


REVIEW

SARS-CoV-2, Covid-19, and the debunking of conspiracy theories

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Summary

The emergence of a novel human coronavirus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has engaged considerable awareness and attention around the world. The associated disease, coronavirus disease 2019 (Covid-19), has now involved virtually all 200 countries. The total number of confirmed cases has been much more than in the two previous outbreaks of human coronaviruses, that is, SARS-CoV and Middle East respiratory syndrome coronavirus. In line with the outbreak escalation, false information about SARS-CoV-2 and its associated disease disseminated globally, particularly through online and social media. Believers in conspiracy theories promote misinformation that the virus is not contagious, is the result of laboratory manipulation or is created to gain profit by distributing new vaccines. The most dangerous effect of this widely disseminated misinformation is it will negatively influence the attitudes and behaviours for preventive measures to contain the outbreak. In this review, I discuss common conspiracy theories associated with SARS-CoV-2 and Covid-19 and consider how we can address and counterbalance these issues based on scientific information and studies.

KEYWORDS

Covid-19, HIV, laboratory generated, SARS-CoV-2, vaccine

1 | INTRODUCTION

We are currently facing a pandemic of an acute respiratory syndrome that first emerged in Wuhan, China. Shortly after the identification of cases, a novel human coronavirus (CoV), officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was identified as the responsible agent of this escalating outbreak.^{1–3} The associated disease, officially termed coronavirus disease 2019 (Covid-19), has been confirmed in more than 75 million cases worldwide with more than 1.6 million fatalities. As the name implied, the virus has similarity with SARS-CoV that caused the SARS

outbreak in 2002–2003. At the whole genomic level, SARS-CoV-2 has $\pm 80\%$ identity with SARS-CoV.²

Since the pandemic arose, online and social media (including Facebook, Twitter, YouTube and others) have been continuously updating and discussing these situations.^{4–7} The government and research communities use social media to update the outbreak situation in real-time regularly.⁸ However, with the increasing popularity of social media, one person's opinions and beliefs can also instantaneously spread across the world.^{9,10} Thus, it is not surprising that the media plays a major role in disseminating false information related to viruses, vaccines, as well as diseases.^{11–13} There is a

Abbreviations: ACE2, angiotensin-converting enzyme 2; AIDS, acquired immunodeficiency syndrome; AIV, avian influenza virus; ART, antiretroviral therapy; BAC, bacterial artificial chromosome; BSL4, biosafety level 4 laboratory; CDC, Centers for Disease Control and Prevention; CEPI, the Coalition for Epidemic Preparedness Innovations; Covid-19, coronavirus disease 2019; CT, cytoplasmic tail; DENV, dengue virus; DURC, dual-use research of concern; E, envelope; EC, extracellular domain; FP, fusion peptide; GOF, 'gain-of-function'; HA, hemagglutinin; HAV, hepatitis A virus; HCV, hepatitis C virus; MERS-CoV, Middle East respiratory syndrome coronavirus; NGS, next generation sequencing; PCR, polymerase chain reaction; PEDV, porcine epidemic diarrhea virus; prM, precursor membrane; RBD, receptor-binding domain; RBM, receptor binding motif; S, spike; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TGEV, transmissible gastroenteritis virus; TM, transmembrane; TMPRSS2, transmembrane protease serine 2; WIV, the Wuhan Institute of Virology; WNV, West Nile Virus.

tendency for conspiracy theories to arise during times of crisis, including during the outbreak of emerging viruses or during a public health crisis in general.^{13,14} Accordingly, these media can have a powerful effect by influencing ways of thinking and behaviour in the general public, thereby creating more chaos and negatively affecting containment measures and behavioural changes needed to halt the pandemic.¹⁵⁻¹⁷ This tendency may be exacerbated by mistrust of governments or health regulatory organisations as well as medical and scientific communities so that the public are less likely to obey and practise proper preventive and containment measures.^{18,19} Indeed, belief in a conspiracy is one of the most important driving factors of mistrust of medical sciences and the medical profession.²⁰

Currently, there are some fictitious and pseudoscientific claims as well as conspiracy theories associated with the Covid-19 pandemic.^{19,21} Some people have alleged that SARS-CoV-2 is of laboratory origin and the result of deliberate genetic manipulation. According to these conspiracy theories, a novel virus is a human-made biological weapon, not the result of natural evolution and selection.²²⁻²⁴ SARS-CoV-2 is said to be engineered by the Chinese government with economic or political background and agenda.^{17,19} There are also rumours that SARS-CoV-2 'leaked' from a famous laboratory in Wuhan working on bat CoVs, the ancestral virus of SARS-CoV-2.²³ Believers in conspiracy theories also alleged that this current pandemic was 'created' by physicians or pharmaceutical industries to distribute new vaccines against SARS-CoV-2 for financial profit. Allegations of collusion between pharmaceutical companies and physicians are present to obtain benefits from vaccines. Even worse, some people (including those holding high political office) believe that SARS-CoV-2 and its associated disease Covid-19 do not exist at all.

It is not surprising that one potential contributing factor to the current outbreak is misunderstanding among the general population of the facts and dissemination of conspiracy theories.²¹ Therefore, counteracting this false information is highly important to decrease the possibilities of the virus spreading and thus, threaten global health.^{4,17} These efforts are also pivotal to reduce panic and paranoia during the epidemic crisis.²⁵ In this review, I discuss common conspiracy theories associated with SARS-CoV-2 and Covid-19 and how we can address and counterbalance these issues based on information and studies gained from science.

2 | IS SARS-CoV-2 GENERATED IN THE LABORATORY?

2.1 | Is it possible to 'make' or 'manipulate' a virus in the laboratory?

It is possible to construct ('to make') or manipulate a virus in the laboratory. Scientists perform these kinds of experiments to study the function of specific viral genes, virulence, cell tropism (cross-species transmission), and infectivity. Additionally, it is also valuable to predict the pandemic potential of certain viruses (e.g., influenza virus and CoVs) and finally, to develop antiviral drugs and vaccines.²⁶

Of note, virus manipulation must consider the biosecurity issue of dual-use research of concern (DURC). DURC applies for any type of manipulation resulting in viruses with increased virulence, transmissibility, or host susceptibility. Additionally, it is also applied to experiments resulting in resistance to antiviral drugs, viral variants capable of avoiding established host immunity, and to regenerate extinct (eradicated) viral pathogens. 'Dual-use' means that in addition to societal benefit and humanity, this kind of 'gain-of-function' (GOF) experiment could be misused to generate a bioweapon. In addition, there is a risk of accidental escape that subsequently leads to human diseases or outbreaks. Therefore, research institutes and laboratories that perform this 'dual-use' biotechnology must guarantee and comply with biosafety and biosecurity practices, and do not intend to threaten individual's safety and general community.^{27,28}

The reverse genetic system is commonly used in 'modern' virological research to manipulate viruses. The reverse genetic approach starts with a gene to create a mutant version of viruses because that gene (or its product) is abnormal (genotype-to-phenotype approach). Vice versa, the forward genetic approach is employed in classical virological research by first identifying mutant viruses to identify the abnormality in their genes or proteins (phenotype-to-genotype approach).²⁹ Reverse genetic approaches have been commonly used to construct or 'to customize' positive-strand RNA virus (polio),³⁰ negative-strand RNA virus (rabies virus),³¹ and segmented negative-strand RNA virus (bunyavirus, influenza A and B viruses).³²⁻³⁵

In the influenza virus, GOF experiments have been controversial issues.²⁸ In 2011, two research groups in the Netherlands and the USA performed genetic alteration of the H5N1 virus that resulted in a highly transmissible virus by serial passage in ferrets.^{36,37} In these 'passage experiments' from one animal to another, viruses can be selected or 'forced' to mutate without direct manipulation of their genomes. These reports indicate that the influenza H5N1 virus could potentially acquire a capacity for human-to-human transmission. Construction of the influenza virus can also be performed by cotransfecting plasmids encoding each gene segment.^{38,39} Additionally, plasmid-based reverse genetics was employed to reconstruct the pandemic H1N1 virus of Spanish flu (1918 pandemic).^{40,41}

Several reverse genetic systems to construct infectious cDNA clones exist for CoV, including by *in vitro* ligation. The cDNA fragments spanning the full-length genome of CoV are cloned into separate plasmids incorporated with unique restriction sites at each terminus. Those contiguous fragments are then assembled into infectious clone cDNA *in vitro*.^{42,43} Reverse genetics were employed to rescue the transmissible gastroenteritis virus,^{44,45} porcine epidemic diarrhoea virus strain PC22A,⁴⁶ human CoV 229E,⁴⁷ SARS-CoV,^{48,49} and Middle East respiratory syndrome coronavirus (MERS-CoV).⁵⁰ Currently, this system was employed to reconstruct infectious cDNA clone of SARS-CoV-2 by yeast-based synthetic and bacterial artificial chromosome platforms.^{51,52}

The reverse genetic system can also be performed by constructing chimeric viruses. Chimeric viruses are constructed by joining genomic fragments from at least two different types of viruses.⁴² One of the examples is the dengue virus (DENV) vaccine of the Sanofi Pasteur

CYD-TDV containing four chimeric live flaviviruses. The chimeric construct backbone is the genome of the yellow fever virus (YFV) 17D strain. Two gene segments of each four DENV serotypes (precursor membrane and envelope [E] genes) replaced the position of the corresponding genes in the YFV genome. A similar construct is also used in the DENVax vaccine (Takeda). However, DENVax used DENV serotype 2 (DENV2) genome as the viral backbone.⁵³

Chimeric constructs are also employed in the study of CoV pathogenesis. The spike (S) gene of bat-derived CoV is inserted to replace the corresponding gene of replication competent SARS-CoV as the backbone. This construct is employed to study the potential of animal CoV-derived-S gene to mediate human infection and diseases.⁴² For example, mouse-adapted (MA) SARS-CoV (MA15 strain) was used as the backbone to construct chimeric viruses by replacing its S gene with those derived from bat CoV SHC014 and WIV1 strains.^{54–56} SARS-CoV MA15 strain was generated by serial passaging of the original human SARS-CoV Urbani strain in the respiratory tract of young BALB/c mice.⁵⁴ Both constructs showed efficient replication in human cells, indicating the potential for bat-derived CoV to cause re-emergence of SARS-CoV in the human population.^{55,56}

2.2 | The characteristics of S protein, the hotspot of CoV evolution

Similar to SARS-CoV, SARS-CoV-2 infection is first mediated by engagement of E-anchored S protein to angiotensin-converting enzyme 2 (ACE2)-expressing cells. Thus, the S protein is a key determinant for viral tropism, infectivity, and transmissibility of these CoVs.⁵⁷ Following the first introduction into the human population, SARS-CoV-2 rapidly evolves by accumulating mutations at the S protein.⁵⁸ Thus, scientists mainly focus on S protein to track the origin and evolutionary history of emerging CoVs.

The S protein is structurally divided into three domains: (1) an extracellular domain (EC), and short (2) transmembrane and (3) cytoplasmic tail domains.⁵⁹ The EC domain contains two functional subunits, S1 and S2 subunits. Within S1 subunits, receptor-binding domain (RBD) is present, which specifically recognises ACE2 via its receptor binding motif (RBM). An early study reported variability in the amino acid residues of the RBD between SARS-CoV and SARS-CoV-2.⁶⁰ Based on the SARS-CoV studies, there are five critical residues in the RBD responsible for optimal binding to human ACE2, that is, Y442, L472, N479, D480, and T487, which correspond to L455, F486, Q493, S494, and N501 in SARS-CoV-2 genome.^{22,61} S2 contains fusion peptide and thus, is a membrane-fusion subunit responsible for the fusion process with the cellular membrane of the target cells.⁵⁹ Importantly, the interaction between RBD and ACE2 regulates both cross-species and subsequent human-to-human transmission of SARS-CoV-2.

During viral entry, the S protein of SARS-CoV-2 is cleaved into two subunits, S1 and S2 by host cell-derived protease(s). This event is similar to the cleavage of hemagglutinin (HA) protein of the avian influenza virus (AIV). Of note, the sequence of the cleavage site in HA is

a key determinant for viral tropism and pathogenicity in AIV.⁶² The cleavage site of low pathogenic AIV (LPAIV), containing a single arginine or lysine, is recognised by the host proteases whose expression is restricted to the gastrointestinal and respiratory tract. In contrast, for highly pathogenic AIV (HPAIV), the cleavage site is recognised by the host (furin) protease ubiquitously expressed in various tissues, leading to systemic viral replication and severe disease.⁶²

Therefore, similar to AIV, the host protease is a key factor determining cell tropism and transmissibility of SARS-CoV-2.⁶³ A previous study in MERS-CoV showed efficient proteolytic cleavage of the S protein by adding exogenous trypsin enabled bat-derived MERS-like CoVs (PDF2180-CoV and HKU5-CoV) to efficiently infect human cells.⁶⁴ SARS-CoV-2 requires the transmembrane protease serine 2 (TMPRSS2) for efficient cleavage of the S protein.⁶⁵ Another in vitro study in VeroE6 cell line showed that constitutive expression of TMPRSS2 enhanced its susceptibility to SARS-CoV-2 infection.⁶⁶ It was found that TMPRSS2 inhibitor (camostat mesylate) could block the entry of SARS-CoV-2, raising a possible treatment option.^{65,67} The genome of SARS-CoV-2 contains four amino acid insertions (PRRA) at the junction of S1 and S2 which represent a unique characteristic of SARS-CoV-2 since it is absent in other lineage B beta-CoVs.²²

2.3 | Current evidence supports the natural emergence of SARS-CoV-2

At the whole genome level, SARS-CoV-2 is most closely related to bat SARSr-CoV RaTG13 (sampled from *Rhinolophus affinis* from Yunnan Province, China) that shares 96.1% nucleotide similarity.² A lower nucleotide sequence similarity (~87%–88%) was observed with bat SARSr-CoV ZC45 and ZXC21, collected in Zhoushan, eastern China in 2018.^{2,60} This sequence similarity suggests that RaTG13-like viruses could be the ancestor of SARS-CoV-2. Noteworthy, there are more than 1000 nucleotide differences between SARS-CoV-2 and RaTG13, dispersed throughout the genome. Thus, it is impossible that RaTG13 was manipulated via targeted mutagenesis to generate SARS-CoV-2. For the S region, RaTG13 shares 97.45% sequence identity with that of SARS-CoV-2 at the amino acid level. However, the identity in the RBD region is lower (89.3%).⁶⁸ Bat SARSr-CoV RaTG13 differs from SARS-CoV-2 in four out of five critical amino acid residues in the RBD interacting with ACE2.⁶⁹ Moreover, RaTG13-based pseudovirus is much less efficient in employing human ACE2 to infect cells than that of SARS-CoV-2 pseudovirus.⁷⁰ Collectively, RaTG13 could be the origin of SARS-CoV-2, although it is less likely that RaTG13 is the immediate ancestor of SARS-CoV-2.

Subsequently, pangolin-derived CoVs were identified that share about 85%–91% sequence identity with that of SARS-CoV-2 at the whole genome level.^{69,71} This identity is lower compared to RaTG13 with SARS-CoV-2 (96.1%). However, pangolin-derived CoV has identical residues in five critical amino acids of the RBD region directly interacting with ACE2.^{69,71,72} These identical residues support that those five amino acids can be naturally found in animal CoVs. However, RaTG13 and pangolin CoVs have no furin cleavage site as identified in

SARS-CoV-2. These notable features indicate that it is impossible to manipulate pangolin CoVs to generate SARS-CoV-2. Additionally, pangolin CoVs were identified after the initial outbreak in Wuhan.

Bat sampling in Nengla County, Yunnan Province identified a novel bat CoV from *Rhinolophus malayanus*. This bat-derived CoV, designated as RmYN02, is very closely related to SARS-CoV-2 in most of the genomic region. At the whole genome level, RmYN02 displayed 93.3% nucleotide sequence identity with that of SARS-CoV-2, compared to 96.1% identity between RaTG13 and SARS-CoV-2. In most of the genomic region, particularly in the longest 1ab gene, RmYN02 had 97.2% nucleotide sequence identity with SARS-CoV-2. In the S gene, RmYN02 demonstrated much less nucleotide and amino acid sequence identities to SARS-CoV-2 (71.9% and 72.9%, respectively) compared to the identities between RaTG13 and SARS-CoV-2 (92.9% and 97.4%, respectively).⁶⁸ However, it is worth noting that RmYN02 contained the insertion of three residues of the polybasic cleavage site (P-AA) at the junction between the S1 and S2 regions. Although this insert is not identical to SARS-CoV-2 (i.e., PRRA), its presence in bat-derived CoV strongly supports the idea that this insert can be naturally obtained via recombination. A previous study in AIV demonstrated an acquisition of HA cleavage site typical of highly virulent strain after serial passages in chickens.⁷³ This study indicates that low pathogenic influenza A virus may convert to highly pathogenic strain while naturally circulating in the chicken population.⁷⁴

It is worth noting that the S protein of SARS-CoV-2 binds to human ACE2 with a stronger affinity than that of SARS-CoV.^{70,75,76} However, structural studies indicated that some critical residues in the RBM of SARS-CoV-2 are not optimal for binding to human ACE2, as compared to SARS-CoV.⁶¹ This finding reduces the possibility that SARS-CoV-2 is a laboratory-generated virus; in other words, SARS-CoV-2 emerged through natural evolution selecting the virus with a high receptor-binding affinity to human ACE2.^{22,72}

In conclusion, there are several arguments supporting the natural emergence of SARS-CoV-2. First, the identification of RaTG13 which is closely related to SARS-CoV-2 at the whole genome level. Secondly, the presence of RBD sequence in pangolin CoVs and polybasic cleavage site in RmYN02 that are both similar to SARS-CoV-2. Third, the absence of a published sequence of progenitor viruses with very high similarity with that of SARS-CoV-2 before the pandemic. Last, SARS-CoV-2 likely interacts with ACE2 from various animals, suggesting that the ancestor of SARS-CoV-2 naturally passed through these animals before introduction to humans.⁶¹ All these pieces of evidence strongly support the natural emergence of SARS-CoV-2.

3 | IS SARS-CoV-2 THE RESULT OF A LABORATORY ACCIDENT?

3.1 | Former laboratory accidents involving live viruses, including SARS-CoV

Running a laboratory that works with dangerous and pathogenic microorganisms requires a strict biosafety management program in

line with a culture of safety to protect laboratory workers and the general community. However, there are multiple reasons why laboratory workers may not comply with these biosafety practices when handling biological agents. Thus, it is important to emphasise that it is always impossible to decrease to zero the risk of a laboratory accident.

One of the most prestigious laboratories in the world, the United States Centers for Disease Control and Prevention (the US CDC) has previously reported major biosafety accidents. These accidents include the unintentional release of viable *Bacillus anthracis* spores due to the implementation of modified and unauthorised inactivation protocols of bacterial spores. About 75 staff were potentially exposed to live *B. anthracis* and were monitored intensively.⁷⁷ Another biosafety event was cross-contamination of a LPAIV H9N2 with a HPAIV H5N1 and subsequent shipment of this contaminated culture.⁷⁸ Cross-contamination also led to the first laboratory-acquired human cowpox virus infection in the US in a laboratory worker conducting research on nonorthopoxvirus.⁷⁹ Importantly, the pandemic H1N1 virus in 1977 was likely associated with accidental laboratory release of the virus isolated in 1950.^{80,81}

Accordingly, any laboratories working with CoVs must have standardised laboratory practices to minimise laboratory-associated infection.⁸² However, several reports have documented transmission of SARS-CoV in laboratory settings. The first case was involved a 27-year-old student working in a laboratory in Singapore. Epidemiologic investigations revealed that it was likely that this patient acquired the infection due to contamination of the West Nile virus sample with SARS-CoV. Fortunately, no further human-to-human transmission was identified.⁸³ The second case was a 44-year-old researcher testing herbal remedies against SARS-CoV. Investigations revealed that this event was likely due to contact with waste liquid spilled in the biosafety level 4 laboratory (BSL4).⁸⁴ The third case was the worst since it spread beyond the affected laboratory personnel. In this case, one graduate and one post-doc student were likely exposed to SARS-CoV at the Institute of Viral Disease Control of the Chinese CDC. Unfortunately, one death of contact cases was reported, eight people were confirmed or suspected, and hundreds were placed in quarantine.⁸⁵ These three cases raised concerns about biosafety issues while handling SARS-CoV in the laboratory following the initial outbreak.

3.2 | SARS-CoV-2 and laboratory release theory

Following the first SARS outbreak in 2002, a lot of efforts were made to conduct years of surveillance in the bat population. Scientists from the Wuhan Institute of Virology (WIV) sampled a particular cave near Kunming city, Yunnan Province, China, inhabited by multiple species of horseshoe bats. For 5 years (April 2011–October 2015), they collected 602 anal swabs and faecal samples and tested for the presence of CoVs. They found 11 novel SARSr-CoVs closely related to SARS-CoV and other bat SARSr-CoVs.⁸⁶ Another exhaustive 5 years bat surveillance (2010–2015) was conducted in numerous

Chinese provinces by the same institute. Importantly, phylogenetic analysis revealed that SARS-CoV-2 may derive from bat CoVs in *Rhinolophus* spp.⁸⁷ Intense bat surveillances were also conducted by various institutes in China.^{88–91}

Wuhan, the epicentre of the outbreak, is home to two research laboratories, that is, the WIV and the Wuhan Centre for Disease Control and Prevention (the Wuhan CDC). Few laboratories in the world are designated BSL4, a maximum security laboratory, and the WIV is one of them and is the first and the only BSL4 laboratory in China. The Wuhan CDC is a BSL2 laboratory facility that also kept bat CoVs. This situation is different from the former SARS outbreak (2002–2003) that first emerged in Guangdong province, China. There are no laboratories working with live viruses near Guangdong province.

Therefore, there are discussions and unjustified theory—promoted by the US President Donald Trump—whether one of the two laboratories in Wuhan could have been the source of SARS-CoV-2.⁹² This theory emerged due to extensive research and collections of numerous bat SARS-CoVs and the close proximity of the WIV and the Wuhan CDC to the Huanan Seafood and Wildlife Market. There is an accusation that these viruses accidentally infected laboratory workers, either from the virus sample or the animal laboratory. Another accusation is that animals in the Wuhan laboratory escaped, or were smuggled, and sold in the Huanan market.⁹³ They also argued that Wuhan is far away (1500-km away) from Yunnan, the home for the horseshoe bats known to harbour SARS-CoV. Should the virus have a natural origin, it would be more likely to first emerge in Yunnan, not Wuhan.^{93,94}

One of the hypothetical origins of SARS-CoV-2 is that of natural selection occurring in humans following zoonotic transfer.²² The first case with SARS-CoV-2 may have had no contact history with the wildlife market, raising a possibility of undetectable chains of human-to-human transmission (infected laboratory worker to people outside the facility) prior to the outbreak.⁹⁵ Hence, there is a suspicion that the ancestral virus of SARS-CoV-2 was derived from the Wuhan Laboratory infecting the laboratory workers and subsequently, led to the outbreaks.

Despite these massive online speculations, scientific evidence does not support this accusation of laboratory release theory. Yet, it is difficult and time-consuming to rule out the laboratories as the original source completely. It is highly unlikely that SARS-CoV-2 was accidentally released from a laboratory since no direct ancestral virus is identified in the current database. The complete genome of SARS-CoV-2 is deposited in the public database shortly after the outbreaks based on advanced next generation sequencing technologies.⁹⁶ There is also no record of laboratory accidents at the WIV, and the former SARS-CoV accident did not occur at the WIV. Additionally, a recent study further supported the natural origin of SARS-CoV-2 from viruses found in *Rhinolophus* sp.⁸⁷ However, an independent forensic investigation is probably the only course of action to prove or disprove this speculation. Finally, we can always learn from the previous SARS-CoV accidents that the best biosafety practices must be implemented to prevent any accidents in the future.⁸²

4 | SARS-CoV-2 AND VACCINE CONSPIRACY

It has been known that social media is a powerful promoter of increasing sentiments of vaccinations.⁹⁷ Conspiracy theory is one of the methods used by anti-vaccine activists to provoke the general population to refuse vaccination.^{9,12,16,11} They are led to believe that the purpose of the vaccination program is solely to make a profit, either from selling the vaccine itself or from treatment due to vaccine side effects.⁹ On the other hand, however, anti-vaccination activists continuously claim themselves as 'pro-science', 'pro-research' and 'pro-information'. Anti-vaccination activists provide 'educational materials', which they claim as scientific evidence for the 'harmful effects of vaccination', to bolster their personal views.^{16,11}

A study reported that anti-vaccine conspiracy beliefs and exposure to anti-vaccine conspiracy theories negatively associate with vaccine intentions.⁹⁸ The effect of an anti-vaccine campaign could be seen from the survey, which showed that only 60% of the respondents contacted in New York stated that they were willing to get SARS-CoV-2 vaccine if it was available.¹⁹ Surely, this condition needs to be taken seriously. Distrust in the SARS-CoV-2 vaccine also increases with the false news reported that one of the clinical trial subjects of Covid-19 vaccine developed by the Oxford University finally died due to disease complication.¹⁹

4.1 | SARS-CoV and MERS-CoV outbreaks were also associated with vaccine conspiracy

CoV outbreaks have not only happened once. There were two previous outbreaks of novel CoVs, that is, SARS-CoV (2002–2003) and MERS-CoV (2012).⁹⁹ These two outbreaks experienced the same association with conspiracy theory. It was said that the SARS-CoV and MERS-CoV were deliberately made and created to 'sell the vaccines'. However, the facts show a big difference.

When the SARS-CoV outbreak started in November 2002, many scientists, academics (universities, research institutes), and pharmaceutical companies were competing to make vaccines. At that time, more than 30 vaccine candidates were made by countries in the world that were designed to control SARS-CoV outbreak.¹⁰⁰

Some of the vaccine candidates had even entered the clinical trial phase (NCT00533741 and NCT01376765). However, the SARS-CoV outbreak was then successfully stopped without a vaccine when that clinical trial phase was still ongoing. Then, all phases of the SARS-CoV vaccine clinical trial were stopped since no new cases were reported, and eventually, SARS-CoV was declared eradicated.^{101,102}

This statement was explained by the Institut Pasteur in France, which was involved in developing the SARS vaccines:

'The vaccine candidate for SARS-CoV was not tested on humans because by the time it was ready, the outbreak had fortunately come to an end and there were no more patients to test it on'.¹⁰³

The same situation also happened to MERS-CoV vaccine candidates. More than 40 MERS-CoV vaccine candidates were developed during the MERS-CoV outbreak.¹⁰⁴ Similarly, some of the vaccine

candidates had even entered the clinical trial phase (e.g., NCT03615911, NCT03399578, NCT04170829, and NCT04119440).

However, the MERS-CoV outbreak was successfully suppressed without vaccines. Currently, there are no SARS-CoV or MERS-CoV vaccines found in the market. These two outbreaks were repressed by applying strict containment measures of isolation, quarantine, contact tracing, intermediate host identification, and lockdown.¹⁰⁵ If a pandemic is always associated with a conspiracy to sell vaccines, the true victims of the SARS-CoV and MERS-CoV outbreaks must be the institutions and the companies who took a lot of effort to develop vaccine candidates that were never used.

4.2 | Bill Gates deliberately created SARS-CoV-2 to make profits by selling vaccines

People who have this idea might be inspired by Bill Gates's statement during a TED Talk in 2015 about the possibility of a global pandemic in the future. However, Bill Gates did not specifically mention that the pandemic will occur in 2020.¹⁰⁶

The predictions about the possibility of a pandemic in the future, especially those involving CoVs, have been known by many scientists (virologists and epidemiologists) throughout the world. This possibility is closely related to CoV characteristics, which are the presence of an animal reservoir (bat) and the frequent occurrence of genetic recombination between different strains of CoV, coupled with the habit of consuming wild animals as food.

The scientists in the WIV China, where the epicentre of the initial Covid-19 outbreak began, are examples of scientists who predict this possibility. They wrote, 'Thus, it is highly likely that future SARS- or MERS-like CoV outbreaks will originate from bats, and there is an increased probability that this will occur in China. Therefore, the investigation of bat CoVs becomes an urgent issue for the detection of early warning signs, which in turn minimises the impact of such future outbreaks in China'.¹⁰⁷

Back in 2006, Larry Brilliant, an epidemiologist with a major role in smallpox eradication also warned of the possibility of a pandemic in the future. At that time, he predicted that one billion people would be infected, and 165 million people would die from it. The prediction is answered now, 14 years later.¹⁰⁸ In the same year, a group of scientists, including those from the WIV, stated that the discovery of SARS-like-CoVs in bats indicates that another SARS epidemic may reoccur in the future.¹⁰⁹ Besides, in 2019 WHO stated that one of the threats to global health was a pandemic of an influenza virus. However, they could not predict when it might happen or how severe it might be.¹¹⁰

The Gates Foundation predicts that a well-tested vaccine will only be available in the next 12–18 months.¹¹¹ However, the misinformation that Gates himself created the virus to deploy vaccines to control people reached Roger Stone, a former adviser to the US President Donald Trump. In April, he stated that he would never trust the vaccine that Gates had funded.¹¹² If SARS-CoV-2 really was the result of Bill Gates' engineering, it surely needs not to have

waited that long. He should have the vaccine ready in 2020 when many countries are at the peak of this pandemic. He would not need to wait for the next few months or years and compete with many countries that are also developing vaccine candidates against SARS-CoV-2 if he really had planned this.

Of note, Bill Gates is a cofounder and funder of the Coalition for Epidemic Preparedness Innovations (CEPI). CEPI is a collaborative approach to improve global preparedness against future pandemics. The main mission of CEPI is developing vaccine candidates for viruses with pandemic potential and ensuring equal access to vaccines during pandemic crises.¹¹³ Currently, there are more than one hundred Covid-19 vaccine candidates from various countries competing to become the first institution or company to succeed in developing an effective vaccine against SARS-CoV-2, some of them have already completed phase 3 clinical trials and three have been licenced so far.¹¹⁴

Another growing conspiracy issue states that Covid-19 vaccine will be contaminated with a microchip to track humans and be connected to supercomputer big data.¹¹² Although it has no sense, this hoax has spread widely. It seems to have come from Bill Gates's statement when he was asked how to maintain the country's economic conditions while still applying social distancing on Reddit March 18, 'Reddit Ask Me Anything session on Covid-19'.¹¹⁵

He suggested a certificate for anyone who is immune from the Covid-19, either because they are infected then recovered, or those who receive the Covid-19 vaccine once it is available. Thus, immune people can support economic activities, and the rest (nonimmune people) can remain to do social distancing. Bill Gates said, 'Eventually, we will have some digital certificates to show who has recovered or been tested recently or when we have a vaccine who has received it'.

This answer was then twisted by a Biohackinfo conspiracy site titled: 'Bill Gates will use microchip implants to fight CoV'.¹¹⁶

Moreover, a microchip for human tracking is not as easy to be implanted through an injected vaccine (zero chance). Obviously, it does not make sense, but this does not prevent it being believed.¹¹²

4.3 | Anti-vaccine movement and its impact on Covid-19 vaccine

The development and approval of vaccines during health emergencies and crises have their own challenges for public acceptance, as we have previously experienced during the pandemic of influenza virus H1N1 in 2009.¹¹⁷ Vaccines of SARS-CoV-2 may be targeted by similar anti-vaccine campaigns. They will say that the SARS-CoV-2 vaccine was made too fast; therefore, it did not pay attention to the safety aspects of the vaccine.^{19,118} Indeed, vaccine harms are commonly used as anti-vaccine advertising messages on Facebook.¹⁸ They will also campaign that Covid-19 'is not dangerous, not as bad as reported', or 'the medical world purposely exaggerates the problem of Covid-19 in order to sell the vaccine'. This situation is similar to the Zika outbreak, where the Zika virus was deliberately 'blamed' as the cause of microcephaly for the successful sale of Zika vaccine.¹⁴

Combined with mistrust of medical sciences and the profession, anti-vaccination activists may oppose any mandatory Covid-19 vaccines if these are implemented.

Due to the massive anti-vaccination campaigns on social media, we need to pay more attention to understanding and counteracting the critical concerns of vaccine hesitancy.¹⁵ We also hope that the Covid-19 pandemic becomes an opportunity to campaign on the importance of vaccination. The general population can see for themselves the impact of a disease outbreak in which a preventive vaccine is not available yet. Indeed, this Covid-19 pandemic is a good reminder of the historical success of vaccines.¹¹⁶

5 | SARS-CoV-2 AND HIV

HIV and its associated disease, AIDS, have been the subject of conspiracy theories for a long period of time. Conspiracy believers have alleged that some types of vaccines, including polio vaccines, have been deliberately contaminated with HIV. Additionally, a significant proportion of the African American community believes that HIV/AIDS is a human-made or federal government-made to 'eliminate' Black people and other minority groups.^{119,120} Indeed, widespread beliefs that HIV is a genocidal conspiracy have a notable impact on HIV prevention and treatment behaviours, including reduced condom use, HIV testing, compliance with antiretroviral therapy, and participation in HIV-related research.^{20,121}

A suggestion that SARS-CoV-2 might be the result of artificial manipulation involving the HIV-1 genome emerged due to the presence of a manuscript deposited in *bioRxiv*, a manuscript sharing website prior to any peer-review process. The authors claimed that SARS-CoV-2 had four HIV-derived insertions in the S protein. The authors further speculated that these HIV-derived insertions may enhance binding affinity to the host cell receptors (ACE2) and also expand the host cell tropism of SARS-CoV-2. The authors then suggest that SARS-CoV-2 might be intentionally generated by genetic manipulation employing gene fragments derived from the HIV-1 genome.¹²²

To my knowledge, there are two rebuttal papers published to dispute these original claims.^{123,124} Comprehensive and careful analysis showed that these insertions are present in multiple eukaryotic and prokaryotic viruses, and thus, not HIV specific. Noteworthy, those four insertions are very rarely found in the HIV-1 sequence database, indicating that these insertions are not derived from the HIV-1 genome.¹²³ In addition, comparative analysis with other CoV strains demonstrated that these insertions are identified in three strains of bat-derived CoVs (ZC45, ZXC21, and RaTG13 strains).^{123,124} These results clearly showed that these inserts had naturally existed before the emergence of SARS-CoV-2. Careful structural analysis also showed that these insertions are not located in the RBD of the S protein, in contrast to original assumptions of the *bioRxiv* paper.¹²⁴ Because of considerable controversies and concerns within the scientific community, the authors have finally withdrawn their original report. However, claims that the virus is laboratory-created are more difficult to withdraw.

6 | SARS-CoV-2 AND EXOSOMES

Exosomes are small endosomal-derived microvesicles secreted by cells to transport biomolecules such as proteins, mRNA, microRNAs, and lipids to the recipient (target) cells. Exosomes are involved in intercellular communications between cells by altering the recipient cell's gene expression and overall function.¹²⁵ Exosomes are released both during normal physiological conditions and during pathologies, including viral infections and malignant transformations.^{126,127} Thus, exosomes have potential to be employed as diagnostic and prognostic molecular biomarkers as well as novel therapeutic modalities.¹²⁵

Exosomes have gained popularity during the Covid-19 pandemic since they are mentioned as one argument by Andrew Kaufman that SARS-CoV-2 does not exist. To support his argument, Andrew Kaufman stated that what was detected by PCR is actually not a specific virus, but exosomes.¹²⁸ It is clearly seen that this claim is extremely illogical and against common sense since SARS-CoV-2 was not solely detected and characterised by PCR but also other modalities, including viral cell culture, whole-genome sequencing, and electron microscopy technologies.

Indeed, the virus (initially named as 2019-nCoV) was first isolated from bronchoalveolar-lavage samples collected on 30 December 2019 by passaging in human airway epithelial cells, Vero E6, and Huh-7 cell lines.¹ The viral structure of SARS-CoV-2 and the cytopathic effect of the infected cells can be clearly visualised by a transmission electron microscopy. Importantly, two nearly full-length and one full-length sequences were then submitted and published in GISAID.¹ Subsequently, the genetic sequences of thousands of SARS-CoV-2 strains isolated from all over the world have also been published in GISAID, which have an approximate length of 30,000 bases.¹²⁹

Interestingly, in his video, Kaufman twisted Dr. James E. K. Hildreth's statement who spoke about HIV in his article, which he quoted as '... the virus is fully an exosome in every sense of the word' to support his claim that a contagious infectious virus does not exist at all.¹²⁸ However, what Dr. Hildreth meant in his paper was that HIV is a virus that hijacks the exosomes in the host cells for both biogenesis of viral particles and viral spread.¹³⁰ It is one common mechanism of immune evasion by pathogenic viruses, including hepatitis A virus (HAV) and HCV, since it may facilitate escape from neutralising virus-specific antibodies.^{126,127} Clearly, Kaufman intentionally skewed Dr. Hildreth's statement to support his claim that SARS-CoV-2 is not a virus, but it is an exosome.¹²⁸

Moreover, since SARS-CoV-2 is an RNA virus, while exosome can also contain RNA, it is possible to be mistakenly detected, according to Kaufman's statement.¹²⁸ Obviously, this is Kaufman's misunderstanding because even though both of them are indeed RNA, the human exosome merely contains human-derived small RNA (mRNA and microRNA) and cannot release another RNA's species (e.g., virus-derived small RNA). The human exosome is also unable to release virus-derived small RNA if the virus itself does not exist in human cells. Exosomes can only release virus-derived small RNA if the cell has been infected with a virus.¹³¹ Exosomes can also transport fully infectious viral particles, including their genetic material, as has been

shown in HCV.¹²⁶ Today's technology has been sophisticatedly developed since deep sequencing technology can distinguish between the chain of virus- and human-derived RNA, so it is impossible to mistakenly confuse these clearly different RNA sequences.

7 | CONCLUSIONS

Conspiracy theories are commonly easy to disseminate and propagate, yet difficult to refute. On one side, 'science' is often used to support conspiracy theories. The believers of conspiracy will continuously search for 'scientific evidence' to defend their claims that SARS-CoV-2 is a human-made virus, such as the case with an HIV-1 bioRxiv paper that has been retracted. On the other side, however, the believers of conspiracy theories criticise sciences when scientific evidence argues against their beliefs. Thus, the issues are clearly on their ideology, not the science. We are now facing over-critical communities which, unfortunately, are not very knowledgeable. The situation is worsened by the lack of trust in government, research institutions, and pharmaceutical industries. Indeed, uncertainty regarding the origin and health consequences of the Covid-19 pandemic may increase the likelihood of people refusing the Covid-19 vaccine once it is approved. Therefore, physicians and health authorities should focus and design targeted interventions to address these issues. The current pandemic of Covid-19 could serve as a starting point for scientists and health authorities to educate the general public and interfere with their decision-making process about vaccination. Finally, governments need to deliver clear, consistent, and transparent information during this pandemic crisis to regain the trust of the general public.

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CONFLICT OF INTEREST

The author declares no conflict of interest.

AUTHOR CONTRIBUTION

Mohamad S. Hakim. *Conceptualisation, writing original draft, editing, and finalisation.*

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