Twitter Thread by Kenny Mathieson

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@KennyMathieson

The "hope" that @krishgm mentions is forlorn, in this case.

A thread in which I prove (using ONLY published Pfizer trial data) that the UK CMOs and JCVI have not so much ignored the science, as left it bleeding at the roadside.

Intrigued?

Read

> The trial data said that after a single dose of the Pfizer vaccine coverage was 52%. Six days after the second dose that rose to nearly 91%. The new policy to delay 2nd dose is based on the idea that the 91% was in fact due to the first dose. We must hope that is true.
>
> — Krishnan Guru-Murthy (@krishgm) December 30, 2020

From the moment, the decision was announced to delay 2nd vaccine doses, I've felt uneasy.

This is not my field of expertise, but I trained as a scientist (two chemistry degrees), worked professionally in IT, and understand the importance of testing.

My principal concern was about the Pfizer vaccine.

As vaccines go, it's "new tech", the first mRNA vaccine and the results are stunning.

Perhaps one should be cautious about deviating from a clinical trial procedure, at least until there is greater experience of mRNA vaccines?

I've been investigating this for over a week and haven't been able to sleep properly since I started.

At best, the 12 weeks strategy was based on one critical assumption, namely that the 2nd dose has NO effect on efficacy in the first 7 days after it is given.

And if it did?

My journey started with a friend pointing me towards an article in @bmj_latest which indicated that a single dose of @pfizer vaccine had an efficacy of 52%.

https://t.co/wAiMlgrRvn

The following day, I heard @NicolaSturgeon say in the Scottish Parliament that the short term efficacy of a single dose of the Pfizer vaccine was 90%.

My head almost exploded. @bmj_latest said the figure was 52%, where did this figure come from? Had it been said by mistake?■■■■■

Where there's a Tweet, there's a way.

I sent a query to @patrickharvie who kindly replied with this:

https://t.co/DZe1pOlltY

Hmmm, OK? ■

It was clearly time to read the Pfizer (Phase 3 trial) paper.

https://t.co/WlkBSoOX1C

> I asked the CMO this question today. The 52% figure comes from looking at the level of protection as soon as the vaccine is administered, ie includes everything from day 0. The higher figure is the level of protection achieved, but which takes time to develop.
>
> — Patrick Harvie \U0001f1ea\U0001f1fa\U0001f308 (@patrickharvie) January 4, 2021

As noted, this is not my field.

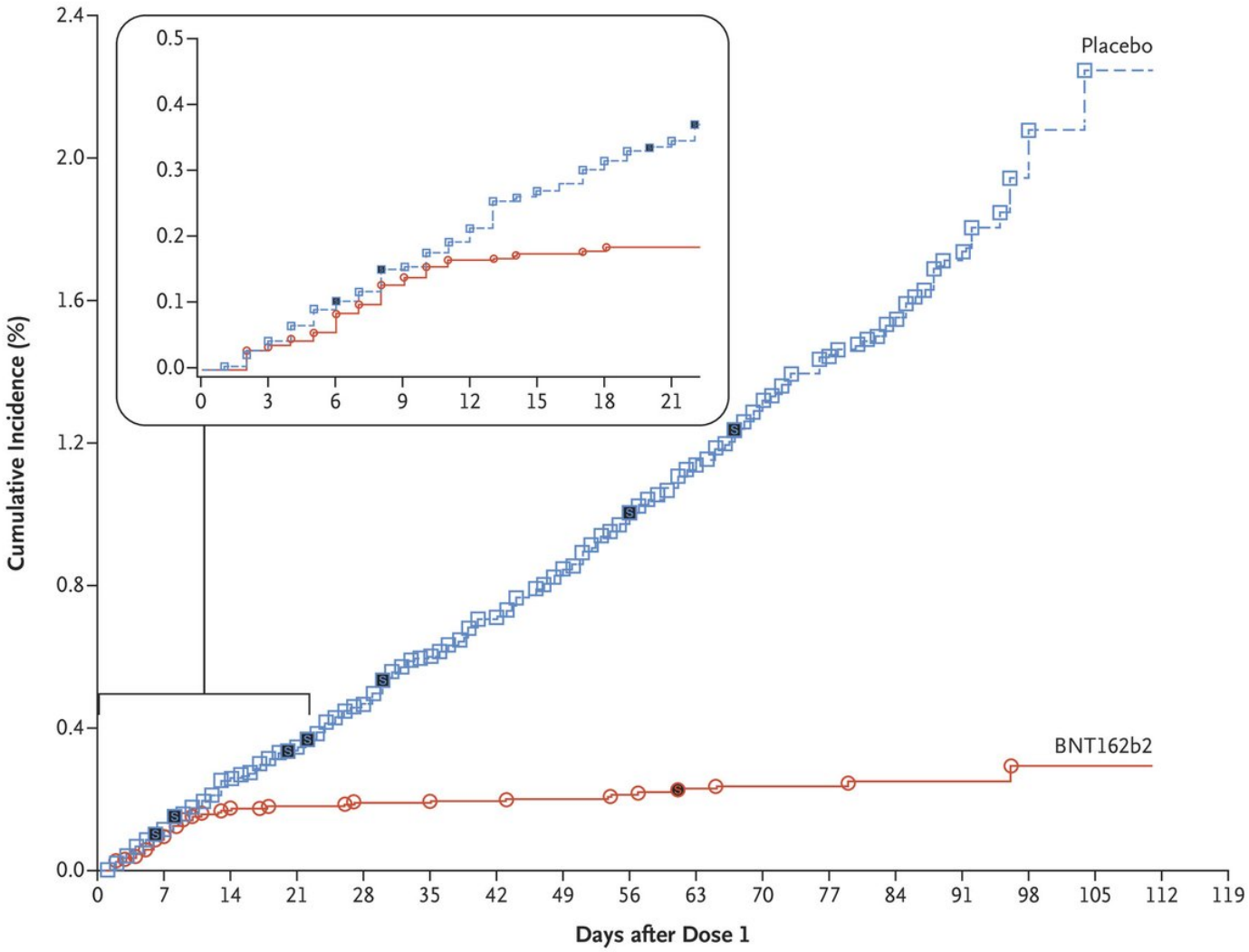
However, I do have three published scientific papers to my name and know how to read them, as long as they are written in something resembling plain English.

High energy physics? Pass.

Vaccine efficacy? Good to go!■■

Helpfully, the key data (in terms of efficacy) in the Pfizer paper is contained in one key graph (with an accompanying table of data).

The 90% efficacy figure is drawn from the 7 day period AFTER dose 2 has been given.



Efficacy End-Point Subgroup	BNT162b2, 30 μg (N=21,669)		Placebo (N=21,686)		VE (95% CI)
	No. of participants	Surveillance time *person-yr (no. at risk)*	No. of participants	Surveillance time *person-yr (no. at risk)*	*percent*
Covid-19 occurrence					
After dose 1	50	4.015 (21,314)	275	3.982 (21,258)	82.0 (75.6–86.9)
After dose 1 to before dose 2	39		82		52.4 (29.5–68.4)
Dose 2 to 7 days after dose 2	2		21		90.5 (61.0–98.9)
≥7 Days after dose 2	9		172		94.8 (89.8–97.6)

Logically, there are 3 possibilities for what happens in the first week after the 2nd dose of Pfizer vaccine is given.

1. It has no effect
2. It has some effect
3. It is the dominant effect

An assumption has been made by the 4 UK CMOs and JCVI that the first is true.

Why?

My guess is that given the first dose is shown to have no effect for 12 days, they have assumed that it will take a similar time to detect any signs of the second dose.

That's one hell of an assumption.

If only there was some data to offer clues?

Gee, there is! ■

I found the final part of the puzzle after watching an interview with @DrPaulOffit on Saturday.

He is concerned about the @joebiden plan to deploy all vaccine doses (rather than holding back enough to ensure 2nd doses can be given on time).

https://t.co/AMiwNisRF4

This section of the interview with Dr Offit supplied the clue I needed.

Phase 1 studies? Well, let's look at that paper.

Obviously, the CMOs and the JCVI must have had a look at it, right? ■

And we have had other experts on our program, even this week, saying, given the surge we're seeing, given this new variant that's more contagious we're seeing, it is time to consider freeing up more of these doses.

In fact, someone I know you have worked with, Dr. Robert Wachter, said to us earlier this week that the data he had seen showed that the first dose could be 80 to 90 percent effective.

This is all very confusing, I think, to the public. Can you clear it up for us?

Dr. Paul Offit:

Sure.

So, these were two-dose — this is a two-dose vaccine. So, if you look, there's a period of time between the first and the second dose — for Pfizer, it's three weeks, and, for Moderna, it's four weeks — when you can see whether or not there's any efficacy. And you could see that, with the Pfizer vaccine, there was about 50 percent efficacy. You could see that, with a Moderna vaccine, it was about 80 percent efficacy.

But that was just for a few weeks. That's when you have just gotten the vaccine and you have an immune response. You don't know whether that's also true for two months later, three months later. It's probably not true.

If you look into phase one studies, where you get one vaccine, and then you get the second dose, there's a dramatic boost with that second dose. So, it's — the first dose does not, frankly, compare all that favorably to the kind of immune response you see with just in convalescent serum for people who've gotten just — survived the infection.

That's why the companies went to a second dose. Otherwise, we could have gone with a one-dose vaccine. So, I think you're taking unnecessary risk here that you're going to have a delay in getting that second dose.

My head almost exploded (again!) when I read this paper.

The UK policy on a 12 week gap between Pfizer doses, is a Damoclean sword, suspended by an assumption that the 2nd dose has no effect for the first 7 days after it is given.

100% incorrect. ■

https://t.co/AaQGc6EnU2

You may recall hearing, "We are following the science"?

Heh.

The Pfizer (Phase 1/2 trials) paper, shows clearly that in this instance, the science is being ripped into tiny pieces, those tiny pieces are then set on fire, and the flames are extinguished by being urinated on. ■■■■■

Speaking as a non-expert, Phase 3 clinical trials are all about testing the efficacy of a particular drug.

Phase 1/2 clinical trials are more about working out the right dose and checking safety.

Pfizer used three separate doses at this stage.

10 μg
30 μg
100 μg

For 10 μg and 30 μg, participants were given 2 doses 21 days apart.

Crucially, for 100 μg, only 1 dose was given.

Two measurements were taken at baseline, at 7 and 21 days after the first dose, at 7 days (day 28) and 14 days (day 35) after the second dose.

As to what those measurements mean specifically, here I am well outside my comfort zone.

Essentially they are related to the strength of the antibody serum levels and receptor binding thingys...or something along those lines. ■■■■■

The larger the numbers, the better. ■■

For the binding thingys, values are:

10 μg dose

Baseline 0.8
Day 7 0.9
Day 21 534 (2nd dose given))
Day 28 4,813
Day 35 5,880

30 μg dose

Baseline 0.9
Day 7 0.8
Day 21 1,536 (2nd dose given)
Day 28 27,872
Day 35 16,166

7 days after the 2nd 10 μg dose has been given, the binding value becomes 9 times larger.

7 days after the 2nd 30 μg dose has been given, the binding value becomes 18 times larger.

Clearly something dramatic is happening in the 7 days AFTER the 2nd dose has been given. ■

Of course, the UK CMOs and the JCVI have assumed that this massive increase has NOTHING to do with the 2nd dose.

Fortunately, this can actually be confirmed by looking at the data for the 100 μg dose, where NO second dose was given.

It's obvious, right?

Clearly, we will expect a massive increase between Day 21 and Day 28 for the 100 μg dose, thus PROVING the assumption underpinning the UK strategy to give Pfizer doses 12 weeks apart, is based on solid foundations.

These guys are experts, right? ■

Still, let's check!

100 μg dose

Baseline 0.9
Day 7 1.2
Day 21 1,778 (NO 2nd dose given)
Day 28 1,260
Day 35

So, as predicted you can see WITHOUT adding a 2nd dose, the value soars by...um...it FALLS, by 30%?

It's almost as if the 2nd dose is significant? ■

This is VERY odd.

I mean the CMOs and JCVI did read the Phase 1/2 Trials paper, right?

Still, this isn't my field, so maybe it's the other measurement that is the important one?

That's probably the one that shows the 2nd dose has no effect in the first 7 days?

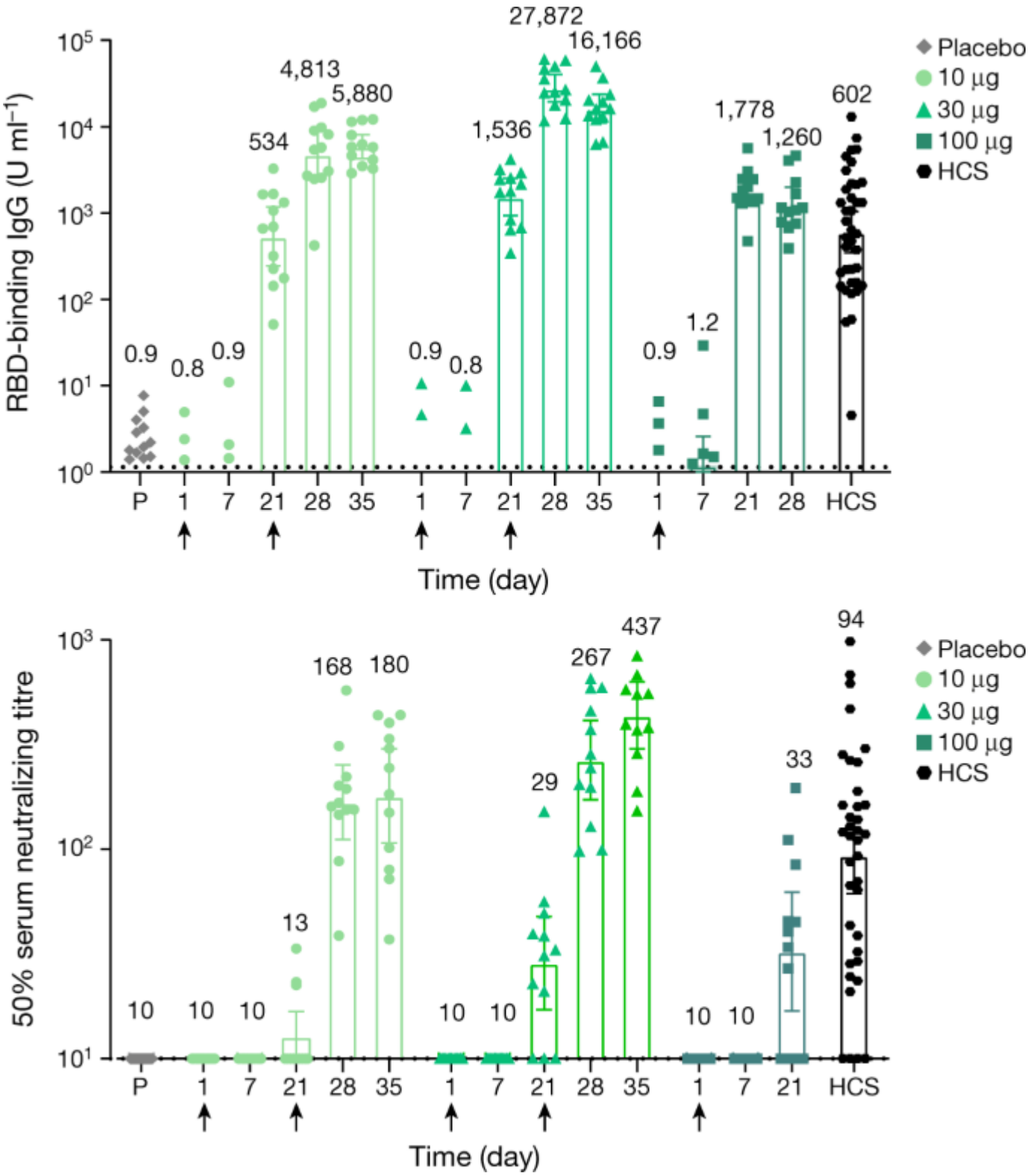
Let's check!

Actually, there's no point.

The second set of values doesn't include any beyond Day 21 (for the 100 μg dose) , because the first set of values have already determined that to be the peak, for that dose.

Gosh, that's kinda awkward.

Here's the data.



Let's review.

The UK is giving doses of the Pfizer vaccine 12 weeks apart (as opposed to the recommended 3 weeks), in the belief that this delivers 90% efficacy, which only increases to 95% efficacy after the 2nd dose.

This is predicated on an assumption that the 2nd dose has NO effect in the first 7 days after it is given.

However, when one looks at the Phase 1/2 Trials data, it clearly shows that the 2nd dose has an immediate turbocharge effect.

It gets worse.

In the first 7 days after Day 21, if no second dose is given, the efficacy goes down.

Two doses of 10 μg given 3 weeks apart, produces a binding thingy value (BTV) of 4,813 at Day 28, while one dose of 100 μg has a BTV of 1,260 at Day 28.

So, you get dramatically more vaccine effect from giving 2 small doses 3 weeks apart, than you do from giving a single dose of 10 times the size of the first smaller dose alone.

Far from increasing between Day 21 and Day 28, the efficacy of a single dose declines significantly.

There are no measurements as to how quickly or how low a single dose of Pfizer vaccine could go after 28 days, but the signs are not encouraging.

We have been told that the first Pfizer dose is the cake (90% efficacy), and the second dose is the icing on top of the cake (95%).

One could scarcely draw a more incorrect conclusion, on the basis of examining the trial data.

The 1st dose is like the cake base and the 2nd dose is the cake.

Oh, and if you don't add the cake after 3 weeks, the cake base starts to disintegrate.

In essence (and to torture this analogy more than an innocent and unsuspecting analogy deserves), the UK's current Pfizer vaccination strategy is one of:

Not having one's cake and not eating it.

Yummy...NOT! ■

If anyone is taking notes for the final exam, let's review the course thus far.

For the Pfizer vaccine:

1. The 2nd dose has a vastly greater effect than the 1st dose on its own.

2. The optimum time to give the 2nd dose is 3 weeks.

Indeed, the indications are that for every week you delay giving the 2nd dose beyond 3 weeks, the efficacy will decline significantly.

In the worst case, by the time you give a 2nd dose at 12 weeks, it may be like a new 1st dose, of limited efficacy and decline quickly.

Oh...and as people are experiencing declining protection after 21 days, they have been told they are 90% protected.

Can one imagine that might lead to behavioural changes which could increase their risk of getting infected?

"I'm fine...been vaccinated...90% protected!”

It gets still worse (surely that can't be possible?)

As well as making people feel they are wearing a suit of vaccine armour, while the reality is they are in a papier-mâché vaccine ensemble, you're kinda wasting two doses of Pfizer vaccine.

Not ideal, is it?

There's also a risk of destroying confidence in the Pfizer vaccine (in the UK), while simultaneously giving a major boost to the anti-vaxxers.

As mass vaccination programs go, this is the Titanic Maiden Voyage Special Edition.

Could there be a more ill-conceived strategy? ■

Time for a quick pop quiz.

Q. Your country is in crisis in the middle of a pandemic. Suddenly, you are given a 95% effective vaccine. Do you:

A. Follow the instructions and improve the situation?

or

B. Use in the least effective way possible, resulting in more deaths?

■

One of my heroes is the late Carl Sagan, who famously said:

“We live in a society exquisitely dependent on science and technology, in which hardly anyone knows anything about science and technology."

Therein lies a problem.

At the moment, I'm tired (couldn't sleep again last night, got up to finish this) and I'm angry.

There are professionals for whom this stuff is their day job.

Literally, this is matter of life and death.

What the hell have they been doing? ■■■■■

Once I navigated my way to the Pfizer (Phase 1/2 trials) paper, it took me about 1 minute to spot that the assumption that the 2nd dose had no significant effect in its first 7 days, was laughably absurd.

Granted, I then spent a couple of hours making sure I was 100% correct.

The data relating to the powerful effect the 2nd dose has (in its first 7 days), would be obvious to a 1st year undergraduate science student, if put in front of them.

So what have the CMOs, the National Clinical Directors and the JCVI been playing at?

This IS their day job.

It's (almost) inconceivable that the CMOs et al, didn't read the Pfizer Phase 1/2 trials paper.

If they DID read it, it's absolutely inconceivable that they didn't understand its significance.

So what's left? Providing cover to justify a political decision?

I have a few apposite words I would like to address to the CMOs, National Clinical Directors and members of the JCVI, who signed off on this ill-conceived strategy.

Those words are:

"Untenable position."

and

“Resign!"

OK, now let's turn to the politicians.

If I hear the phrase, "That's a clinical decision, I can't overturn it." (or words to that effect) once more, I will scream.

Medicine is a branch of science (last time I checked!)

The scientific method is ALL about challenging.

If Albert Einstein published a paper today, firstly, it would be a major breakthrough in paranormal research. ■

However, leaving aside his "mortality challenged" life status, the paper would be judged on its merits and the quality of the ideas it contained.

To the uninitiated, elements of the scientific method can seem brutal.

The peer review process is essentially a form of intellectual kicking.

The quality of your data and ideas will be challenged.

It's not done to be nasty.

It's nothing personal.

It IS a trial by ordeal.

If you're trying to add to the Tree of Human Knowledge, it's better to avoid adding diseased branches, for all of us.

I believe the phrase, "Advisers advise, ministers decide." is quite a familiar one?

OK, so be it.

If ministers have signed off on bad advice, without even challenging it, because it's "a clinical decision", they are equally culpable.

Surely, one does not need to be a clinician to note that the advice one is getting from one's CMO, is VERY much at odds with the advice from Pfizer, Dr. Anthony Fauci, the WHO et al.?

I can think of some obvious questions.

1. Why are you right and Pfizer (who developed and tested this vaccine) wrong?

2. What assumptions have you made and why do you believe they are justified?

3. If you're wrong, what's the worst case scenario?

Oh...and maybe pick up the phone to Pfizer for a chat, as well? ■

OK, so I've dealt with the clinicians and the politicians.

Who's left in this epic catalogue of failure?

Ah yes, the Fourth Estate.

Since I read the Pfizer Phase 3 trials paper, I've been waiting for a journalist to ask a question, which indicated they had.

Still waiting.

My sense has been that Covid-19 is primarily being covered by political journalists and it IS a political story.

However, it's also a science story.

Having said that, I'm not sure how many journalists who cover science, actually have a science background?

Carl Sagan also said:

“Science is a way of thinking, much more than it is a body of knowledge.”

Indeed, it is.

Once you have that training, it will usually point you in the right direction in terms of questions to ask, even in areas that are new to you.

#CarlSaganRocks

In the last 10 months, I've learned so much about vaccines and efficacy via watching @CNN

In particular, my thanks are due to Dr. Anthony Fauci, @drsanjaygupta, @DrPaulOffit, @ChrisCuomo, @andersoncooper, @jaketapper and @wolfblitzer

This thread wouldn't exist without them.

As I've been digging into this, at times, I've felt somewhere between Woodward and Bernstein at Watergate and a tinfoil hat wearing conspiracy theorist.

My bulwark against the latter feeling has always been, "I agree with Dr. Fauci."

Phew!

While this thread is primarily about the 12 weeks gap between Pfizer doses in the UK, it may also have relevance for the USA.

The new Biden plan is to deploy all vaccines held in reserve and ramp up manufacturing to be able to give 2nd doses on time.

That's risky.

Given what I now understand, it's obvious (and unsurprising) as I watch Dr. Fauci, that I don't know any more than he does.

However, when I listen to the UK CMOs, it's far from obvious that they have looked at the Pfizer Phase 1/2 trials data. ■

Surely a national policy on mass vaccination has not been based on the Brodie's Notes version of published research? ■■■■■

So, if I only know what many others already know, what can I bring to this (socially distanced) virtual party?

Well, I'm as geeky as they come, science background and a career in IT.

However, I'm also a photographer and think in terms of images.

In my career, I was generally regarded as having skills in communicating technical matters in a way that was understandable to business people.

Scientists are mostly used to communicating with fellow scientists.

Like every profession, they have their own code in terms of language.

A phrase like, "There's no data to support that.", might (in a certain context) actually translate as:

"Are you utterly forking insane?”

My nightmare vision has been of solemn press conferences in 6 months time, where Boris Johnson, Nicola Sturgeon and the other leaders, say:

"We take full responsibility for the disastrous Pfizer vaccine rollout, but we sincerely believed..."

Essentially, Blair after Iraq.■

There's a major difference.

It was impossible to prove the non-existence of that which didn't exist.

In the case of the Pfizer vaccine, we have VERY clear and understandable published research.

Just RTFM!

This is not how I envisaged 2021 beginning.

I'm shattered.

For 9 nights, I've had trouble sleeping (and I normally sleep VERY soundly).

My Science-sense was tingling from the moment the 12 weeks gap between doses was announced.

When I read the Pfizer (Phase 3 trials) paper, the potential worst case scenario was instantly obvious to me.

This has taken a lot of energy and determination, but I had the best motivation in the world.

I want to keep my Mum safe.

If you've read this far, I salute your courage, your strength, your indefatigability...

Oh wait, that line doesn't have the greatest history, does it? ■

I've tried to make my case as clearly as I can, because I am certain lives depend upon it being understood.

What do I want?

That's easy.

I want the UK Governments to "follow the science" and give doses of the Pfizer vaccine, 3 weeks apart, as per clinical trial.

The 12 weeks strategy for this vaccine will be a disaster and cost lives.

It's now over to all of you.

I've done all I can and hope it will make a difference.

If you've found my arguments persuasive, please share this thread.

If you're unpersuaded, thanks for reading.

On y va, mes amis!