Reinfection and variants

Reinfection: is it possible?

- **Dozens of cases of 'reinfection' were discovered in South Korea early in the pandemic** and caused a great deal of panic. All of these turned out to be **testing errors** (false positives) due to inability of the standard PCR test to distinguish between a live virus and its residual genetic material (more on this in the Asymptomatic Transmission section).
- **Hong Kong** scientists reported the case of a healthy man in his 30s who became reinfected with coronavirus four and a half months after the first infection. **Genome sequencing showed the two strains of the virus were clearly different, i.e. it was an early variant.** (Parry J. Covid-19: Hong Kong scientists report first confirmed case of reinfection. BMJ2020;370:m3340.)
- A Qatari study which carried out genomic testing showed that reinfection seemed to be a mixture of the original strain and variants. (Abu-Raddad LJ, et al. Severity of SARS-CoV-2 Reinfections as Compared with Primary Infections. N Engl J Med. 2021 Dec 23;385(26):2487-2489)
- **We need to be clear, when talking of reinfection, whether we mean reinfection by the exact same strain as the first infection or whether we are looking at a variant.** Unless the study specifically carries out genomic testing to determine whether it is a true reinfection by the same strain, **it is likely that reinfection is with a variant**.

However, reinfection with the original strain is possible through viral reactivation

- **Viral reactivation occurs where the original virus has not been eliminated from the body but is preserved in viral reservoirs, often in the gut.** Plasma concentrations of the virus are below the level of conventional detection.
- **If the immune system is distracted, viral reactivation from these reservoirs is possible.**
- **We need to be careful about claims of viral reactivation:** an early Chinese study claimed that that 5% suffered viral reactivation, yet the methods show **no evidence of genomic testing** to ensure that it was not a variant (Ye G, et al. Clinical characteristics of severe acute respiratory syndrome coronavirus 2 reactivation. J Infect. 2020 May;80(5):e14-e17).

Implications of viral reactivation

- **It has been hypothesised that true viral reactivation may be the cause of severe and lingering COVID and also of Long Covid.**
- It has been found **in some Long Covid patients that there is reactivation either of the original strain of SARS-CoV-2 or another virus** such as Epstein Barr, which can mirror the symptoms of Long Covid.
- Studies have found SARS-CoV-2 reservoirs in Long COVID patients in multiple organs including the brain, lung, myocardium, lymphoid tissue (gut, lymph nodes and spleen) but also in the central nervous system. (Matschke, J., et al. (2020). Neuropathology of patients with COVID-19 in Germany: a post-mortem case series. Lancet Neurol. 19, 919–929; Gaebler, C. et al. (2021). Evolution of antibody immunity to SARS-CoV-2. Nature 591, 639–644; Neurath MF, et al. Gut as viral reservoir: lessons from gut viromes, HIV and COVID-19 Gut 2021;70:1605-1608)
- However, a recent UK study of ONS data showed that 0.1-0.5% of people had persistent infections lasting >60 days with evidence of ongoing viral replication. These individuals had >50% higher odds of self-reporting long COVID (Ghafari M, et al. Prevalence of persistent SARS-CoV-2 in a large community surveillance study. Nature. 2024 Feb;626(8001):1094-1101).

We will assume that we are principally dealing with reinfection with a mutation/variant

- **All viruses mutate randomly all the time due to errors in transcription during replication.** They tend to evolve toward **a milder strain because that maximises their transmissibility.**
- The fact that many of them fail to gain traction in the population, does not mean that they don't exist. **Apparently, SARS-CoV-2 mutates a little every 10 hours.**
- RNA viruses mutate more slowly than DNA viruses and coronaviruses mutate more slowly than other RNA viruses, because they have a 'proof-reading' enzyme (3'-5' exoribonuclease) which prevents copying mistakes.
- **SARS-CoV-2 has around 30,000 elements of genetic code. Alterations to a few of these will not change its shape to any significant degree.** Mutations in RNA viruses rarely lead to changes in function or pathogenicity. Many thousands of mutations had already occurred before anyone bothered to assign a name to them.
- **Nor will a mutation alter its broad general recognition by the adaptive immune system.** The immune system records a large number of different features for each pathogen to build up immune memory; changing five or six elements out of 30,000 will not prevent its recognition by the immune system.

(Cosar B, et al. SARS-CoV-2 Mutations and their Viral Variants. Cytokine Growth Factor Rev. 2022 Feb;63:10-22; Hou YJ, et al. SARS-CoV-2 D614G variant exhibits efficient replication ex vivo and transmission in vivo. Science. 2020 Dec 18;370(6523):1464-1468; Sciscent BY, Eisele CD, Ho L, King SD, Jain R, Golamari RR. COVID-19 reinfection: the role of natural immunity, vaccines, and variants. J Community Hosp Intern Med Perspect. 2021 Nov 15;11(6):733-739).

Dr Mike Yeadon on variants

- According to Dr Mike Yeadon, former Pfizer VP, **no variant is more than 0.3% different from the ancestral strain,** i.e. no variant is less than 99.7% identical to the Wuhan sequence.
- **"…it's literally impossible and absurd to pretend to the British people that a mere 0.3% mutation is a problem. It's not a problem."**

(https://www.lifesitenews.com/blogs/five-reasons-not-to-fear-coronavirus-variants/)

SARS-CoV-2 variants of concern (VOCs)

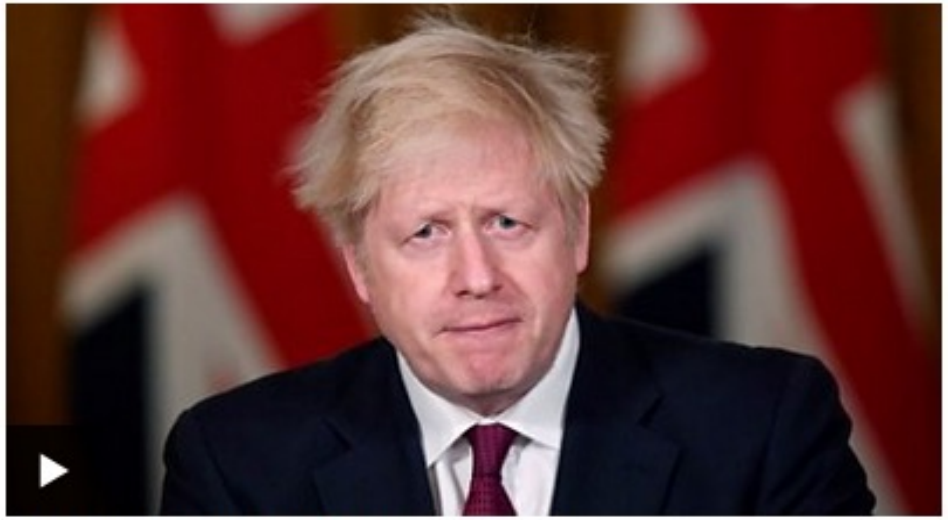
- By early 2022, over 4,000 mutations in the spike protein gene had been observed but there are many other areas of the SARS-CoV-2 genome which can and do mutate.
- Mutations in the spike protein can impact disease pathogenesis (usually weakening disease severity) and susceptibility to antibody neutralisation (usually evading antibodies more effectively).
- Several of these mutations were designated **'variants of concern (VOCs)'**: Alpha (the Kent variant: B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Lambda (C.37), Epsilon (CAL.20C), the Brazil variant (B.1.1.248, Omicron (B.1.1.529) and its later sub-variants.
- **These represent perhaps 10 variants out of tens of thousands of mutations.**
- **As at 5 January 2024, the European Centre for Disease Prevention and Control stated that there are currently no VOCs.** (https://www.ecdc.europa.eu/en/covid-19/variants-concern)

What started the variant of concern panic?

Covid-19: Christmas rules tightened for England, Scotland and Wales

20 December 2020 • Comments

Coronavirus pandemic



'Tier 4 residents must stay at home' as PM announces tighter restrictions

The planned relaxation of Covid rules for Christmas has been scrapped for large parts of south-east England and cut to just Christmas Day for the rest of England, Scotland and Wales.

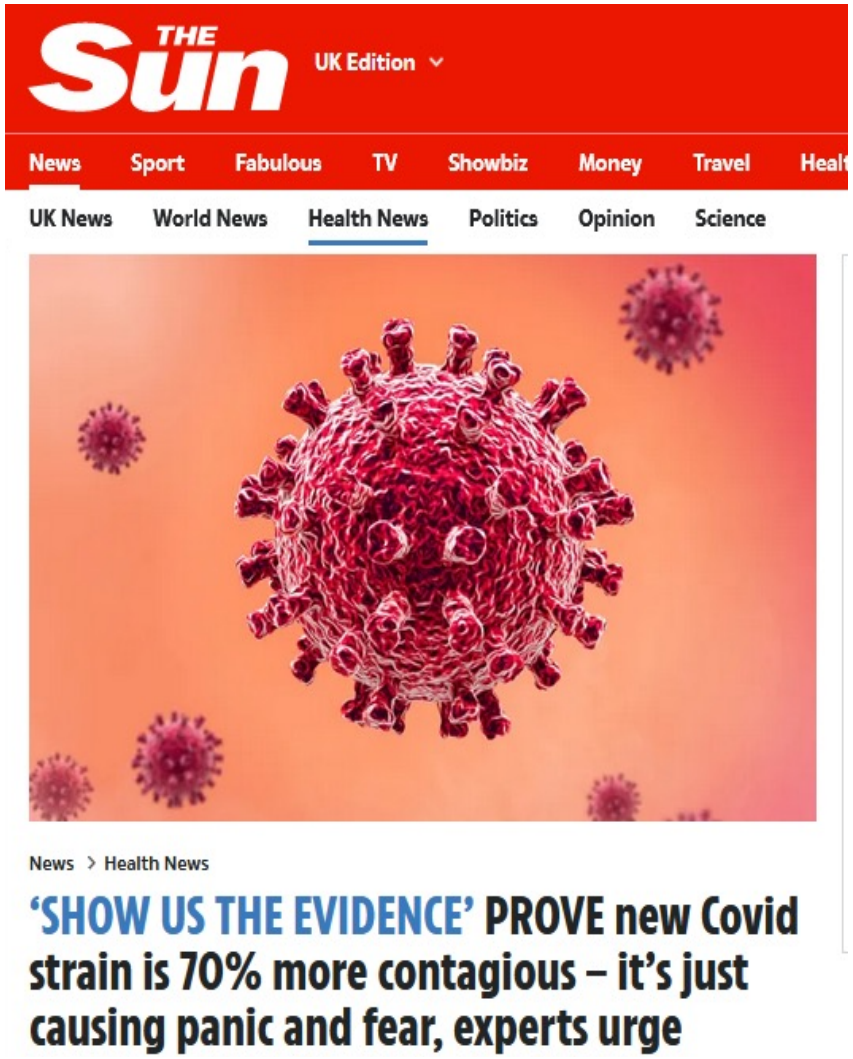
From midnight, a new tier four will be introduced in areas including London, Kent, Essex and Bedfordshire.

Those in tier four cannot mix indoors with anyone not from their household.

https://www.bbc.co.uk/news/uk-55379220

- The Kent variant, aka the Alpha Variant (B.1.1.7).
- The Prime Minister warned **the mutation could be 70% more contagious than the original version and is "spreading rapidly".**
- **So this variant was behaving exactly as we would expect it to: more transmissible but less severe disease.** There was no evidence to the contrary.
- The fuss over the Kent variant set the scene for **more panic every time a new variant was discovered.** Even though it was to be expected.
- **Although all viruses produce variants, we have never had this hysteria before about any other virus.**

But not everyone was concerned about the alpha variant



- **Dec 2020**: 'Boris Johnson has been urged to publish clear evidence on the mutant strain of coronavirus after **dramatically scaling back Christmas plans.'**
- **'Leading academics have demanded more data on the Kent Variant, which prompted swathes of the country to be placed into Tier 4 restrictions.'**
- Even Chief Scientific Adviser **Patrick Vallance said: "There's no real evidence of an increase in mortality for those in hospital".**
- The Zoe App study reported: "We found no changes in reported symptoms or disease duration associated with [the Kent Alpha variant]….There was **no evidence that the frequency of reinfections was higher for the [Kent] variant than for pre-existing variants**".

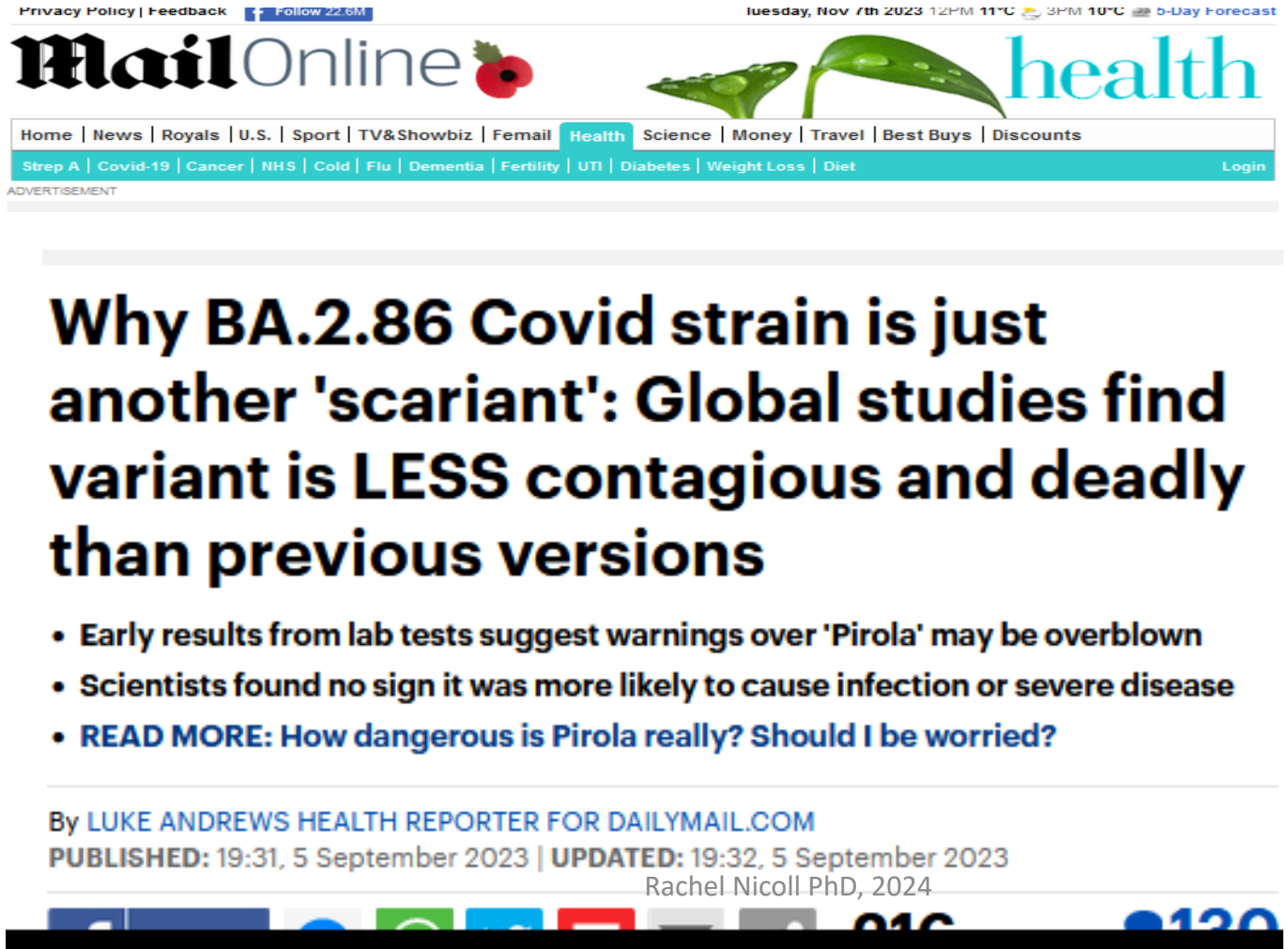
(https://www.thesun.co.uk/news/13535213/prove-new-covid-strain-70-more-contagious-experts-urge/; https://www.reuters.com/article/uk-health-coronavirus-britain-idUSKBN29R0R0; Graham MS, et al. Changes in symptomatology, reinfection, and transmissibility associated with the SARS-CoV-2 variant B.1.1.7: an ecological study. Lancet Public Health. 2021 May;6(5):e335-e345)

How serious were the ‘variants of concern’?

- These variants proved ultimately **not to be of great concern.**
- They mostly proved to be **milder, more transmissible and less virulent** (any resultant infection is milder) compared to the ancestral Wuhan strain. Focus on these obscured the fact that these were a few out of thousands which were not of concern.
- **This means that SARS-CoV-2 variants were behaving exactly as we would expect variants to behave based on other virus behaviour.**
- A study that investigated all mutations up to Autumn 2020 reported “We do not identify a single recurrent mutation in this set convincingly associated with increased viral transmission....At this stage we find no evidence for significantly more transmissible lineages of SARS-CoV-2 due to recurrent mutations.”

(Chen S, et al. The role of B cells in COVID-19 infection and vaccination. Front Immunol. 2022 Aug 30;13:988536; Laidlaw BJ, Ellebedy AH. The germinal centre B cell response to SARS-CoV-2. Nat Rev Immunol. 2022 Jan;22(1):7-18; Wiegand T, https://www.biorxiv.org/content/10.1101/2021.12.16.473096v1; Grubaugh ND, et al. We shouldn't worry when a virus mutates during disease outbreaks. Nat Microbiol. 2020 Apr;5(4):529-530; van Dorp L, et al. No evidence for increased transmissibility from recurrent mutations in SARS-CoV-2. Nat Commun. 2020 Nov 25;11(1):5986; Frampton D, et al. Genomic characteristics and clinical effect of the emergent SARS-CoV-2 B.1.1.7 lineage in London, UK: a whole-genome sequencing and hospital-based cohort study. Lancet Infect Dis. 2021 Sep;21(9):1246-1256; Pierson BC, et al. Severe Acute Respiratory Syndrome and Coronavirus Disease 2019. In: Jong EC, Stevens DL, eds. Netter’s infectious diseases. 2nd ed. Philadelphia: Elsevier, 2021)

And some variants are actually less contagious than the original strain



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Why BA.2.86 Covid strain is just another 'scariant': Global studies find variant is LESS contagious and deadly than previous versions

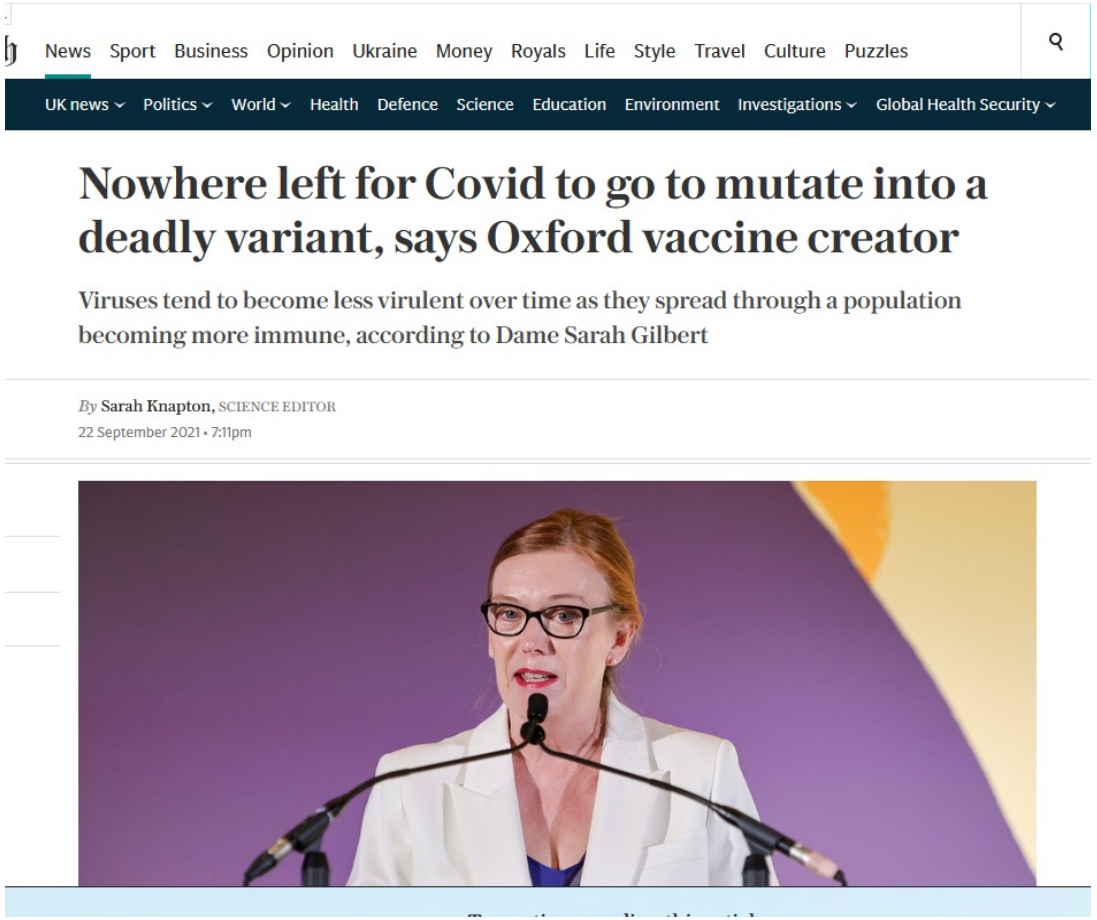
- Early results from lab tests suggest warnings over 'Pirola' may be overblown
- Scientists found no sign it was more likely to cause infection or severe disease
- READ MORE: How dangerous is Pirola really? Should I be worried?

By LUKE ANDREWS HEALTH REPORTER FOR DAILYMAIL.COM

PUBLISHED: 19:31, 5 September 2023 | **UPDATED:** 19:32, 5 September 2023

https://www.dailymail.co.uk/health/article-12483255/pirola-ba286-covid-variant-contagious-deadly-strain.html

Even the Astra Zeneca vaccine creator was not concerned….



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Nowhere left for Covid to go to mutate into a deadly variant, says Oxford vaccine creator

Viruses tend to become less virulent over time as they spread through a population becoming more immune, according to Dame Sarah Gilbert

By Sarah Knapton, SCIENCE EDITOR
22 September 2021 • 7:11pm

- Reported in the Telegraph, Dame Sarah Gilbert of Astra Zeneca, said in September 2021 that **Covid-19 was unlikely to mutate into a much deadlier variant and would eventually become like other seasonal coronaviruses, which cause the common cold.**
- Speaking on a Royal Society of Medicine webinar, Dame Sarah said: “The virus can’t completely mutate because its spike protein has to interact with the ACE2 receptor on the surface of the human cell, in order to get inside that cell….If it changes its spike protein so much that it can’t interact with that receptor, then it’s not going to be able to get inside the cell. So there aren’t very many places for the virus to go to have something that will evade immunity but still be a really infectious virus.”

https://www.telegraph.co.uk/news/2021/09/22/nowhere-left-covid-go-mutate-deadly-variant-says-oxford-vaccine/?li_source=LI&li_medium=liftigniter-rhr

So how did our immune systems cope with variants?

- Studies looking at the immune response to the later variants, such as Delta and Omicron, are not necessarily using the 'ancestral strain' as a comparator. Immunity could have been gained from infection by Alpha or any later mutation.
- And bear in mind that the ancestral Wuhan strain would have been considerably mutated by the time it reached the UK!
- **There is an alarmist tone to many of the studies showing how the VOCs can successfully evade elements of the immune system,** particularly the adaptive immune system. Furthermore, VOCs have evolved reduced sensitivity to interferons, by suppressing viral proteins located outside the spike protein, which reduce the induction of interferons.
- **But that's really the definition of a variant: it has evolved to be able to survive a little better in the human body.**
- But **overall there seems to have been little to worry about….**

Reinfection studies of the unvaccinated

- **Not all studies distinguish between the vaccinated and unvaccinated.** Unless otherwise stated, the results are likely to have been a combination.
- Studies of the specifically unvaccinated showed a **reinfection rate between 0% and 1.1%** with no study reporting an increase in the risk of reinfection over time.
- There was an **87% lower risk of COVID-19 hospitalisation** for up to 20 months of follow-up compared to risk for the primary infection.
- Protection against reinfection was lower for those aged ≥60 years.

(Murchu E, et al. Quantifying the risk of SARS-CoV-2 reinfection over time. Rev Med Virol. 2022 Jan;32(1):e2260; Ridgway JP, et al. Rates of COVID-19 Among Unvaccinated Adults With Prior COVID-19. JAMA Netw Open. 2022 Apr 1;5(4):e227650; Nordström P, et al. Risk of SARS-CoV-2 reinfection and COVID-19 hospitalisation in individuals with natural and hybrid immunity: a retrospective, total population cohort study in Sweden. Lancet Infect Dis. 2022 Jun;22(6):781-790; Kojima N, et al. Incidence of SARS-CoV-2 infection among previously infected or vaccinated employees. Int J Infect Dis. 2022 May;118:21-23; Spicer KB, et al. Protective Immunity after Natural Infection with Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) - Kentucky, USA, 2020. Int J Infect Dis. 2022 Jan;114:21-28; Lind ML, et al. Evidence of leaky protection following COVID-19 vaccination and SARS-CoV-2 infection in an incarcerated population. Nat Commun. 2023 Aug 19;14(1):5055)

How common is reinfection with a variant?

- The UK COVID-19 Forecasting Team carried out a large meta-analysis and showed **>85% protection against Alpha, Beta, Delta and some Omicron variants for the outcomes of infection, any symptomatic disease, hospitalisation and death.** At 10 months, protection against hospitalisation and death remained at c90% for pre-Omicron variants.
- **A systematic review of 10 studies** to August 2021 showed that the weighted average **risk reduction against reinfection was 90.4%** with a standard deviation of 7.7% (p-value: <0.01). Protection against SARS-CoV-2 reinfection was observed for up to 10 months.
- **A UK study of 11,000 healthcare workers** who had evidence of infection between March and April 2020, **none had symptomatic reinfection in the second wave of the virus between October and November 2020**.
- **Pooled reinfection rates range from 0% to 6.8%** after, normally, 8-12 months. The reinfection rate was higher in high-risk populations. Reinfection risk may increase slightly with Delta and Omicron variants.
- Compared to antibodies, T cell responses are generally less affected by the mutations of SARS-CoV-2 variants.

How severe is the reinfection?

- In general, **the 1st wave of viral infection tends to be more severe but the 2nd and later wave variants tend to be less severe but more infectious. The virus has a shorter clearance time, shortening the duration of the second infection.**
- **And in general, that is what we have seen.**
- The Qatari study found that for a person who has already had a primary infection, **the risk of having a severe reinfection is only approximately 1% of the risk of a previously uninfected person having a severe primary infection. There were no cases of critical disease or death at reinfection.**
- Deng et al (2023) calculated severity risk and found that only **0.58% of cases manifested as severe illness and 0.04% cases as critical illness**. Compared with SARS-CoV-2 primary infection cases, reinfection cases were more likely to present with mild illness (OR = 7) and the risk of severe illness was reduced by 86% (OR = 0.14).
- A US case of reinfection gained a lot of publicity because the **second infection was more severe** than the first but it turned out that the patient had developed **secondary bacterial pneumonia**.

(Abu-Raddad LJ, et al. Severity of SARS-CoV-2 Reinfections as Compared with Primary Infections. N Engl J Med. 2021 Dec 23;385(26):2487-2489; Kissler SM, et al. Viral kinetics of sequential SARS-CoV-2 infections. Nat Commun. 2023 Oct 5;14(1):6206; https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3681489; https://www.statnews.com/2020/08/28/covid-19-reinfection-implications/; Halstead SB. Dengue hemorrhagic fever: two infections and antibody dependent enhancement, a brief history and personal memoir. Rev Cubana Med Trop2002;54:171-9.pmid:15846943)

Sometimes it's impossible to be reinfected!

- **An Oxford study tried to reinfect 36 young people with a SARS-CoV-2 variant and followed them up after 12 months.** There was a mixture of vaccinated and unvaccinated subjects but all had previously caught COVID.
- **In every subject, the attempt to reinfect them with COVID failed.**
- **Researchers then increased the dose until it was 10,000 times the initial dose; still no-one became infected, demonstrating that they had developed robust immunity from previous infection.**
- A similar study at Imperial College has also failed to reinfect sufficient subjects.
- As one scientist pointed out, if people can't be reinfected with COVID in a challenge trial, it raises questions about their usefulness for testing vaccines, drugs and other therapeutics.

(Jackson S, et al. Safety, tolerability, viral kinetics, and immune correlates of protection in healthy, seropositive UK adults inoculated with SARS-CoV-2: a single-centre, open-label, phase 1 controlled human infection study. Lancet Microbe. 2024 Apr 26:S2666-5247(24)00025-9https://www.nature.com/articles/d41586-024-01284-1)

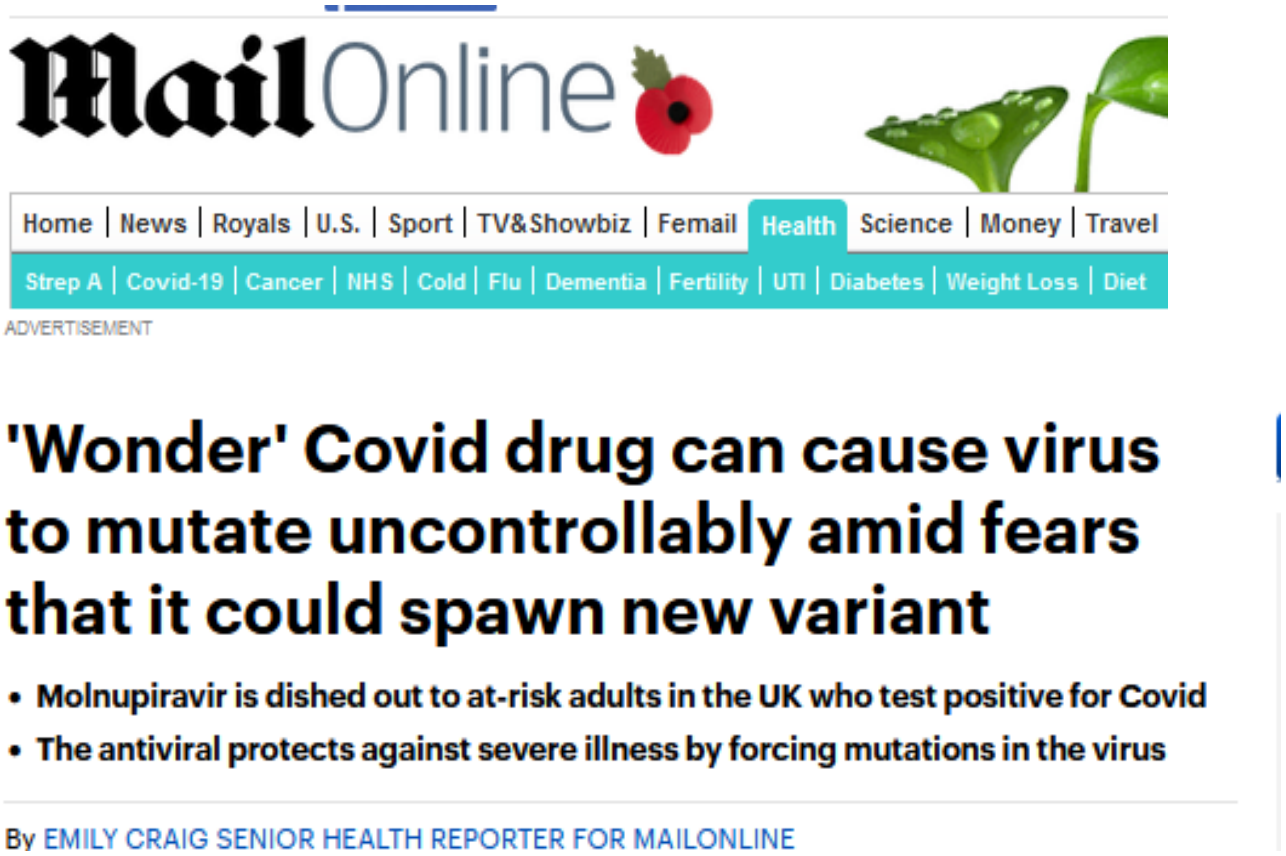
VOCs: comforting thoughts (which were never conveyed to us by the government or its advisors)

- **It's not in a virus' best interest to kill its human hosts** as it can't then reproduce. Infection followed by recovery is what it is aiming for.

- **No-one has yet demonstrated that these VOCs can evade <u>every</u> element of the immune system to run rampant in society.**

- **Even if the immune memory failed to recognise a new variant, it would simply mount a fresh immune response,** which we know it can do very effectively. Yes, the immune response would take longer but it would still be there.

But then we had the antiviral drug Molnupiravir, which could induce mutations



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'Wonder' Covid drug can cause virus to mutate uncontrollably amid fears that it could spawn new variant

- Molnupiravir is dished out to at-risk adults in the UK who test positive for Covid
- The antiviral protects against severe illness by forcing mutations in the virus

By EMILY CRAIG SENIOR HEALTH REPORTER FOR MAILONLINE

https://www.dailymail.co.uk/health/article-12558155/Wonder-Covid-drug-cause-virus-mutate-uncontrollably-sparking-fears-spawn-new-variant.html

Molnupiravir: worth the risk?

- The antiviral drug **molnupiravir was authorised for use in November 2021 and was prescribed widely on the NHS** for Covid-infected people who were at higher risk.
- It works by inserting nonsensical code into the virus's own genetic sequence to turn it into gibberish. This is supposed to lead to "catastrophe error" and prevent the virus from replicating, effectively killing the infection in patients, allowing them to recover quickly.
- **A study from UK Health Security Agency found the virus sometimes survived with the inserted mutations from the drug, which fast-tracked the evolution of Covid variants.**
- They pointed out that some of the mutations created by the drug were similar to those found in delta and omicron variants, although there was no direct evidence that molnupiravir created any known variants of concern.

(Sanderson T,) https://www.medrxiv.org/content/10.1101/2023.01.26.23284998v3.full.pdf) Note: still a pre-print

Isn't Omicron supposed to be more serious?

- The Omicron variant was first detected in November 2021 and subsequently **diverged into a number of sub-variants.**
- In late 2022, the WHO announced that there were then more than 300 Omicron sub-variants.
- These Omicron variants were **not causing more severe disease but they were developing some qualities 'of concern', including 'increased transmissibility and immune escape'.**
- Immune escape: Omicron has been observed to have **high resistance to antibodies and can downregulate antigen presentation to T cells. But there is no evidence that Omicron can evade every element of the immune system.**
- It showed higher infectiousness and immune escape, but significantly **lower severity and mortality. Compared to the Delta variant, the Omicron variant has a 90% lower death rate.**

How results can be differently interpreted from a Review of protective immunity studies

What the review authors said

- **"….previous infection provides remarkable immunity with a shallow reinfection incidence rate and hospitalization frequency."**

(Kojima N, Klausner JD. Protective Immunity After Recovery From SARS-CoV-2 Infection. Lancet Infect Dis (2022) 22:12–14)

How Mainstream Media (ITV News) interpreted it

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Covid: Past coronavirus infection 'does not fully protect young people against reinfection'

HEALTH | CORONAVIRUS | Friday 16 April 2021 at 9:38am

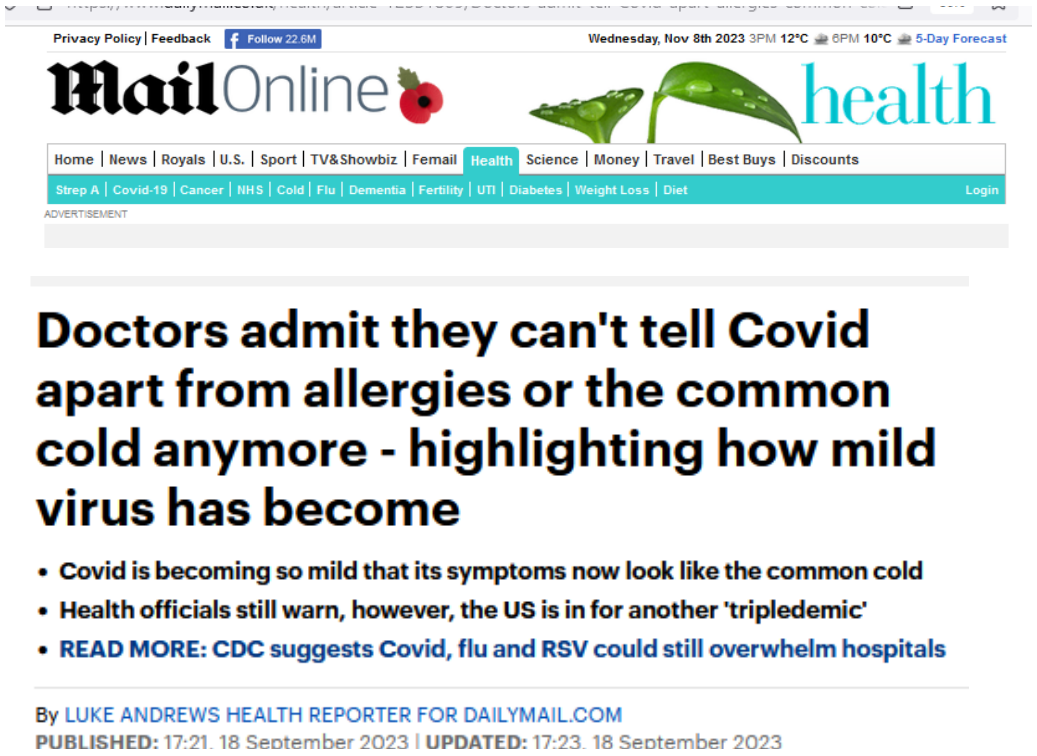
Having Covid before does not guarantee immunity, researchers found.
Credit: PA

Young people who have had coronavirus are not fully protected against reinfection, research suggests.

Scientists said that despite previous Covid 19 infection and the presence of antibodies, vaccination is still

https://www.itv.com/news/2021-04-16/covid-past-coronavirus-infection-does-not-fully-protect-young-people-against-reinfection

But by September 2023….



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Doctors admit they can't tell Covid apart from allergies or the common cold anymore - highlighting how mild virus has become

- Covid is becoming so mild that its symptoms now look like the common cold
- Health officials still warn, however, the US is in for another 'tripledemic'
- READ MORE: CDC suggests Covid, flu and RSV could still overwhelm hospitals

By LUKE ANDREWS HEALTH REPORTER FOR DAILYMAIL.COM
PUBLISHED: 17:21, 18 September 2023 | UPDATED: 17:23, 18 September 2023

- Covid patients are becoming harder to distinguish from those suffering from allergies or the common cold, doctors say.
- The most common symptoms of the virus are now sore throat, sneezing or congestion — the same as RSV, asthma or a pollen allergy.
- Dr Erick Eiting, a senior emergency medicine doctor, at Mount Sinai, New York City, told NBC News: “Just about [every Covid patient] who I've seen has had really mild symptoms…**The only way that we knew it was Covid was because we happened to be testing them.”**

https://www.dailymail.co.uk/health/article-12531809/Doctors-admit-tell-Covid-apart-allergies-common-cold-anymore-highlighting-mild-virus-become.html

Reinfection and variants: summary

- Reinfection with the original strain is very rare due to the continual mutation of the virus.
- SARS-CoV-2 variants are all genetically very similar to the original strain, so our immune system has little problem dealing with them.
- Typically, variants are more infectious but give less severe disease, as proved to be the case.
- ‘Variants of concern’ (VOCs) were in fact of little concern.
- We had around 90% protection against variants after an initial infection and any disease was generally mild.

Meta-analysis and reviews

- Nguyen NN, et al. SARS-CoV-2 Reinfection and Severity of the Disease: A Systematic Review and Meta-Analysis. Viruses. 2023 Apr 14;15(4):967
- Carabelli AM, et al. SARS-CoV-2 variant biology: immune escape, transmission and fitness. Nat Rev Microbiol. 2023 Mar;21(3):162-177
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