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Review scientific paper

BACTERIAL, FUNGAL AND VIRAL ZOONOSES OF PETS

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Summary

Today, pets are the source of numerous infectious diseases that can be transmitted to humans, as a result of their increasingly frequent contact. The most important viruses with zoonotic potential include rabies and influenza viruses as well as rotaviruses and noroviruses. However, the importance of individual viruses varies depending on the climate and infectious disease control systems in certain countries. Dogs, cats, and other increasingly popular types of pets can transmit bacterial zoonotic agents to humans in various ways. In addition to known pathogens such as the bacteria causing leptospirosis, salmonellosis, campylobacteriosis, or brucellosis, the bacteria *Pasteurella multocida* and *Bartonella henselae* transmitted by bites or scratches are also significant in human pathology. There has been a significant increase in the prevalence of methicillin-resistant strains of *Staphylococcus aureus* in isolates originating from pets and the transmission of these strains between humans and animals requires special attention. Furthermore, fungi causing diseases such as sporotrichosis or dermatophytosis are linked to long-term and persistent infections in humans. The epidemiological situation caused by SARS-CoV-2, and the assumption of an interspecies jump of this virus from animals to humans, including its documented presence in domestic cats, dogs, tigers, and martens, have raised the question of the possibility of virus transmission from pets to humans. However, the current pandemic is caused exclusively by SARS-CoV-2 transmission in the human population, and these animals are not a source of infection for humans. A significant number of zoonoses originating from pets is a threat to public health, thus requiring the "One Health" approach through close cooperation between human and veterinary medicine to develop and implement effective health measures for both humans and animals. As part of responsible ownership, pet owners must be informed by veterinarians about measures to prevent infectious diseases and certain risks that are related to keeping certain species of animals.

Keywords: pets, zoonoses, bacteria, fungi, viruses

INTRODUCTION

Zoonoses are defined as infections/diseases that can be transmitted from wild and domestic animals to humans, and pose a constant threat to public health globally (Kahn, 2006). However, certain infections of bacterial, fungal, and viral etiology that are transmitted from animals to humans are considered zoonoses, although they pose a danger to human health only in certain cases. Over the past 15 years, humanity has faced more than 15 deadly zoonotic epidemics that have resulted in a loss of human lives and have had a detrimental effect on the global economy (Gebreyes, 2014). Despite the constant advances in biomedical sciences, infectious diseases considerably contribute to human morbidity and mortality worldwide and it has been estimated that zoonoses are responsible for 2.5 billion cases of diseases and 2.7 million deaths worldwide annually. Also, it is estimated that 75% of the emerging and reemerging infectious diseases have zoonotic potential (Krnjaić and Vuković, 2017; Gibbs, 2005). In the last few decades, the relationship between humans and pets has grown, supported by the fact that 23% of European households keep dogs as pets, 22% keep cats as pets, while in the USA, 1/3 of the population owns a pet (Cito et al., 2016). The relationship between humans and pets has health, emotional and social benefits (Hodgson, 2015). In addition, there is evidence of the impact of pets on the prevention of cardiovascular disease and stress reduction (Rabinowitz, 2007). In recent years exotic pets such as rabbits, ferrets, birds, guinea pigs, hamsters, and reptiles have become increasingly popular (Mani and Maguire, 2009). Zoonotic agents can be a source of infection for healthy people. However, the risk of infection is more pronounced in the immunocompromised people, children, pregnant women, and the elderly. Also, at increased risk are professionals who are professionally exposed, such as pet caregivers, veterinarians, butchers, farmers, zookeepers, and laboratory researchers (Kahn, 2006).

The increased incidence of emerging and reemerging zoonotic infectious diseases is caused by various anthropogenic factors, which include: environmental factors with an emphasis on climate change that affect the distribution of vector; changes in the ecosystem and human and animal population density; socioeconomic and political factors such as increased international travel and trade, social and economic inequality, poverty, conflicts and changes in economic development, as well as the increasing number and increasing intensity of interaction with pets (Gebreyes, 2014). Although zoonoses represent a global problem, their impact is more severe in developing countries due to high population density, lack of infrastructure and skilled workforce to control zoonoses, as well as a high percentage of immunocompromised people due to comorbidities, such as human immunodeficiency virus (HIV) (Gibbs, 2005).

Bacterial zoonoses

Bacterial zoonotic infections can be transmitted from animals to humans in various ways: animal bites and scratches, through feces, urine, and other secretions and excretions, via vectors such as mosquitoes, fleas, and ticks that can transmit the pathogen to humans in which case pets represent reservoirs for these pathogens (Cantas and Suer, 2014). The spread and importance of some bacterial zoonoses is growing globally, and some may

reemerge after having been considered eradicated or put under control. The development of antimicrobial resistance greatly contributes to this phenomenon, however, changes in people's lifestyle and closer contact with animals play an important role as well.

Bacterial zoonoses transmitted by bites and scratches

Healthy dogs and cats carry hundreds of different pathogenic bacteria in their oral cavities, therefore bacterial zoonoses are most commonly transmitted to humans through bites and scratches (Cantas and Suer, 2014). However, it is considered that the risk of infection is significantly higher after cat bites (60%) compared to dog bites (20%). Wound infections occurring due to dog bites are most often caused by aerobic microorganisms such as *Pasteurella multocida* (50%), alpha-hemolytic strains of streptococcus (46%), *Staphylococcus* spp. (46%), *Neisseria* spp. (32%), and *Corynebacterium* spp. (12%). However, there have been some cases in which anaerobic microorganisms have been the cause of wound infections: *Fusobacterium nucleatum* (16%), *Prevotella heparinolytica* (14%), *Propionibacterium acnes* (14%), *Prevotella intermedia* (8%), and *Peptostreptococcus anaerobius* (8%) (Abrahamian and Goldstein, 2011). Although these infections are generally treatable with antibiotics, complications in the form of bacteriemia or septic arthritis and osteomyelitis that arise as a result of a penetrating bite near the joints and bones are also possible (Cantas and Suer, 2014).

Cat scratch fever is a clinical syndrome caused by *Bartonella henselae,* a bacterium that is most often transmitted by cat scratches and bites, as well as by direct contact of damaged skin or sclera with cat saliva (Cantas and Suer, 2014). *Bartonella* spp. are aerobic, Gram-negative, intracellular bacilli. There are approximately 20 species of *Bartonella* spp, of which, at least 8 cause disease in humans (Mani and Maguire, 2009). These bacteria are transmitted and maintained in the cat population through the cat flea *Ctenocephalides felis*. During feeding, the fleas ingest these bacteria, which are then excreted through their feces. Human infection occurs by direct inoculation of contaminated flea feces into a wound, most often by cat scratches. Dogs and cats can be asymptomatic carriers, while in some cases, various clinical symptoms can be detected. Human bartonellosis may be present in a subclinical form, while common symptoms of cat scratch fever include the appearance of papules and pustules at the inoculation site, lymphadenopathy, fever, and malaise (Chomel et al., 2006). It has been noted that in the USA alone, around 22.000 people get infected by this bacterium annually (O'Neil, 2018).

Pasteurella multocida and *Pasteurella canis* are facultative anaerobic Gram-negative bacilli and are part of the normal microflora of the oral cavity and upper respiratory tract of dogs and cats. Through dog and cat bites this pathogen penetrates deep into the soft tissue, sometimes even reaching the bone tissue and in some cases in immunocompromised individuals, the process can become generalized, accompanied with bacteriemia. It has been suggested that the risk of human infection after cat bites is up to 10 times higher compared to dog bites (Morgan, 2005).

Capnocytophaga spp. are Gram-negative rods, part of the normal oral microflora in dogs and cats, and consequently, these animals are reservoirs for *C. canimorsus*, *C. cyanoderma* and *C. cynodegmi*. Transmission to humans occurs through bite and scratch

wounds. Sepsis, shock, disseminated intravascular coagulation and death can occur as a consequence of an infection in immunocompromised individuals, while healthy individuals rarely develop serious symptoms (Janda et al., 2008).

Gastrointestinal zoonoses

Infectious diarrhea of bacterial etiology in pets is most often caused by *Salmonella* spp. *Escherichia coli*, *Shigella* spp., *Campylobacter* spp., and *Yersinia enterocolitica*. Bacteria that cause enteropathogenic zoonoses can be present in both diseased and clinically healthy animals and can be transmitted from pets to humans by the fecal-oral route (Cantas and Suer, 2014). Data has shown that raw pet foods increase the risk of human exposure to enteropathogenic bacterial species.

Campylobacter spp. are microaerophilic, Gram-negative, motile microorganisms, with *C. jejuni* and *C. coli* being the most common species infecting dogs, cats, and humans (Greene, 2011). The risk of infection with these bacteria is higher in young animals and pets from shelters or kennels (Mani and Maguire, 2009). The clinical symptoms of this infection in dogs and cats are most often manifested in the form of gastroenteritis accompanied by diarrhea, although hepatopathies and abortions can occur. In addition to the mentioned clinical manifestations, certain complications in the form of septic arthritis, septicemia, meningitis, Guillain Barre syndrome, and myocarditis are possible in humans (Greene, 2011). The prevalence of *C. jejuni* in animal feces is high and is about 40% in dogs and cats (Wieland et al., 2005), while in birds it is about 19% (Lopez et al., 2002).

Salmonella spp. are Gram-negative, facultatively anaerobic bacilli and cause a large number of diseases in both animals and humans. Cats are most commonly infected through infected birds, while dogs get infected by ingesting pig-based foods or by consuming raw food (Cantas and Suer, 2014). Pets are most often asymptomatic carriers of these bacteria, while the clinical manifestation of this disease can occur if there is a decline in the immune response. The disease manifests with acute diarrhea, gastroenteritis, less often with septicemia with a lethal outcome. Complications such as osteomyelitis, endocarditis and meningitis are more common in humans (Greene, 2011).

Vector-borne bacterial zoonoses

Many vector-borne zoonoses are considered emerging infectious diseases, which either appear for the first time or spread rapidly in a certain area. The ecology of zoonotic bacterial diseases transmitted by vectors is complex, given that climate factors affect the distribution of vectors, and thus the dynamics of pathogen transmission (Cantas and Suer, 2014). The most common bacterial pathogens identified as causes of vector-borne infections in recent decades in the EU are *Rickettsia* spp., *Anaplasma phagocytophilum*, *Borrelia burgdorferi*, *Bartonella* spp., and *Francisella tularensis* (Vorou et al., 2007).

Lyme disease, the most commonly diagnosed zoonosis transmitted by ticks, is an infectious disease caused by spirochetes from the *Borrelia burgdoferi sensu lato* group, which in Europe is predominantly transmitted by ticks of the genus *Ixodes*. The presence of the agent of Lyme disease has been detected in 20-40% of *Ixodes ricinus* ticks in Serbia (Potkonjak et al., 2016).

In the last two decades, the extent and importance of tick-borne rickettsiae have increased, and the complex of diseases they cause has become an ideal paradigm for understanding and studying emerging and reemerging infections. The agent of granulocytic anaplasmosis is *Anaplasma phagocytophilum*, a Gram-negative, obligatorily intracellular bacteria maintained between ticks and vertebrate hosts in nature. In the Republic of Serbia, the presence of its genome in the tick species *Ixodes Ricinus* and *Dermacentor reticulatus* has been documented (Potkonjak et al., 2013).
Francisella tularensis is a Gram-negative aerobic bacillus, whose natural hosts are subclinically infected rodents. Cats are more susceptible to infection than dogs. The transmission of the mentioned pathogen to humans from infected animals occurs through fleas and ticks (Greene, 2011).

Bacterial zoonoses transmitted by secretions and excretions

Bordetella bronchiseptica is one of the causative agents of infectious cough in dogs and is especially important in kennels or shelters. Tracheobronchitis is the most common clinical manifestation in dogs, while immunocompetent individuals usually do not develop clinical symptoms when infected with this pathogen (Mani and Maguire, 2009).
Leptospira spp. are spiral bacteria that cause many diseases important for veterinary medicine, and dogs can act as reservoirs of *L. canicola*, *L. batavie*, and *L. icterohemorrhagiae* (Greene, 2011). These bacteria are excreted through urine, and infection in humans occurs through direct contact with contaminated excretions, water, or soil. Cats are usually asymptomatic carriers of these bacteria, while in dogs, the disease manifests with fever, accompanied by hepatitis, kidney inflammation, and pneumonia. Exotic pets can also be a source of infection for humans, given that the bacteria have also been isolated from the urine of reptiles (Ebani et al., 2017).
Brucella canis is an intracellular coccobacillus that causes reproductive disorders in infected dogs and is transmitted and maintained in dog populations by direct contact. Humans are most often infected by contact with secretions and excretions of infected animals, however, the disease is most often asymptomatic, except in immunocompromised individuals (Adler et al., 1977).
Mycobacteria are acid-alkali-resistant, aerobic, and facultatively anaerobic bacteria. *M. avium subsp. Avium* is widespread in domestic and wild bird populations, including canaries, parrots, and pigeons. Clinical signs in birds and carnivores are nonspecific and depend on the location of the granuloma. *M. avium complex*, as well as *M. genavense*, can colonize the airways of humans causing pneumonia, which is especially important in patients with chronic diseases (Greene, 2011). Parrots can be infected with *M. tuberculosis*, while cattle can transmit *M. bovis* and *M. tuberculosis* to dogs and cats which can consequently represent a source of infection for humans (Krnjaic et al., 2014; Mani and Maguire, 2009). Furthermore, reptiles can be an infection source for non-tuberculous mycobacteria that cause granulomatous changes in humans. Symptoms in reptiles are mostly nonspecific and manifested as loss of appetite and weight loss (Ebani et al., 2017).

Antibiotic resistant bacteria

The main cause of the increase in antimicrobial resistance is considered to be the evolutionary response to selective pressure resulting from excessive and improper use of antibiotics in veterinary clinical practice (WHO, 2020). In addition to farm animals, pets have an important role in spreading antimicrobial resistance, primarily due to their close contact with humans. Moreover, some antibiotics banned for farm animals, are allowed in pets. This primarily refers to antibiotics used in human medicine (Todorović et al., 2015; Krnjaić et al., 2005; Guardabassi et al., 2004). Various studies have shown that pet owners have a 6-fold higher risk of coming into contact with ESBL (extended-spectrum beta-lactamases) producing *E. coli*, in comparison with people who do not own pets (Meyer et al., 2012). In addition, several species of carbapenemase-producing bacteria have been isolated from clinical material of pet origin (Johnson and Woodford et al., 2013). Recently, an increased prevalence of antimicrobial resistance of isolates originating from infected human wounds resulting from animal bites has been reported. The most commonly isolated species of bacteria are methicillin-resistant staphylococci, which, in most cases, originate from pets. This is one of the reasons for pets being considered as the main source of methicillin-resistant strains of *Staphylococcus aureus* (O'Neil, 2018).

Fungal zoonoses

Systemic fungal infections occur in both animals and humans, some of the most common etiologic agents of these mycoses being *Blastomyces dermatiditis*, *Histoplasma capsulatum*, and *Coccidioides immitis*. Infection with *B. dermatiditis* in humans and animals can occur by inhalation of infectious conidia, whereas in rare situations, infected dogs can transmit it through bites (Greene, 2011). The dimorphic saprophytic fungus *Sporotrix schenckii* is the agent of sporotrichosis, which is manifested through the appearance of ulcerative nodules and papules on the skin of infected cats and humans. Humans are most often infected through direct contact with cats or contaminated material.

The etiologic agents that cause dermatophytosis, *Microsporum* spp. and *Trichophyton* spp. can be present on the skin of healthy cats and dogs. Transmission to humans can occur through direct contact with infected animals (Mani and Maguire, 2009). The disease is clinically manifested as erythematous, circular, or oval lesions accompanied by pruritus and hair loss (O'Neil, 2018). *Malassezia pachydermatis* is part of the normal cutaneous microflora of dogs and cats. However, there have been reports of granulomas and infections in young and immunocompromised individuals infected with this microorganism (Mani and Maguire, 2009).

Cryptococcus neoformans var. neoformans is a fungus most often isolated from bird feces, especially pigeons, which are consequently the most common source of infection for cats. The infection can occur through inhalation of infectious forms or the skin. *C. neoformans* is a significant opportunistic pathogen that causes meningitis in immunocompromised individuals (Greene, 2011; Mani and Maguire, 2009).

Viral zoonoses

One of the most significant viral zoonoses is caused by the rabies virus belonging to the genus Lyssavirus and Rhabdoviridae family. It is estimated that more than 60,000 human lives are lost globally every year as a result of this viral infection. However, it is considered that this data is not relevant on a global level since occurrences of this infection are more frequent in some Asian and African countries (Baxter, 2012). It has been estimated that in areas where rabies is endemic, a person dies of rabies every 10-20 minutes, and 40-50% of these victims are children under the age of 15. In over 99% of cases, rabies virus transmission occurs after a dog bite (Fooks et al., 2014). Infected foxes are considered especially dangerous in terms of virus transmission to domestic animals and humans because infected animals change their behavior when approaching populated areas. The last case of human rabies in the Republic of Serbia was recorded in 1980 (Lalošević and Lalošević, 2001).

Noroviruses and rotaviruses are transmitted by direct contact between humans, as well as contaminated food and water. Since these are RNA viruses with relatively high mutation rates, they are considered potential zoonoses (Drummond et al., 2003). Rotavirus infections are some of the most common causes of acute gastroenteritis in humans and numerous animal species worldwide. These viruses belong to the family *Reoviridae* and possess a genome consisting of segmented double-stranded RNA, which is considered to be a predisposition for frequent occurrence of point mutations and genetic recombination. According to literature, there is a possibility of genetic rearrangement between animal and human rotaviruses as a consequence of cohabitation and close contact. Moreover, there have been indications that the virus can cross the species barrier (Martella et al., 2010). However, even in extremely rare cases when a virus does cross the species barrier, a sufficiently high viral titer is not established, which is crucial for its further transmission in the novel host population (Malik et al., 2020). Noroviruses belong to the family *Caliciviridae* and represent one of the most common causes of gastroenteritis of viral etiology in the world. Due to their great genetic and antigenic diversity, as well as the fact that they have been detected in numerous different hosts such as humans, wild and domestic animals, including pets, noroviruses are considered to have the ability to cross the species barrier. Nevertheless, to date, the presence of animal noroviruses in human samples has not been recorded, and the only available data refer to individual serological tests which suggested a certain level of seroprevalence against canine noroviruses in humans (Villabruna et al., 2019; Mesquita et al., 2013).

Lymphocytic choriomeningitis is a zoonotic disease caused by viruses of the *Arenaviridae* family, in which pet rodents are the primary source of infection for humans. Transmission takes place through direct contact with secretions and excretions of infected animals, or bites from infected animals. Immunocompromised individuals and pregnant women are considered to have a higher risk of infection (Mani and Maguire, 2009).

In the last 20 years, two new influenza virus variants pathogenic for dogs have been detected, with the H3N8 virus having been detected in the United States as a variant of equine influenza, and H3N2 in Asia as a consequence of transmission of an avian influenza virus to the canine population. Both viruses cause mild respiratory disease in

susceptible hosts and are important in large agglomerations of animals (Parrish and Voorhees, 2019). Influenza viruses possess a high degree of variability but one of their most significant traits is the ability to cross the species barrier. For this reason, the literature suggests that the possibility of human infection with a newer strain cannot be completely ruled out, which implies that immunocompromised individuals should avoid contact with infected dogs (Mani and Maguire, 2009).

Viruses from the *Coronaviridae* family possess a single-stranded and non-segmented RNA genome inside the capsid, whereas their coat contains glycoproteins arranged in the appearance of a crown (lat. *corona*), among which the most important and most variable is the S protein whose characteristics determine the ability of coronaviruses to adapt to new hosts (Nišavić et al., 2020; Nišavić and Milić, 2017). SARS-CoV-1 and MERS-CoV viruses are thought to have originated from animals that have been in close contact with humans and have acted as reservoirs of the virus. Given the current global epidemiological situation caused by SARS-CoV-2 and the presumption that this virus crossed from animals to humans further emphasizes the importance of coronaviruses in both veterinary and human medicine. There are several hypotheses about the origin of SARS-CoV-2 and the potential reservoir host, however, bats are considered the most likely source of this virus. Furthermore, snakes, turtles, and certain rodents have been suggested as potential virus hosts. The presence of SARS-CoV-2 has also been detected in domestic cats, dogs, tigers, and martens, and it is necessary to emphasize that these animals do not represent a source of infection for humans and that the current pandemic is solely due to virus transmission in the human population (Nišavić et al., 2020).

Most common zoonoses of exotic pets

Keeping exotic birds as pets has become increasingly popular in Europe in recent decades. The most common bacterial infections transmitted from birds to humans are chlamydiophilosis, campylobacteriosis, and salmonellosis (Evans, 2011).

Chlamydiosis or psittacosis is caused by the Gram-negative, coccoid intracellular parasite *Chlamydophila psittaci* found in the respiratory tract of birds. Transmission occurs via feces and other secretions originating from these animals, however, dust inhalation, dandruff, and nasal secretions of infected birds are most important for transmission to humans. Animals can be asymptomatically infected, although the development of a wide range of clinical symptoms has been well documented (Mani and Maguire, 2009). Besides birds, reptiles are potential reservoirs of chlamydia given that *C. psitaci, C. abortus, and C. pneumoniae* have been isolated from clinical material of turtle origin (Ebani, 2017). It is estimated that the population of reptiles kept as pets in Europe exceeds 7 million (Corrente et al., 2017). The results from one study suggest that 74,000 salmonella infections per year have been associated with reptiles and amphibians acting as infection sources (Mermin et al., 2004). However, most of these infections have been observed in children, the elderly, or immunocompromised individuals (Corrente et al., 2017). The infection caused by *S. enterica* in reptiles is most often asymptomatic, which does not diminish their importance in the transmission of this pathogen to humans (Bošnjak et al., 2016; Rijks et al., 2016). Examination of cloacal swab samples from

different reptile species revealed the presence of salmonella in clinically healthy animals, namely in 54.2% of snakes, 66.6% of lizards, and 30% of turtles (Corrente et al., 2017).

CONCLUSION

Pets are a potential source for more than 70 diseases important to human medicine, however, this number is thought to be underestimated given the molecular and epidemiological evidence of interspecies pathogen exchange, especially for antibiotic-resistant bacterial strains. Additionally, in many cases, animals are subclinically infected carriers of certain pathogenic microorganisms. One of the crucial aspects related to the control of zoonoses is the development of adequate risk management methods based on scientific data. To achieve this task, a tripartite initiative has been launched by the international organizations Food and Agriculture Organization (FAO), World Health Organization (WHO) and World Organization for Animal Health (OIE), which jointly follow a holistic multidisciplinary approach "One Health“. Namely, the fact that zoonotic agents can infect both animals and humans, as well as the consequent need to develop an effective implementation plan for the "One Health" program, indicate the necessity for analyzes that will aid in the development and sustainability of synergies between human and animal health and the ecosystem. For this reason, veterinarians and physicians need to constantly assess and monitor the dynamic state of infectious diseases. Contributions from these professions and adherence to the recommendations highlighted in the “One Health” concept should result in improved zoonosis surveillance, prevention, and control strategies. The problem of zoonosis control has also been recognized by the European Union as the funder of a project called Companion animal multi-sectorial interprofessional and interdisciplinary strategic think tank on zoonoses (CALLISTO) aiming to reduce zoonotic diseases in pets. The project aimed to promote principles of responsible ownership, informing the public about the risk and prevention of zoonoses, political and research actions, development of a system for identification and registration of pets, zoonotic surveillance program, as well as an increased focus on the health status of animals entering the EU from developing countries. Also, testing for pathogens in less studied, exotic animals has been increased, as well as constant monitoring of the potential presence of antibiotic-resistant bacteria in pets. In this regard, control of the treatment of pets with antibiotics used in human medicine has been established, with the parallel development of new approaches to antimicrobial therapy of animals. Strategies for the prevention of human zoonotic infections, in addition to the mentioned systemic solutions, also include various mechanisms that are realized at the individual level. For example, careful monitoring of the interaction between children and animals, mandatory reporting of bites, public education on responsible ownership, regular shortening of claws, and improved oral care for pets is necessary, all to reduce human exposure to potentially pathogenic microorganisms. Personal hygiene is certainly one of the most important factors in preventing infections and washing hands thoroughly with soap after having been in contact with animals, as well as before meals or drinks, avoiding mouth-to-mouth contact, can help prevent the potential transmission of infectious agents to humans. Important prevention measures include isolation of sick animals before discovering the

etiology of the disease, education of owners by veterinarians, rational use of antibiotics in pets, and respect for the principle of responsible ownership, which, among other things, include regular vaccination and regular treatment with antiparasitic drugs.

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