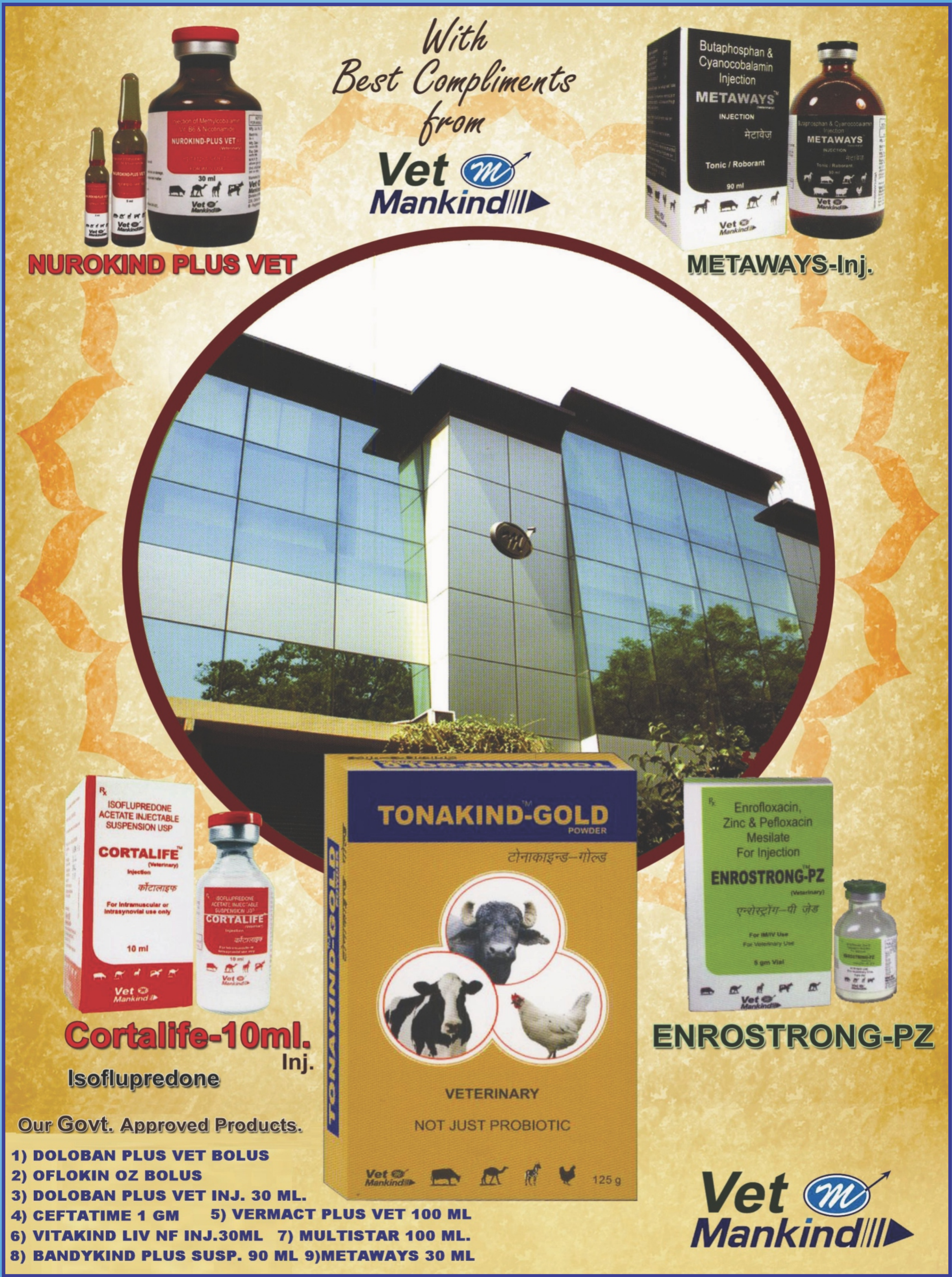
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