The microbiome of bat guano: for what is this knowledge important?

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Abstract
Bats as flying mammals are potent vectors and natural reservoir hosts for many infectious viruses, bacteria, and fungi, also detected in their excreta such as guano. Accelerated deforestation, urbanization, and anthropization hastily lead to overpopulation of the bats in urban areas allowing easy interaction with other animals, expansion, and emergence of new zoonotic disease outbreaks potentially harmful to humans. Therefore, getting new insights in the microbiome of bat guano from different places represents an imperative for the future. Furthermore, the use of novel high-throughput sequencing technologies allows better insight in guano microbiome and potentially indicated that some species could be typical guano-dwelling members. Bats are well known as a natural reservoir of many zoonotic viruses such as Ebola, Nipah, Marburg, lyssaviruses, rabies, henipaviruses, and many coronaviruses which caused a high number of outbreaks including ongoing COVID-19 pandemic. Additionally, many bacterial and fungal pathogens were identified as common guano residents. Thus, the presence of multi-drug-resistant bacteria as environmental reservoirs of extended spectrum β-lactamases and carbapenemase-producing strains has been confirmed. Bat guano is the most suitable substrate for fungal reproduction and dissemination, including pathogenic yeasts and keratinophilic and dimorphic human pathogenic fungi known as notorious causative agents of severe endemic mycoses like histoplasmosis and fatal cryptococcosis, especially deadly in immunocompromised individuals. This review provides an overview of bat guano microbiota diversity and the significance of autochthonous and pathogenic taxa for humans and the environment, highlighting better understanding in preventing emerging diseases.

Key points
• Bat guano as reservoir and source for spreading of autochthonous and pathogenic microbiota
• Bat guano vs. novel zoonotic disease outbreaks
• Destruction of bat natural habitats urgently demands increased human awareness

Keywords Bat guano · Microbiota · Zoonoses · Pathogens · Disease outbreaks

Introduction
Bats (Chiroptera) are a diverse group of mammals with more than 1400 different species with abilities to inhabit various ecological niches and environments (Winter et al. 2016; Gorbunova et al. 2020). Although bats are geographically widespread, the ecology of their microbial communities and the role involved in bat health and behavior are scarce, especially on the microbiota residing in bat’s excreta accumulated in the form of guano, which could be potentially involved in pathogen transmission to humans (Dietrich et al. 2018; Dietrich and Markotter 2019). Bats revealed versatile feeding behavior; they have a flying capacity and inherent characteristics which makes them as highly potent vectors and natural reservoir hosts for many pathogens. Furthermore, it is quite clear that humans and bats are cross-visitors of each other’s habitats! The main assumption is that these flying mammals visit human settlements more often than humans visit their...
natural habitats. Based on this hypothesis, the question arising is "Could the frequent visitations of these animals in urban areas affect human health?" Accelerated urbanization and the destruction of natural habitats inevitably lead to increased risk of zoonotic diseases. It is known that zoonotic pathogens, especially new or still unexplored, can easily spread to humans through any contact point with animals or their excreta, as well as through markets selling the meat or by-products of wild animals (WHO 2020). Also, deforestation and encroachment of natural habitats leads to reduced feeding bat habitats forcing them to find alternative sites in peri-urban landscapes and with simultaneous less awareness in building communities’ resilience to future outbreaks can increase human exposure to zoonotic disease reservoirs allowing pathogens transfer to other species (United Nations Environment Programme and International Livestock Research Institute 2020). Additionally, climate changes as a force of nature can rapidly influence the geographic distribution and abundance of bats species and increase the incidence of the vector-borne and zoonotic diseases (Wells and Clark 2019). Inter-species transmission of the pathogens is a consequence of the contact between bats and other animals including humans, which potentially could result in disease outbreaks. Primarily, bats are contemplated as the reservoir of many viruses and diseases outbreaks caused by SARS coronavirus (SARS-CoV) (Tsang et al. 2003), Marburg virus (MARV) (Calisher et al. 2006), MERS coronavirus (MERS-CoV) (Kupferschmidt 2013), Nipah virus (NiV) (Luis et al. 2013), Ebola virus (EBOV) (WHO Ebola Response Team 2014), Australian bat lyssavirus (ABLV), Hendra (HeV) and Menangle (MenPV) viruses, and current COVID-19 pandemic, for which is not yet proved that bats transmit SARS-CoV-2 to humans (United Nations Environment Programme and International Livestock Research Institute 2020). Contrary to it, bat guano has been recognized as a potential source of bacterial and fungal pathogens. Furthermore, it is well known that, in many regions of the world, bat guano is precisely used in agriculture, frequently as patented and presented on the market, as organic biofertilizer in order to positively affect overall soil fertility (Grantina-Ievina and Levinsh 2015; De Leon et al. 2018). However, in areas with a high use of guano as biofertilizer, agricultural workers could be at increased risk by contact with guano-harbored foodborne pathogens, which also could easily contaminate food products or infect livestock. Due to easy spread of pathogens into the environment with the interaction with other animals, intake of raw food, or water contamination and possible infection of humans, knowledge on the bats guano microbiota is highly important (Wolkers-Rooijackers et al. 2019). The presence of pathogenic enteric bacteria and other bacterial pathogens common in human and animal diseases such as species of Pasteurella, Salmonella, Shigella, Escherichia, Klebsiella, Proteus, Yersinia, Hafnia, Serratia, Staphylococcus, and Campylobacter genera among many others in different cave- and building–dwelling bat guanos (Sridhar et al. 2006; Mühldorfer 2013; Banskar et al. 2016; Wolkers-Rooijackers et al. 2019; Dimić et al. 2020; Gerbáčová et al. 2020) has already been confirmed. Furthermore, some other bacterial species from genera Bartonella, Borrelia, Leptospira, Pseudomonas, Enterobacter, Acinetobacter, Bacillus, Arthrobacter, and Micrococcus, related to bat guano, can indicate novel species-specific bat-dwelling bacteria with medical importance to humans (Lei and Olival 2014; Veikkolainen et al. 2014; Banskar et al. 2016; Dimić et al. 2020). Additionally, guano has also been recognized as a potential source of various dimorphic fungal pathogens, including endemic Histoplasma capsulatum, Coccidioides spp., Blastomyces dermatitidis, Cryptococcus neoformans, and opportunist pathogens from genera Candida, Meyerozima, Trychophyton, Trychosphoron, Microsporum, Sporotrix, Chrysosporium, Geomyces, Aspergillus, Penicillium, and Fusarium (Sugita et al. 2005; Ulloa et al. 2006; Ogórek et al. 2016; Cordero et al. 2016; Dimić et al. 2020; Rodrigues et al. 2020). It should be pointed out that bats themselves are reservoirs for many infectious agents, including viruses, bacteria, and fungi, which could also be detected in guano (Fig. 1). Hence, the sampling of guano is a noninvasive and more convenient approach, in contrast to direct examination of bats, which can also be carried out even when bats hibernate (Ogóreck et al. 2016).

This paper provides a new systematic review of the literature within the context of various quantitative and qualitative bat guano microbiota diversity researches, emphasizing the presence and significance of autochthonous phylogenetically different lineages and potential pathogenic taxa for humans and the environment. This could be very important in terms of biodiversity preservation and understanding how we can provide a protection of humans from emerging infectious diseases.

**Bat (guano) virome**

Bats are well known as a natural reservoir of many zoonotic viruses, including lyssaviruses, causative agents of rabies, henipaviruses, severe acute respiratory syndrome coronavirus, and Ebola virus (Li et al. 2010a). Their ability to host different viruses is enabled by their wide geographical distribution, migratory and feeding habits, and in many cases, high population density (Wibbelt et al. 2009). In several recent studies based on metagenomic analyses and other methods, more than 80 species of viruses were isolated or detected. Besides already mentioned, these species include adenoviruses, adenovirus–associated viruses, herpesviruses, astroviruses, and polyomaviruses (Chu et al. 2008; Misra et al. 2009; Li et al. 2010b). The study of the presence of viruses in guano samples...
from several insectivorous species of bats revealed a great diversity of identified virus species (Li et al. 2010a). These groups include animal viruses from the families Parvoviridae, Circoviridae, Adenoviridae, Poxviridae, Picornaviridae, Astroviridae, and Coronaviridae and bacteriophages from the families Siphoviridae and Microviridae. The same study also showed that bat guano virome contained plant and fungal viruses from Luteoviridae, Secoviridae, Tymoviridae, and Partitiviridae families, and the Sobemovirus genus. Within detected families, some species are particularly interesting; Cyclovirus, a new genus from the family Circoviridae contains viruses with covalently closed circular single strand DNA (ssDNA) genomes. These viruses were detected in cerebrospinal fluid samples from patients with unexplained paraplegia in Malawi (Smits et al. 2013). In the case of bat cyclovirus GF-4 identified in the samples of guano, a phylogenetic analysis of the Rep protein sequence placed this virus within the group of known cycloviruses as the distinctive species. In another study, metagenomic analysis of insectivorous bat guano in Hungary showed the presence of viruses from the order of Picornavirales. In tested samples, the aphid lethal paralysis virus (ALPV) and Big Sioux River virus (BSRV) were detected in Hungary for the first time (Zana et al. 2018). Additionally, among others, rabies viruses also are the part of the bats’ virome. Rabies is the zoonotic disease that is, if not treated, fatal for all mammals including humans. The causative agent of disease is the rabies virus (RABV), an RNA virus that belongs to the genus Lyssavirus within the family Rhabdoviridae. Bats are the main natural reservoirs of the rabies viruses; until now, 64 species of bats were reported positive for RABV worldwide, including insectivorous, frugivorous, and hematophagous species (Jiménez et al. 2017). Bat species that can carry rabies virus can be found in South and North America, as well as in Africa, in Western and Southeastern Europe. There have been only several recorded deaths of humans in Europe caused by the bite of rabies-infected bats (Lina and Hutson 2006). In most cases, humans can be infected if bitten by the domestic cats that are the main predators of bats. Although the rabies is a generally eradicated disease, in the United States, bats are responsible for 7 out of 10 rabies deaths, according to the U.S. Centers for Disease Control and Prevention.

**Bat’s coronaviruses**

Bat’s virome and relationships between bats and viruses, including more than 200 novel coronaviruses are very likely specific to the bat species (Calisher et al. 2006; Vijaykrishna et al. 2007; Ksiazek et al. 2003).
Since the new bat viruses, isolation has already proven to be difficult, current SARS-CoV-2 pandemic, still unexplored in transmission to humans, required extent detection in bats and sequencing of their genomes. Coronaviruses are the group of lipid-enveloped, single-strand RNA viruses (positive strand) with the genome size from 27 to 32 kb, among the largest of all RNA viruses’ genomes. Several recent studies indicated that bat coronaviruses represent the source of human coronaviruses such as SARS-CoV and MERS-CoV. Coronaviruses were isolated from the samples of bat guano of common flying fox (Pteropus medius) in Sri Lanka (Kudagammana et al. 2018). These viruses showed more than 97% of nucleotide sequence identity with coronaviruses detected in fruit bat Cynopterus sphinx and insectivorous bats Scotophilus heathii and Scotophilus kuhlii bats in Thailand. Although the lineage D of betacoronaviruses detected in this study represent the group of coronaviruses that was until now confined to bats, they might evolve to new strains potentially pathogenic to humans, since in some parts of South Asia, they are hunted and consumed as food. Besides that, bat guano is also collected and sold as fertilizer in some countries, including Thailand, Indonesia, Mexico, Cuba, and Jamaica. In samples of bat guano fertilizer in Thailand, a betacoronavirus from group C was isolated (Wacharapluesadee et al. 2013). This practice can represent the serious health risk to guano miners and, without the use of preventive measures, expose them to zoonotic pathogens. Coronaviruses were also detected in the bat guano samples and rectal swabs in Myanmar (Valitutto et al. 2020). In this study, three novel alphacoronaviruses, three novel betacoronaviruses, and one previously identified alphacoronavirus were detected for the first time in bats in Myanmar. Novel lineages of alphacoronaviruses were also detected in bat guano samples collected from caves on several locations in Kazakhstan (Mendenhall et al. 2019).

**Bat (guano) bacteriome**

In the last decade, composition of bacterial communities from bat guano has begun to intensively be characterized. In the focus of investigations were guano sampled from fresh fecal samples or guano piles in different places such as caves, buildings, and church towers. Also, surveys were based on bats’ gu as the primary source of guano bacteria. Significant bacterial diversity was detected in guano samples that varied in detected genera among analyzed bat species, sample types (fresh feces or guano piles), and sampling points of investigated caves or guano layers (Table 1).

In general, representatives from the phyla Proteobacteria and Firmicutes were detected as dominant groups in the bat guano or fresh feces samples collected from mist-netted bats. Culture-based analysis indicated that common genera in guano, regardless of the sample and sampling location, were *Staphylococcus*, *Lactococcus*, *Enterobacter*, and *Bacillus* (Banskar et al. 2016; Newman et al. 2018; Gerbáčová et al. 2020). These common genera are also detected as dominant in the gut of *Rhinolophus monoceros* (Selvin et al. 2019), with the exception of *Lactococcus* sp., which could be explained by culture method bias. Identified common taxa in guano from different bat species and sample types indicate that bat gut is the basis of the dominant bacterial genera. Other bacterial representatives are probably influenced by environmental factors. Besides valuable information provided by cultivation methods, traditional use of culturable media has limitations to comprehensively analyze whole microbial diversity (Abdelfattah et al. 2018). Thus, using high-throughput sequencing (HTS) as a tool to investigate bacterial communities of guano enabled detailed studies of these extreme microhabitats (Knight et al. 2018). In guano samples, originated from bats with different diets and different geographic regions (the USA, India, and China), by HTS genera *Weissella*, *Lactococcus*, *Enterococcus*, *Bacillus*, and *Arthrobacter* as common were detected (Banskar et al. 2016; Li et al. 2018; Newman et al. 2018). That indicated these species as potential typical members of guano.

From the aspect of clinical significance, bacteria originating from guano could be divided into four groups. Enteric foodborne and other pathogens includes genera *Escherichia*, *Enterobacter*, *Yersinia*, *Hafnia*, *Serratia*, *Staphylococcus*, *Streptococcus*, *Pseudomonas*, *Rahnella*, *Micrococcus*, *Acinetobacter*, and *Arthrobacter*. Among common zoonotic pathogens, following genera *Bartonella*, *Borrelia*, *Leptospira*, *Campylobacter*, *Clostridium*, and *Bacillus* were recognized. Group of unusual Gram-negative bacterial pathogens, in relation to atypical cell structure, includes genera *Mycoplasma*, *Ureaplasma*, *Rickettsia*, *Anaplasma*, and *Chlamydia*. Extended spectrum beta-lactamase (ESBL) and carbapenemase-producing *Enterobacteriaceae* (CPE) as a group of multiple drug-resistant bacterial pathogens are detected in several studies in guano which originated from different bat species. Many studies have, so far, identified pathogens as common guano residents (Veikkolainen et al. 2014; Banskar et al. 2016; Wolkers-Rooijackers et al. 2019; Gerbáčová et al. 2020). Therefore, guano piles are recognized as potential reservoirs of spreading zoonoses. Recently, two studies have characterized and compared the composition of bacterial communities in different layers of guano piles (Newman et al. 2018; Dimkić et al. 2020). Bacterial population shift was detected throughout the guano pile as nutritional composition and environmental factors have changed, from aerobic to anaerobic. Different distributions of bacterial taxa in layers were detected between studied caves, but common genera were identified as *Bacillus* and *Enterococcus*. Microbial diversity of bat guano is driven by different factors such as diet type and reproductive stage of the host (Phillips et al. 2012; Gaona et al. 2019). Also, caves as typical bat
| Reference                     | Sample origin                                                                                                                                                                                                 | Identification method                        | Distribution of most abundant taxa                                                                 |
|-------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------------------------------------------------------|
| Banskar et al. 2016           | Bat feces samples of *Roussetus leschenaultii* collected at the Robber’s Cave, Maharashtra, India                                                                                                              | Cultivation method                            | Enterobacter, Enterococcus, Escherichia, Lactococcus, Staphylococcus, Serratia, Weissella, Citrobacter, Acinetobacter |
| Selvin et al. 2019            | Samples from *Rhinolophus monoceros* gut, The Arwah Cave, Meghalaya, India                                                                                                                                     | Cultivation method                            | Staphylococcus, Bacillus, Hafnia, Brevibacillus, Pseudomonas, Serratia, Enterobacter               |
| Newman et al. 2018            | Bat guano sampled from different guano layers, lava tube cave, Sierra County, United States                                                                                                                   | Cultivation method                            | Microbacterium, Enterococcus, Bacillus, Pantoena, *Bacillus* spp., Bacillus, Staphylococcus, Weissella, Streptomyces, Deinococcus |
| Gerbačová et al. 2020         | Feces samples, building–dwelling insectivorous bat species (*Myotis myotis*, *Rhinolophus hipposideros*), twelve locations in central Slovakia                                                              | Cultivation method                            | Enterococcus, Lactococcus, Lactobacillus, Pseudomonas, Paenibacillus, Bacillus, Staphylococcus   |
| Dimkić et al. 2020            | Bat guano sampled from different layers in Ogořelčíka Pećina Cave, Serbia                                                                                                                                    | Cultivation method                            | Bacillus, Enterococcus, Staphylococcus, *Voridibacillus*, Lysinibacillus, Pseudomonas, Escherichia, Serratia, Citrobacter |
| Borda et al. 2014             | Bat guano sampled from 7 caves in Romania                                                                                                                                                                | Cultivation method                            | Escherichia, Chryseomonas, Burkholderia                                                        |
| Vandžurová et al. 2013        | Guano samples from mixed *Myotis myotis* and *M. blythii* colony, the church tower in the Slovak Lupca village, Slovakia                                                                                     | Cultivation method                            | Staphylococcus nepalensis                                                                       |
| Tomova et al. 2013            | Bat guano samples from the Gallery with prehistoric drawings in Magura Cave, Bulgaria                                                                                                                        | Cultivation method                            | Serratia, Pseudomonas, Enterobacter, *Sphingobacterium*                                          |
| Wolkers-Rooijackers et al. 2019 | Bat guano samples of 10 insectivorous bats of different species sampled from limestone mines, province of Limburg, Netherlands                                                                              | 16S rRNA cloning and sequencing                | *Carnobacterium*, Serratia, Pseudomonas, Enterococcus, *Yersinia*                              |
| Afonso and Goydadin 2018      | Feces samples from 23 lesser horseshoe bat maternity roosts located in buildings (churches, barns), Franche-Comté region, France                                                                               | *msp2* (major surface protein gene) sequencing | *Anaplasma phagocytophilum*                                                                      |
| Hornok et al. 2018            | Bat feces samples from 19 bat species collected at Hungary and Netherlands                                                                                                                                     | PCR screening focused on vector-borne bacteria | *Rickettsia*, Neorickettsia, *Mycoplasma*                                                       |
| Vengust et al. 2018           | Feces samples of 12 different bat species, captured during autumn migration across central Europe at 8 different parts of Slovenia                                                                            | High-throughput 16S rRNA sequencing            | Pseudomonas, *Staphylococcus*, *Carnobacterium*, Acinetobacter, an unclassified Enterobacteriaceae |
| Veikkolainen et al. 2014      | Feces samples from *Myotis daubentoni*, Finland                                                                                                                                                                | High-throughput 16S rRNA sequencing            | *Leuconostoc*, Enterobacter, Lactococcus, *Chlamydia*, Citrobacter, Aeromonas, Klebsiella       |
| Li et al. 2018                | Fresh fecal pellets from bats with different diets randomly collected in Guangdong, Guangxi, and Yunnan, China                                                                                              | High-throughput 16S rRNA sequencing            | Enterobacter, Fructobacillus, Ureaplasmata, Klebsiella, Weissella, Plesiomonas, Enterococcus, Lactobacillus, Bacillus, Streptococcus, Actinobacillus, Nesterenkonia |
habitat are specific, extreme environments with low level of UV radiation, high gaseous ammonia levels, and could reach temperatures up to 43 °C (Newman et al. 2018). Different caves ensure the development of taxa specifically adapted for conditions in this environment. On the other hand, variations in the microbial community are conditioned by the geographic location, geological characteristics, and other environmental factors (Wiseschart and Pootanakit 2020).

Bacterial diversity of guano from building-dwelling bats was rarely studied (Vandzurová et al. 2012, 2013; Gerbáčová et al. 2020). Nevertheless, composition of their bacteriome is especially interesting considering the vicinity of human residence. Gerbáčová et al. (2020) reported presence of several possible human pathogens including *Hafnia alvei*, *Staphylococcus nepalensis*, *Serratia fonticola*, and *S. liquefaciens* in two building-dwelling bat species in Slovakia. Earlier, *Staphylococcus nepalensis* was detected by Vandzurová et al. (2013) from the summer colony bats from the church tower, also in Slovakia. *Staphylococcus nepalensis* is a potential human pathogen with presence of antibiotic-resistant strains (Nováková et al. 2006). Constant presence of *S. nepalensis* over a long period of time observed on bat populations in Slovakia indicates a persistence of potential pathogens in the bat population.

**Bats as a natural reservoir of antibiotic multi-resistant bacteria**

The existence of antibiotic multi-resistant bacteria in terrestrial mammals has been previously documented in multiple studies, providing an important insight into their potential role as reservoirs of resistant bacteria. Antibiotic-resistant bacteria have been detected in bat isolates across the globe, suggesting the possibility of them being one of the environmental reservoirs of resistant bacteria (Adesiyun et al. 2009; Allocati et al. 2016;).

McDougall et al. (2019) described the presence of bacteria resistant to several antibiotic families in gray-headed flying fox (*Pteropus poliocephalus*) populations across Australia. Isolated bacteria were found to carry genes responsible for resistance to aminoglycosides, trimethoprim, and beta-lactams. This study also provided evidence of resistome transfer between humans and bats, as well as from environment to bats. Studies in Nigeria also detected bacterial isolates from bat fecal droppings with resistance to multiple antibiotics (Oluduro 2012; Ajayi et al. 2020). Among Gram-positive isolates, most were resistant to amoxicillin, streptomycin, and erythromycin, while most of Gram-negative isolates were resistant to penicillins and cephalosporins.

Recent studies have detected presence of extended spectrum beta-lactamases (ESBLs) in *Enterobacteriaceae* isolates from bat guano. Mbehang Nguema et al. (2020) reported for the first time the presence of multi-resistant ESBL-producing *Enterobacteriaceae* in fruit bats in Makokou. Their strains showed higher resistance to tetracycline, ciprofloxacin, and ofloxacin compared with the studies carried out in Nigeria (Oluduro 2012; Ajayi et al. 2020). Main enterobacterial species that showed resistance to ESBLs were *Escherichia coli*, followed by *Klebsiella pneumoniae* and *E. cloacae*. Genetic analysis of ESBL resistance genes by PCR and sequencing identified only two genes responsible for observed resistance phenotype: *blaCTX-M* and *blaSHV-11*. Both genes are recognized as plasmid-mediated resistance genes (Cantón et al. 2013; Liakopoulos et al. 2016). In addition, *blaCTX-M-15* beta-lactam resistance gene is the most widely distributed and the most prevalent ESBL gene in human strains worldwide (Ewers et al. 2012; Janatova et al. 2014). ESBL-producing *E. coli* isolates from bat guano, carrying the same resistance genes, were also detected in Peru, Poland, and Portugal (Benavides et al. 2018; Garcés et al. 2019; Nowakiewicz et al. 2020). During 2019, carbapenemase-producing *Enterobacteriaceae* (CPE) were detected in bat guano (Gharout-Sait et al. 2019). CPE isolates were identified as *K. pneumoniae* and were found to carry *blaOXA-48* gene (CS34) and *blaKPC-3* gene (CS63). *K. pneumoniae* isolate carrying *blaKPC-3* gene was found to belong to the ST512 clonal group, subcluster of ST258 (Gharout-Sait et al. 2019). Strains belonging to this sequence types are recognized as a major
contributor to the spread of carbapenemases and have been frequently associated with hospital outbreaks. In Gabon, phylogenetic analysis of bat guano isolates revealed that they were clustered with previously described human bacterial strains from Turkey and Tunisia, but without information on their relatedness to clonal groups (Mbehang Nguema et al. 2020). All these and other studies suggest that antibiotic resistance in bat microbiome may vary locally and could be influenced by contact with wastes of antibiotic treatments of animals and humans (Swift et al. 2019).

Bat (guano) mycobiota

Since many bat species are nocturnal animals that roost in caves, much more often than in tree cavities, caves could be considered natural habitats for Chiroptera (Kunz 1982). Although fungi in caves could colonize a variety of substrata, such as cave sediments, vermiculations on cave walls, carcasses, and droppings of troglobites or troglophiles (Nováková 2009), bat guano is according to Ogórek et al. (2016) the most suitable substrate for fungal growth and proliferation. Since caves are usually regarded as oligotrophic, without primary production, bat guano piles are an important source of organic matter (Ferreira 2019). Depending on Chiroptera diet, three types of bat guanos are described. The majority of troglobilous microbats (former Microchiroptera) from the northern temperate regions are insectivorous; hence, their guano is finely granulated and consists of small pieces of insect cuticle. Chitin-degrading saprobes could be regarded as the first colonizers of newly established guano piles in caves roosted with insectivorous bats. On the other hand, megabats (Pteropodoidea or Yinpterochiroptera) are predominantly frugivorous, and their geographical distribution encompasses tropical regions of the Old world as well as Australia. Guano of frugivorous bats contains small undigested seeds easily colonized by saprobes. Hemopathagous or vampire bats (Desmodontinae) are native to Central and South America, and their guano is with a pasty consistency and reddish color or sometimes black with powdery consistency (Gnaspin 2012). All types of guano (from insectivorous, frugivorous, and hemopathagous bats) are suitable substrata for fungal colonization. Investigation conducted in a sandstone cave Meu Rei located in the Catimbau National Park (Brazil) showed that fungal richness does not differ greatly between insectivorous, frugivorous, and hemopathagous bats or between fresh and non-fresh guano, while regarding fungal propagules abundance guano types were in ascending order: frugivorous< haematopathagous< insectivorous (Cunha et al. 2020). Once pioneer fungal community is established further heterotrophic succession goes on, followed by changes in community structure and physicochemical properties of guano (Ferreira 2019). Guano communities are very simple and consist of only a few trophic levels (mostly of two with guanophages and their predators); however, they can harbor a large number of fungal propagules (Gnaspin 2012). Previous studies suggest that fungal density in bat guano piles could be high. Ogórek et al. (2016) reported very high fungal density in guano samples in Harmanecká cave in Slovakia (3498.3 CFU/g), while even higher fungal density in guano samples from Ogorelička Pečina Cave (Serbia) of 6384.61 CFU/g were presented by Dimkić et al. (2020). Apart from high fungal density, the mycobiota documented in guano samples can also be moderate to high (Vaughan 2012). Previous studies suggest the presence of a broad spectrum of fungal species documented in guano (Novákova 2009). Although the majority of guano-dwelling species are saprobes, guano can also be a reservoir of pathogenic fungi harmful to animals and humans. Opportunistic pathogens, causative agents of severe or mild mycoses, and toxigenic molds can be documented in bat guano worldwide. Larcher et al. (2003) documented the high fungal diversity in bat guano samples from caves in the region of Pays de la Loire (Western France). Their findings included pathogenic yeasts (Candida glabrata and Meyerozyma guilliermondii) and eight species of pathogenic keratinophilic fungi (Trichophyton terrestre, Scapulariopsis brevicaulis, Aphanoeascus fulvescens, Myceliophthora thermophila, Chrysosporium lobatum, Ch. merdarium, Ch. pseudomerdarium, and Ch. pnuinosum). Sugita et al. (2005) reported the presence of nine species of genus Trichosporon, causative agent of white piedra and opportunistic trichosporonosis, from guano of bat-inhabited limestone and volcanic caves in Japan. Other opportunistic pathogens presented in this work were Candida lusitaniae and Debaryomyces hansenii. Ulloa et al. (2006) reported the presence of pathogens Aphanoeascus fulvescens, Candida catenulata, C. ciferrii, M. guilliermondii, and Sporothrix sp. in tested guano samples from different caves in State of Guerrero in Mexico. The presence of Aspergillus fumigatus, known causative agent of invasive pulmonary mycosis in immunosuppressed individuals, was documented in guano samples from Domica Cave and Čertova Cave in Slovakia (Novákova 2009). Pathogenic yeast M. guilliermondii was isolated from guano samples collected in Ogorelička Pečina Cave in Serbia (Dimkić et al. 2020). According to Ogórek et al. (2016) bat guano is a “hidden treasure” of fungi that may be hazardous for mammal health, such as Candida, Geomyces, Microsporum, Trichosporon, and Trichophyton species.

The most important attention regarding guano-dwelling fungi is paid to dimorphic human fungal pathogens, which are the causative agents of severe diseases within specific geographic areas of known endemicity. It is already known that endemic mycoses manifested as focal and systemic diseases in a limited geographical area and remain a major public health problem in several countries. However, over the past
few decades new epidemiological reports have indicated that endemic fungi in certain areas are thought to be “non-endemic” (Ashraf et al. 2020). Interestingly, these pathogens could be the cause of various infections outside these areas. Endemic mycoses diagnosed outside of their established geographic ranges could be the main causes of morbidity and mortality in immunocompromised individuals, especially AIDS patients and patients with other immunosuppressive medical conditions (Wheat 1995; Ashraf et al. 2020). In this regard, due to the significant fact that there are many asymptomatic cases, the occurrence and development of these mycoses in such patients can be an important benchmark for the detection of these pathogens beyond endemic areas. The most prominent guano-associated dimorphic fungus is *Histoplasma capsulatum*, causative agent of systemic histoplasmosis also known as cave disease (Rodrigues et al. 2020). In addition to histoplasmosis, endemic mycoses are also caused by other dimorphic fungi such as *Coccidioides immitis*, *Co. posadasii*, *Blastomyces dermatitidis*, *Paracoccidioides brasiliensis*, *P. lutzii*, and *Talaromyces marneffei* (formerly known as *Penicillium marneffei*) (Sil and Andrianopoulos 2014). The above-mentioned species are more or less related to the guano and bat habitats, but perhaps the largest number of reports and scientific papers in recent two decades is related to *Coccidioides* species (Barker et al. 2007; Brown et al. 2013; Engelthaler et al. 2016; Kollath et al. 2019; Van Dyke et al. 2019; Oltean et al. 2020) and *B. dermatitidis* (Saccente and Woods 2010; Smith and Gauthier 2015; Slomka and Doub 2020).

*Coccidioides immitis* and *Co. posadasii* are causative agents of potentially fatal coccidiomycosis, known as valley fever, endemic for southwestern USA, northern Mexico, Central America, and some regions of South America (del Rocio Reyes-Montes et al. 2016). The first report regarding the presence of *Co. immitis* in bat guano samples, originated from roosting places deep within deserted mine tunnels in southern Arizona (Krustsch and Watson 1978). Later, Cordeiro et al. (2012) proved that several chiropteran species from Brazil (*Carollia perspicillata*, *Glossophaga soricina*, and *Desmodus rotundus*) could be infected with *Co. posadasii* and these authors also hypothesized that the ability of bats daily to travel long distances in their search for food and the social behavior could introduce this fungus in previously non-disease-endemic areas. The predominant route of infection with *Coccidioides* spp. is inhalation. The majority of cases are asymptomatic, but in some patients, a complicated form of pneumonia can also develop (Saubolle et al. 2007). In the last decades, the incidence of *Coccidioides* infections is increasing in endemic areas, with >90% in Arizona and California between 2001 and 2006 (Hector et al. 2011). The result of this increase has a significant impact on public health around the world.

*Blastomyces dermatitidis* is known as endemic species in the Mississippi and Ohio River Valleys, the Midwestern states, and the area of New York and Canada (Klein et al. 1986a, 1987; Cano et al. 2003; Dworkin et al. 2005; Sil and Andrianopoulos 2014). In the endemic region, this species is not uniformly distributed. It is known that it inhabits an ecological niche that is characterized by forested, sandy, and moist soils with an acidic pH; decaying vegetation or organic material; and rotting wood areas rich in organic debris, located near water sources (e.g., rivers and lakes) (Smith and Gauthier 2015). Similar to *H. capsulatum* and *Cryptococcus* species, this fungus may also persist in bird guano (Klein et al. 1986b; McBride et al. 2017). The first report on isolation of *B. dermatitidis* from liver of species *Rhinopoma hardwickei* (the “lesser rat-tailed bat”) found within the basement of Safdar-Jang Tomb, a historical monument in New Delhi, was reported by Randhawa et al. (1985). Previous means that *Chiroptera* could be the vectors of blastomycosis, a systemic disease caused by this pathogen, which is also called Gilchrist’s disease (Pappas and Dismukes 2002) or North American blastomycosis. The clinical manifestations of this mycosis are broad, ranging from asymptomatic infection to acute respiratory distress syndrome and lethal outcome (McBride et al. 2017).

In contrast to previously discussed fungi, there are only few reports regarding the presence of *Cryptococcus neoformans*, causative agent of potentially fatal cryptococcosis, in bats and bat guano. *Cryptococcus neoformans* var. *neoformans* was documented in an old abandoned house inhabited by bats in Rio de Janeiro, Brazil (Lazera et al. 1993). Furthermore, Montagna et al. (2003) reported the presence of *Cr. neoformans* in the upper layers of the bat guano in three caves in the Apulia region in Italy. Although cryptococcosis is regarded as a deadlier disease than histoplasmosis, *Cr. neoformans* does not spread as easily, and outbreaks have never been documented. Nevertheless, caves and bat guano generate sheltered conditions that prevent desiccation and protect *Cr. neoformans* from environmental stresses, i.e., UV radiation and extreme temperatures and wind (Montagna et al. 2003).

**Histoplasma capsulatum**

*Histoplasma capsulatum* is often regarded as “the main culprit from the Kingdom Fungi” that could be concealed in bat guano. There are two varieties which were initially distinguished on the basis of symptoms they cause. *Histoplasma capsulatum* var. *capsulatum* is found globally (mainly North, South, and Central America, Southeast Asia, and Africa) and is associated with pulmonary and systemic (i.e., classical) histoplasmosis, while *H. capsulatum* var. *duboisii* is predominantly found in Western and Central Africa and
causes skin and bone lesions (Cockshott and Lucas 1964; Sil and Andrianopoulos 2014).

It is well known that spelunkers should be aware of the risk bat-inhabited caves pose for developing histoplasmosis caused by H. capsulatum, especially if they are immunocompromised in any way (Lyon et al. 2004). Pulmonary histoplasmosis is a common disease of residents of the Ohio and Mississippi river valleys, where the fungus prevails and is the cause of the most common endemic fungal infection in the USA (Paul and Kuhlenschmidt 2018). However, new epidemiological reports indicate that regions other than the disease-endemic areas (midwestern and southeastern USA and Central and South America) are also affected, which indicates that H. capsulatum is wider spread than originally acknowledged (Deepe Jr 2018). Furthermore, in response to deforestation and urbanization, bats populations are adapting and setting up in the anthropized rural and urbanized environments, closer to human dwellings, leading to shift in the pattern of disease outbreaks to cover urban areas as well, with the number of infected individuals exceeding that found in rural areas (Jung and Threlfall 2018; Deepe Jr 2018). Though most of these infections are clinically silent and resolve without any consequence in immunocompetent individuals, H. capsulatum has been known to be behind such unusual cases as puzzling sickness of the pastor that cleaned copious amounts of bat guano from belfry of the church (Wynbrandt and Crouser 2007), outbreak of an unknown severe febrile illness of workers in the Dominican Republic tasked with cleaning accumulated bat guano from access tunnels to a hydroelectric dam inhabited by large bat colonies (Armstrong et al. 2018) or an outbreak affecting American tourists in a hotel in Acapulco (Guerrero, Mexico) where hotel’s ornamental potted plants, fertilized with guano compost, were determined as the infectious source (Taylor et al. 2005). In the period from 1938 to 2013, a total of 105 outbreaks involving 2,850 cases were reported in 26 states and the territory of Puerto Rico (Benedict and Mody 2016). Two outbreaks of extreme proportions have occurred in Indianapolis in the twentieth century, first associated with construction of a tennis stadium in the downtown area and other construction of a new natatorium on the IUPUI campus, with approximately 200,000 infected individuals in total (Deepe Jr 2018). Since H. capsulatum is known to exist within environmental pockets, i.e., “hotspots” (Armstrong et al. 2018), disruption of these soil reservoirs and release of large quantities of microconidia into the air can be possible cause of these outbreaks. Monitoring and data on histoplasmosis occurrence in Europe, as a non-endemic disease area, is very scarce. Disease has been reported among different risk groups in Germany, Italy, United Kingdom, France, Belgium, Sweden, Switzerland, Austria, Bulgaria, and Turkey (Ashbee et al. 2008) with only one case report of rare pulmonary histoplasmosis complicated with bronchocentric granulomatosis in Greece (Botsa et al. 2017). Histoplasma capsulatum infections are quite heterogeneous and may have significant consequences for immunological response and disease progression. Co-infections are also another important aspect to consider, since some of them could have a lethal outcome, such as reported human co-infections with C. neoformans (Cordero et al. 2016) and Blastomyces and Coccidioides spp. (Jehangir et al. 2015). In light of current pandemic, it is important to emphasize that two cases of histoplasmosis co-infection on immunocompromised AIDS patients with COVID-19 have been reported recently (Messina et al. 2020; Basso et al. 2020).

Open questions for the future

The current pandemic demands thinking about human impact on the natural system that increases the contact between humans and animals. Disturbing natural bat habitats, often to expand agricultural land, unleash pathogens that were sealed in the wild. Bearing in mind that bats and bat guano are the natural reservoir of pathogenic microorganisms, causative agents of serious diseases with epidemic and pandemic potential, it is quite clear that mankind is almost always responsible for the spillover of new diseases. Expanding the knowledge of guano microbiome is nowadays of utmost importance considering the presence of antibiotic multi-resistant bacteria, as well as pathogenic fungi with potential of outbreaks and “silent” viruses queuing for epidemics or eventually pandemics. Advances in microbiome-enabling technologies will help in better understanding of the community composition, function, and activity of both cultivable and non-cultivable microorganisms in the bat (guano) microbiome globally and could give an answer on the important question: “How can a microbiome be disclosed to increase human awareness and decreased all potential new disease outbreaks in the future?”

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