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Summary

Zusammenfassung



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Coronaviruses in Bats

Coronaviren in Fledertieren

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This article summarizes current detections of coronaviruses in bats in different geographic regions worldwide, and underlines the potential role of bats as ancestor and reservoir hosts of different coronaviruses. Bats can be found in almost all global habitats with the notable exception of the high arctic and a few isolated oceanic islands. First, we give an overview on the potential role of bats as carriers of zoonotic viruses, underlining the relevance of specific physiological traits of representatives of this mammalian order, that are supporting the transmission of these disease agents. Research in this field was predominantly initiated by the SARS coronavirus event in 2003, and in the meantime, bats are assumed to be the ancestor hosts for numerous alpha and beta coronaviruses. Bat associated coronaviruses have been detected on all continents where bats are distributed. Since the beginning of the COVID-19 pandemic, coronavirus research has again been considerably intensified, leading to a gain of knowledge regarding the interaction between bats and coronaviruses that will be valuable in the management of potential future outbreaks originating from bats. Finally, an outlook is given on research gaps that could be invaluable when dealing with future pandemic events.

Keywords: Coronavirus, bats, PCR detection, geographical distribution, reservoir host

Dieser Artikel gibt einen Überblick über die bisherigen Nachweise von Coronaviren in Fledertieren in verschiedenen geografischen Regionen weltweit. Darüber hinaus wird auch die potenzielle Rolle der Fledertiere als Ursprungs- und Reservoirwirt für die verschiedenen Coronaviren erörtert. Bemerkenswerterweise kommen Fledertiere weltweit in fast allen Habitaten vor, mit Ausnahme der hohen Arktis und einiger isolierter Ozeaninseln. Zunächst wird ein Überblick über die Bedeutung der Fledertiere als potenzielle Überträger von Viren mit zoonotischem Potenzial gegeben und dabei die Bedeutung der speziellen physiologischen Charakteristika dieser Säugetier-Ordnung hervorgehoben, die die Verbreitung solcher Erreger unterstützen. Die Forschung auf diesem Gebiet wurde erst durch das SARS-Coronavirus-Geschehen 2003 angestoßen, wobei derzeit davon ausgegangen wird, dass Fledertiere als Ursprungswirt für zahlreiche alpha- und beta-Coronaviren eine bedeutende Rolle spielen. Auf allen Kontinenten mit Fledertiervorkommen wurden inzwischen auch Fledertier-assoziierte Coronaviren nachgewiesen. Seit dem Beginn der COVID-19 Pandemie wurden die Arbeiten nochmals deutlich intensiviert, wodurch ein Wissensgewinn in Bezug auf die Interaktion zwischen Fledertieren und Coronaviren erreicht wurde, der auch zukünftig bei der Bekämpfung pandemischer, möglicherweise von Fledertieren ausgehender Infektionsgeschehen von Nutzen sein wird. Schließlich wird ein Ausblick auf noch offene Forschungsfragen gegeben, deren Beantwortung beim Umgang mit zukünftigen pandemischen Ereignissen von Nutzen sein könnten.

Schlüsselwörter: Coronaviren, Fledertiere, PCR-Nachweis, geografische Verbreitung, Reservoirwirt

Introduction

This article summarizes the currently known detections of coronaviruses in bats in different geographic regions worldwide, and underlines the potential role of bats as ancestor and reservoir hosts for different coronaviruses. This information therefore complements what has been summarized in other recently published review articles regarding different aspects of infectiology, bat immunology, virus/bat interactions and bat ecology (Banerjee et al. 2019, 2020, Gorbunova et al. 2020, Irving et al. 2021, Letko et al. 2020). It includes a short insight into published *in vitro* and *in vivo* work, followed by a discussion of public health relevance of these findings, as well as the research gaps in this field.

Bats as potential reservoirs for zoonotic diseases agents

In recent years, bats have increasingly moved into public and scientific attention after they have been identified as reservoir hosts of a number of disease agents. Bats form the second largest order of mammals aside from rodents, with more than 1300-1400 known species. This already partly explains their role as reservoir hosts for a number of relevant viruses, a perception which has been supported by a recent article discussing the relevance of mammals and birds as possible reservoir hosts (Mollentze and Streicker 2020). Following morphological, behavioural and molecular characteristics, the order chiroptera divides into Yinpterochiroptera (comprising the family Pteropodidae (fruit bats, formerly known as megabats), and the Rhinolophoidae superfamily with 5 families) and Yangochiroptera (comprising the remaining 14 bat families, that all use laryngeal echolocation). In general, bats exist in highly diverse habitats on six continents, but with the notable absence in the high Arctic, the Antarctic and a few isolated oceanic islands (Fenton 2015). The different bat families and species display considerable differences in their habitat, lifestyle, diet and social structure, resulting in large variations in the potential risk they may pose to public and veterinary health. In general, bats harbour specific life traits that increases their relevance as virus reservoirs: Bats are the only flying mammals and are thus able to cover large distances within short periods of time, with the annual migration of some species covering up to 1500 kilometres (Thomas 1983). Bats are also very gregarious and tend to form large colonies of up to tens of thousands of individuals, increasing the risk of virus spread through the colony. Some bat species even share their roosts with other animal species or roost close to humans, (e.g. in roofs of buildings) increasing the risk for a spillover infection (Kemenesi et al. 2015, Steyer et al. 2013). Interestingly, their body temperature can span a wide range between <math><10^{\circ}\text{C}</math> during torpor and hibernation, up to 43°C in hot roosts (Bronrier et al. 1999, Maloney et al. 1999) or during flight. It has been postulated that the elevated body temperature during flight activity (‘flight as fever’) may mimic the fever reaction of other mammals, thereby activating the immune responses (O’Shea et al. 2014). On the other hand, the activity of the immune system

is downregulated during the torpor phases (torpor bouts during summer and torpor during hibernation) of temperate zone bats, which may hamper virus clearance. Finally, by mechanisms that are still not fully understood, their immune system is able to protect them from developing disease after infection with a large number of viruses that are highly pathogenic to most other mammalian species. The current knowledge of the interaction of viral pathogens with the bat immune system has been summarized in a number of recent reviews (Banerjee et al. 2020, Gorbunova et al. 2020, Letko et al. 2020).

Many zoonotic viruses from bats may carry high pathogenic potential for humans, livestock or companion animals, especially in bats of tropical regions. The most prominent examples are filoviruses that are highly pathogenic to humans (e.g. Marburg and Ebola virus), henipaviruses that are highly pathogenic to pigs, horses and humans (e.g. Nipah and Hendra virus), lyssaviruses that are fatal to livestock, companion animals and humans (e.g. Rabies and Lagos Bat virus) as well as coronaviruses that are pathogenic to livestock, companion animals and humans (SARS-CoV, MERS-CoV and SARS-CoV-2) (Calisher et al. 2006, Moratelli and Calisher 2015, Nabi et al. 2021). In general, bats are capable of propagating and shedding viruses of all Baltimore classifications (Chen et al. 2014, Hayman 2016). Moreover, bats have been postulated as ancestral hosts for the most relevant mammalian paramyxoviruses (Drexler et al. 2012), alpha- and beta-coronaviruses (Woo et al. 2012) as well as lyssaviruses (Badrane and Tordo 2001, Delmas et al. 2008).

However, despite the abundance of viruses detected in bats, spillover events are still relatively rare, as viruses need to overcome a number of barriers imposed by ecological, geographical and social factors. This leads to variable levels of pathogen pressure, probability of virus survival in the environment, probability of exposure, and finally probability of infection of the host. These spillover cascades have been comprehensively summarized in two articles published by Plowright and colleagues (Plowright et al. 2015, 2017).

Coronaviruses (CoVs)

As classified by the International Committee on Taxonomy of Viruses (ICTV, 2019) Coronaviridae form the largest family in the order Nidovirales with the highest relevance to human and animal health. They harbour a single-stranded positive-sense RNA genome, ranging among the largest RNA virus genomes. The family is split into two subfamilies, the first of which, Letovirinae contains only one known species, *Microhyala letovirus 1*, which infects amphibia. The other subfamily, Orthocoronavirinae, comprises four genera: alpha-, beta-, gamma- and delta-CoVs. While alpha- and beta-CoVs infect mammals, infections with gamma- and delta-CoVs are mainly confined to birds. Therefore, in the following, we focus our review on infections of bats with alpha- or beta-CoVs. Interestingly, in each subgenus of both alpha- and beta-CoV genera, at least one virus species has been found in bats, highlighting the relevance of bats as hosts for CoVs, and again pointing to a coevolution of bats with these two genera (Woo et al. 2012).

Human CoV infections are of high importance to public health, with the emergence of SARS-CoV in 2003 (Drosten et al. 2003), and MERS-CoV in 2012 (Zaki et al. 2012) causing significant outbreaks. The most notable human coronavirus is SARS-CoV-2 which emerged in 2019 (World Health Organization 2020b) leading to an unprecedented pandemic. Aside from the new emergence of CoV species, others with relatively low pathogenicity play a key role in seasonal respiratory infections with global distribution. The most relevant virus species are hCoV NL63, hCoV 229E (alpha CoV) and hCoV OC43, hCoV HKU1 (beta CoV). On the other hand, a number of CoV infections, addressed in detail in other articles of this Special Issue, have a strong relevance for veterinary medicine.

Coronavirus infections in bats

Prior to the SARS-CoV epidemic, bats were not known to be hosts for CoVs. Since then they have been found to carry many more CoVs, with 30 complete genomes sequenced, and many more partial genome sequences (Wong et al. 2019). They were shown to be the group of mammals harbouring the largest number of CoVs (Fig. 1). To date, only alpha- and beta-CoVs have

been detected in bats which have been identified in Asia, Europe, Africa, North and South America, as well as Australasia. With higher detection rates, alpha-CoVs appear more widely distributed than beta-CoVs (Wong et al. 2019). Bats are hosts for many alpha- and beta-CoVs (Shi 2013, Woo et al. 2012) and phylogenetic analysis suggest, that bat-CoVs may be the ancestors for many CoVs in other mammals (Wong et al. 2019).

In general, bat CoVs are characterized by a distinct species-, genus- or family-specificity, while showing a wide geographic distribution across continents (Chu et al. 2006, Drexler et al. 2014, Gloza-Rausch et al. 2008, Pfefferle et al. 2009, Poon et al. 2005, Tang et al. 2006, Woo et al. 2006a). Interestingly, the diversity of bat related CoVs seems to be correlated with the diversity of bat species in a certain geographical region (Anthony et al. 2017b). It could be shown that the same alpha-CoV (*Miniopterus* bat coronavirus HKU8), which had previously been reported in *Miniopterus* species in China and Hong Kong, occurred in *M. schreibersii* in Bulgaria, over 8000 km away (Drexler et al. 2010).

In the following, we summarize the current knowledge regarding alpha- and beta-CoVs in bats in the different geographical regions and climatic zones worldwide (Tab. 1). Detection of CoV-related RNA has been

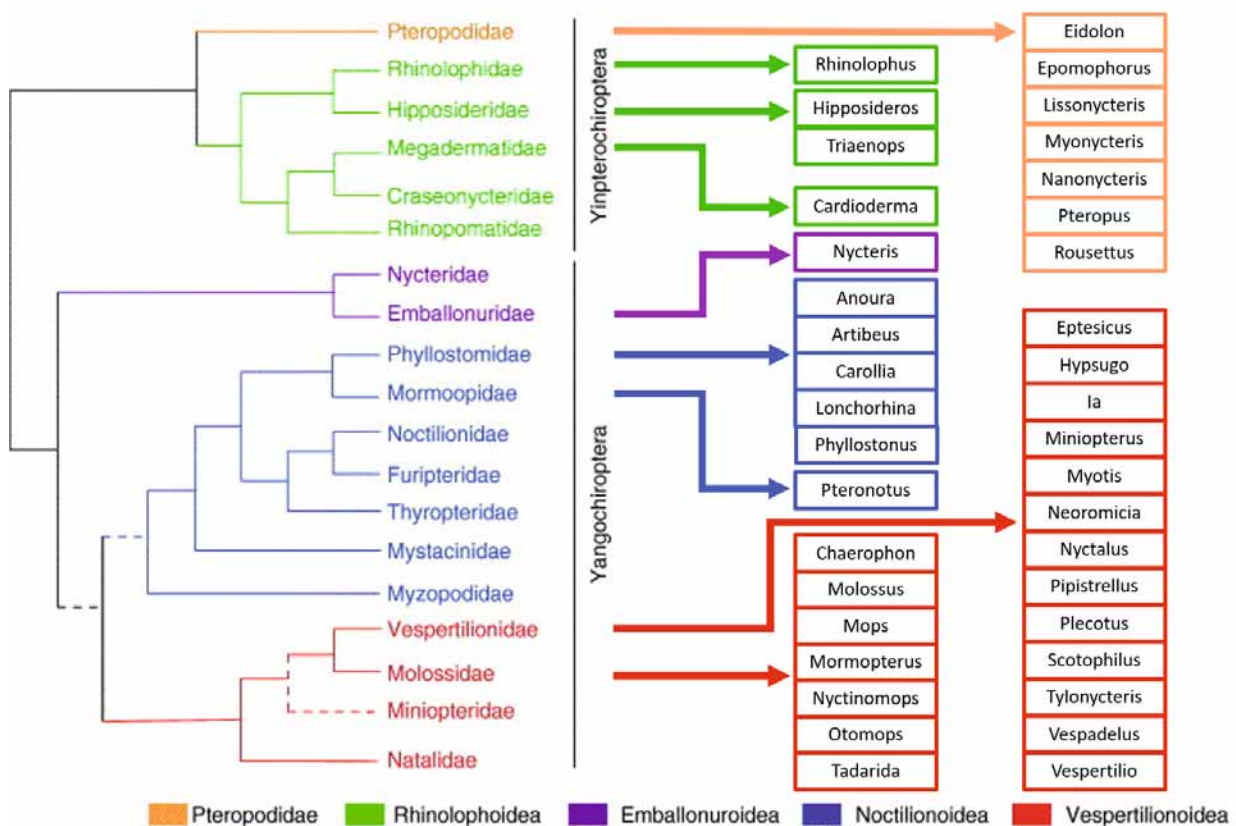


FIGURE 1: Bat CoVs detected in different bat taxa. Illustration of both chiroptera suborders (Yinpterochiroptera, Yangochiroptera), five superfamilies Pteropodidae (orange), Rhinolophoidea (green), Emballonuroidea (purple), Noctilionoidea (blue), Vespertilionoidea (red), and 19 bat families and respective bat families, where bat-related CoVs have been detected so far. Note that the bat-CoV findings are not evenly distributed among the bat families, which may well be biased by an uneven research focus on different bat families. Figure based on Jones and Teeling (2006), modified by the authors.

most successful from faecal samples in all previous studies, indicating a tropism to the digestive system in *Chiroptera* (Anthony et al. 2013, Pfefferle et al. 2009, Tang et al. 2006). We include an extensive list of references for further reading where the detailed information goes beyond the scope of this short review article.

TABLE 1: CoV sequence detections in bats mentioned in this review, grouped by the continent of detection, country of detection, bat species, and reference

Continent	Country	Bat species	Reference	
Europe	Italy	<i>Rhinolophus ferrumequinum</i>	Balboni et al. 2011	
		<i>Hypsugo savii</i>	Moreno et al. 2017	
		<i>Pipistrellus kuhlii</i>		
		<i>Pipistrellus kuhlii</i>	De Sabato et al. 2019	
		<i>Hypsugo savii</i>	Lelli et al. 2013	
		<i>Nyctalus noctula</i>		
		<i>Pipistrellus kuhlii</i>		
		<i>Rhinolophus hipposideros</i>		
		<i>Myotis blithii</i>	De Benedictis et al. 2014	
		<i>Eptesicus serotinus</i>		
	Bulgaria	<i>Miniopterus schreibersii</i>	Drexler et al. 2010	
		<i>Nyctalus leisleri</i>		
		<i>Rhinolophus euryale</i>		
		<i>Rhinolophus blasii</i>		
		<i>Rhinolophus ferrumequinum</i>		
		<i>Rhinolophus mehelyi</i>		
		Denmark	<i>Eptesicus serotinus</i>	Lazov et al. 2018
			<i>Myotis daubentonii</i>	
			<i>Myotis dasycneme</i>	
			<i>Myotis nattereri</i>	
	<i>Pipistrellus pygmaeus</i>			
	France	<i>Miniopterus schreibersii</i>	Monchatre-Leroy et al. 2017	
		<i>Myotis emarginatus</i>		
		<i>Myotis nattereri</i>		
		<i>Pipistrellus pipistrellus</i> <i>Pipistrellus sp.</i>		
	Germany	<i>Myotis dasycneme</i>	Gloza-Rausch et al. 2008	
		<i>Myotis daubentonii</i>		
		<i>Pipistrellus nathusii</i>		
		<i>Pipistrellus pygmaeus</i>		
		<i>Myotis bechsteinii</i>	Fischer et al. 2016	
		<i>Myotis nattereri</i>		
		<i>Pipistrellus nathusii</i>		
<i>Pipistrellus pygmaeus</i>				
Hungary		<i>Myotis daubentonii</i>	Kemenesi et al. 2014	
	<i>Myotis myotis</i>			
	<i>Myotis nattereri</i>	Balboni et al. 2012		
	<i>Pipistrellus pygmaeus</i>			
	<i>Rhinolophus euryale</i>			
	<i>Rhinolophus ferrumequinum</i> <i>Rhinolophus hipposideros</i>			
Europe	Luxembourg	<i>Myotis emarginatus</i>	Pauly et al. 2017	
		<i>Rhinolophus ferrumequinum</i>		
		Netherlands	<i>Myotis daubentonii</i>	Reusken et al. 2010
			<i>Myotis dasycneme</i>	
			<i>Pipistrellus pipistrellus</i>	
			<i>Nyctalus noctula</i>	
		Romania	<i>Pipistrellus nathusii</i>	Annan et al. 2013
			<i>Pipistrellus pipistrellus</i>	
			<i>Pipistrellus pygmaeus</i>	
		Slovenia	<i>Rhinolophus hipposideros</i>	Rihtarič et al. 2010
	Spain	<i>Eptesicus isabellinus</i>	Falcón et al. 2011	
		<i>Hypsugo savii</i>		
		<i>Myotis daubentonii</i>		
		<i>Myotis myotis</i>		
		<i>Nyctalus lasiopterus</i>		
		<i>Pipistrellus kuhlii</i>		
		<i>Pipistrellus sp.</i>		
		UK	<i>Myotis daubentonii</i>	August et al. 2012
	<i>Myotis nattereri</i>			
	Ukraine	<i>Pipistrellus nathusii</i>	Annan et al. 2013	
North America	Canada	<i>Eptesicus fuscus</i>	Misra et al. 2009	
		<i>Myotis lucifugus</i>		
		<i>Myotis lucifugus</i>	Subudhi et al. 2017	
	US	<i>Eptesicus fuscus</i>	Dominguez et al. 2007	
		<i>Myotis occultus</i>		

Continent	Country	Bat species	Reference	Continent	Country	Bat species	Reference
North America		<i>Eptesicus fuscus</i>	Osborne et al. 2011	Africa	Kenya	<i>Cardioderma cor</i>	Tong et al. 2009
		<i>Myotis evotis</i>					
		<i>Myotis lucifugus</i>					
		<i>Myotis volans</i>					
		<i>Tadarida brasiliensis</i>	Bonny et al. 2017			<i>Chaerophon pumilus</i>	
Asia	China	<i>Rhinolophus ferrumequinum</i>	Li et al. 2005			<i>Chaerophon sp.</i>	
		<i>Rhinolophus macrotis</i>					
		<i>Rhinolophus pearsoni</i>					
		<i>la io</i>	Luo et al. 2018			<i>Eidolon helvum</i>	
		<i>Pipistrellus abramus</i>					
		<i>Pipistrellus minus</i>					
		<i>Pipistrellus pipistrellus</i>					
		<i>Pipistrellus spp.</i>					
		<i>Tylonycteris pachypus</i>					
		<i>Tylonycteris spp.</i>					
		<i>Vespertilio superans</i>					
		<i>Rousettus leschenaulti</i>	Xu et al. 2016			<i>Hipposideros commersoni</i>	
		<i>Rhinolophus sinicus</i>					
	<i>Myotis daubentonii</i>						
	<i>Hipposideros cineraceus</i>						
	<i>Rhinolophus ferrumequinum</i>		<i>Miniopterus africanus</i>				
	Hong Kong	China	<i>Rhinolophus sinicus</i>	Lau et al. 2005	<i>Miniopterus inflatus</i>		
			<i>Miniopterus magnater</i>	Poon et al. 2005	<i>Miniopterus minor</i>		
			<i>Miniopterus pusillus</i>		<i>Miniopterus natalensis</i>		
			<i>Miniopterus schreibersii</i>		<i>Otomops martinsseni</i>		
Africa		Gabon	<i>Hipposideros caffer ruber</i>	Maganga et al. 2020	<i>Rousettus aegyptiacus</i>		
			<i>Hipposideros gigas</i>				
			<i>Miniopterus inflatus</i>				
Ghana	<i>Hipposideros caffer ruber</i>	Pfefferle et al. 2009	<i>Chaerophon pumilus</i>	Waruhiu et al. 2017			
	<i>Nycteris cf. gambiensis</i>	Annan et al. 2013	<i>Eidolon helvum</i>				
Guinea		<i>Eidolon helvum</i>	Lacroix et al. 2020		<i>Hipposideros caffer</i>		
		<i>Epomophorus gambianus</i>					
		<i>Hipposideros sp.</i>					
		<i>Lissonycteris angolensis</i>					
		<i>Nanonycteris veldkampii</i>					
		<i>Nycteris sp.</i>					
		<i>Rhinolophus sp.</i>					
		<i>Rousettus aegyptiacus</i>					
		<i>Cardioderma cor</i>	Tao et al. 2017				
		<i>Chaerophon sp.</i>					
		<i>Eidolon helvum</i>					
		<i>Epomophorus labiatus</i>					
		<i>Epomophorus wahlbergi</i>					
		<i>Hipposideros vittatus</i>					
		<i>Hipposideros sp.</i>					
		<i>Miniopterus inflatus</i>					
		<i>Miniopterus minor</i>					
		<i>Miniopterus natalensis</i>					
		<i>Miniopterus sp.</i>					
		<i>Otomops martinsseni</i>					
		<i>Rhinolophus hildebrandtii</i>					
		<i>Rhinolophus landeri</i>					
		<i>Rhinolophus sp.</i>					
		<i>Rousettus aegyptiacus</i>					
		<i>Scotophilus dingani</i>					
		<i>Triaenops afer</i>					

Continent	Country	Bat species	Reference
Africa	Madagascar	<i>Mops midas</i>	Joffrin et al. 2020
		<i>Mormopterus jugularis</i>	
		<i>Rousettus madagascariensis</i>	
		<i>Triaenops menamena</i>	
		<i>Eidolon dupreanum</i>	Razanajatovo et al. 2015
		<i>Pteropus rufus</i>	
	Mayotte	<i>Chaerephon</i> sp.	Joffrin et al. 2020
		<i>Chaerephon pusillus</i>	
	Mozambique	<i>Hipposideros caffer</i>	Joffrin et al. 2020
		<i>Miniopterus mossambicus</i>	
		<i>Mops condylurus</i>	
		<i>Nycteris thebaica</i>	
		<i>Rhinolophus lobatus</i>	
		<i>Rhinolophus rhodesiae</i>	
		<i>Rhinolophus</i> sp.	
		<i>Triaenops afer</i>	
	Nigeria	<i>Hipposideros commersoni</i>	Quan et al. 2010
	Reunion	<i>Mormopterus francoismoutoui</i>	Joffrin et al. 2020
	Rwanda	<i>Rhinolophus clivosus</i>	Markotter et al. 2019
		<i>Chaerephon pumilus</i>	Nziza et al. 2019
		<i>Eidolon helvum</i>	
		<i>Epomophorus labiatus</i>	
		<i>Hipposideros caffer</i>	
<i>Myonictes angolensis</i>			
<i>Rhinolophus clivosus</i>			
<i>Rousettus aegyptiacus</i>			
South Africa	<i>Miniopterus natalensis</i>	Geldenhuys et al. 2013	
	<i>Mops midas</i>		
	<i>Neoromicia capensis</i>		
	<i>Neoromicia</i> cf. <i>zuluensis</i>	Ithete et al. 2013	
Uganda	<i>Pipistrellus</i> cf. <i>hesperidus</i>	Anthony et al. 2017	
Zimbabwe	<i>Hipposideros caffer</i>	Bourgarel et al. 2018	
South-East Asia and Australia	Australia	<i>Miniopterus australis</i>	Smith et al. 2016
		<i>Miniopterus schreibersii</i>	
		<i>Myotis macropus</i>	
		<i>Pteropus alecto</i>	
		<i>Rhinolophus megaphyllus</i>	

Continent	Country	Bat species	Reference
South-East Asia and Australia		<i>Rhinonictes aurantia</i>	
		<i>Vespadelus pumilus</i>	
	Thailand	<i>Hipposideros larvatus</i>	Gouilh et al. 2011
		<i>Hipposideros armiger</i>	
South America	Brazil	<i>Molossus molossus</i>	Lima et al. 2013
		<i>Tadarida brasiliensis</i>	
		<i>Carollia brevicauda</i>	Corman et al. 2013
		<i>Carollia perspicillata</i>	
	Costa Rica	<i>Anoura geoffroyi</i>	Corman et al. 2013
		<i>Carollia perspicillata</i>	
	Ecuador	<i>Carollia brevicauda</i>	Corman et al. 2013
		<i>Carollia perspicillata</i>	
	Mexico	<i>Artibeus lituratus</i>	Anthony et al. 2013
		<i>Artibeus phaeotis</i>	
		<i>Artibeus jamaicensis</i>	
		<i>Carollia sowelli</i>	
<i>Carollia perspicillata</i>			
<i>Eptesicus fuscus</i>			
<i>Lonchorhina aurita</i>			
<i>Myotis velifer</i>			
<i>Nyctinomops laticaudatus</i>			
<i>Pteronotus parnellii</i>			
<i>Tadarida brasiliensis</i>			
Panama	<i>Artibeus jamaicensis</i>	Corman et al. 2013	
	<i>Artibeus lituratus</i>		
	<i>Carollia perspicillata</i>		
	<i>Phyllostomus discolor</i>		

Bat-related CoV livestock and companion animals

As mentioned before, bats have been postulated as ancestor hosts for a number of relevant alpha- and beta-CoVs. Moreover, a common ancestor has been postulated for most relevant CoVs in veterinary medicine, namely TGEV (transmissible gastroenteritis virus) in pigs, CCoV (canine coronavirus) in dogs and FCoV (feline coronavirus) in cats (Le Poder 2011). Although the host species of this ancestor virus has not been identified yet, it may have been bat-related. In 2017, a novel HKU2-related CoV, later reported as SADS-CoV (Swine acute diarrhoea syndrome coronavirus, or porcine enteric alphacoronavirus), caused a fatal diarrhoea syndrome in pigs in China and resulted in the loss of almost 25.000 piglets (Gong

et al. 2017, Zhou et al. 2018). SARS-CoV shows a 95% sequence homology to a bat-related HKU2-CoV, that has been detected in *Rhinolophus* bats in Southern China in 2007 (Lau et al. 2007).

Coronaviruses in temperate bats

Europe

Three alpha-CoVs, fully sequenced by next generation sequencing, were detected in *Pipistrellus kuhlii* bats in Italy, of which one strain showed a high level of sequence similarity to a Chinese bat-CoV (De Sabato et al. 2019). In another study in Italy, alpha- and beta-CoVs were detected using a pan-CoV-PCR assay in different vespertilionid and rhinolophoid bat species, with *Pipistrellus kuhlii* bats carrying both, alpha- and beta-CoVs (Lelli et al. 2013). In Spain, 14 alpha- and beta-CoVs were detected in nine bat species (Falcón et al. 2011) and in the Netherlands the overall estimated prevalence of CoVs in *Myotis*, *Nyctalus* and *Pipistrellus* bats was 16.9% (Reusken et al. 2010). In 2012 the first CoVs were detected in bats in the United Kingdom by PCR, with particularly high prevalence in *Myotis nattereri*, which have been found living in close proximity to humans (August et al. 2012). Testing of 315 bats in northern Germany by PCR revealed four lineages of alpha-CoVs in *Myotis* and *Pipistrellus* bats with an overall prevalence of 9.8% (Gloza-Rausch et al. 2008). In another study the average detection rate for CoVs in *Myotis* and *Pipistrellus* bats by PCR was only 1.4% of 957 analysed samples from different regions in Germany (Fischer et al. 2016). In Hungary a detection rate of 1.79% was found in *Myotis*, *Pipistrellus* and *Rhinolophus* bats, testing 447 samples from 24 bat species (Kemenesi et al. 2014). Alpha-CoVs were also detected by PCR in *Myotis*, *Pipistrellus* and *Eptesicus* bats in Denmark, of which some are showing a close resemblance to coronavirus sequences obtained from bats in Germany and the UK (Lazov et al. 2018). Twelve out of 504 bat intestinal samples from France were tested positive by PCR, revealing alpha-CoVs in *Myotis*, *Pipistrellus* and *Miniopterus* bats with high sequence similarities to CoV sequences obtained from other European countries such as Germany, Luxembourg, Hungary and Bulgaria (Monchatre-Leroy et al. 2017).

A study on Rhinolophids in Bulgaria showed, that these bats carried SARS-related beta-CoVs at high frequencies and RNA levels (26% of 389 animals were positive; up to 2.4×10^8 copies per gram of feces) (Drexler et al. 2010). In Italy (Balboni et al. 2011, 2012, Lecis et al. 2019), Luxembourg (Pauly et al. 2017), Slovenia (Rihtarič et al. 2010) and Hungary (Kemenesi et al. 2014) SARS-like CoVs were detected by PCR in *Rhinolophus* bats. In another study, beta-CoV sequences obtained from *Pipistrellus* bats in Romania and Ukraine showed relatedness to hCoV EMC/2012 (Annan et al. 2013), while MERS-like CoVs were detected in *Eptesicus*, *Pipistrellus*, *Nyctalus* and *Hypsugo* bats from Italy (De Benedictis et al. 2014, Lelli et al. 2013, Moreno et al. 2017), with two complete CoV genome sequences obtained from a *Pipistrellus kuhlii* and *Hypsugo savii* bat (Moreno et al. 2017).

North America

To allow a science-based risk assessment regarding CoV infections of bats in North America, a small number of

bats of seven Rocky Mountain vespertilionid bat species were screened for CoVs by PCR. In 17% of fecal samples of big brown bats (*Eptesicus fuscus*) and 50% of *Myotis occultus* alpha-CoVs were detected (Dominguez et al. 2007). In a larger follow-up study, more than 1000 samples collected from 17 bat species in Colorado were analysed, with alpha-CoVs detected in up to 10% of fecal samples of four species. The highest detection rate was seen in *E. fuscus*. The authors concluded, that given the exclusive detection of alpha-CoVs in these bats, there appears to be a much more limited CoV diversity in New World bat species than in Old World bat species (Osborne et al. 2011). A later study was consistent with the restriction of North-American bat populations to infections with alpha-CoVs by PCR analysis of fecal samples of two out of 19 Brazilian free-tailed bats (*Tadarida brasiliensis*) in Florida (Bonny et al. 2017). A study summarizing the analysis of 31 vespertilionid bats also confirmed the presence of alpha-CoVs in these species in Canada (Misra et al. 2009). Persistent infections with *Chiroptera*-alpha-CoVs were detected in the intestines and lungs of some North American little brown bats (*Myotis lucifugus*) after four months of hibernation (Subudhi et al. 2017, 2019).

Asia

After the SARS-CoV epidemic, CoV research in bats intensified, and a large number of studies was performed in Asia. In 2005, two independent teams reported the discovery of SARS-like CoVs (SL-CoVs) in bats and suggested that bats are natural reservoirs of SARS-CoV (Lau et al. 2005, Li et al. 2005). Of the various bat species, horseshoe bats (*Rhinolophus* spp.) were suggested as a reservoir of SARS-CoV.

While the previously known human CoVs (HCoV-229E, HCoV-OC43, HCoV-HKU1 and HCoV-NL63) usually cause mild symptoms, the more recently discovered human CoVs have higher virulence and as a result have a more significant public health impact. The emergence of the beta-CoV SARS-CoV occurred in 2003 after a possible transmission from civet cats or raccoon dogs as an intermediate host to humans (Peiris et al. 2003). Within a few months, SARS-CoV infected around 8000 people in more than 30 countries with a lethality rate of ~10% (Peiris et al. 2003). Another beta-CoV, MERS-CoV emerged in 2012, causing more than 2500 cases in 27 countries with a lethality rate of 35% (World Health Organization 2019, Zaki et al. 2012, Zumla et al. 2015). Dromedary camels seem to represent a natural reservoir of MERS-CoV (Killerby et al. 2020, Lau et al. 2017, Paden et al. 2018, Wernery et al. 2017), but again bats have been postulated as the original reservoir host (Killerby et al. 2020), as several closely related CoVs were detected in different bat species (Corman et al. 2014, Hu et al. 2015). A recent PCR-based study testing more than 1000 bats from >30 different species in South China revealed 89 different beta-CoV strains from eight vespertilionid bat species, of which a number of sequences showed high similarities to MERS-CoV (Luo et al. 2018). Two full-length sequences indicate a natural recombination event between this bat MERS-related CoV and another bat coronavirus, HKU4. Moreover, this study expands the known host range of MERS-related CoVs and confirms the geographical distribution of MERS-like CoVs outside the Old World and North America.

A screening survey of bat intestinal samples collected from 21 different bat species in the Tibet Autonomous Region revealed an overall CoV positivity rate of more than 5%. Interestingly, 84% of these sequences belonged to beta-CoVs that are generally less frequently reported in bats, while the remaining 16% were related to alpha-CoVs (Xu et al. 2016).

Next, the HKU2-related SADS-CoV has frequently been described in *Rhinolophus* bats in China before the first SADS outbreaks in Chinese pig farms were reported (Gong et al. 2017, Zhou et al. 2018). The current CoV findings in Chinese bats have been comprehensively summarized by (Fan et al. 2019).

Then in December 2019, a novel SARS-CoV, later designated SARS-CoV-2, was first detected in Wuhan, China, and was possibly epidemiologically associated to a seafood market (Zhu et al. 2020). SARS-CoV-2 represents the seventh CoV to be identified in humans since the 1960s (Su et al. 2016, Ye et al. 2020). The recent SARS-CoV-2 outbreak has an estimated case-fatality rate lower than that seen during the SARS-CoV outbreak, but its distribution and speed of its spread resulted in a much higher disease burden (He et al. 2020). By March 11th 2020, the WHO declared the ongoing outbreak a pandemic (World Health Organization 2020a). To date (April 2, 2021), 130 million COVID19-cases have been reported worldwide, with more than 2.8 million fatalities (Johns Hopkins University – Coronavirus Resource Center 2020). All seven HCoVs are zoonotic viruses with likely evolutionary origins in bats (Corman et al. 2018, Huynh et al. 2012, Pfefferle et al. 2009, Vijaykrishna et al. 2007). Whilst some have been directly transmitted from bats to humans, for other CoVs an intermediate host was implicated, for example, camels for MERS-CoV or civets for SARS-CoV (Corman et al. 2014, Guan et al. 2003, Lau et al. 2005, Li et al. 2005, Luo et al. 2018). For SARS-CoV-2, the closest relative (RaTG13) has been identified in a *Rhinolophus affinis* bat from China with 96.2% sequence homology to SARS-CoV-2. Therefore, bats have been also postulated as the natural reservoir for this virus (Guo et al. 2020, Zhou et al. 2020). The role of an intermediate species, is still not fully understood (Lam et al. 2020, Zhou et al. 2020).

Coronaviruses in tropical and subtropical bats

Africa

It was shown in a number of studies that insectivorous and frugivorous bats across Africa harbour a diverse number of CoVs. Antibodies against SARS-CoV antigen were detected in 6.7% of 705 bat serum specimens comprising 26 species collected in South Africa and the Democratic Republic of Congo (DRC) (Müller et al. 2007). In 11% of 319 tested bats from 14 genera in Guinea, numerous different alpha- and beta-CoVs were found using PCR (Lacroix et al. 2020). Testing of bats from Mozambique, Madagascar, Mayotte and Reunion Island revealed a large diversity of alpha- and beta-CoVs (Joffrin et al. 2020). Another study showed a significant diversity of CoVs circulating in bats in Kenya, which are phylogenetically distant from any previously described human and animal CoV (Tao et al. 2012). In *Pteropus* and *Eidolon* bats in Madagascar 14 CoVs were detected, forming distinct clusters within the beta-CoVs (Razana-jatovo et al. 2015) and in Rwanda new beta-CoVs were recently discovered in *Rhinolophus* and *Hipposideros* bats (Markotter et al. 2019, Nziza et al. 2019). Three unique alpha-CoV species were identified in the tissues of the South African bats *Neoromicia capensis*, *Miniopterus* spp. and *Mops midas*, of which the CoV *Mops* BtCoV1364/SA/11 is closely related to the CoV *Chaerephon*-BtKY22 from Kenya (Geldenhuys et al. 2013, Tong et al. 2009). The two bat genera, *Mops* and *Chaerephon*, are closely related and share an overlapping geographical distribution, sometimes even sharing same roosts, so interspecies transmissions of these alpha-CoVs could easily occur between these two host genera (Geldenhuys et al. 2013). *Mops condylurus*, in which a new ebolavirus, Bombali virus (BOMV), was recently discovered in Sierra Leone (Goldstein et al. 2018), Kenya (Forbes et al. 2019) and Guinea (Karan et al. 2019), was also shown to harbour alpha-CoVs (Waruhiu et al. 2017).

Some of these described alpha- and beta-CoVs are closely related to human CoVs such as hCoV-229E, SARS- and MERS-CoVs (Lacroix et al. 2020). In Ghana, fecal samples of insectivorous leaf-nosed bats of the

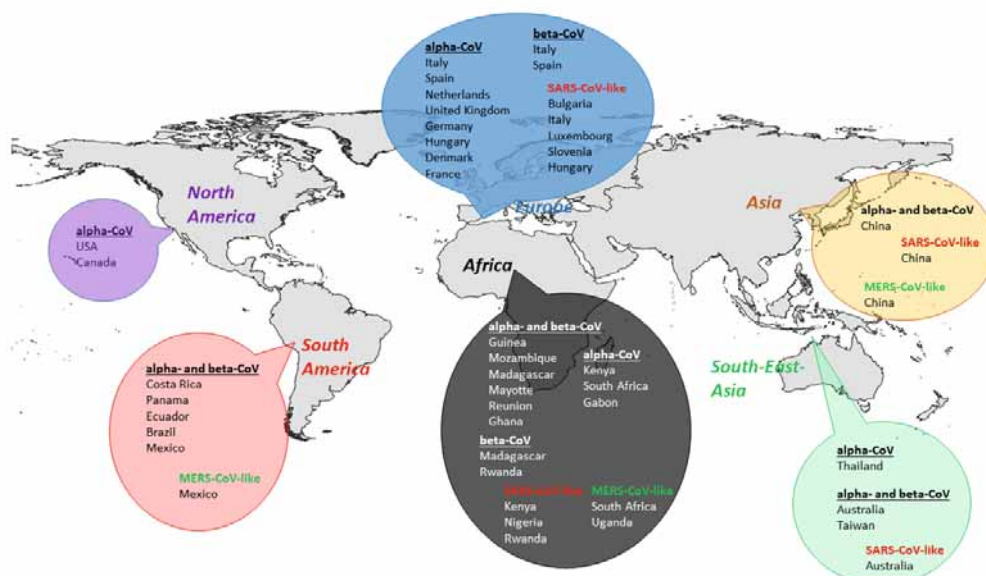


FIGURE 2: Detection of bat CoVs in geographical regions worldwide. Only alpha- and beta-CoVs have been detected in bats so far, with the majority of findings in the alpha-CoV group. Note that no beta-CoV has been reported in bats in North America so far. Besides Asia, SARS-CoV like sequences have been detected in Africa, Europe, and South-East-Asia, while MERS-CoV like sequences have been reported from Asia, Africa and South America. Figure created by the authors.

genus *Hipposideros* tested positive for alpha- and beta-CoVs, with the most closely related member of the GhanaBt-CoVGrp1 clade sharing 91.90% nucleotide identity with hCoV-229E in the analysed fragment (Pfefferle et al. 2009). In other studies alpha-CoV sequences obtained from *Hipposideros* bats in Gabon (Maganga et al. 2020) and Zimbabwe (Bourgarel et al. 2018) grouped with hCoV-229E (Maganga et al. 2020). The evolutionary origin of 229E-related CoVs seem to be in hipposiderid bats (Corman et al. 2015), while sequences closely related to human CoV NL63 were identified in *Triaenops* bats (Tao et al. 2017). Sequences closely related to SARS-like CoVs were detected in *Chaerophon* bats in Kenya (Tong et al. 2009) and *Hipposideros* bats in Nigeria (Quan et al. 2010). Also, in Rwanda, novel beta-CoVs were shown to cluster with SARS-CoV (Nziza et al. 2019). In *Nycteris* bats in Ghana novel clade 2c betacoronaviruses were detected that are phylogenetically related to the novel hCoV EMC/2012 (Annan et al. 2013). Close relatedness of CoV PML/2011, detected in *Neoromicia* cf. *zuluensis* in South Africa, and MERS-CoV support the hypothesis that, like human CoV-229E and SARS-CoV, ancestors of MERS-CoV may exist in Old World insectivorous bats belonging to the family Vespertilionidae, to which the genera *Neoromicia* and *Pipistrellus* belong (Ithete et al. 2013). NeoCoV, obtained from a South African *Neoromicia capensis* bat, and MERS-CoV even belong to one viral species (Corman et al. 2014). Phylogenetic analysis of a MERS-like CoV (strain PREDICT/PDF-2180), detected in a *Pipistrellus* bat in Uganda, showed that it is closely related to MERS-CoV across much of its genome, further supporting the hypothesis that bats are the evolutionary source of MERS-CoV (Anthony et al. 2017a). In conclusion, there is a large pool of different alpha- and beta-CoVs detected in African bats with presumably many more to be discovered. This is particularly important as some prominent human CoVs seem to originate from CoVs in these bats.

South-East Asia and Australia

A PCR- and serology-based study analysing more than 2000 bats from over 40 different species in the Australasian region revealed a wide-spread presence of CoVs in this area (Smith et al. 2016). Four different CoV genotypes were detected including three potentially new species, whilst no SARS-like beta-CoVs were identified, despite targeting rhinolophid bats. Interestingly, *Miniopterus* bat coronavirus HKU8 was detected, which had previously been described in *Miniopterus* bats in China, Hong Kong and Bulgaria, supporting the virus-host coevolution hypothesis. A recent serological survey of *Pteropus poliocephalus* bats in Southern Australia revealed, that 42.5% of the analysed 301 sera were reactive to SARS-CoV or a related antigen, providing evidence that these flying foxes had previously been in contact with a SARS like coronavirus, but no reactivity to a MERS-CoV antigen could be demonstrated (Boardman et al. 2020). In another PCR-based study performed on *Hipposideros* bats in Thailand, bat CoV sequences could be detected that were closely related to those detected earlier in Africa (beta-CoV) or in Europe (alpha-CoV and beta-CoV). This evidence again supports the coevolution theory of bats and CoVs, further supporting the hypothesis of a beta-CoV spillover from Hipposideridae to Rhinolophidae bats, and subsequently from Rhinolophidae to civets and humans (Gouilh et al. 2011).

South America

A pilot study to evaluate the general presence of CoVs in Brazilian bats was performed on > 500 samples from two insectivorous bat species, *Molossus molossus* and *Tadarida brasiliensis*, and revealed alpha-CoV sequences in 29 of 150 pooled fecal samples (Lima et al. 2013). Another study revealed alpha- and beta-CoV RNA in 50 of >1500 bats from nine different frugivorous and insectivorous species in Costa Rica, Panama, Ecuador and Brazil, underlining the broad distribution among different bat species (Corman et al. 2013). Meanwhile, alpha- and beta-CoV related RNA was detected in samples from nine frugivorous and four insectivorous bat species in Mexico, with one beta-CoV sequence isolated from an insectivorous bat (*Nyctinomops laticaudatus*) showing 96.5% identity to MERS-CoV (Anthony et al. 2013), again emphasizing the global distribution of closely related bat-associated CoVs among different bat species.

In summary, the cumulated data in this article show, that CoVs are detectable in all global areas, where bats can be found (Fig. 2). While SARS-like CoVs have not only been detected in Asia, but also in Europe, Africa, and South-East Asia, MERS-like CoVs have so far been identified in Asia, Africa and South America. Moreover, in the temperate zones of Europe, North America, and Asia as well as in the tropical and subtropical zones of South-East Asia and South America, most studies confirmed the presence of CoV lineages, showing relatedness to other already known CoV clades. Some distinct novel alpha and beta-CoVs have been detected in a number of African countries.

Virus isolation from bats and in vivo experiments in bats

While the vast majority of CoV detection in bats is based on molecular detection by PCR, there are comparably few isolates available that allow the analysis of the biological properties of these strains. While attempts to isolate the progenitor viruses of human CoV epidemics were so far unsuccessful for both SARS-CoV and SARS-CoV-2, the isolation of beta-CoVs that are closely related to SARS-CoV in China facilitated in vitro analysis of cell entry and susceptibility (Ge et al. 2013, Yang et al. 2015). Such studies are crucial to gain a better understanding of the biological properties of these agents. However, isolation of CoVs from free-ranging bats does not allow a profound analysis of the clinical picture and virus shedding in these animals. To be able to analyse this, challenge experiments in relevant bat species that are available for such experiments are necessary. This was first carried out in *R. aegyptiacus* fruit bats using SARS-CoV isolated from *R. sinicus* bats (Ge et al. 2013, van Doremalen et al. 2018). In this study, *R. aegyptiacus* bats did not develop any clinical signs, displayed a mild involvement of the respiratory tract and only produced low levels of antibodies against the viral proteins. A challenge study using a human SARS-CoV-2 isolate in the same bat species again revealed results indicating a potential role of these bats as a reservoir host, since the animals also showed no clinical signs, but shed virus, transmitted the infection to contact animals and seroconverted (Schlottau et al. 2020). In a different study *Eptesicus fuscus* bats were experimentally challenged

with SARS-CoV-2 (Hall et al. 2020): In contrast to *R. aegyptiacus*, *E. fuscus* bats seem to be resistant to infection with SARS-CoV-2. No virus was detectable in tissues and no viral excretion was observed, demonstrating that certain bat species serve as reservoirs for certain viruses. Such challenge experiments are indispensable for the assessment of the role of the infected bat species or closely related bat species in the epidemiology of the different bat CoVs. It must however be kept in mind, that bat species available for such experiments are not necessarily the most relevant species for a certain disease agent, which may compromise the interpretation of the results.

Conclusions and Outlook

Relevance for public health

CoVs infect a wide variety of animals and humans, causing diseases of the respiratory, enteric, hepatic and neurological systems with different severity (Wong et al. 2019). Because of their special mechanisms of viral replication with possible recombinations and mutation (Graham and Baric 2010, Lau et al. 2010, Tian et al. 2014), CoVs may adapt rapidly to new hosts upon spill-over infections. On the other hand, with 1300-1400 species (American Society of Mammalogists 2020, Fenton 2015, Teeling et al. 2018), bats account for about 20% of all mammalian species (Teeling et al. 2018), and harbour a large number of viruses (Han et al. 2015). In bat colonies the physical proximity facilitates viral transmission among bats, supporting the virus circulation within the population (Han et al. 2015).

With more than 30 complete bat-CoV genomes sequenced within the last 17 years, bats are the group of mammals harbouring the largest number and variety of CoVs, and bat-CoVs may in fact be the ancestors for alpha- and beta-CoVs (Wong et al. 2019). *Rhinolophus* bats were shown to be natural reservoirs for SARS-like CoVs (Ge et al. 2013, Lau et al. 2005, Li et al. 2005) and several beta-CoVs detected in bats are closely related to MERS-CoV (Anthony et al. 2017a, Corman et al. 2014) and SARS-CoV-2 (Boni et al. 2020, Wacharapluesadee et al. 2021). Spill-over events of CoVs from bats to humans have led to devastating outbreaks, so intense surveillance of bats and their CoVs has tremendous relevance for public health. The worldwide distribution, roosting behaviour of bats close to or even in human settlements resulting in close contacts to humans may expose the public to a general risk of infection with bat-borne viruses (Han et al. 2015), such as bat-CoVs. The ability of bats to fly thousands of kilometres (Neuweiler 2000), may also contribute to long-distance dispersal of viruses (Mandl et al. 2018, Smith and Wang 2013). However, these findings should not be misinterpreted in a way to support programmes aimed at a decrease or removal of bat populations in the vicinity of human populations. Bats play a crucial role in the ecosystem (Kunz et al. 2011) and their protection should be a primary goal when implementing public health measures.

Research gaps

As a reaction to the SARS-CoV and lately the SARS-CoV-2 outbreaks, research on bats and CoVs has been intensified. A literature search shows that the SARS-CoV emergence resulted in the publication of approxi-

mately 4000 scientific articles within the first five years, while almost 11.000 articles related to SARS-CoV-2 have already been uploaded as preprint or peer-reviewed article within the last 10 months (bioRxiv 2020). This is a perfect example for event driven research that can obviously only react to outbreaks that have occurred in the past. Due to their high frequency of recombination and the large number of CoV species, a number of studies have highlighted the possible relevance of CoVs for future pandemic situations prior to the COVID19-pandemic, even predicting „disastrous consequences“ (Woo et al. 2006b), and considering CoVs a „time bomb“ (Cheng et al. 2007). To decrease the risk of future pandemic situations caused by CoVs or other disease agents, a preventive approach would be more beneficial, e.g. identifying general replication strategies of virus families or virus genera that are suspected to carry a pandemic risk, in order to develop intervention strategies that will at least provide us with initial measures to control a disease outbreak in its early stage and gain time to develop more targeted interventions. At the same time, vaccine strategies should be developed that can quickly and easily be adapted to any virus, so called “virus X”, that may emerge or re-emerge in the future. Such activities have been ongoing for the last years, and have now considerably accelerated the development of promising vaccine candidates against COVID-19.

Necessary measures and precautions

In order to get to a situation where we are able to act in a preventive manner instead of being forced to react to new outbreaks, we need to monitor the emergence of new viruses. Surveillance should be focused in regions and putative reservoir species that have been the origin of large disease outbreaks in the past. Of particular focus are tropical and subtropical regions (e.g. the Chinese Guangdong Wuhan regions as the putative regions of origin for SARS-CoV and SARS-CoV-2; African countries as the origin of Ebola disease outbreaks and South-East-Asian regions as regions, where outbreaks with highly pathogenic Nipah and Hendra viruses have occurred). All these viruses have been postulated to be transmitted directly or indirectly from bats to humans. Therefore, regular monitoring of bats and other potential reservoir hosts, especially, but not exclusively in tropical and subtropical regions, enables a science-based risk assessment. Factors like habitat destruction, human encroachment or climate change as potential drivers for viral spill-over events and disease emergence should be included in the evaluation. Given the high-throughput sequencing methods that are now available often as portable devices, such screening activities no longer need to be focused on specific disease agents, but can be performed in a more general, unbiased approach.

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Conflict of interest

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