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Rodent Borne Zoonosis and Its Epidemic Surveillance - An Overview

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Abstract
Human health has been continually challenged from many years with a variety of pestilences and infections. Majority of the diseases are of zoonotic origin with different animal host range including reptiles, mammals, pet animals, livestock and wild animals. Among these, the species of the rodents are highly prevailed and distributed globally and hosts for variety of zoonotic pathogens. Until now, investigations of disease outbreaks have mostly been recorded with limited or non-availability of prior information. Due to the non-specific symptoms caused by these rodent-borne zoonotic pathogens and lack of clinical suspicion, transmission to human population probably left under-diagnosed or non-diagnosed and leads to spill over of disease. Identification of suspecting zoonotic pathogen along with reservoir host and transmission of emerging infectious diseases in different geographical regions are the important steps toward a preemptive approach to minimizing zoonotic disease risk in humans. In this review, we summarized the significance of rodent species as zoonotic carriers, associated diseases and their epidemic surveillance.

Keywords
Rodents; Zoonotic Pathogens; Epidemic Survey; Hantavirus; Bacteria.

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INTRODUCTION
Zoonoses are the diseases and infections which are transmitted through a wide range of animals. More than half of the human pathogens are zoonotic and emerging infectious diseases (EIDs), which cause no significant signs or illness in their host species (1). The high impact spill over in past and present pandemic outbreaks are resulted from wildlife zoonotic pathogens and led to distressing global health and economic effects when transmit to human and livestock (2). Previous studies reported that 60-80% of EIDs in human are originated from wildlife animals and two thirds of EIDs are originated from rodents, bats, and other wildlife (3).
However, the order Rodentia is highly prevailed mammalian group on the earth comprising approximately 42% of the global mammalian population (4). Rodents are small in size with short reproduction period and biologically, morphologically adoptable to different ecological lifestyles and environments including aquatic, semiaquatic and dry environments (5). Because of this compatibility rodents can live in different habitats than any other animal species. Despite of this, rodents are well known for zoonotic risk of human health by serving as reservoir hosts and transmitting a wide variety of microbial pathogens and cause diseases including plague, leptospirosis, brucellosis, leishmaniosis, bartonellosis, salmonellosis, and viral infections, haemorrhagic fevers (5-7). The zoonotic diseases transmitted directly by rats through bites, urine faeces and arthropod vectors, which affect 7-10 million people per year globally. The prevalence of the diseases may associate with rodent population and

socioeconomic lifestyle of humans, and human related activities such as urbanization and agriculture (8). The rodent species including *Ratts rattus*, and *Rattus norvegicus* are widely distributed to different geographical locations and live in urban and rural areas in close contact with humans and are of viewed to spread diseases more than other rodent species (9). The major bacterial pathogens associated to rodents include *Anaplasma, Borrelia, Leptospira, Coxiella, Bartonella, Francisella, Ehrlichia* and *Rickettsia*.
The increasing outbreaks of emerging and re-emerging infectious diseases in the world require the exploration of reservoir hosts of zoonosis to understand transmission dynamics and to develop buoyant response strategies. Moreover, it helps to predict and reduce the risk of future emergence of zoonotic diseases. Viral zoonotic pathogens can cause epidemic and pandemic outbreaks. The Integrated Disease Surveillance Program (IDSP) survey reported that in 2017, a total of 1683 outbreaks were reported in India and 71% of them were caused by viral pathogens, and nearly 72,000 individuals were affected in these outbreaks (10). In this review, we discuss the different diseases which are transmitting by rodent species and their epidemic surveillance.

Rodent Borne Diseases
The order Rodentia with 33 families and 2,277 species is the largest mammalian group on earth, representing 43% of all mammalian species, which are widely distributed in all continents (3). It forms a bridge between humans and wildlife animal by being in close contact with humans. Among rodent species, Norway and black rats (*Rattus* spp.) are distributed globally. The expansion in global transportation networks lead to consequences of infectious disease pandemics, vector invasion events and vector-borne pathogen importation. The initial disease outbreaks such as *Yersinia* spp. and Hanta virus in ports are very common than any other routes. Rodents transmit disease in 2 different ways such as either by (1) contaminating the food and water taken by humans or (2) by serving as host for pathogens can bring them to direct contact with humans. Rodents help pathogen transmission to diverse environments and landscapes including urban area to rural area as well desert lands. However, climate change and urbanization are noted to increase the risk of with rodent-borne diseases as the distribution of rodent species (11). Major zoonotic bacterial species and viruses associated with rodents and their diseases are given in Table 1.

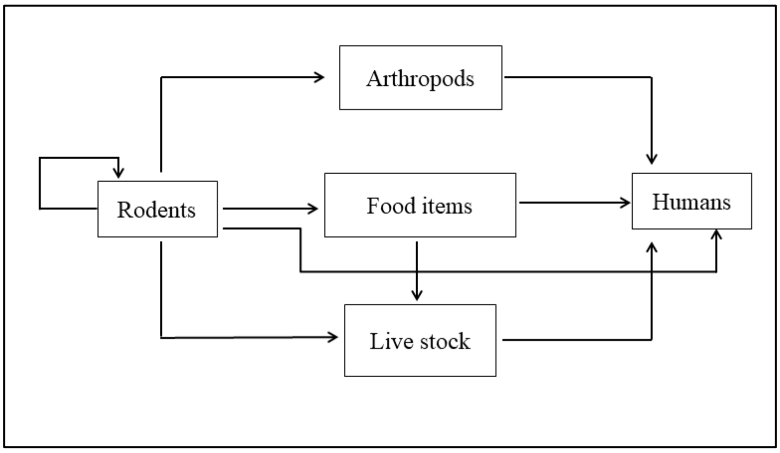

Figure 1. Transmission strategies of zoonotic pathogens from rodents.

Plague
The zoonotic pathogen which causes plague and responsible for three pandemics was attributed to *Yersinia pestis*. It is a Gram-negative bacterium belongs to Enterobacteriaceae. It was isolated by Alexandre Yersin during third pandemic plague. Other species of this genus *Y. pseudotuberculosis* and *Y. enterocolitica* were also found to infect humans (12). These pathogens spread from fleas, which were associated with live rodents and/or products that led to the plague spread. Since 2014, a total of 14 major outbreaks of Africa and Asia were reported to the WHO (13). The zoonotic pathogen *Yersinia pestis* was found to transmit by respiratory droplets and uncooked contaminated food and also transmitted through contact with pet animals. Based on the mode of infection, this disease can be described as bubonic, pneumonic and septicaemic plague. Bubonic plague symptomized by common flu, fever, malaise, chills and headache, and if not treated it can develop into pneumonic and septicaemic plague. The early recognition and treatment with antibiotics for the patients is the recommended procedures. It will become fatal for the patients if the treatment is delayed by 24 hours. Though *Yersinia* species are sensitive to streptomycin, multi-drug resistant strains were identified in Madagascar. Fortunately, these

strains were never emerged naturally in these regions (14).

Hantavirus Pulmonary Syndrome

In 1993 in the Southwestern parts of the United States, this disease appeared due to anomalous weather patterns. It is a deer mouse borne disease caused by different strains of viruses belong to the genus of Hantavirus (15). Hantavirus is a single genus comprising 40 species with single stranded RNA which belong to bunyaviruses family. Presently, more than 50 hantavirus strains have been identified and 24 of those strains are having pathogenic relevancies to humans. Other hantaviruses may remain undetected, as infections are likely to go unreported in many areas, particularly in Africa, the Middle East, Central America, the Indian subcontinent and Mongolia (16). Based on the geographical and clinical manifestation, these species are grouped into 2 categories of strains. One variant strain causes pulmonary edema and effusions with respiratory failure and cardiovascular depression whereas another variant strain causes haemorrhagic shock and renal failure by targeting kidneys and vascular system. In a study conducted at the United States revealed that an average of 11% of SNV prevalence was observed. Moreover, the California mouse (*Peromyscus californicus*), cactus mice (*Peromyscus eremicus*), harvest mice (*Reithrodontomys megalotis*) and California voles (*Microtus californicus*) species of rodents were also found to have SNV antibody prevalence positive (17).

Leptospirosis

Leptospirosis is most common zoonotic, rodent-borne mainly, the brown rat (*Rattus norvegicus*) disease globally. It is also classified as re-emerging infectious disease by CDC and WHO. The zoonotic bacteria *Leptospira* spread all over and habitat in reservoir kidneys without causing any disease. These bacteria spread through the reservoir urine and acquire a new host. Once enter through the glomerulus or peritubular capillaries into the kidney and colonizes at proximal renal tubular epithelium (18). It is a nonspecific symptomatic and characterized by fever, myalgia and headache. Disruption of hepatocytes by disrupting the intracellular junctions leads to elevated bilirubin levels, as a results of it leaking of bilirubin out of bile canaliculi (19). In 1995, the first outbreak of leptospirosis in Colombia occurred in its principal sea-port, Barranquilla and resulted in four deaths. Later, the sea-port city of Colombia has been identified as "hot spots" for leptospirosis due to rodents transported on these visiting commercial ships (Romero-Vivas *et al*., 2013). A 2012 study reported that annually 4713·5 cases in America (Costa *et al*., 2012), 1.03 million human cases and 58,900 deaths occur globally (Costa *et al*., 2015).

Bartonellosis

The members of the genus *Bartonella* are vector borne pathogens infect humans and a number of mammal species. *Bartonella* are facultative intracellular, gram-negative bacteria belong to the α- proteobacteria (20). They are able to parasitize in endothelial and erythrocytes of the mammals. A wide variety of mammalian species including bats, dogs, cats, rodents, ruminants and terrestrial animals have identified as potential reservoirs and hosts for *Bartonella* species. Rodents found to serve as hosts for a majority of *Bartonella* species including zoonotic species like *B. elizabethae, B. vinsonii arupensis* and *B. washoensis* (21). Moreover, A high prevalence of *Bartonella* was also reported in rodents from different geographical areas. Rodent species such as *Rattus norvegicus* and *Rattus rattus* are the most frequent studied ones for *Bartonella* prevalence. *Bartonella* was also detected in other species rodents such as *Apodemus*, *Microtus*, *Bandicota*, *Mus* and *Myodes* (21).

The infections associated with *Bartonella* are mild to lethal conditions, which are collectively called as bartonellosis. A wide verity of infections often caused by *Bartonella* species in humans including endocardial, myocardial, vascular infections, ophthalmological and lymph infections. The rodent associated species *B. elizabethae, B. vinsonii arupensis* and *B. washoensis* were reported to cause endocarditis (22). The other species including *B. grahamii* was suspected to cause neuroretinitis and *B. tribocorum* was suspected to cause symptomatic fever, apathy and chronic fatigue (23). The list of rodents- borne zoonotic pathogens, their host reservoir and disease are given in Table 1.

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Table 1. Major zoonotic pathogens associated with rodents and their responsible diseases.

Zoonotic Pathogen		Microbial species	Rodent species	Associated diseases	Reference
			Bacterial		
1.	*Bartonella*	*B. tribocorum,* *B. queenslandensis,* *B. elizabethae*	*Rattus satarae* *Mus booduga* *Mus musculus*	Infective endocarditis, Neuroretinitis	(6, 24)
2.	*Coxiella*	*Coxiella burnetii*	*Apodemus* spp. *R. norvegicus* *Eutamias sibiricus*	Q fever	(25)
3.	*Orientia*	*O. tsutsugamushi*	*R. rattus* *S. murinus* *B. bengalensis.*	Scrub typhus	(26, 27)
4.	*Rickettsia*	*Rickettsia typhi* *R. rickettsii*	*R. rattus,* *A. agrarius*	Rickettsiosis, Murine typhus, Rocky mountain spotted fever	(26, 28, 29)
5.	*Leptospira*	NA	*Mus musculus,* *R. rattus*	Leptospirosis	(26, 30)
6.	*Yersinia*	*Yersinia pestis* *Y. pseudotuberculosis* *Y. enterocolitica*	*R. rattus,* *Indian Gerbil* *Rattus rattus,* *R. norvegicus*	Plague, Yersiniosis	(31-33) (34)
7.	*Borrelia*	*B. burgdorferi,* *B. afzelii* *B. garinii*	*P. xanthopygus,* *O. longicaudatus*	Lyme disease,	(35)
8.	*Mycobacterium*	*Mycobacterium tuberculosis* complex	*Mus musculus*	Tuberculosis	(5)
9.	*Listeria*	*Listeria* spp.	*Apodemus spp.* *Rattus spp.* *Bandicota indica*	Listeriosis	(36)
10.	*Salmonella* spp.	*Salmonella* spp.	*Mus Musculus, R. rattus, R. norvegicus*	Salmonellosis	(5)

11.	*Campylobacter*	*Campylobacter* spp.	*Sciurus anomalus*	Campylobacteriosis	(5)
12.	*Francisella*	*Francisella tularensis*	*Microtus paradoxus, Tatera indica*	Tularemia	(37)
13.	*Escherichia*	*E. coli*	*R. rattus, R. norvegicus*	*E. coli* enteritis	(38)
14.	*Ehrlichia*	*Ehrlichia* spp.	*Apodemus spp.*	Ehrlichiosis	(39)
15.	*Anaplasma*	*A. phagocytophilum*	*Apodemus spp.*	Anaplasmosis	(39)
16.	*Brucella*	*Brucella* spp.	*Apodemus spp Myodes glareolus*	Brucellosis	(40)
Viral					
1.	Hanta virus	Hantaan virus, Puumala virus, Dobrava virus, Seoul virus	Murinae rodents	Haemorrhagic fever with renal syndrome (HFRS)	(41, 42)
2.	Hepatitis virus	Hepatitis E virus	*Rattus spp.*	Hepatitis E	(42, 43)
3.	Rabies virus	Rabies virus	Rabid rodents	Rabies	(44)
4.	Nairovirus	Nairovirus	*Allactaga williamsi, Mus musculus, Meriones crassus*	Crimean-Congo haemorrhagic fever	(45)
5.	Lassa virus	Lassa virus	*Mastomys natalensis Mastomys erythroleucus Hylomyscus pamfi Mus baoulei*	Lassa fever	(46)
6.	Orthopoxvirus	Orthopoxvirus	*Myodes glareolus*	Smallpox	(39)
7.	Dobrava hantavirus	Dobrava hantavirus	*Apodemus flavicollis*	Hemorrhagic fever with renal syndrome (HFRS)	(39)

Epidemic Survey of Rodent Borne Diseases

Prevalence of diverse astroviruses, paramyxoviruses, hepeviruses and arenavirus was reported in both wild and synanthropic Kenyan rodents and shrews. Interestingly, majority of these viruses are found to be novel strains, and some belong to the families that contain important human viral pathogens. A novel arenavirus was detected in *Grammomys macmillani,* a rodent species newly identified to harbor arenavirus, and it potentially represent a novel arenavirus species (1). It was suggested that ChRCoV HKU24 represent the murine origin of *Betacoronavirus* 1, with interspecies transmission from rodents to other mammals having occurred centuries ago, before the emergence of human coronavirus (HCoV) OC43 in the late 1800s (Susanna K. P. Lau et al 2015). Rodents are likely an important reservoir for ancestors of lineage A *βCoVs* (47). Accumulating data suggest that some *Bartonella* spp, being evolutionary and ecologically associated with rats of the genus *Rattus*, have been dispersed from Asia to many seaports around the globe, where these bacteria have subsequently become established among domestic rats. Recent investigations in Thailand, China, Vietnam, Bangladesh, and Nepal have demonstrated that rats harbour strains genetically related to *B. elizabethae*, a species firstly identified from a human patient in the USA.

In Vietnam, rodents and bats liver and serum samples were examined for viral detection and found virus homologous to human hepatitis B, C, E viruses. Pegivirus and Hepacivirus-like viruses were frequently detected in the bamboo rat, *Rhizomys pruinosus*. The rodent hepacivirus-like viruses significantly diverged from currently classified variants and potentially represent a new species in the Hepacivirus genus (48). In a survey conducted in Iran, fast expansion of industry and agriculture and climate change throughout the globe led to change or increase in incidence of rodent-borne diseases (49). Considering the distribution of rodents throughout Iran, out of 70 known rodent-borne diseases 34 were reported in Iran. The rat borne diseases including plague, leishmaniasis and hymenolepiasis were the most frequent diseases occurred, and notable diversity in rodents was also observed, The survey suggested that it is crucial to pay more attention to control the spread of EIDs (49). Orthohanta viruses are the re-emerging rodent-borne pathogens circulating globally. In Germany, two stable PUUV strains were isolated from Central Europe and glycoprotein-specific monoclonal antibodies for this PUUV isolate was developed for future reservoir host studies (50).

The plague outbreak in Himachal Pradesh in 2002 was due to unhygienic lifestyle, hunting practices on rodents, and treatment practices through faith healers (51). The delay in the initiation of effective treatment of plague cases was a major factor that led to the spread of the disease (52). This report explained the unawareness of people resides in remote areas and emergency of survey on rodent-borne pathogens. Balakrishnan *et al*. (2008) suggested that zoonotic agents, especially *Bartonella* spp. are prevalent causative organisms of blood culture-negative endocarditis in India and recommended serologic screening for antibodies to zoonotic microorganisms as diagnostic tools for this disease in India (52).

High prevalence of leptospirosis in rodents in Mumbai and southern part of India (Kerala and Tamil Nadu) was detected, which proved possible role of these animals in transmission of leptospiral organisms to humans. Hence, it is imperative to take necessary control measures to prevent human leptospirosis (53). The zoonotic risks associated with *R. norvegicus* in wetland agroecosystems such as Kerala cannot be ignored in the wake of emerging zoonotic and fungal potent carrier of dermatophytes and other opportunistic fungi (54).

Gaps in Surveillance and Future Perspective

Rodents and bats are the largest group of mammalian species in the world, distributed globally and harbour a wide range of zoonotic pathogens. However, it has been neglected to investigate the prevalence and diversity of bacterial populations and viral pathogens distributed in rodent species. For example, discovering the entire viral diversity is estimated to cost about $6.4 billion. The cost of the 2002 SARS outbreak has been pegged at $54 billion and a severe flu pandemic could cost about $3 trillion. This may be due to poor domestic research and lack of international collaborations in this area, of which the latter driven by restrictive policies on sharing clinical and research materials are responsible for these incidences.

Surveillance and discovery programs of emerging infectious diseases in wildlife have identified rodents and shrews as natural reservoirs of diverse viruses such as hantaviruses, arenaviruses, astroviruses, picornaviruses, paramyxoviruses and others (55). For the first time, feline astrovirus was detected in rodent species, but this virus cause infections domestic cats only. These findings indicate possible cross-species infection of astroviruses between cats and rodents. Urbanization and disturbance of natural habitats have brought rodents in close contact with humans. Based on the literature survey, rodents might be the next source of zoonotic disease outbreaks.

Identification of known and novel pathogens in rodents and prevention strategies to control zoonosis transmission are the emerging and essential tasks for public health significance. As the frequency and prevalence of zoonotic diseases increase globally, investigation of how distribution of rodent hosts determines the patterns of disease transmission to human, and predicting which regions are at greatest risk for emergence of future zoonotic disease are two goals, which both require better understanding of the current distributions of zoonotic hosts and pathogens. Hence, there is a need to move from being reactive to proactively understanding zoonotic pathogens before they cause human disease. This will require preparedness by prior survey reports and strengthening inter-sectorial research on rodent borne zoonoses. Such type of research is useful in public health point of view.

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CONFLICT OF INTEREST
No conflict of Interest was found between authors.

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