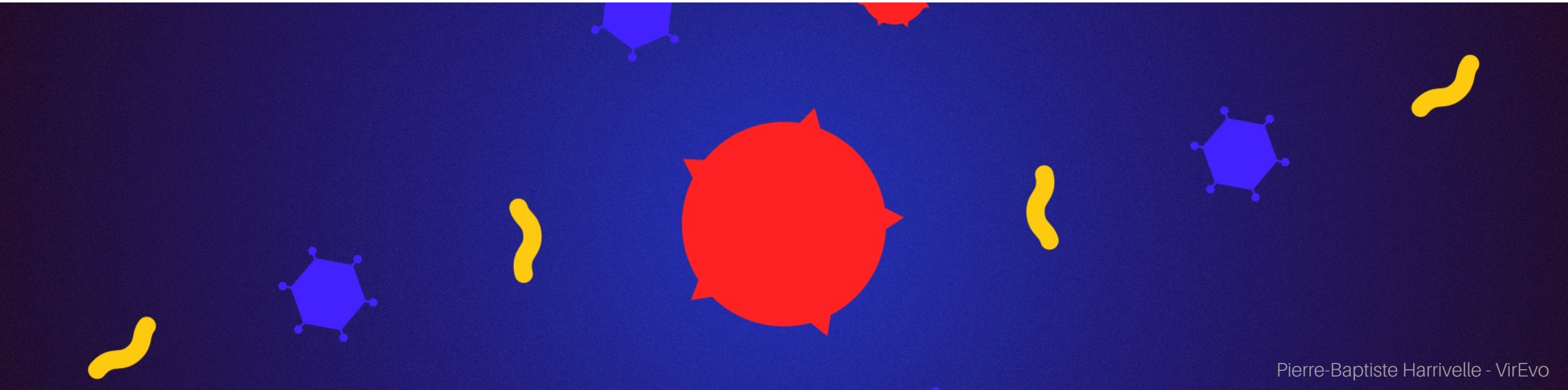
university of groningen / faculty of science and engineering / groningen institute for evolutionary life sciences / Virus Ecology & Evolution

The constant change of viruses

– evolutionary biology in action

Sebastian Lequime (Assistant professor) *s.j.j.lequime@rug.nl*



Pierre-Baptiste Harrivelle - VirEvo

Outline

1. What are viruses?
2. SARS-CoV-2
3. How do RNA viruses evolve?
4. Evolution and future of SARS-CoV-2

Outline

1 What are viruses?

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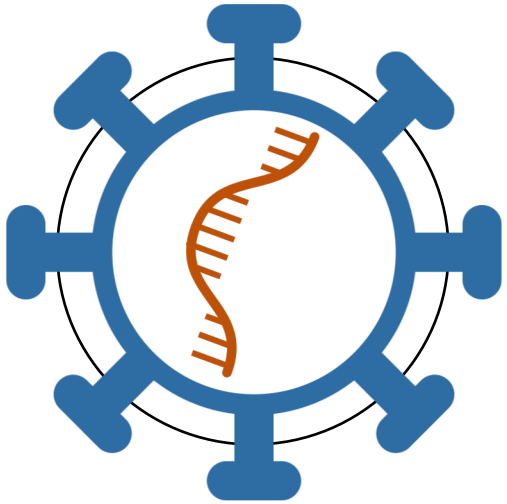
"A virus is a piece of (bad) news wrapped in protein".
– Peter Medawar (Nobel Prize 1960)

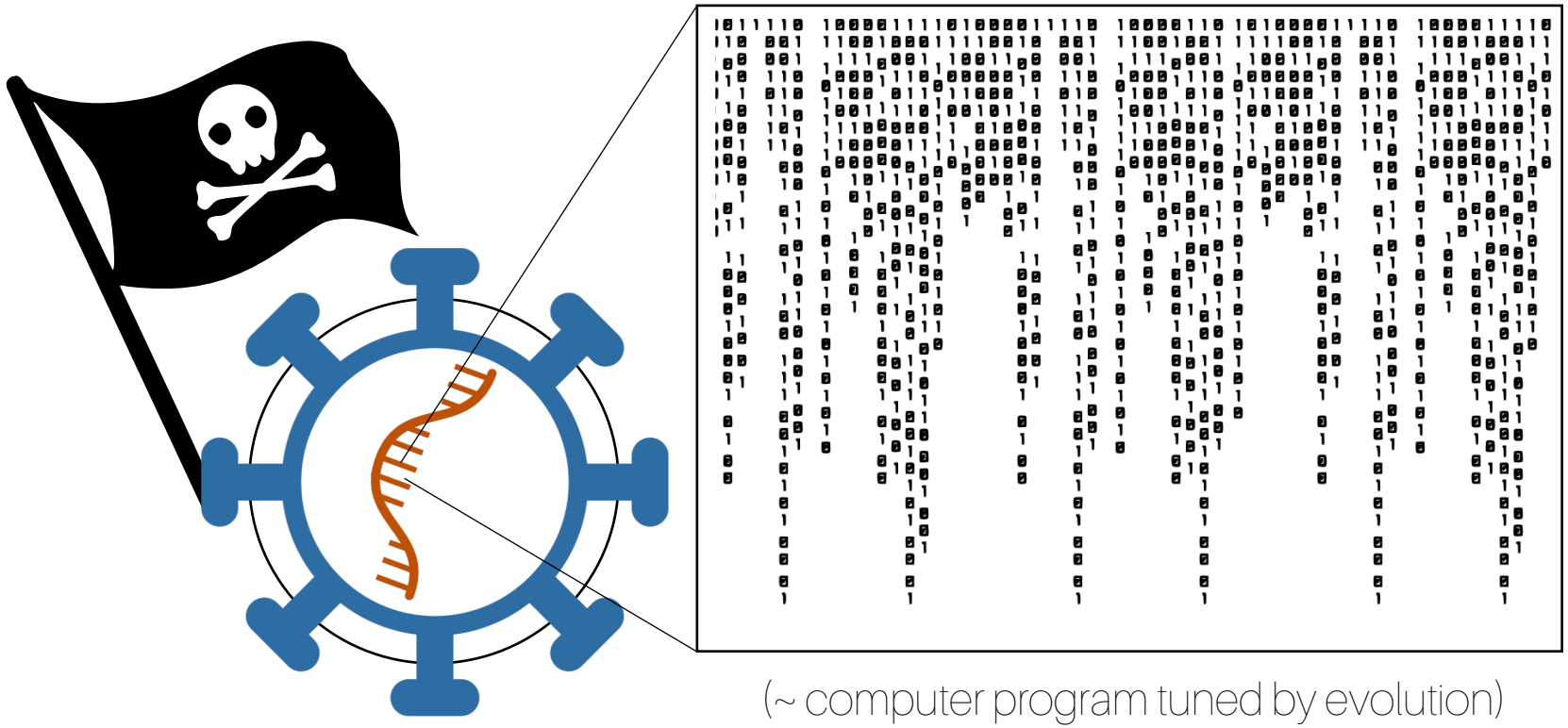


"Viruses appear to be obligate parasites in the sense that their reproduction is dependent on living cells".

– Thomas Milton Rivers (1926)

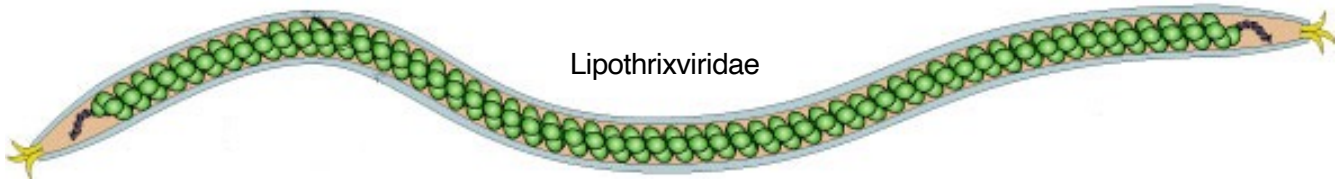
Viruses are passive agents!

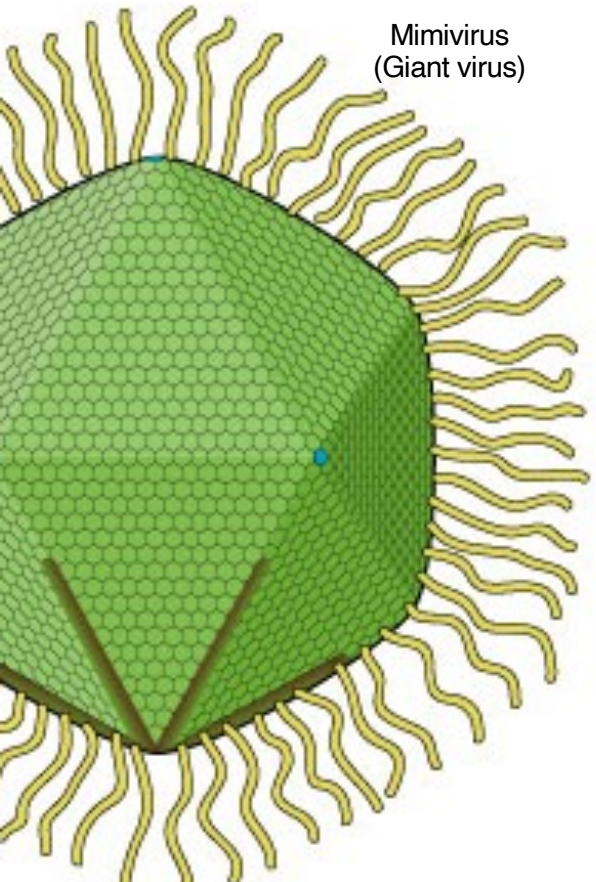
– Vincent Racaniello (at least 2012)

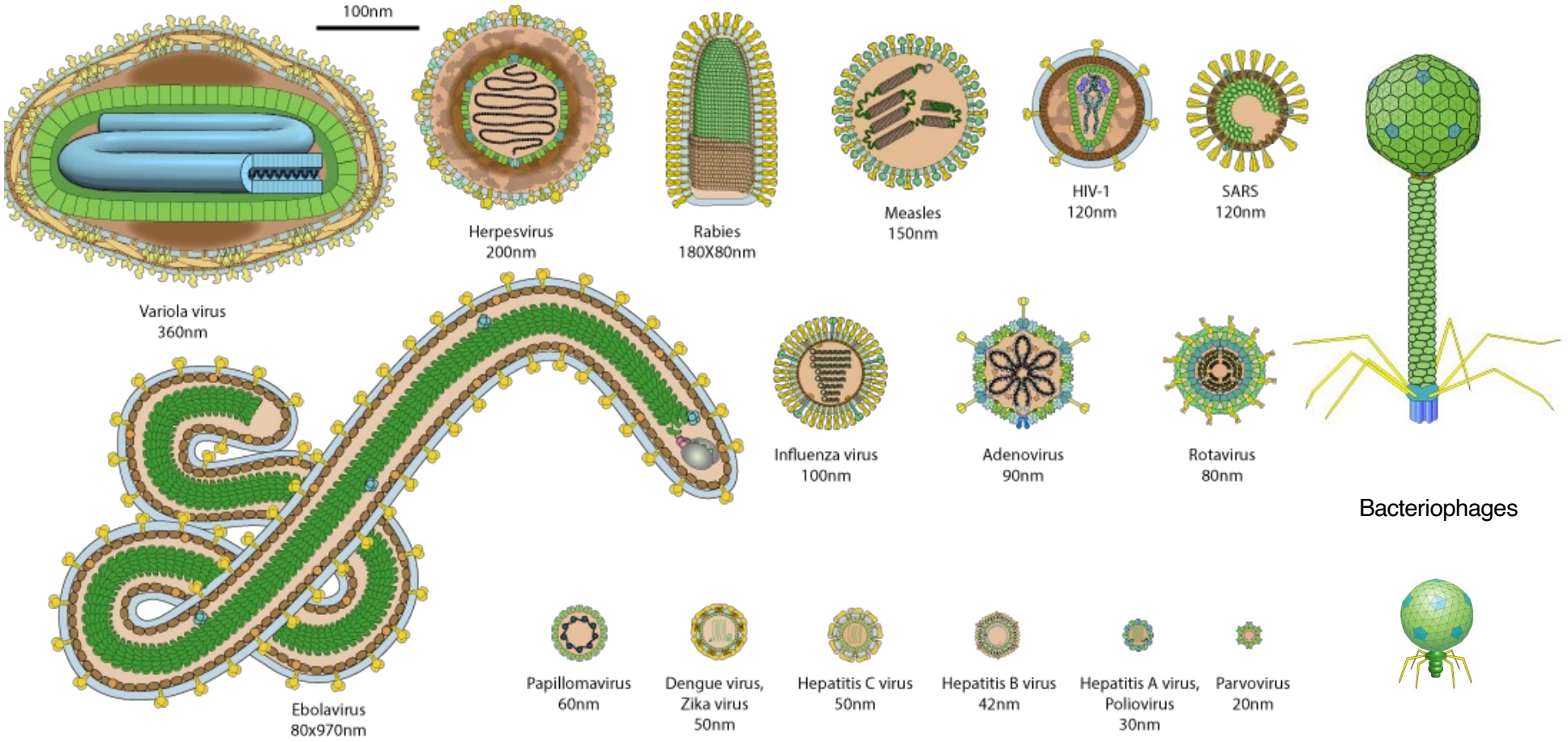


(~ computer program tuned by evolution)

Diversity







Hulo et al. (2011) Nucleic Acids Res – ViralZone
https://viralzone.expasy.org/

Abundance

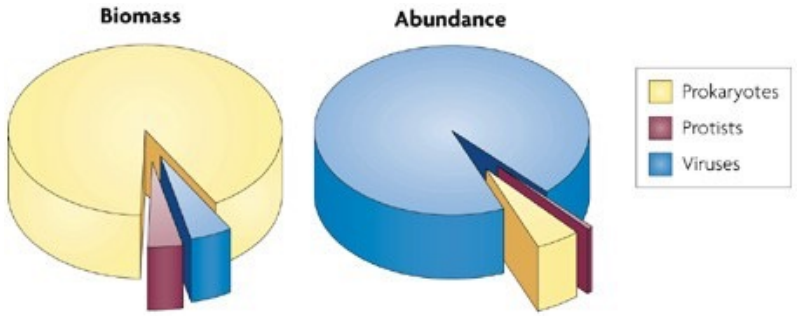
All three domain of life have been found infected by viruses

For example, marine viruses:

10^{30} viruses in the entire marine biota (estimate)

10^{23} viral infections every second (estimate)

Viruses kill about 20% of the total microbial biomass every day forcing a constant and large-scale turnover

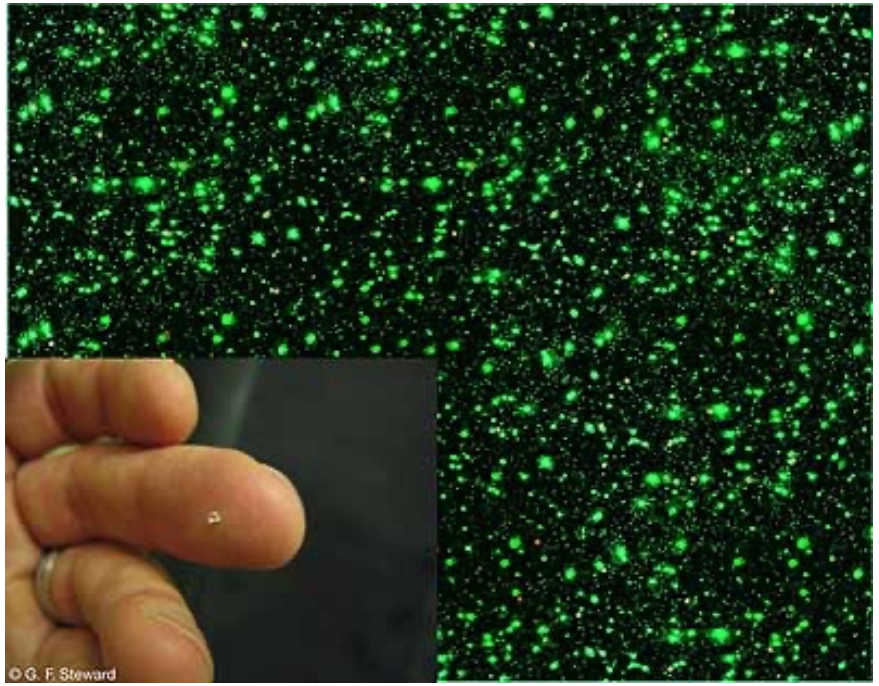


Suttle 2007 Nature Rev. Microbiol.
https://doi.org/10.1038/nrmicro1750

Nature Reviews | Microbiology

Suttle 2005 Nature
https://www.nature.com/articles/nature04160

Wietz et al 2017 Nature
https://www.nature.com/articles/nature23295



Abundance

Gray whale ~10^6 calicivirus per gram of feces

Excretes 10^{13} (10,000,000,000,000) viral particles every day

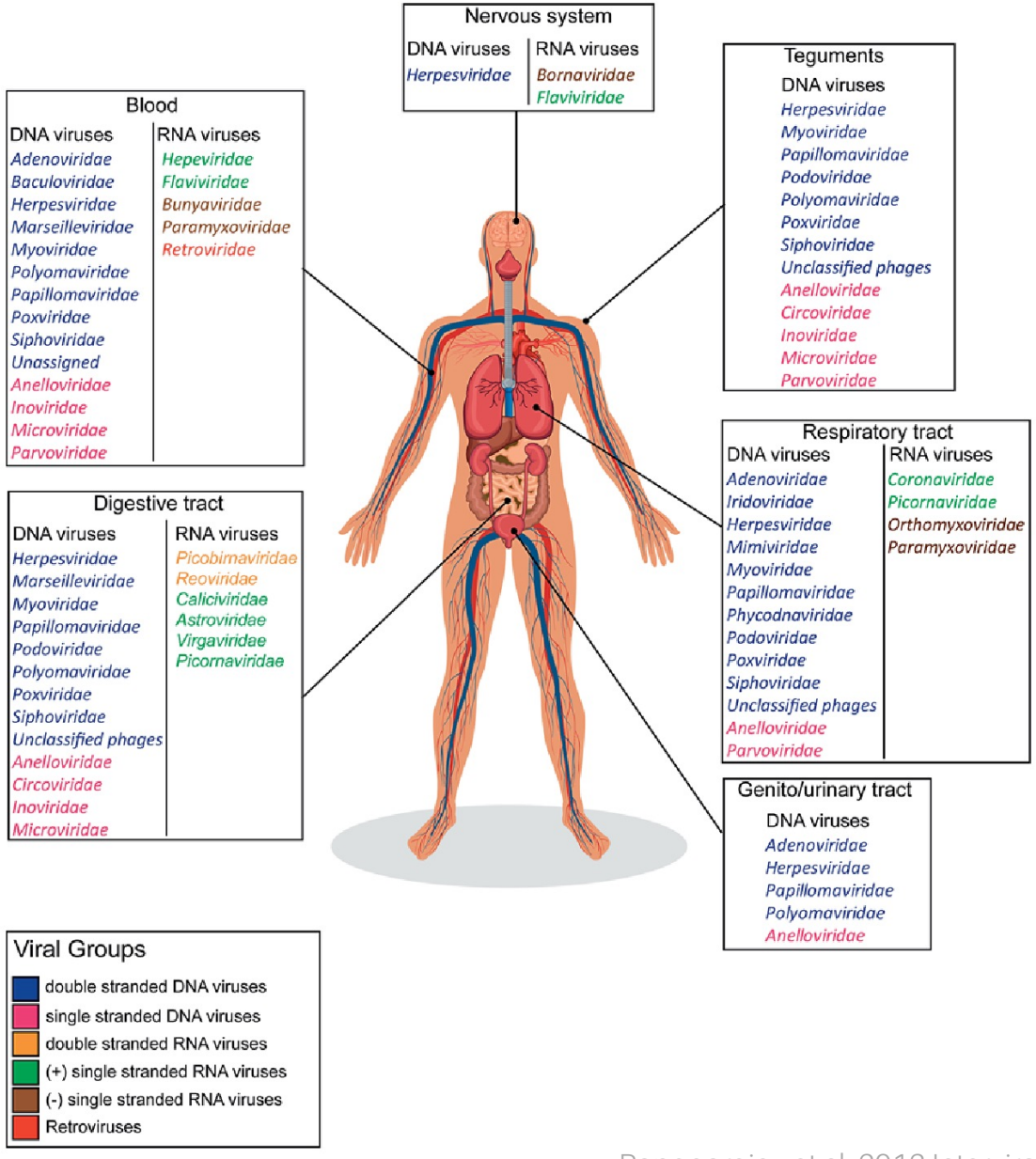
Smith et al. 1998 EID
https://dx.doi.org/10.3201%2Feid0401.980103

Abundance

Viruses are part of any microbiome

Infecting directly the host (*e.g.* Herpesviruses)

Infecting other members of the microbiome



Popgeorgiev et al. 2013 Intervirology
https://doi.org/10.1159/000354561

Viruses...

...are everywhere

Especially when you study biology :

- Molecular biology
- Cell biology
- Genetics
- Ecology
- Evolution
- Medical sciences (diseases and treatments)
- Biochemistry
- Epidemiology
- Computational biology

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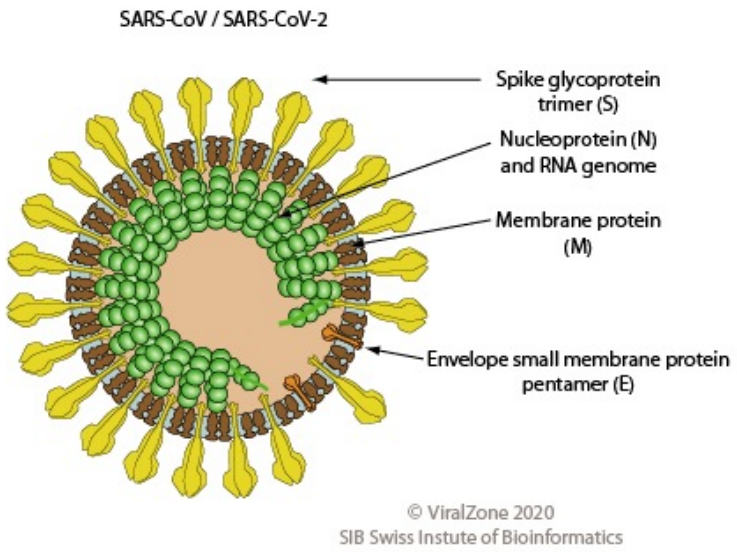
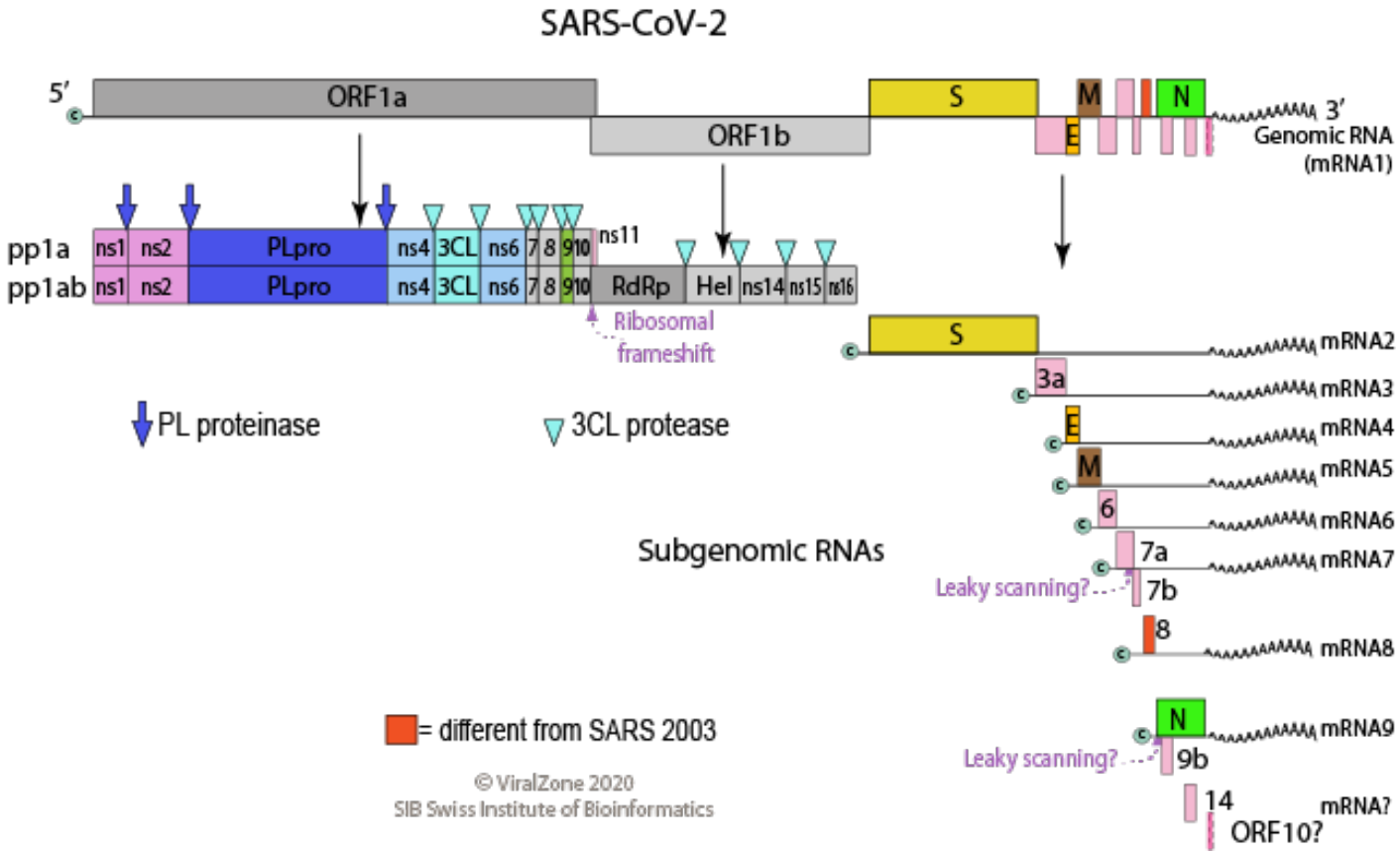
SARS-CoV-2

Betacoronavirus

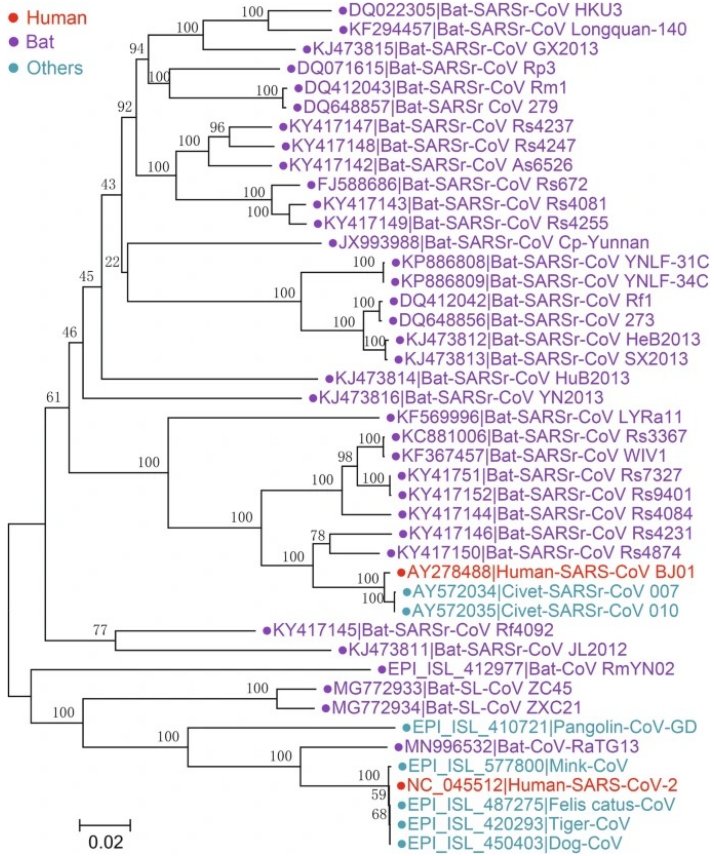


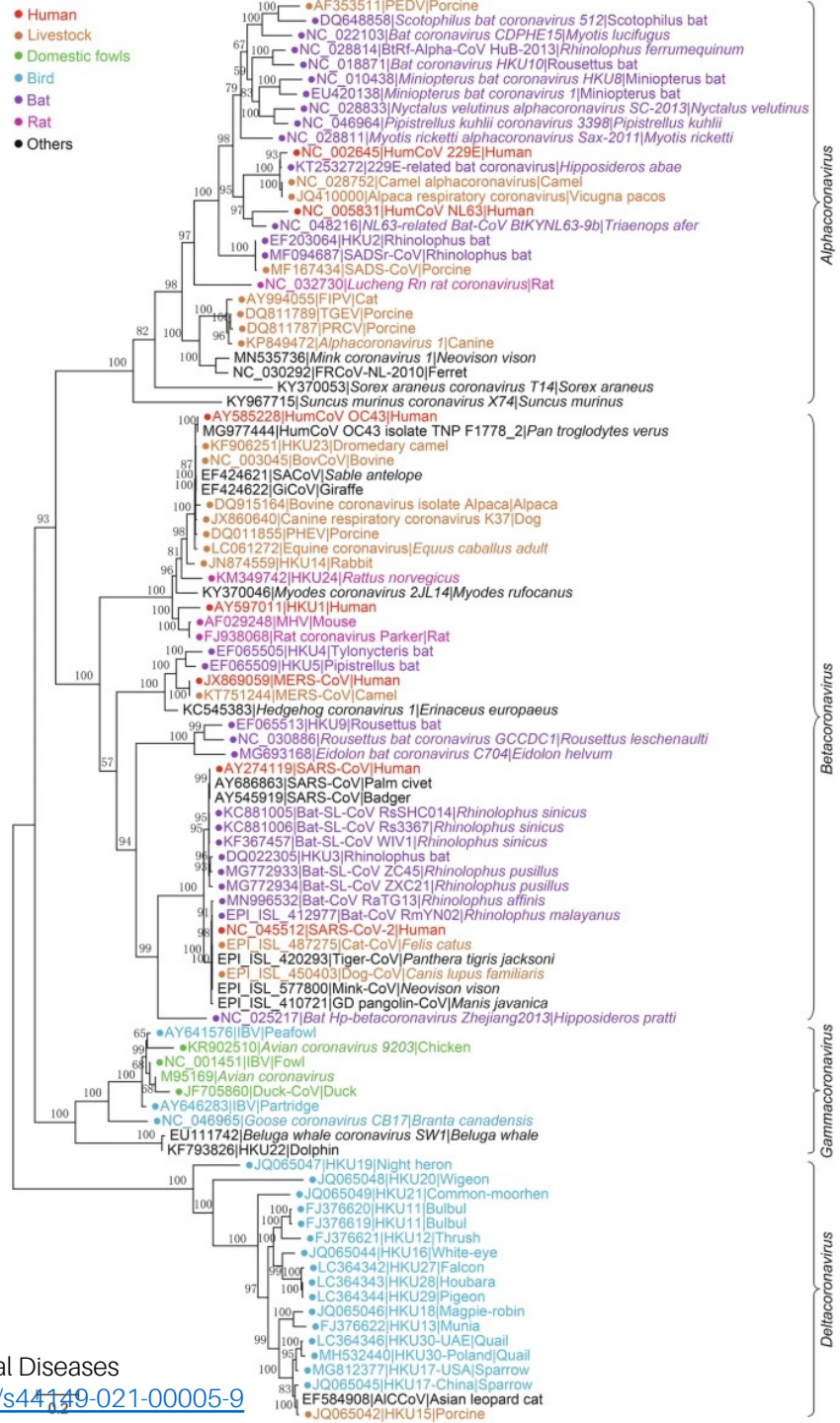


Monopartite
Linear ssRNA(+) genome
29.9 kb in size
13 Open reading frames

Betacoronavirus

Diverse sets of hosts (mammalians)





Zhou et al (2021) Animal Diseases
https://doi.org/10.1186/s44149-021-00005-9

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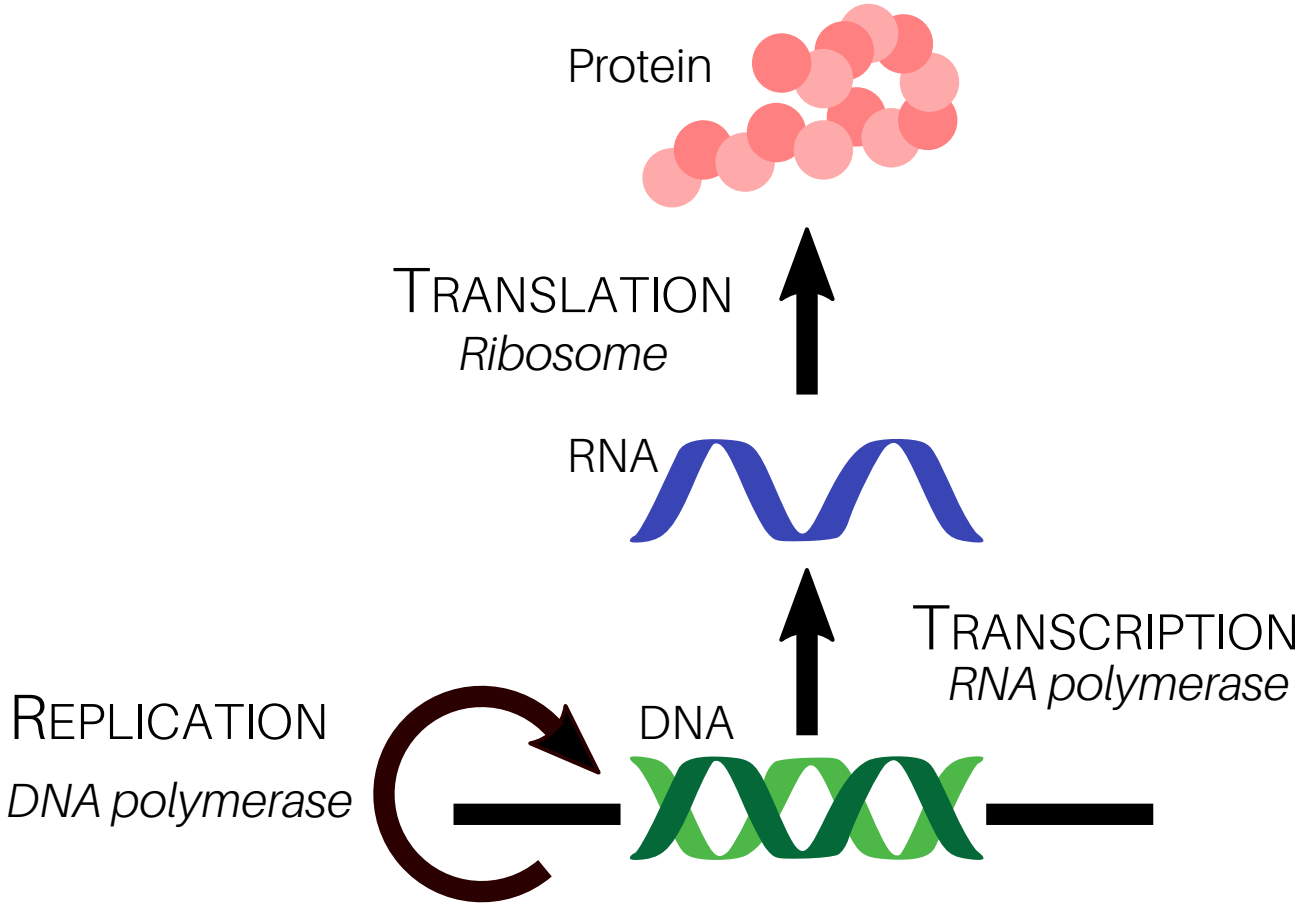
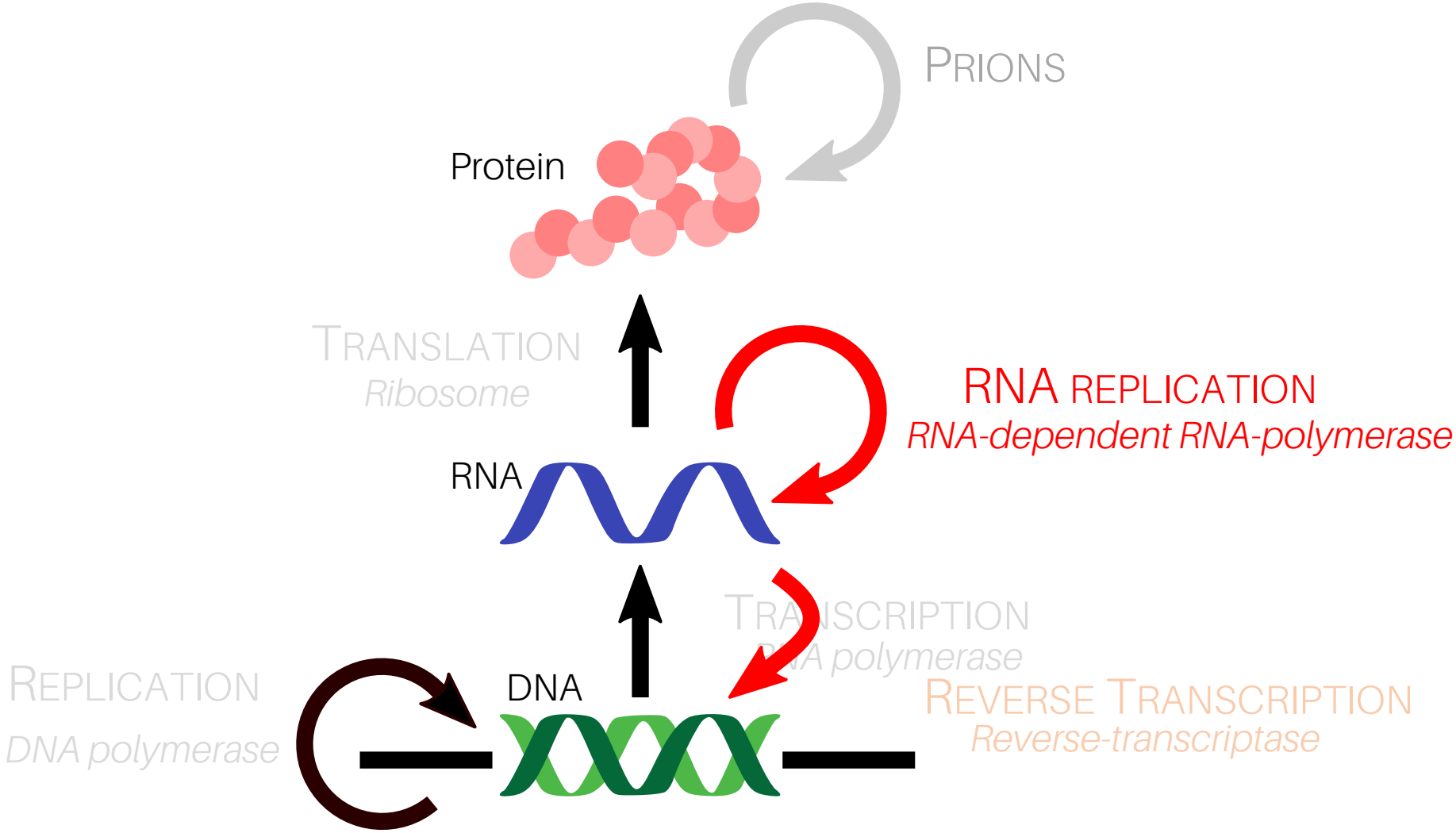
Central dogma of molecular biology



Viral heretics



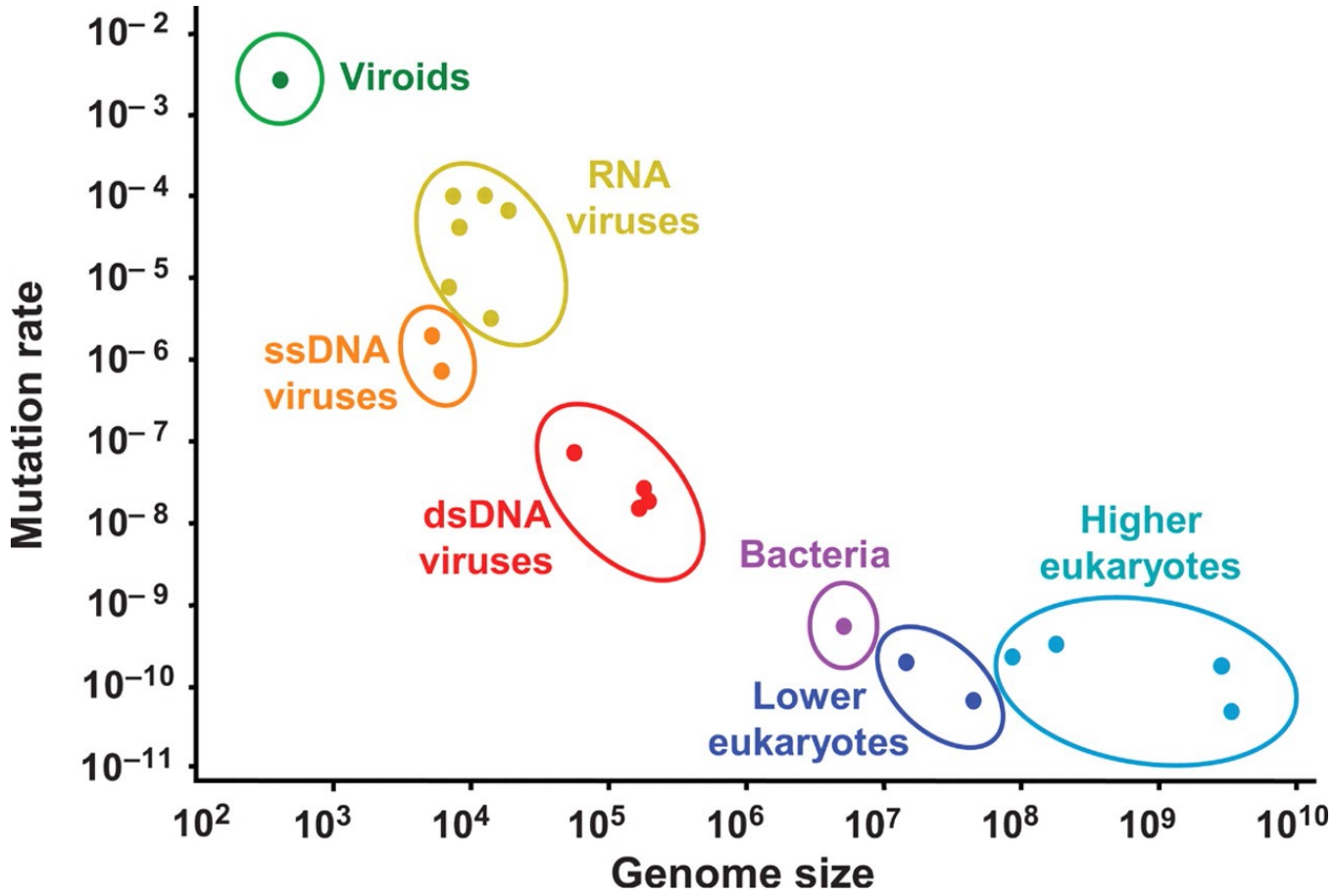
RdRP is error-prone

DNA polymerase: 10^{-7} to 10^{-9} error/nt replicated

RdRP: 10^{-3} to 10^{-5} error/nt replicated

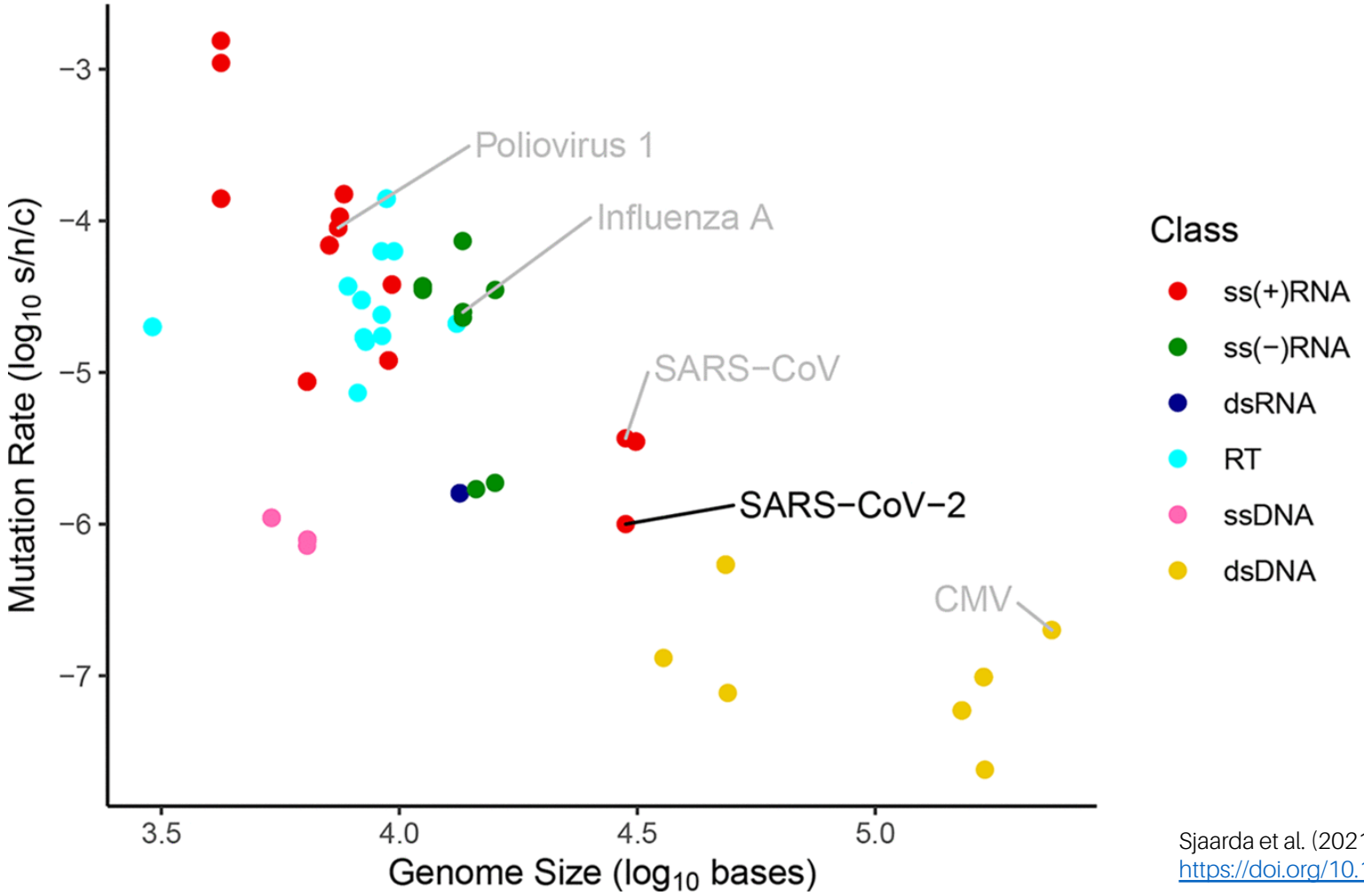
lack of proofreading ability in RNA polymerases

Virus mutation rate



Gago et al. 2009 Science
https://doi.org/10.1126/science.1169202

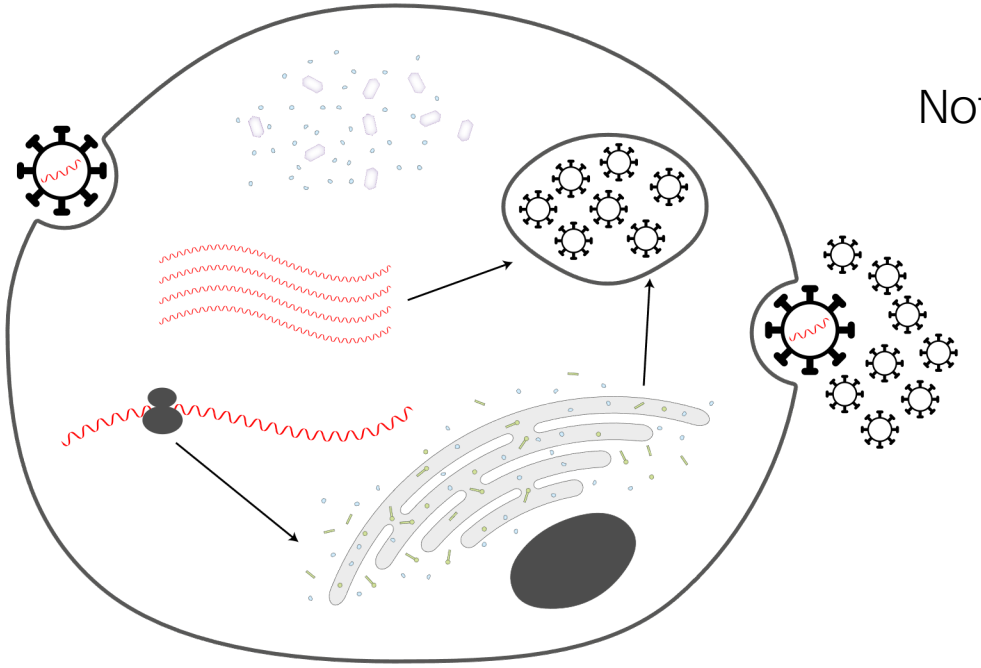
SARS-CoV-2's RdRP is slightly less error-prone



Proof reading activity!

Sjaarda et al. (2021) mSphere
https://doi.org/10.1128/mSphere.00011-21

Within-host evolution



Replication mechanism

Not totally random

Not totally clonal

Population

Fitness does not directly relate to replication success

Allows “hitchhikers”

“Quasispecies theory”

Lauring and Andino (2010) PLoS Pathogens

Between-host evolution

Viral population is shaped by:

Bottleneck,

Immune response,

Host genetic background & physiology,

Environment...

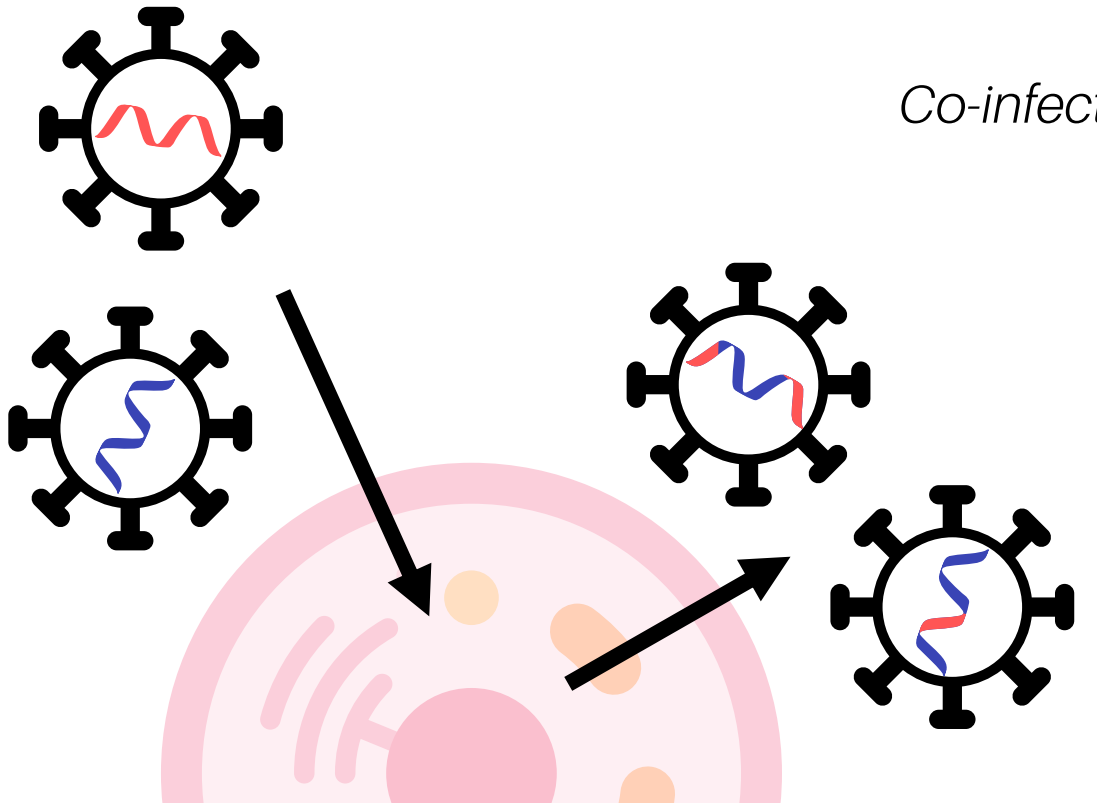
~ It's a complex mess.

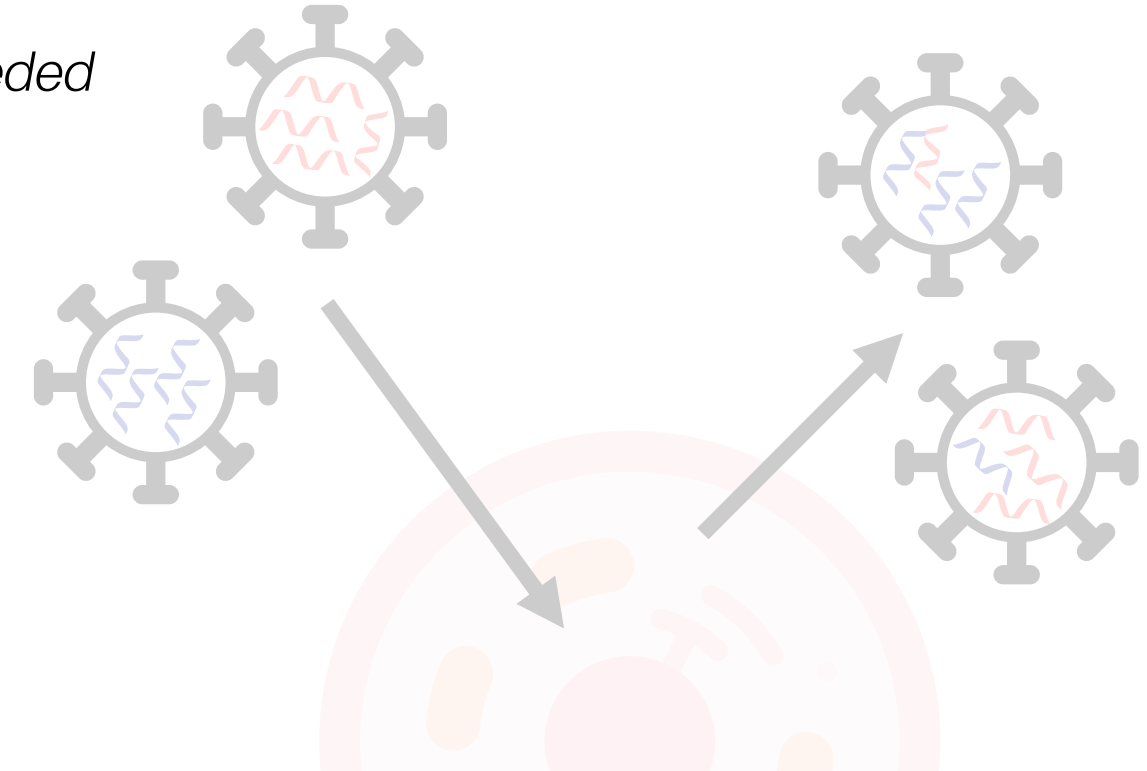
Other mechanisms of virus evolution

Recombination

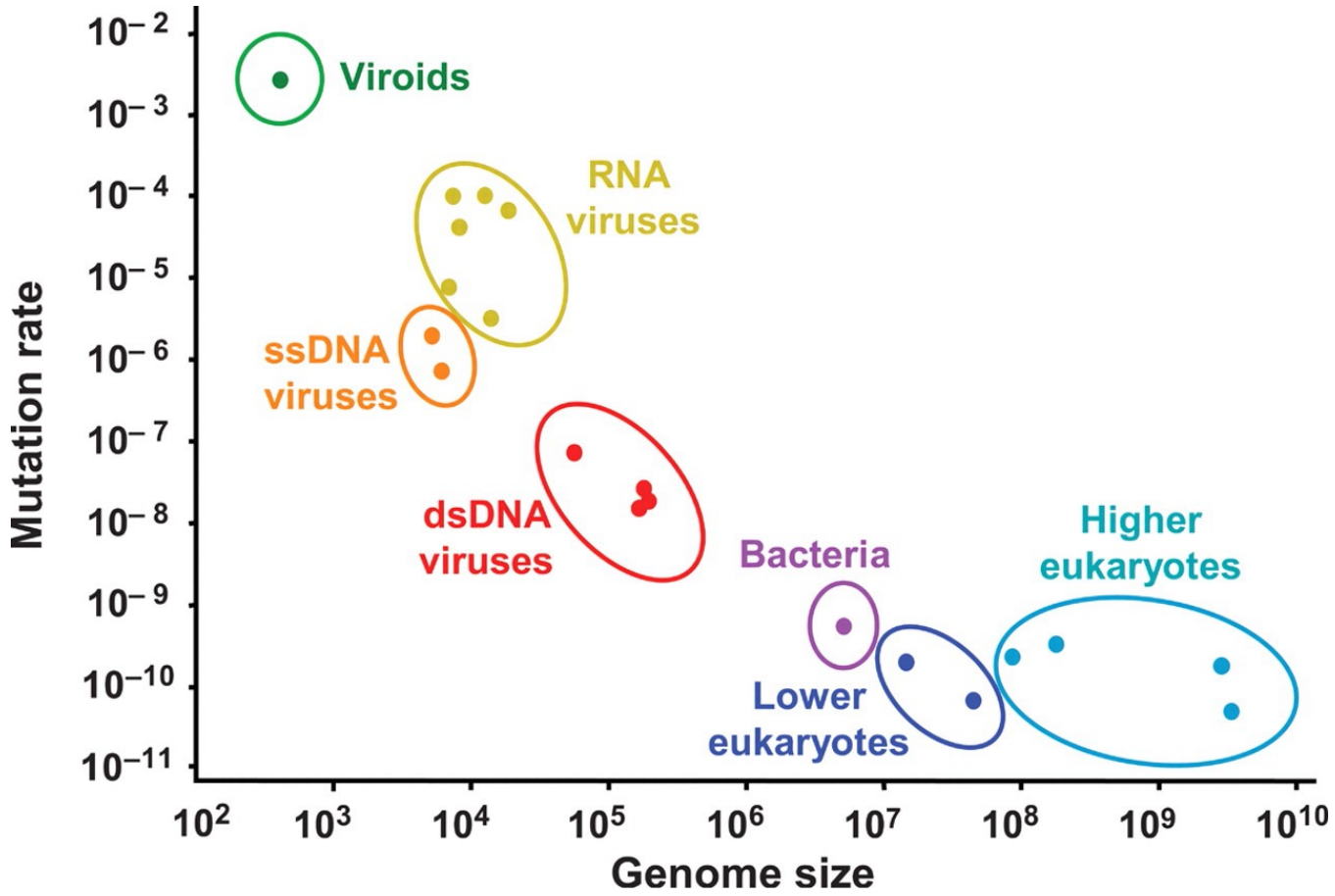
Reassortment

Co-infection is needed



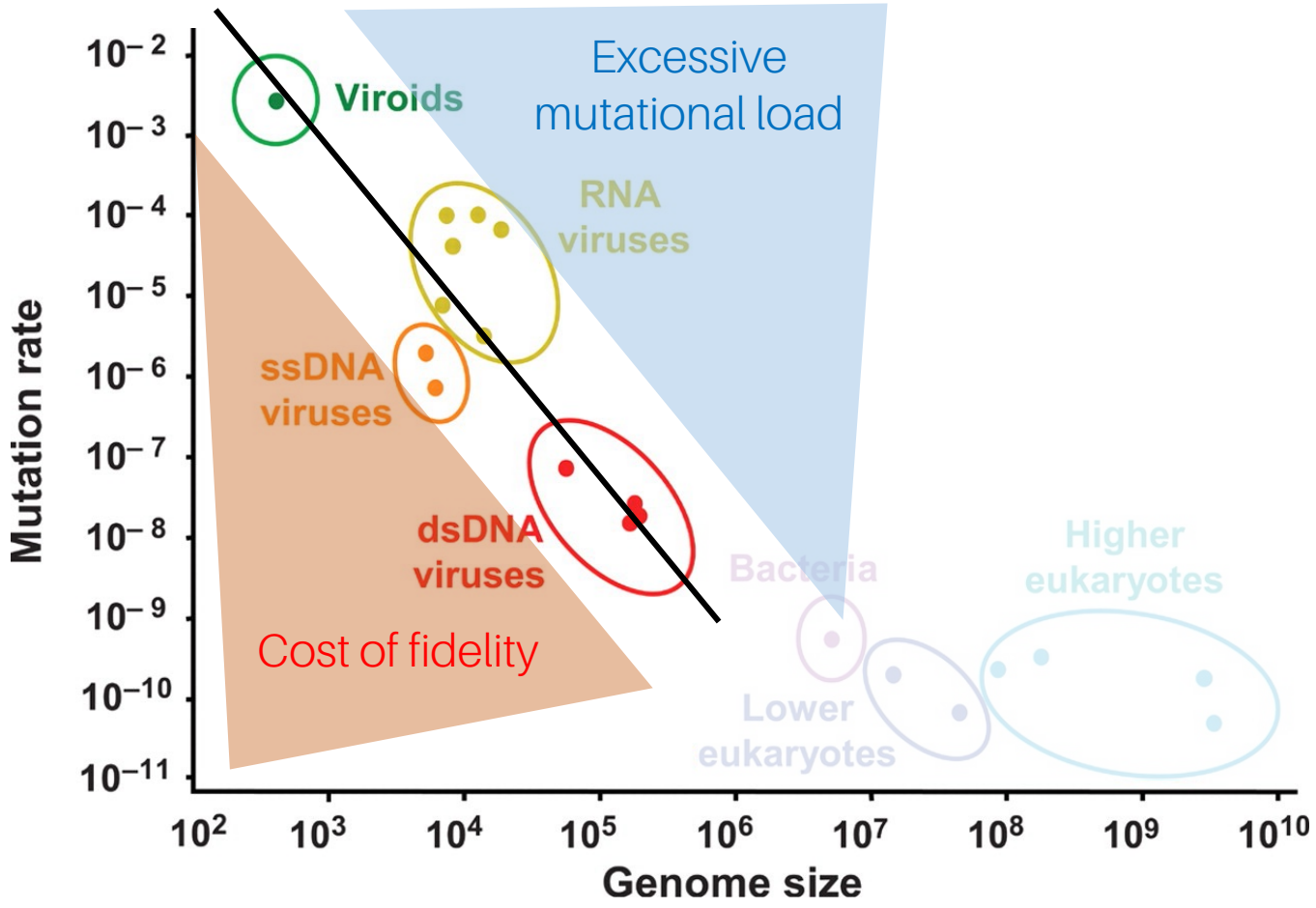


Virus mutation rate



Gago et al. 2009 Science
https://doi.org/10.1126/science.1169202

Constraints on virus evolution

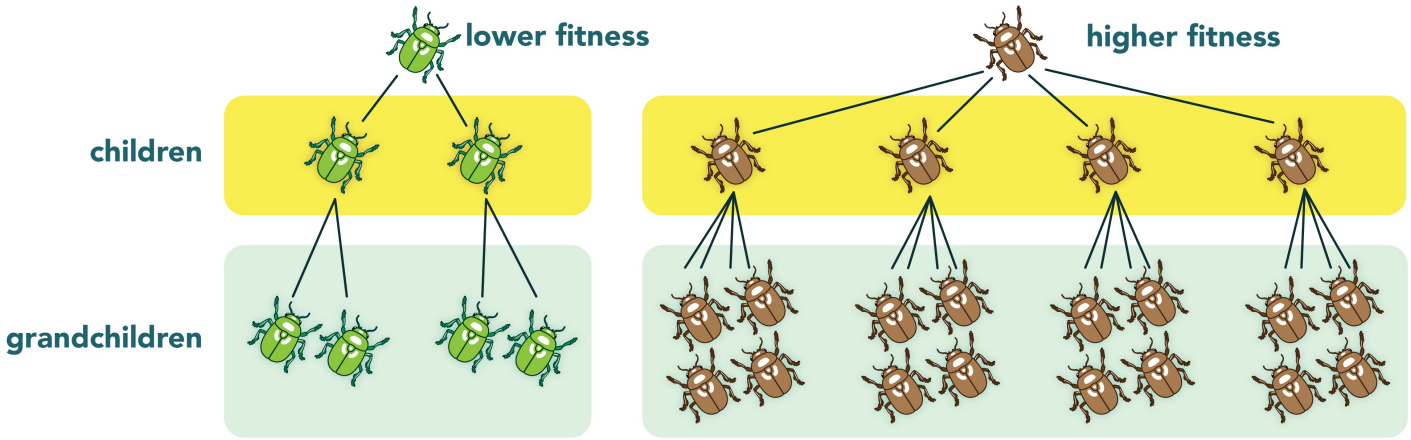


Gago et al. 2009 Science https://doi.org/10.1126/science.1169202
Holmes 2011 J. Virol. https://doi.org/10.1128/jvi.02203-10

Fitness?

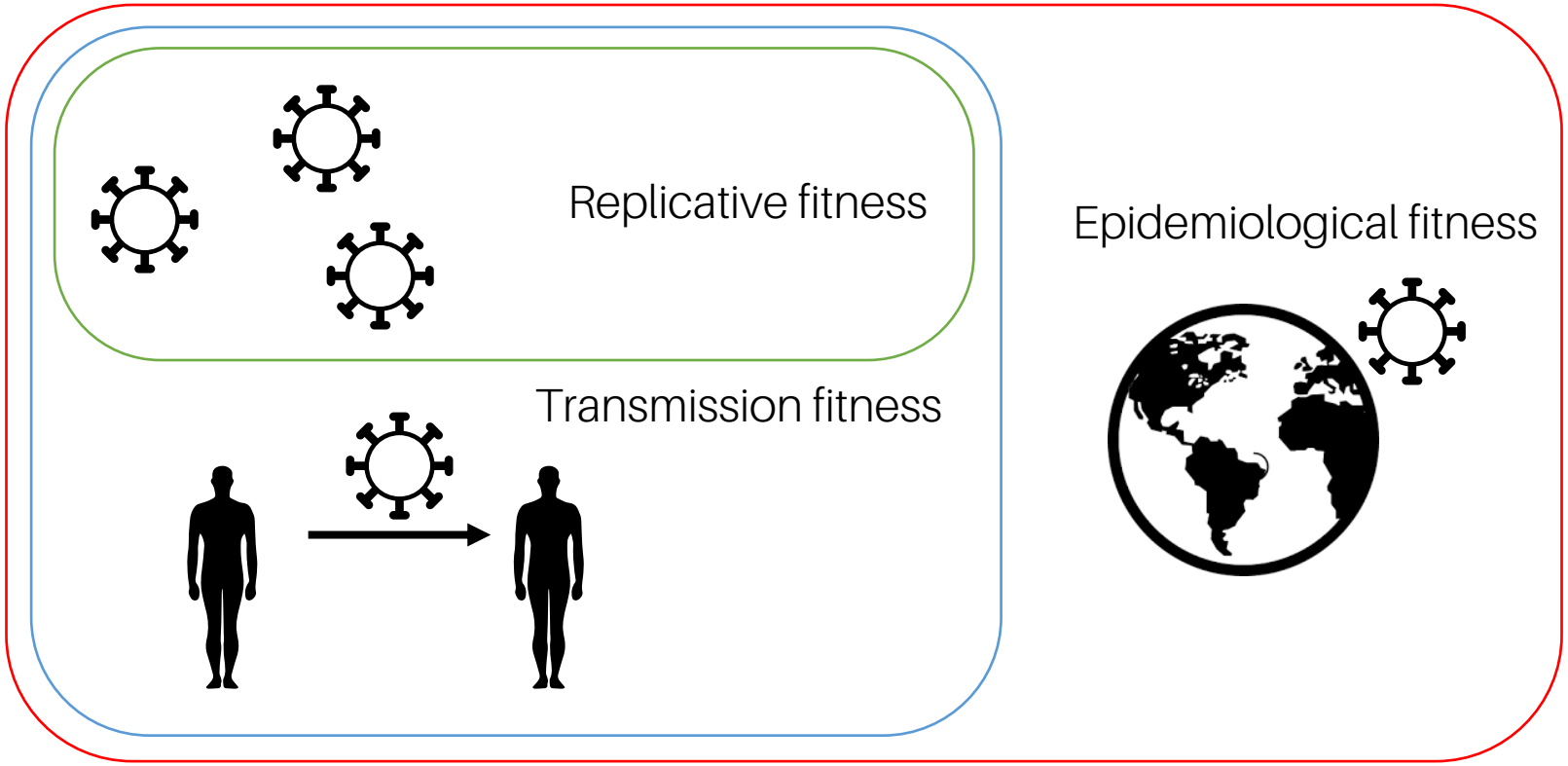
Evolutionary biologists use the word fitness to describe how good a particular genotype is at leaving offspring in the next generation relative to other genotypes

Of course, fitness is a relative thing.



https://evolution.berkeley.edu/evolution-101/mechanisms-the-processes-of-evolution/evolutionary-fitness/

Fitness of viruses



Wargo & Kurath (2012) Curr Opin Virol

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Why study virus evolution?

https://nextstrain.org/

For what it leads to

Genetic flexibility

Adaptation
Emergence

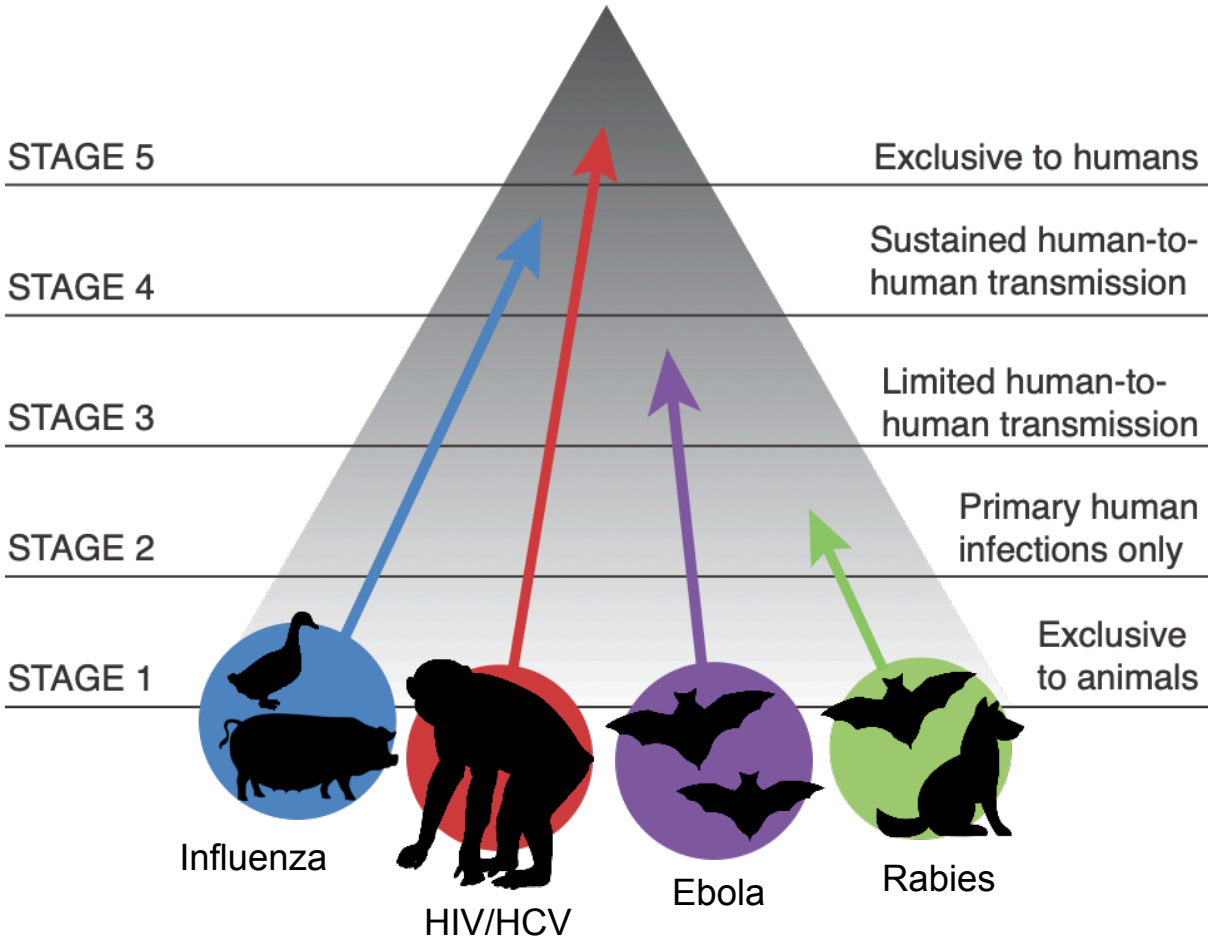
Drug resistance

For what it tells us

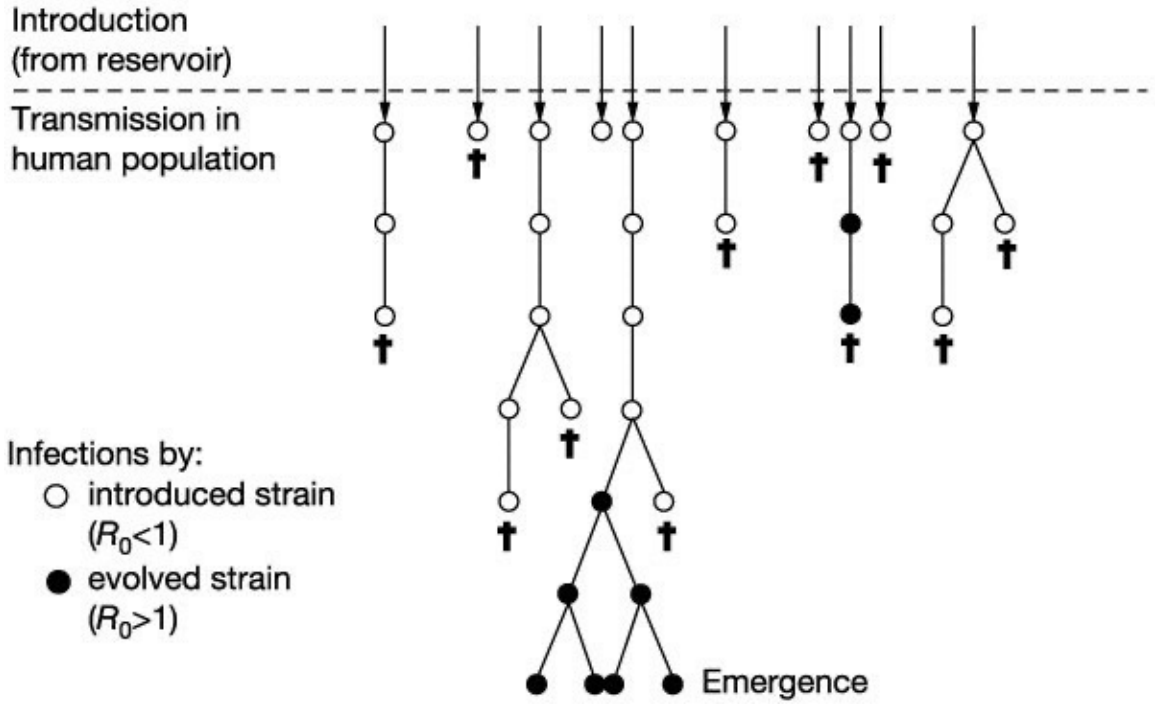
Insights into their epidemiology

Understanding the trajectory of SARS-CoV-2

Genetic changes (can) trigger/follow epidemiological change

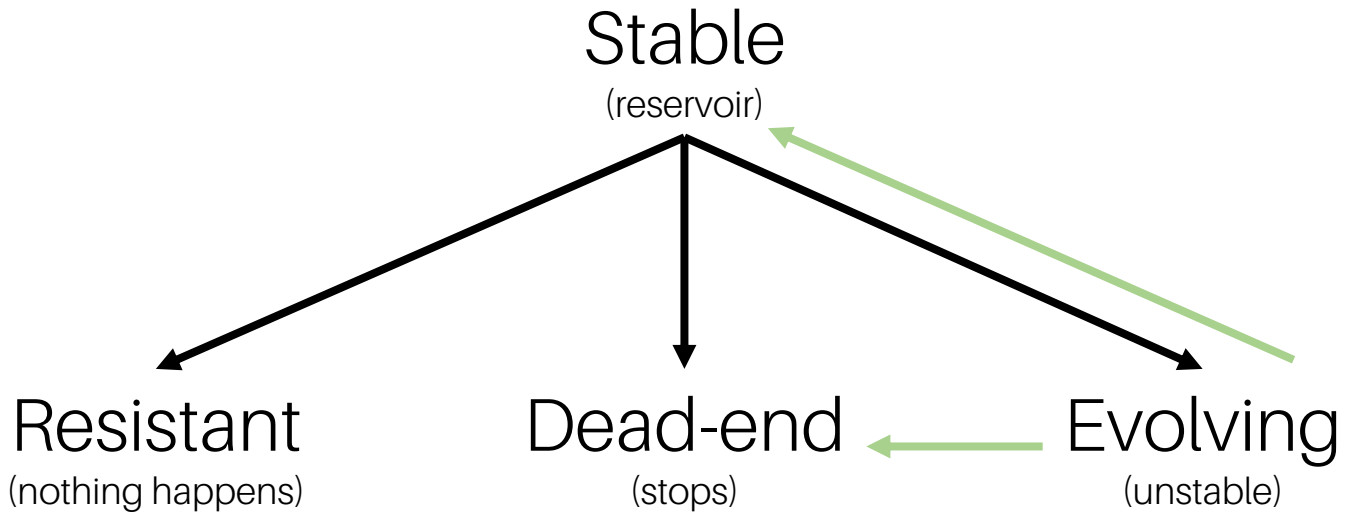


Wolfe et al. Nature 2007 https://doi.org/10.1038/nature05775
Pike et al. CID 2010 https://doi.org/10.1086/652860



Antia et al. 2003 Nature
https://doi.org/10.1038/nature02104

Virus-host interaction



May take some time!

Transmission and emergence

R_0 "R nought" or "R zero"

Reproduction number
(in an idealized, naïve population)

R_t Effective reproduction number
(takes into account immunity, etc)

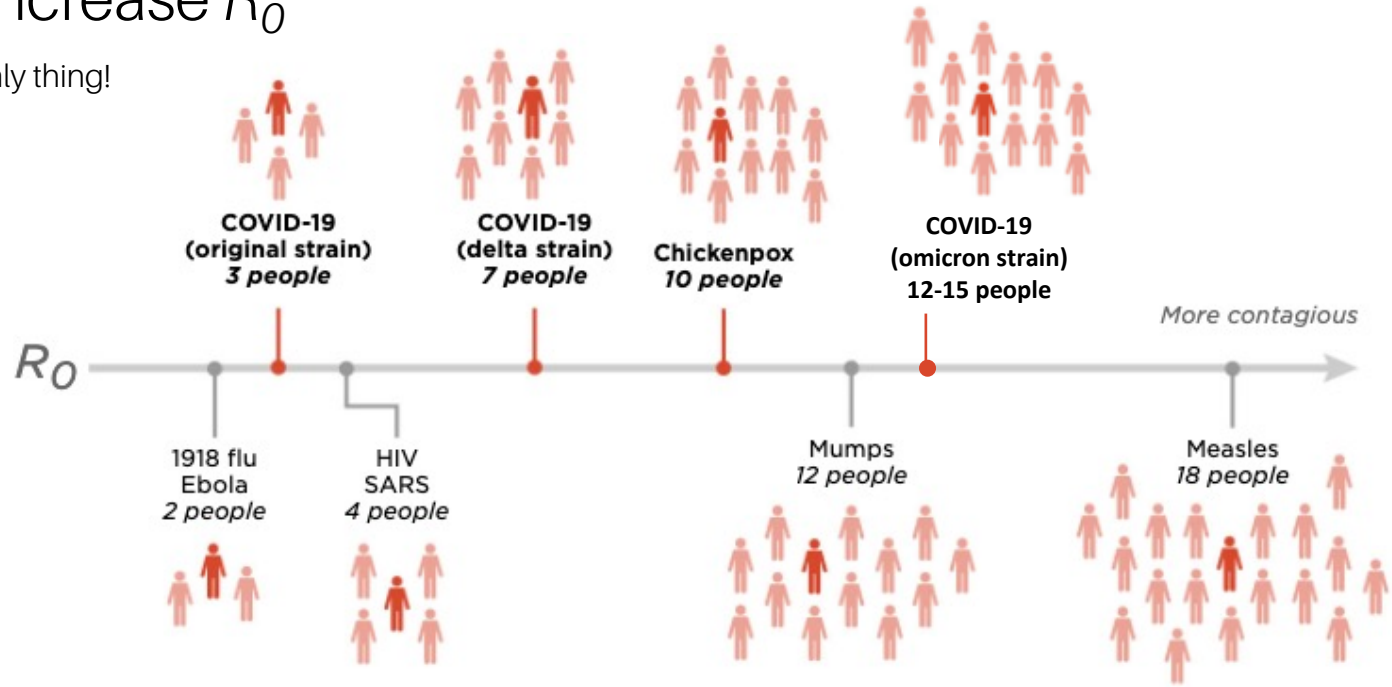
average number of people who will contract the disease from one infected person

$R_0 < 1$	$R_0 = 1$	$R_0 > 1$
Decline, eventually dies out	Maintenance, endemicity	Epidemic

Transmission and emergence

Increasing transmission can increase R_0

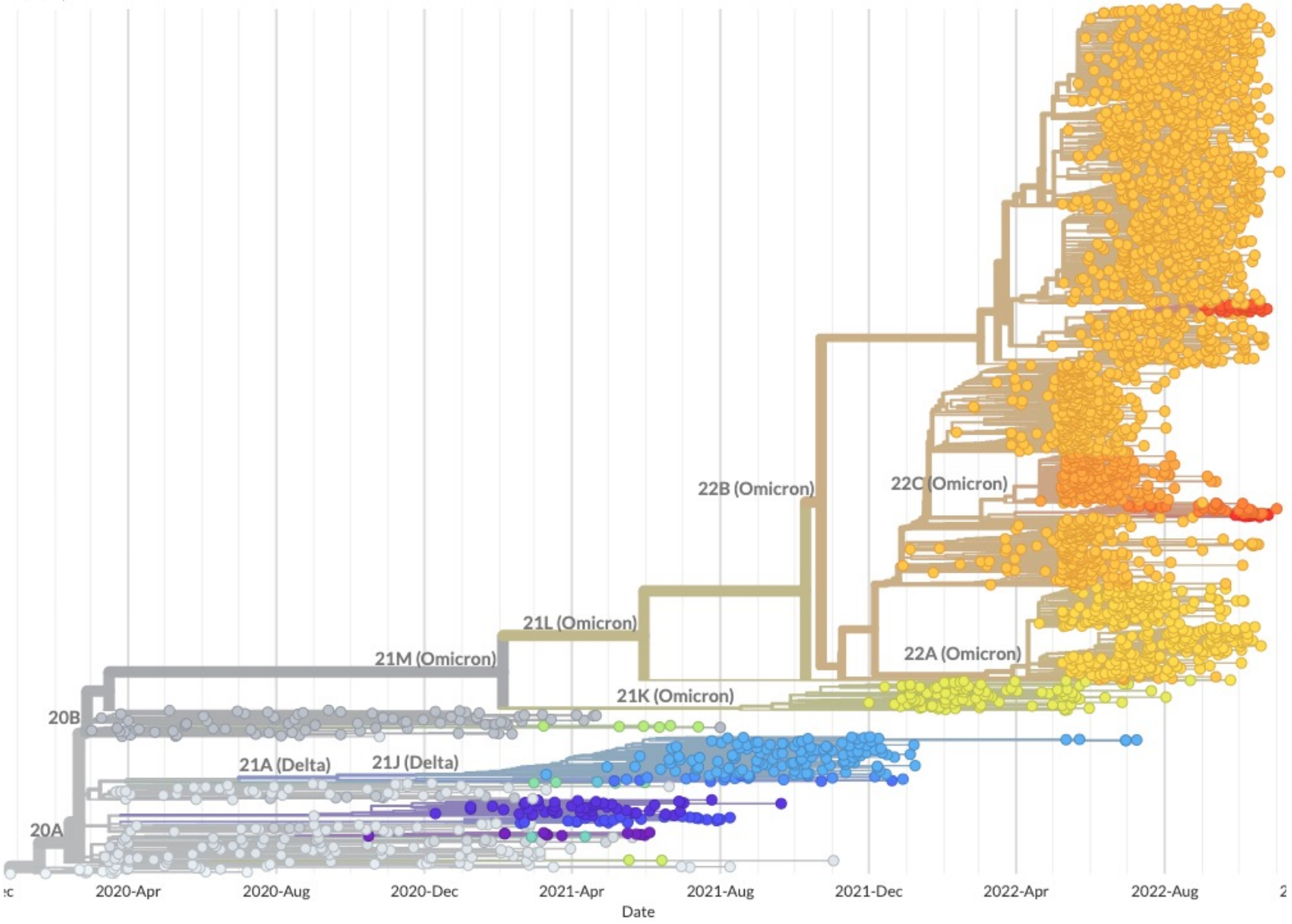
BUT it's not the only thing!



Michaeleen Doucleff, Alyson Hurt and Adam Cole/NPR, link

It is also dynamics; changes in the virus or else can change R_0

SARS-CoV-2 variants

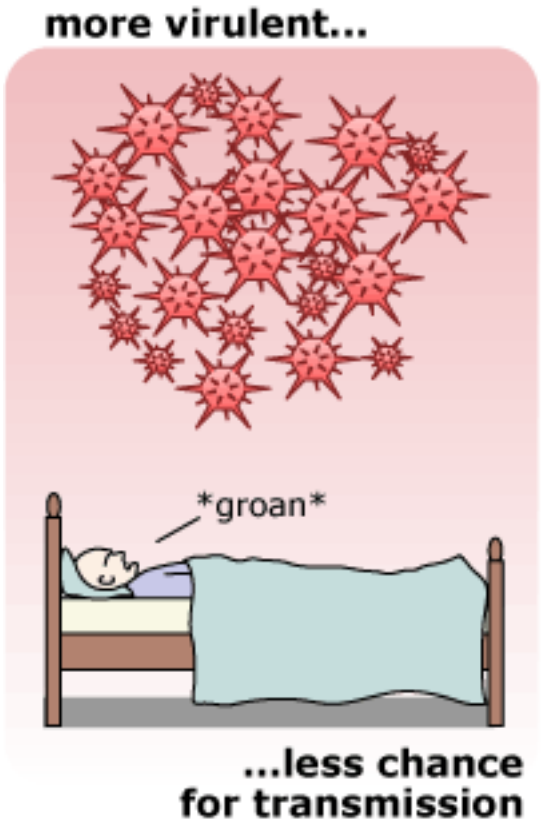


https://nextstrain.org/ncov/gisaid/global/6m

SARS-CoV-2 variants

It’s just a mild flu…

Future of COVID



https://evolution.berkeley.edu/evo-news/evolution-from-a-viruss-view/

Why is it hard to treat viral infections?

Why so few antivirals?

Reason 1 Inhibiting virus growth can affect the host cell

Virus replication engages host function Side effects

Reason 2 Difficult to grow or have an animal model (or dangerous)

Reason 3 A compound must block virus replication **completely**

Partial inhibition is not acceptable

Also…

Acute infections are short

When patient feels ill, usually too late

Antivirals for these infections must be given early or prophylactically

But safety issues?

Giving drugs to healthy people?

One counter example though?

Resistance

Resistance to ANY antiviral drug must be anticipated

Special concern for chronic infection

Patient cannot be treated with the same drug

If no other drug available... infection cannot be stopped

Viral mutants resistant to every antiviral drug in arsenal

Genetic analysis of resistance provides insight into mechanism, and may reveal new strategies to reduce or circumvent problem

High mutations rates

RNA viruses have an error prone RNA polymerase

no correction mechanism Except one order (Nidovirales)…

One mutation in 10^4 – 10^5 nucleotide

in RNA viruses of ~10kb, that makes 1 mutation per 1 to 10 genomes.

DNA virues: most DNA polymerase have proofreading mechanisms

Slower evolution

Maths of drug resistance

Consider a unique drug resistance provided by a single mutation

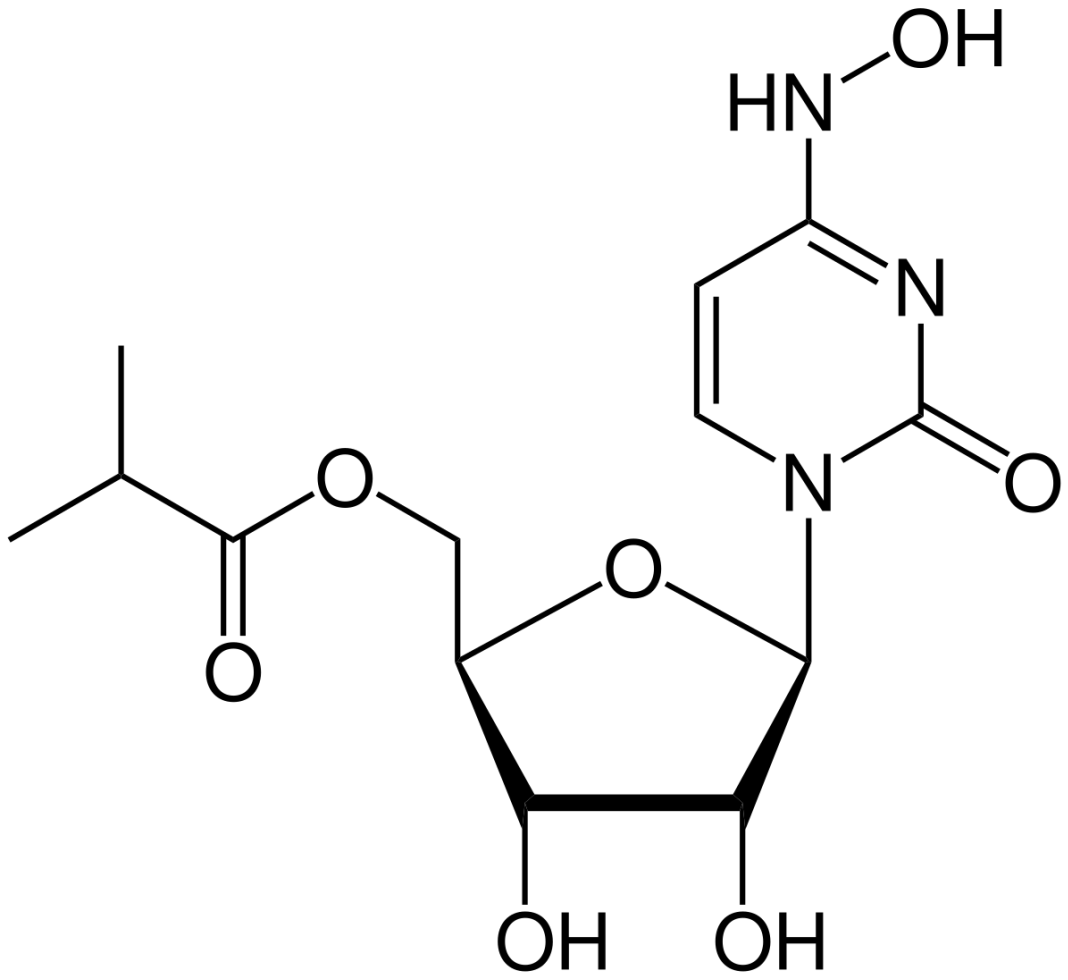
$\mu = 10^{-4}$ mut/base Each base is substituted in every 10^4 viruses

Each person has 10^9-10^{11} virions during pick viremia (SARS-CoV-2)

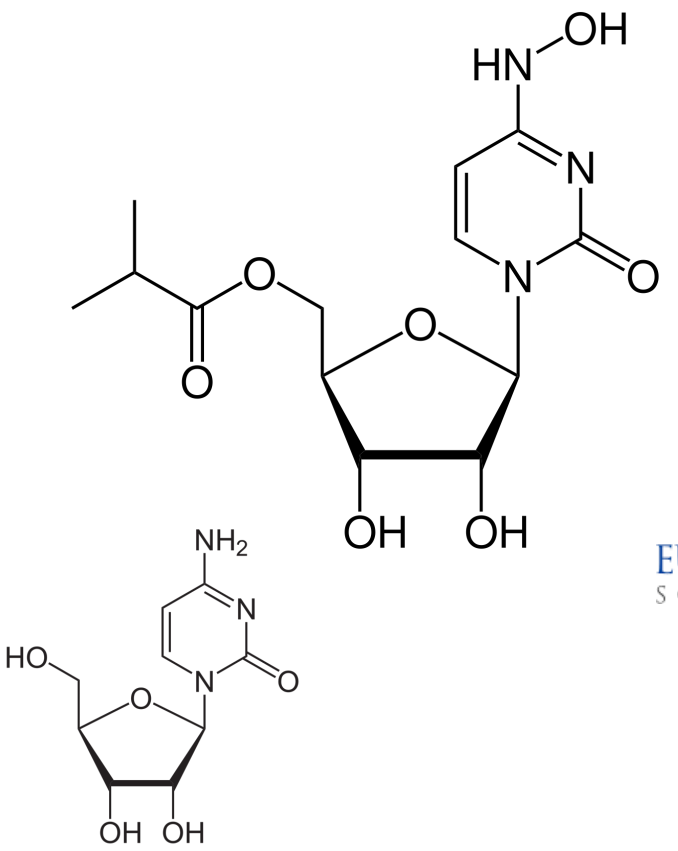
Sender et al. 2021 PNAS
https://doi.org/10.1073/pnas.2024815118

$$\frac{10^{10}}{10^4} = 10^6 \text{ viruses with resistance to the one drug...}$$

Molnupiravir (Lagevrio®$_{MSD}$)



Molnupiravir (Lagevrio®$_{MSD}$)



Cytidine

As soon as possible after diagnosis of COVID, within 5 days of the start of the symptoms, for 5 days

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

" About one month after treatment started 7.3% of patients (28 out of 385) who took Lagevrio compared with 14.1% (53 out of 377) of patients who took placebo (a dummy treatment) had been hospitalised or had died; none of the patients in the Lagevrio group died compared with eight patients in the placebo group. "

https://www.ema.europa.eu/en/news/ema-issues-advice-use-lagevrio-molnupiravir-treatment-covid-19

Molnupiravir (Lagevrio®$_{MSD}$)

Incorporates into replicating RNA

Induces C→U mutations

Mutagenic!

Molnupiravir (Lagevrio®$_{MSD}$)

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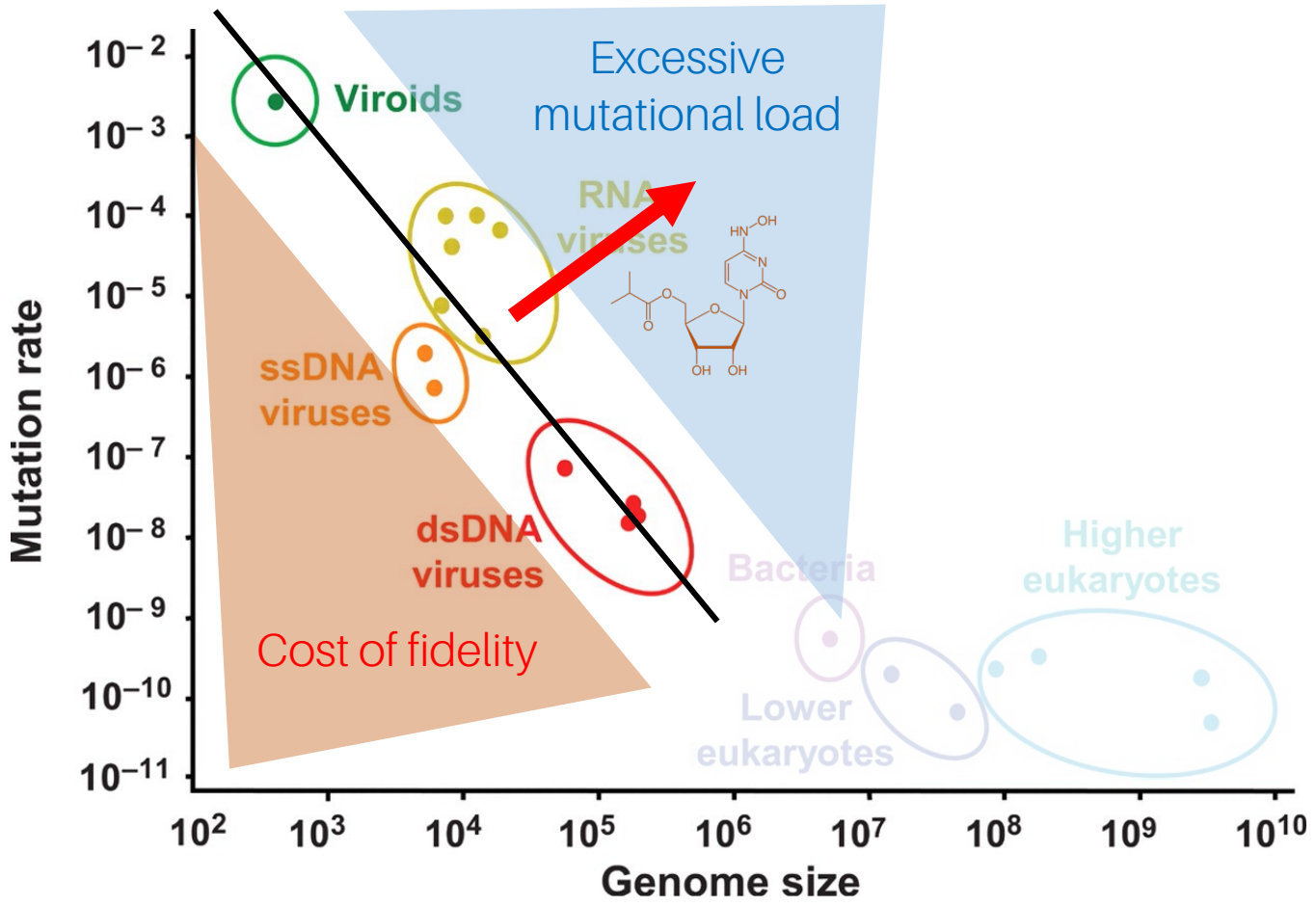
Mutagenic!

Lethal mutagenesis

"error catastrophe"
"mutational meltdown"



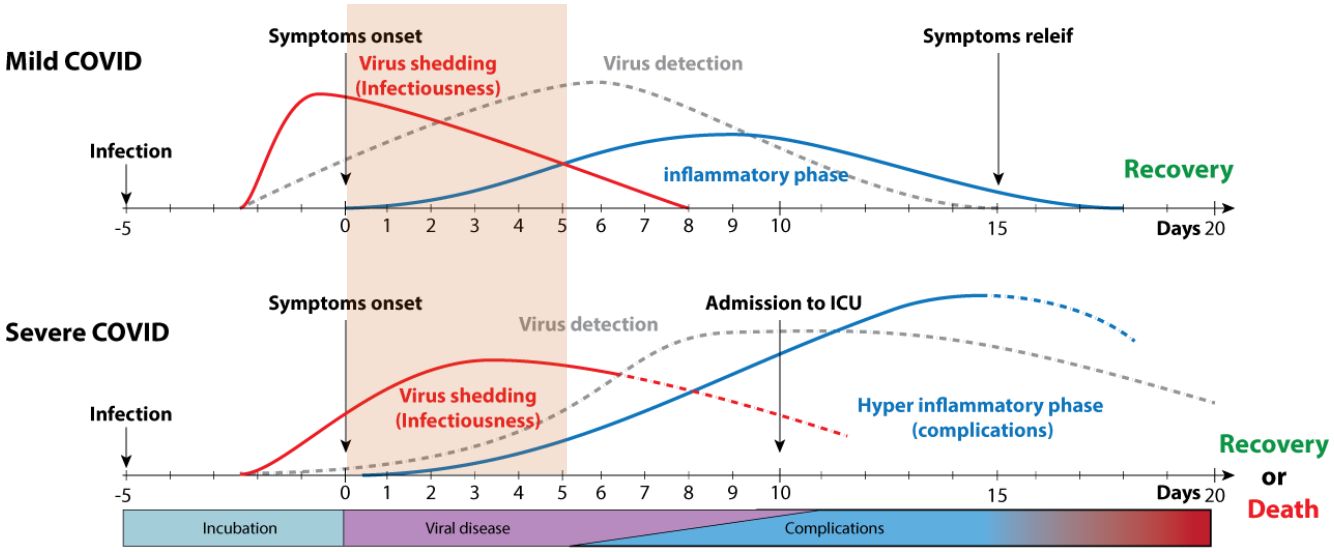
Gago et al. 2009 Science https://doi.org/10.1126/science.1169202
Holmes 2011 J. Virol. https://doi.org/10.1128/jvi.02203-10

Molnupiravir (Lagevrio®$_{MSD}$)

What about low drug concentration?

increase the mutation rate without error catastrophe: sublethal mutagenesis

Peak viral shedding is likely to coincide with low initial drug concentration



ViralZone, link

Molnupiravir has a short plasma half-life.

1 hour

Sequence content limits mutation rate elevation.

Pre-existing bias for C→U mutations
genomic G:C content of 38%
plus-strand C content of 18%

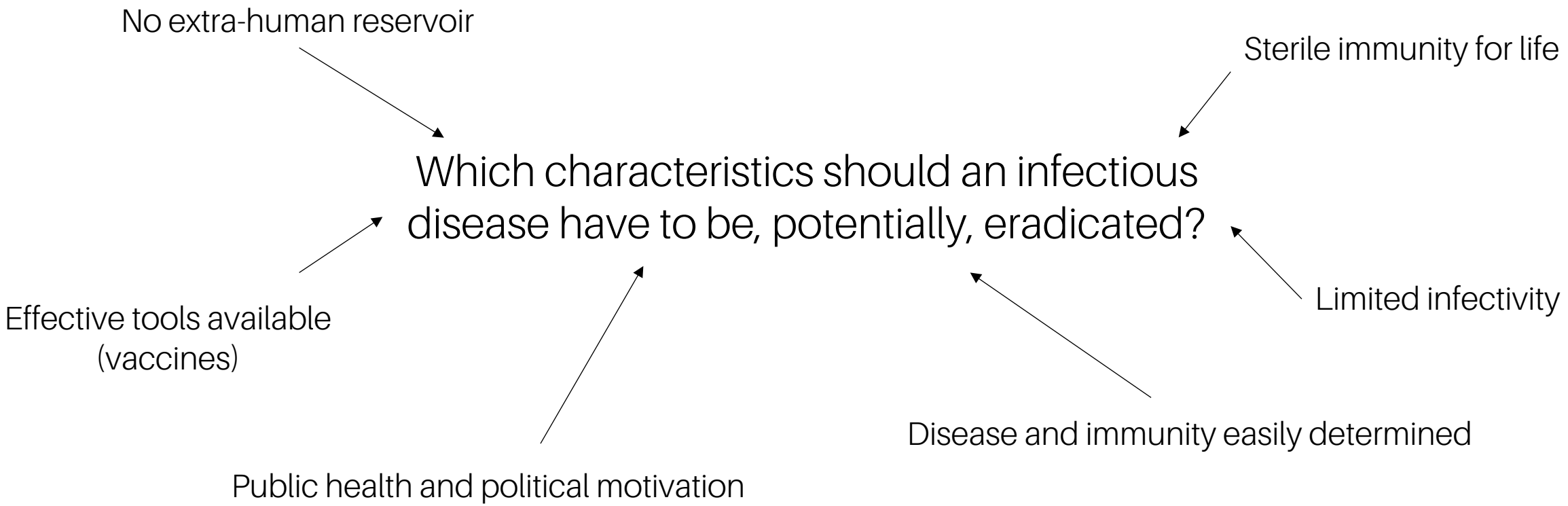
Nelson & Otto (2021), link

Eradicating SARS-CoV-2

Eradication of infectious diseases

Which characteristics should an infectious disease have to be, potentially, eradicated?

Eradication of infectious diseases




Virevo
virevo.lequimelab.eu