Received: 17 June 2023 | Revised: 10 August 2023 | Accepted: 30 August 2023

DOI: 10.1002/hsr2.1590

PERSPECTIVE

Health Science Reports Open Access WILEY

The abstraction of potentially zoonotic SARS-like coronavirus (BtSY2): A threat to global health

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Abstract

This article highlights the discovery of a new virus lurking in bats in Yunnan province of China. The virus shows phylogenetic and genomic similarity to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, which was the cause of the COVID-19 pandemic. The virus, named Bat SARS-like virus BtSY2, along with four other viruses, has been named a "virus of concern." Recombination events in the viral genome due to coinfection by multiple viruses in related animal hosts can lead to disease emergence, a process that has repeated itself innumerable times throughout history and has given rise to some major viral pandemics. Zoonotic infections, if not contained at the right time, can cause significant harm to the public health sector as well as the global economy. Studies like this are required to acquire a good understanding of the phylogeny of the virus, mechanisms of its transmission, carriers, probable clinical picture, and similarity to previous outbreaks. This will help to devise preventive strategies and, in case of higher probability and hazardous potential of the disease, develop prototype vaccines and drugs to face the outbreak with adequate preparedness.

KEYWORDS

bats, coronavirus, public health, viral zoonoses, virome, zoonoses

The last two decades have seen the emergence of a number of novel viral diseases such as Severe acute respiratory syndrome coronavirus-1 (SARS-CoV-1), Middle East respiratory syndrome-related coronavirus (MERS-CoV), Influenza A virus subtype H1N1, Ebolavirus disease, Nipah henipavirus disease, and the latest of all, SARS-CoV-2. The overpowering effect of such viruses, known to have been transmitted from animals to humans, on health and the economy has brought forth the potential of zoonotic diseases being a major public health problem. Zoonoses is derived from the words "zoon," meaning animal, and "nosos," meaning illness. The World Health Organization defines zoonoses as any infection or disease that is naturally transmissible from vertebrate animals to humans.[1] With 61% of pathogens causing diseases in humans being zoonotic, the chances of zoonotic diseases being "emerging diseases" is twice as compared to non-zoonotic diseases.[2]

Over two-thirds of human viruses are zoonotic in origin,[3] indicating that the spillover of viruses from animals to humans is a more frequent occurrence than one may anticipate. The majority of spillover events end in self-limited infections with no additional human-to-human transmission, as is the case, for instance, with Nipah and rabies viruses.[4] Other zoonotic infections can be transmitted among humans resulting in secondary cases and even establishing chains of transmission. These chains of transmission may remain limited to a few secondary cases, as is the case with Marburg

& monkeypox viruses, or they might result in long-standing outbreaks like MERS-CoV, SARS-CoV-1, COVID-19, and certain avian flu viruses.[4] Finally, as happened with the HIV virus that caused the AIDS epidemic, a few spillover incidents can lead to the microbe's final adaption to the new host, which forms a new stable reservoir. The majority of infections that are currently exclusive to humans, like measles, mumps, rubella, and syphilis, were presumably once spread by other animals.[4] A possible explanation for this could be infection by an ancestral species of the pathogen in the common ancestor of hominins and other primates, which coevolved and cospeciated over time when the lineages diverged.[3,4]

Bats harbor the majority of zoonotic viruses[5] among mammals, which have given rise to several outbreaks in the recent past, the latest being the SARS-CoV-2. This predisposition of bats to act as asymptomatic carriers can be attributed to a specialized immune system, flight-related ecological traits, global distribution, and the ability to flourish in an anthropogenic environment.[6] Bats are known to possess a number of viruses, most of which are acquired from other bat species. The most important factor facilitating inter-species transmission of bat-associated viruses is that bat species are mostly gregarious, leading to greater contact and increased chances of transmission.[6] Other factors contributing to this transmission are the phylogeny (virus originated in a common ancestor and evolved over time), frugivory (virus shared from fruits which are shared or dropped on the ground), and migration (facilitating spatial transmission of the virus).[6]

In light of the pandemic of 2019, the findings of a study conducted by scientists at the Yunnan Institute of Endemic Disease Control are particularly daunting.[7] The southwest Chinese province of Yunnan has been noted as a hub for a variety of bat-borne viruses. Rectum specimens were gathered from 149 different bats of 15 representative species over a duration of 5 years by extensive field sampling in six cities of Yunnan. They extracted and subsequently sequenced RNA separately for each bat. The researchers noticed a high rate of occurrence of numerous viruses affecting a bat at the same point in time. Out of the 149 different samples, 70 tested positive for a minimum of one virus species. Strikingly, approximately 33% were infested by more than one viral species. According to Wang et al., two viral species, namely bat SARS-like virus BtSY1 and bat SARS-like virus BtSY2, are at particular risk for anthropozoonotic transmission (Table 1). Both of these were detected in more than one species of *Rhinolophus* bats and had a relatively high prevalence. A phylogenetic analysis using the conserved nucleotide sequence of the replicase (RNA-dependent RNA polymerase) revealed that both these viruses belong to the subgenus *Sarbecovirus* of the genera *Betacoronavirus*.[7]

TABLE 1 Viruses of concern with their host species.

Name of the virus	Bat host species
Bat SARS-like virus BtSY1	*Rhinolophus thomasi*
	Rhinolophus macrotis
Bat SARS-like virus BtSY2	*Rhinolophus marshalli*
	Rhinolophus pusillus

Coronaviruses are a group of related viruses of the subfamily Orthocoronavirinae. They have a positive sense, single-stranded RNA genome. The first two-thirds of the genome is occupied by sequences known as the open reading frames (ORF 1a & 1b) which encode the replicase polyprotein, which is later cleaved to form 16 nonstructural proteins (nsp1−nsp16). The remaining one-third encodes the four major structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) (Figure 1A provides a schematic representation of the structure and genomic organization of betacoronaviruses). The most distinguishing feature of coronaviruses is the spike proteins. Each spike is a homotrimer of the S protein, which, in turn, is composed of S1 and S2 subunits. The S1 subunit has the receptor-binding domains (RBD) named the N-terminal domain (S1-NTD) and the C-terminal domain (S1-CTD), which help in binding to host cell receptors (Figure 1A,B).

Subsequent analysis of key genes displayed that BtSY1 clustered with SARS-CoV in the RBD, S1-NTD, and N gene trees to form the S-1 clade, whereas BtSY2 & SARS-CoV-2 came together to form the S-2 clade.[7] Intriguingly, BtSY2 also belonged to the S-1 clade in the tree of the RdRp gene, while BtSY1 continued to do so. BtSY2, therefore, seems to represent a crossover between the two lineages. In fact, Wang et al. were able to uncover potential sites of recombination at base pairs 12035−20708, which encodes the nsp7−nsp14. The sequence of this region displayed a significant degree of similarity to SARS-CoV (92.3%). In contrast, the remaining genetic makeup, particularly the sequence encoding the NTD and RBD, exhibited substantial similarities with SARS-CoV-2 (95.15% and 93.70%, respectively). BtSY2 and SARS-CoV-2 have a 92% overall similarity according to whole genome sequencing.[7] However, the presence of whole genome similarity does not necessarily indicate human pathogenicity.

On the other hand, BtSY1, in comparison to previously reported SARS-related viruses like WIV16 and Rs4231, showed the most substantial genetic similarity to human SARS-CoV (93%) at the scale of the entire genome, particularly in the ORF1b (nsp13 and nsp15) and the NTD regions. However, it was comparatively farther away in the ORF1a, RBD, and S2 regions. In the NTD domain, it showed a 98.13% resemblance to SARS-CoV, which is higher than the 88.61% resemblance seen in the RBD domain.[7]

Bat-associated viruses also have the ability to tolerate substitutions in receptor sequences.[8] For example, *Ebolavirus* and MERS-CoV can bind to receptors having up to three substitutions, while SARS-CoV and SARS-CoV-2 can tolerate up to seven substitutions.[8] This facilitates their entry into host cells of new species after a spillover event. Wang et al.[7] used molecular dynamics simulations and a homology prediction method to infer the structure of RBD of BtSY2 to assess the protein's capacity to bind to human ACE-2 receptors. They demonstrated that the RBD had changes in just five amino acids when compared to the SARS-CoV-2, with three of them occurring at the interface, that is, the receptor-binding motif. It has been noted that these three alterations, Q498H, N501Y, and H519N, improve affinity to human ACE-2. Interestingly, the N501Y substitution has also been found in the successional variants of SARS-CoV-2 (Alpha, Beta, Gamma, and Omicron). Moreover, the binding energy & stability of the RBD-human ACE-2 complex between BtSY2 and SARS-CoV-2

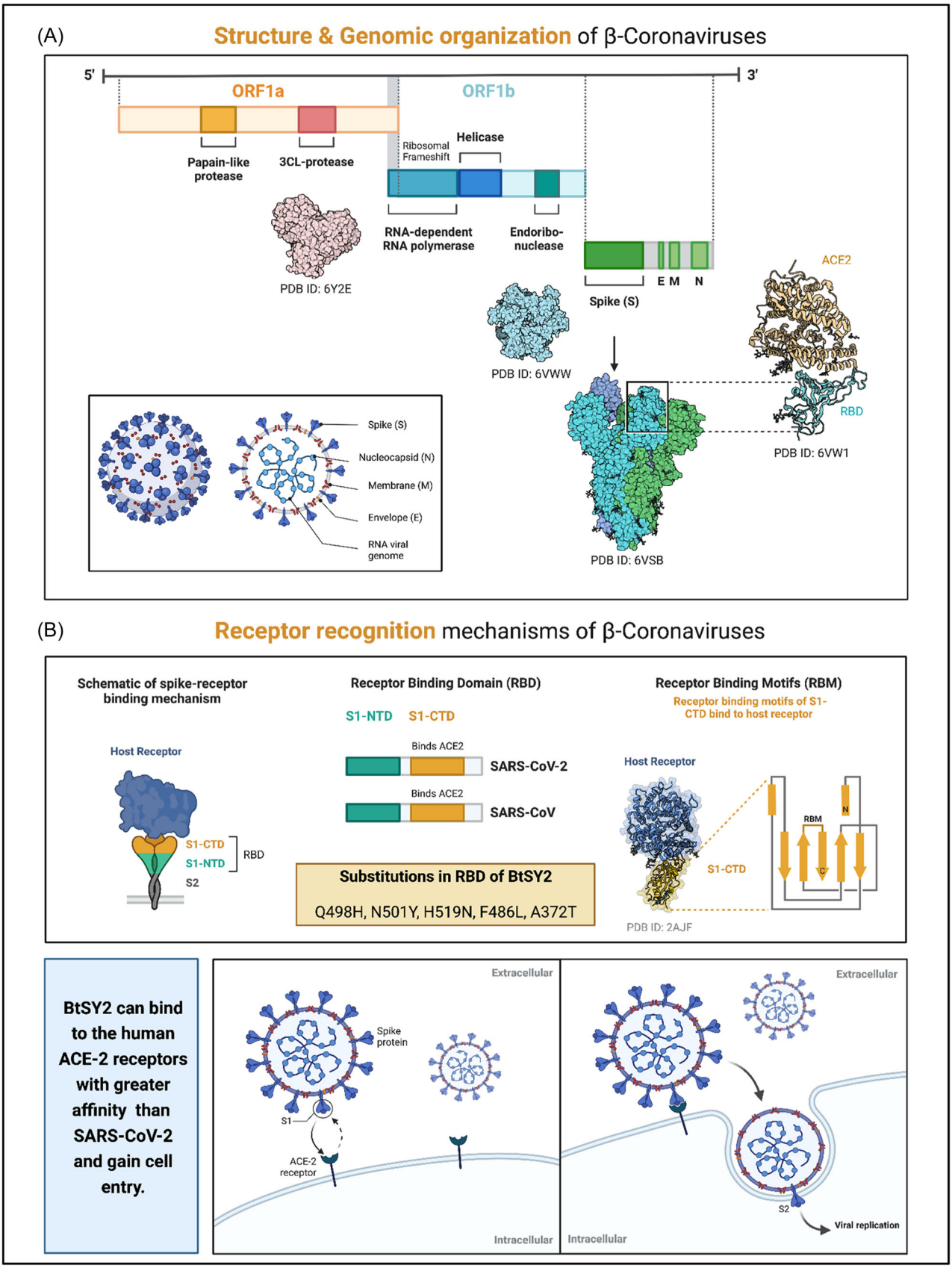

FIGURE 1 (A) Schematic diagram representing the structure and genomic organization of β-coronaviruses. (B) Schematic representation of receptor recognition & binding of coronaviruses. ACE-2, angiotensin-converting enzyme-2; CTD, C-terminal domain; NTD, N-terminal domain; PDB, Protein data bank; RBD, receptor binding domain. *(created with Biorender.com by Agrawal V; Publication license acquired).*

are also extremely comparable, according to molecular dynamics simulations, indicating that BtSY2 may be able to exploit the human ACE-2 receptor for cell invasion (Figure 1B). Furthermore, non-structural proteins nsp7-nsp14 (including nsp12, the replicase) of BtSY2 are closely related to the SARS-CoV proteins.[7] Comparative analysis has revealed that SARS-CoV can multiply more quickly than SARS-CoV-2 in vitro.[9] Additional research indicated that nsp14 is probably linked to virulence.[10] When interpreting all these findings together, it is plausible to infer that BtSY2 may be able to enter the human host cells through ACE-2 receptors and risk an anthropozoonotic outbreak owing to its high virulence and greater affinity.

The study also reports the incidence of coinfection in almost one-third of the virus-positive bats. Coinfection of single host cells with viruses acquired from different species provides the opportunity for recombination among different viral genomes, increasing the genetic diversity of viruses. This high number of diverse viromes circulating among bat species, given the term "known unknowns,"[11] puts public health in jeopardy in the form of emerging diseases, with their characteristics not being accurately predicted. Predicting from the great diversity in the genetic constitution and the geographical distribution of recent bat-associated virus-mediated diseases, these viruses carry the potential of many more such outbreaks in the future.

Given the risk that such viral outbreaks pose to public health and the world economy, it is imperative that measures are taken before the rise of a health crisis. A legalized control over the trading and consumption of potential hosts must be formulated. Screening of the locals and their livestock living in areas where new viral genomes have been discovered can prevent its transmission to other areas. Tian et al.[8] suggested the collaboration of the public and private sectors to develop prototype drugs on viral targets such as the replicase, receptors, or other viral enzymes. Apart from these preventive measures, population-based models are being used to aid in prediction studies to effectively control outbreaks. These models may incorporate data based on previous outbreaks to predict how transmission varies over time or make use of artificial intelligence in predicting epidemic peak and subsequent control time.[12] Such measures can be helpful in prevention as well as preparedness for control of outbreaks before they become unmanageable.

AUTHOR CONTRIBUTIONS

Vibhor Agrawal: Conceptualization; project administration; resources; software; validation; visualization; writing—original draft; writing—review and editing. **Yashita Khulbe**: Conceptualization; validation; writing—original draft; writing—review and editing. **Vikash Jaiswal**: Resources; supervision; writing—review and editing. **Kusum Paudel**: Funding acquisition; resources; writing—review and editing. All authors have read and approved the final version of the manuscript.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors. The lead author, Vibhor Agrawal, had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The lead author, Vibhor Agrawal, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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How to cite this article: Agrawal V, Khulbe Y, Jaiswal V, Paudel K. The abstraction of potentially zoonotic SARS-like coronavirus (BtSY2): a threat to global health. *Health Sci Rep*. 2023;6:e1590. doi:10.1002/hsr2.1590