Animal models play key role to develop novel drugs

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The increase in resistance of bacterial pathogens, to commonly used antibiotic drugs, is reaching alarming proportions globally. This phenomenon, globally referred to as Antimicrobial Resistance (AMR), has important health and economic consequences.

An estimated 700,000 people die annually around the world due to infections caused by multidrug resistant pathogens. This is in addition to millions of people suffering from morbidities caused by serious infectious. Annual deaths attributable to AMR are estimated to reach 10 million by 2050, which is more than mortalities caused by cancer, diabetes, and road accidents.

Physicians treating patients with infections, caused by multi-drug resistant pathogens, are left with very limited options as the existing first choice anti-bacterial drugs (such as the Fluoroquinolones, Penicillins, Carbapenems, Aminoglycosides, Macrolides) are ineffective. This results in treatment with second-line drugs such as Polymixin B and Colistin which are efficacious but have un-acceptable side effects. The situation becomes even worse when the bacteria become resistant to virtually all the existing anti-bacterial drugs, which ultimately leads to death due to lack of any alternate treatment options.

Complicated infections caused by resistant pathogens in patients having diabetes and kidney injury (complicated urinary tract infections –cUTI), diabetic or burn wounds and medical implants further complicate treatments.

The lack of effective drugs for the treatment of patients with drug resistant pathogens leads to a significant increase in costs for hospitalisation, treatment of morbidities, and poor outcomes due to often ineffective second-line drugs.

Some of the important factors contributing to the development of AMR are indiscriminate use of antibiotics (poultry), sub-optimal treatment schedules, non-compliance, and empirical treatments without accurate diagnosis. Appropriate steps taken (raising awareness, education of physicians, development of rapid diagnostics, regulations such as ban of use of antibiotics in poultry) to address these factors will help in significant reduction in development of resistance and therefore lead to effective treatments. Although these steps have helped reduce the development and spread of resistance, there is still the pressing problem of treating MDR infections in populations globally.

There is an urgent need to bring novel broad- spectrum or narrow –spectrum anti-infective drugs to the market to counter the AMR threat. Unfortunately, in the recent years many large pharmaceutical companies have dropped anti-infective research and development programs due to economic reasons or due to the perception that there is no need for novel anti-infective drugs (e.g. tuberculosis). However, there are a few big, medium and small sized pharmaceutical companies who are active in this area. Novel

chemical entities for anti-infective therapy are in different stages of preclinical and clinical development, and a few were recently approved for marketing (Delafloxacin, Plazomicin, Eravacycline, Omadacycline). Some of the areas where new antibiotics (narrow spectrum or broad spectrum) are needed are in the treatment of acute bacterial skin and skin structure infections, sexually transmitted infection, infections in cystic fibrosis patients, treating infections caused by *P. aeruginosa*, *Acinetobacter*, and *Klebsiella* species.

The development of narrow spectrum agents poses major challenges in clinical testing.

Infections caused by multidrug-resistant or extensively-drug-resistant pathogens are not common and are encountered mostly in critically ill patients who are difficult to include in clinical trials. Nevertheless, these organisms are being increasingly found in patients. Some examples are patients diagnosed with Ventilator Associated Bacterial Pneumonia (VABP) and Hospital Acquired Bacterial Pneumonia (HABP), cUTI and bloodstream infections. In recently conducted trials, the prevalence of *Pseudomonas* and *Acinetobacter* was ~ 10% in VABP/HABP and ~ 2% in cUTI patients. The number of patients required (for demonstrating statistical significance) for evaluating the efficacy of new agents in clinical trials will be very high. Given the low incidence of these pathogens, it is a herculean task to find such patients in large numbers and is also un-ethical to put these patients at risk. Fortunately, animal models of infectious diseases provide a solution to solve this problem.

It has been widely recognised that animal models of infectious disease have a vital role in the development of narrow spectrum agents. Regulatory agencies such as the Food and Drug Administration, USA (FDA) have indicated (Guidance document -*Product Development Under the Animal Rule Guidance for Industry* (October 2015) that if efficacy of these agents are demonstrated in animal models of disease that mimic the human disease conditions, in a robust manner, then the agents can be given conditional approval for marketing without conducting the pivotal phase three trials. This stems from the fact that animal models of infectious diseases predict the efficacy of anti-bacterial agents in humans with reasonable accuracy. This has been well documented for Fluoroquinolones, Penicillins, Carbapenems, Aminoglycosides, and Macrolides in the murine thigh infection, lung, bacteremia and urinary tract infection models. However, validated animal models for cUTI, IAI, CABP, HABP and VABP are lacking. There is an urgent need for development and validation of these models.

The main criteria for validation of animal models for infectious diseases are a) the species of animal used should adequately produce the clinical symptoms observed in humans when infected with the pathogen, b) the efficacy of reference anti-bacterial drugs should be demonstrated in the animal models, c) the efficacy (curing of the clinical symptoms) of the anti-bacterial agent in the animal model should be linked to its pharmacokinetics (time course of concentration of the anti-bacterial agent at the site of infection), and d) the relationships of pharmacokinetics and efficacy for the reference drug in the animal models should be similar to its corresponding relationships observed in humans.

AMR is a real threat and is affecting the human population in significant ways. This must be tackled on a war footing. There is an urgent need for new anti-bacterial medicines to add to the list of existing drugs (for which AMR has developed). Anti-bacterial discovery and development in turns needs financial support (e.g. funding of small to medium companies with anti-infective drug discovery programs by the consortium Combatting Anti-Bacterial Resistance of Bacteria - CARB-X) and incentives. Animal models play a vital role in development of novel anti-bacterial agents indicated for treatment of complicated infections. Animal models for cUTI, IAI and HAVP/VABP need to be validated urgently to help progress these lifesaving medicines rapidly to the clinic and eventually to save the lives of millions of patients.

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