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**Arijit Chakravarty**  
@arijitchakrav



Let 'er rip leads to rapid SARS-CoV-2 evolution. How bad could things get, really?

We take a closer look at that question in our latest review (preprint below).

(h/t @lfwhite14, @ManishSagar\_MD, @madistod, @debravanegeren)

[osf.io/k4hb3/\(1\)](https://osf.io/k4hb3/(1))

5:19 AM · Feb 25, 2023 · **138.3K** Views



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**Arijit Chakravarty** @arijitchakrav · Feb 25



Replying to @arijitchakrav

A point that is often made is that widespread transmission and rapid viral evolution should make the virus become milder over time. We and others have pointed out that this is not the case for this virus (h/t [@ariskatzourakis](#), [@tryangregory](#)). (2)

4

77

333

9,566



**Arijit Chakravarty** @arijitchakrav · Feb 25



There's no reason to expect the virus to "settle in" due to rapid evolution- we showed in a recent paper that the virus could kill almost everyone it infects with minimal impact on its fitness (ability to succeed evolutionarily): [mdpi.com/2673-8112/2/12...](https://mdpi.com/2673-8112/2/12...) (3)



mdpi.com

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The strategy of relying solely on current SARS-CoV-2 vaccines to halt SARS-CoV-2 transmission...

3 101 325 12K



**Arijit Chakravarty** @arijitchakrav · Feb 25

Our paper above suggested that virulence may be under drift, at a minimum (meaning that it may increase or decrease over time, based on luck). But what if there were biological advantages to increased virulence? (4)

1 20 198 5,915



**Arijit Chakravarty** @arijitchakrav · Feb 25

That's not something that can be addressed in a modeling paper, but fortunately for us, there is an enormous body of literature on this virus at present (193k papers), making it (already) one of the most studied pathogens of all time! (5)

	<i>Pubmed entries</i>	
	<u>Total</u>	<u>2020-2023</u>
<b>HIV</b>	408,125	52,179
<b>Tuberculosis</b>	285,281	29,201
<b>Hepatitis</b>	285,070	32,432
<b>SARS-CoV-2</b>	193,440	193,440
<b>Influenza</b>	153,351	23,038
<b>Malaria</b>	108,899	14,686
<b>Cholera</b>	37,010	2,504
<b>Dengue</b>	28,491	6,304
<b>Smallpox</b>	11,613	816
<b>SARS-CoV-1</b>	151,388	148,494

1 32 209 9,674



**Arijit Chakravarty** @arijitchakrav · Feb 25

So, we dug into that literature a bit for clues to this question, using a simple lens- what changes in virus biology are likely to lead to both an

increase in virulence and viral fitness (transmission potential)? This is a simple question, but a powerful one.(6)

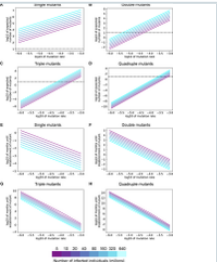
1 19 185 5,247



**Arijit Chakravarty** @arijitchakrav · Feb 25

Over 2yrs ago we predicted rapid immune evasion of the spike based on a similar observation- the virus had essentially unlimited mutational space to increase its immune evasion without impacting fitness.

So here we asked the question more broadly. (7)



[journals.plos.org](https://journals.plos.org)  
 Risk of rapid evolutionary escape from biomedic...  
 The spike protein receptor-binding domain (RBD) of SARS-CoV-2 is the molecular target for many ...

1 39 207 6,577



**Arijit Chakravarty** @arijitchakrav · Feb 25

In this review, we looked at the biological processes involved in viral pathogenesis (infection, replication) & immune evasion/suppression. We found many examples where the virus could increase fitness by increasing its ability to suppress/evade the immune system, e.g. (8)

1 36 176 6,308



**Arijit Chakravarty** @arijitchakrav · Feb 25

Both loss-of-function immune evasion & gain-of- immune suppression have been reported extensively in the literature. There is a whole panoply of viral genes whose function it is to suppress the immune system directly. (9)

1 31 191 5,625



**Arijit Chakravarty** @arijitchakrav · Feb 25

Notably, mutations in these genes are not expected to the efficiency of infection or transmission, meaning that the virus is free to fine-tune this machinery without impacting fitness. That's a lot of evolutionary whitespace for the virus to explore!(10)

2 25 169 5,736



**Arijit Chakravarty** @arijitchakrav · Feb 25



Another potential way in which the virus can access increased virulence is through antibody-dependent enhancement (ADE), where non-neutralizing antibodies help the virus enter host cells- in effect, playing for the wrong team!(11)

2 32 174 4,915



**Arijit Chakravarty** @arijitchakrav · Feb 25



ADE occurs in dengue, for example- when Abs from a 1st infection bind to an infecting viral particle during a 2nd infection with a different serotype, they can't neutralize the virus, but instead, help the virus infect immune cells more efficiently. (12)


1 24 159 4,614



**Arijit Chakravarty** @arijitchakrav · Feb 25



We've pointed out in a separate preprint that the risk of serotype formation (and hence ADE) is very much on the table for this virus, given enough time for viral evolution). It hasn't happened yet, but the risk remains real. (13)

 <p>medRxiv THE PREPRINT SERVER FOR HEALTH SCIENCES</p>	<p>medrxiv.org Antibody escape, the risk of serotype formation, ... As the COVID-19 pandemic progresses, widespread community transmission of SARS-...</p>
--	--

1 36 167 5,262



**Arijit Chakravarty** @arijitchakrav · Feb 25



Several aspects of SARS-CoV-2 biology also factor into the intrinsic virulence of viral variants. Many of these aspects are likely to have a neutral impact on transmissibility (and hence, from an evolutionary standpoint, be under drift rather than natural selection).(14)

1 14 132 3,906



**Arijit Chakravarty** @arijitchakrav · Feb 25



But some changes may yield a benefit to the virus for fitness, while also increasing virulence. For example, tighter binding of the viral spike protein to ACE2, or an increase in the viral load, or the ability to enter host cells through other pathways (altered tropism).(15)

1 23 148 4,006



**Arijit Chakravarty** @arijitchakrav · Feb 25



The thing is- none of these mechanisms is theoretical. They've all been demonstrated at one point or the other, just not at the same time in an evolutionarily successful SARS-CoV-2 variant. Lucky for us- so far, but luck is not a good basis for a public health strategy.(16)

1 51 204 6,870



**Arijit Chakravarty** @arijitchakrav · Feb 25



The rapid pace of viral evolution means deadlier variants can- by dumb luck alone- be outcompeted by less deadly variants. If virulence and transmissibility are uncorrelated, or weakly correlated, you could expect viral interference to do some of the heavy lifting for us. (17)

1 18 148 3,722



**Arijit Chakravarty** @arijitchakrav · Feb 25



But viral evolution is not our friend (📖👉). And viral recombination is afoot already, letting the virus access big changes in properties in a relatively short span of time. Recombination makes things even more volatile- it's not hard to see why! (18)



**Arijit Chakravarty** @arijitchakrav · Feb 5

Viral evolution is not our friend: a 📖 about the future of covid-19.

What does the future hold for us with COVID-19?

In a recent preprint (h/t @madistod), we continue to explore a question that's concerned us since the beginning of the pandemic: (1)

[medrxiv.org/content/10.1101...](https://medrxiv.org/content/10.1101/2023.02.05.23020001)

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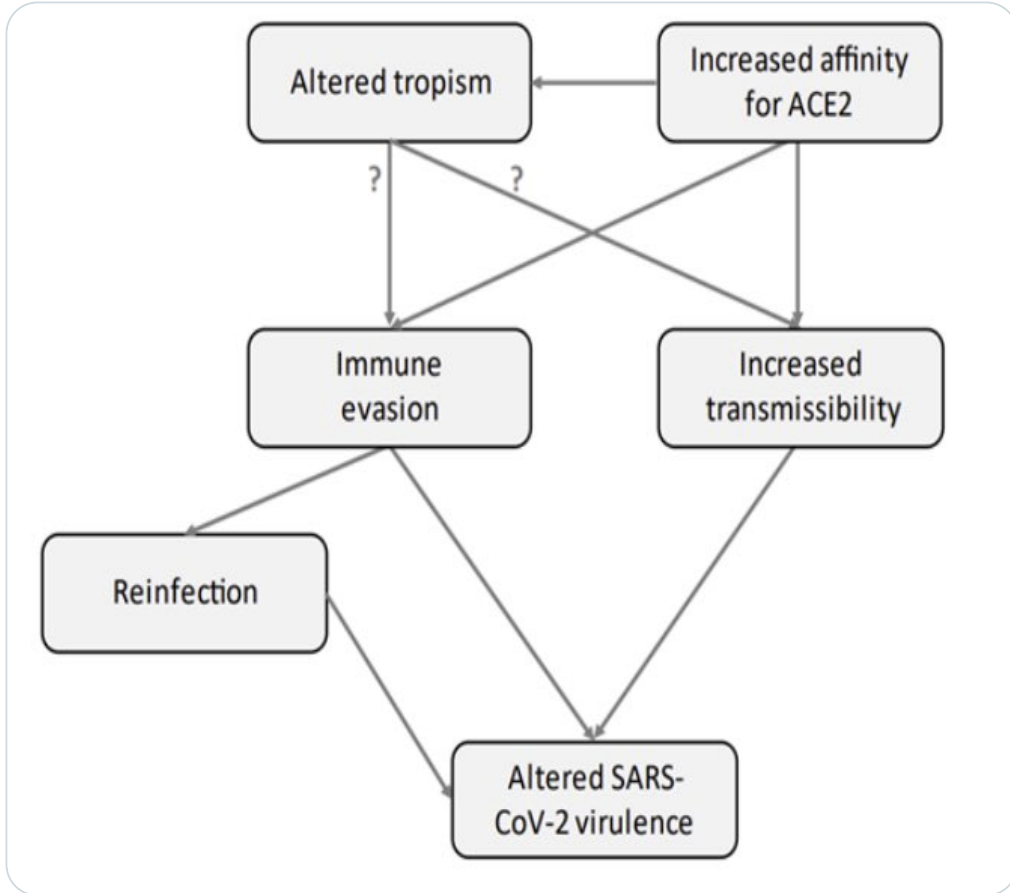
2 38 176 7,685



**Arijit Chakravarty** @arijitchakrav · Feb 25



Our review suggests that one of these days, along will come a variant with properties that \*we've seen before\*. And these properties may well lead to a higher infection fatality rate for a highly transmissible variant. There are many ways in which this could all go sideways. (19)




1 44 172 5,240



**Arijit Chakravarty** @arijitchakrav · Feb 25



A point we've made before is that under 'let it rip', even relatively small increases in IFR could be devastating. So, such a situation, while entirely predictable, will also be something that we are caught reacting to. (20)



mdpi.com  
 Endemicity Is Not a Victory: The Unmitigated Do...  
 The strategy of relying solely on current SARS-CoV-2 vaccines to halt SARS-CoV-2 transmission...

1 42 192 4,468



**Arijit Chakravarty** @arijitchakrav · Feb 25



Because increases in fatality rates are a lagging indicator, and only become apparent after a ton of people have been infected.

Unfortunately, a reactive public health strategy in the face of rapid viral evolution is just not good enough. It's a disaster waiting to happen.(21)


1 63 238 6,988



**Arijit Chakravarty** @arijitchakrav · Feb 25



We are in year 4 of what looks like a long-term pandemic & only a few months into the scenario where countries worldwide have opted for unlimited viral transmission. We know that relying on vaccines alone will not slow the evolution of this virus. (22)

 <p>medRxiv THE PREPRINT SERVER FOR HEALTH SCIENCES</p>	<p>medrxiv.org Vaccines alone cannot slow the evolution of SAR... The rapid emergence of immune-evading viral variants of SARS-CoV-2 calls into question the ...</p>
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4 61 223 5,728



**Arijit Chakravarty** @arijitchakrav · Feb 25



The virus still has explored only a vanishingly small portion of its evolutionary space. Our review suggests that the quadrillion monkeys on typewriters working tirelessly to improve the virus are not done with us yet. We could still be in for some really nasty surprises! (23)

1 49 232 7,389



**Arijit Chakravarty** @arijitchakrav · Feb 25



This review is not aimed at predicting what will happen next. No one knows that.

It's simply pointing out that the biological basis (direct gain or loss of function resulting from mutations) for accessing higher virulence has been documented for this virus already.(24)

1 23 181 3,740



**Arijit Chakravarty** @arijitchakrav · Feb 25



The bottom line (again!) is that we need to take viral evolution seriously. Our work suggests the virus has showed behaviors that should be cause for concern already. Rather than explaining why we shouldn't panic, public health should focus on mitigating worst-case scenarios.(25)

5 93 337 12.4K



**Arijit Chakravarty** @arijitchakrav · Feb 25



This is the link:

	<p>osf.io Pathways to altered virulence of SARS-CoV-2 The recently emerged SARS-CoV-2 virus has led to a prolonged pandemic characterized by ongoing ...</p>
--	--

8   34   155   5,361  



**Arijit Chakravarty** @arijitchakrav · Feb 25



Replying to @arijitchakrav

Looks like this is the right link:

	<p>osf.io Pathways to altered virulence of SARS-CoV-2 The recently emerged SARS-CoV-2 virus has led to a prolonged pandemic characterized by ongoing ...</p>
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2   27   103   3,523  

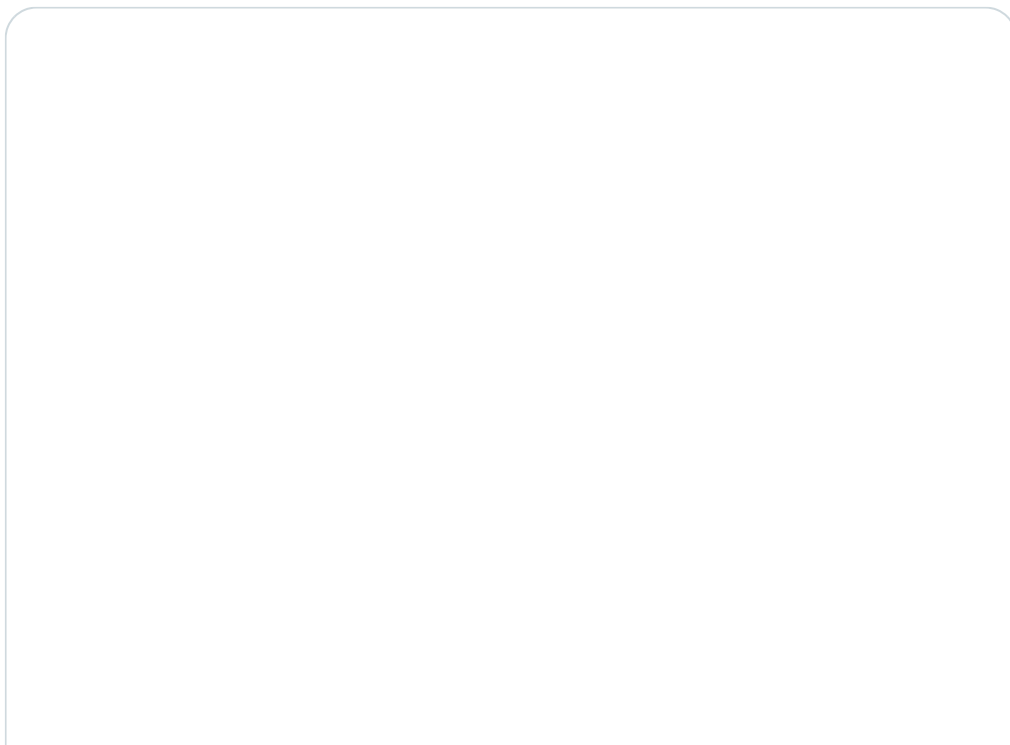


**SharonBC,Canada** @SharonBurnabyBC · Feb 25



Replying to @arijitchakrav @ToshiAkima and 4 others

That's all I got when I clicked on the link





2 2 1 931



**Arijit Chakravarty** @arijitchakrav · Feb 25

Replying to @SharonBurnabyBC @ToshiAkima and 4 others



osf.io

Pathways to altered virulence of SARS-CoV-2

The recently emerged SARS-CoV-2 virus has led to a prolonged pandemic characterized by ongoing ...

2 2 11 633

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**Negawatts are best** @JoelTH · Feb 25

Replying to @arijitchakrav @TRyanGregory and 4 others

It says not available at the moment?

1 2 1,291



**KDog** @MouseionScholar · Feb 26

Replying to @arijitchakrav @lfwhite14 and 3 others

@Harvard2H fits pretty well with your paper Dan. ADE still on the menu.

2 1 135



**lexextom@law.builders** @lexextom · Feb 25

Replying to @arijitchakrav @lfwhite14 and 3 others

> Let 'er rip

All we did was lock everyone in their houses for 18 months until the entire population had been vaccinated. I just find this trivializing phrasing really disrespectful to all the hardships that lockdown imposed.

7 2 521




**Federico MCuadra, MS** @GringoGranadino · Mar 7

Replying to @arijitchakrav @lfwhite14 and 3 others



**Federico MCuadra, MS** @GringoGranadino · Mar 6

A NEW  on SARSCoV2 effects on the immune system: immune dysregulation, aging of immune cells, cell apoptosis, risk for autoimmune disease, oncogenic (cancer causing), harming immune system, susceptibility to secondary infections, coinfections, inflammation.

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**Waldhexe** @Waldhexe6 · Feb 25



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[@RWittenbrink](#)



**TheyPlagueHorsesDon'tThey?** @Ride4Truth · Feb 25



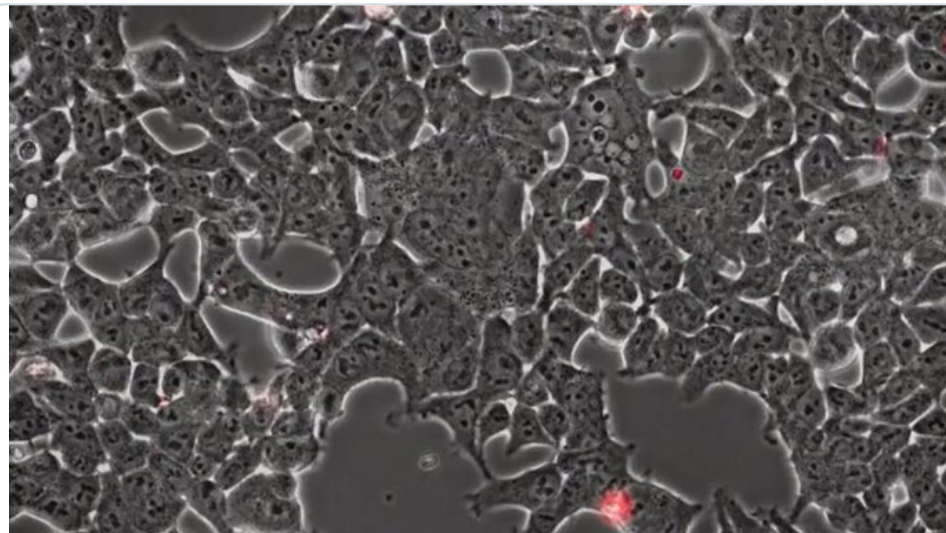
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[@threadreaderapp](#) unroll please



**BeliTsari** @BeliTsari · Feb 25




Replying to @arijitchakrav @lfwhite14 and 3 others








[web.archive.org](http://web.archive.org)


A microscopic video shows the coronavirus on the rampage. Inside a bat's brain, the pathogen destroys cells, but not before it forces them to build more invaders.








 **Norma 'l Bürgerin** @LooftSabine · Feb 25 ...  
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 1       2    755   

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 **Don Ford - The People's Strategist -** @DonEford · Feb 25 ...  
Replying to @arijitchakrav @lfwhite14 and 3 others  
Dear everyone... drop the (1) on the link to get it to work

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