COMMENTS to FDA VRBPAC Meeting January 26, 2023

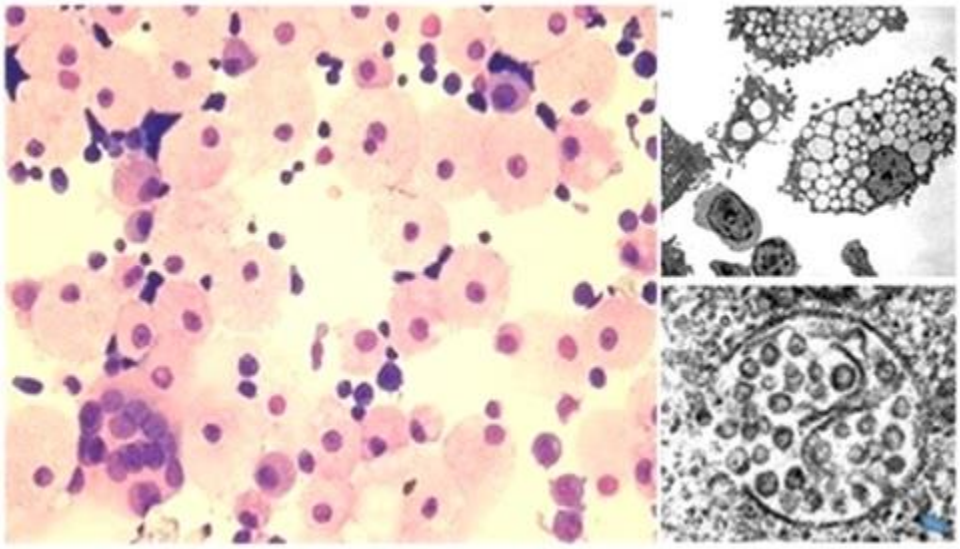

Figure 1. The lipid body negative foamy macrophages (LB$^-$FMs; *WDR74 positive*) producing the protective HERV-K102 particles for trained INNATE immunity *critical* to counteract SARS-CoV-2, an RNA pandemic virus.[1]

I have just completed the first revision of a 19,383-word document with 255 references entitled "**Controversies Concerning the Immunology of the COVID-19 Adaptive Immunity Vaccines**" with 5 Tables, 16 images and 2 appendices which is very relevant to your upcoming discussions. One should note that my background involves regulatory experience at Health Canada and also of relevance, I was the Research Manager for the Blood Zoonotics Unit at the Public Health Agency of Canada where my team discovered the replication competence of human endogenous retrovirus K102 (HERV-K102) (**Figure 1**) and identified it as the elusive foamy virus **UNIQUE TO** humans.[1,2,3]

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[1] Laderoute MP. Clues to finding correlates of risk/protection for HIV-1 vaccines [version 2; peer review: 2 approved with reservations] F1000 Research 2018, 6:868. https://doi.org/10.12688/f1000research.11818.2.

2 Laderoute MP, Giulivi A, Larocque L, et al. The replicative activity of human endogenous retrovirus K102 (HERV-K102) with HIV viremia. AIDS. 2007 Nov 30;21(18):2417-24.

3 MP, Larocque LJ, Giulivi A, Diaz-Mitoma F. Further evidence that human endogenous retrovirus K102 is a replication competent foamy virus that may antagonize HIV-1 replication. Open AIDS J. 2015 Dec 7;9:112-22. doi: 10.2174/1874613601509010112.

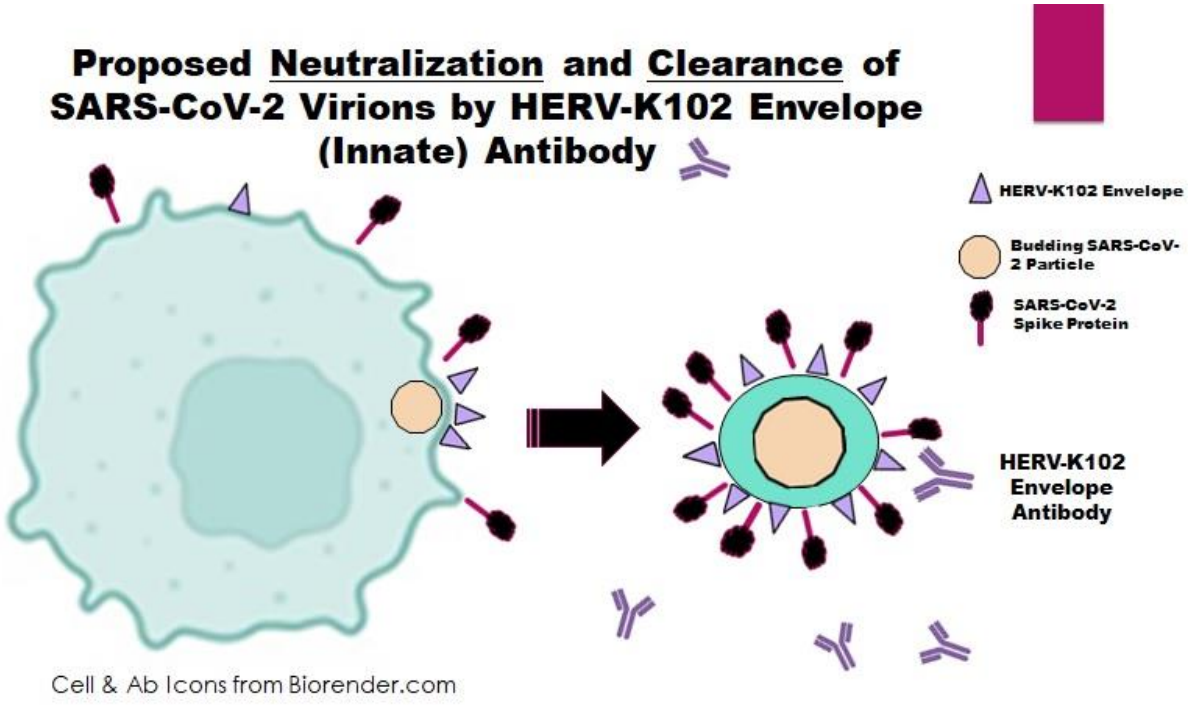

Figure 2. Enveloped viruses like HIV-1 and SARS-CoV-2 When Produced in Human Cells But Not NON-Human Cells Display HERV-K102 Envelope on Their Virions So the HERV-K102 Innate Protector System Includes the Ability to Neutralize Virions Through HERV-K102 Envelope Antibodies[2] in the Upper Respiratory Tract[4]

I have validated in this 149 page report[5] that the HERV-K102 INNATE protector system is the only way to handle an RNA virus pandemic. On the other hand, the use of adaptive immunity vaccines to SARS-CoV-2 spike protein, is dangerous and prolongs the pandemic.

What is unique about this *POWERFUL* trained innate protector system which may be only 700,000 years old is that it:

1) is **a virus anti-virus response** including the ability to neutralize enveloped viruses (**Figure 2**) which constitute many of the emerging and/or pathogenic viruses,

[4] Apostolou E, Rizwan M, Moustardas P, et al. Saliva antibody-fingerprint of reactivated latent viruses after mild/asymptomatic COVID-19 is unique in patients with myalgic-encephalomyelitis/chronic fatigue syndrome. Front Immunol. 2022 Oct 20;13:949787. doi: 10.3389/fimmu.2022.949787.

2) is **an autologous innate vaccination system** producing both T cell and B cell (antibody) *temporary* responses with specificity to HERV-K102 envelope antigens,
3) is **constitutive and positioned in the mucosa** with HERV-K102 particles being continuously produced and released as sebum from the sebaceous glands; sebocytes have been discovered to be specialized **LB-FMs**,[5]
4) displays **memory of short-term duration (epigenetic associated with trained innate immunity; 3-6 months)**, but also longer term associated with increased integration of HERV-K102 proviral genomic copies (genetic alterations to human genome just like adaptive T cells and B cells) that can provide sterilizing immunity (**Figure 3**), and
5) possibly responsible at least in part, for the **survival of *Homo sapiens* over the extinct hominins, Neanderthal and Denisovans** (**Figure 4**)[5]

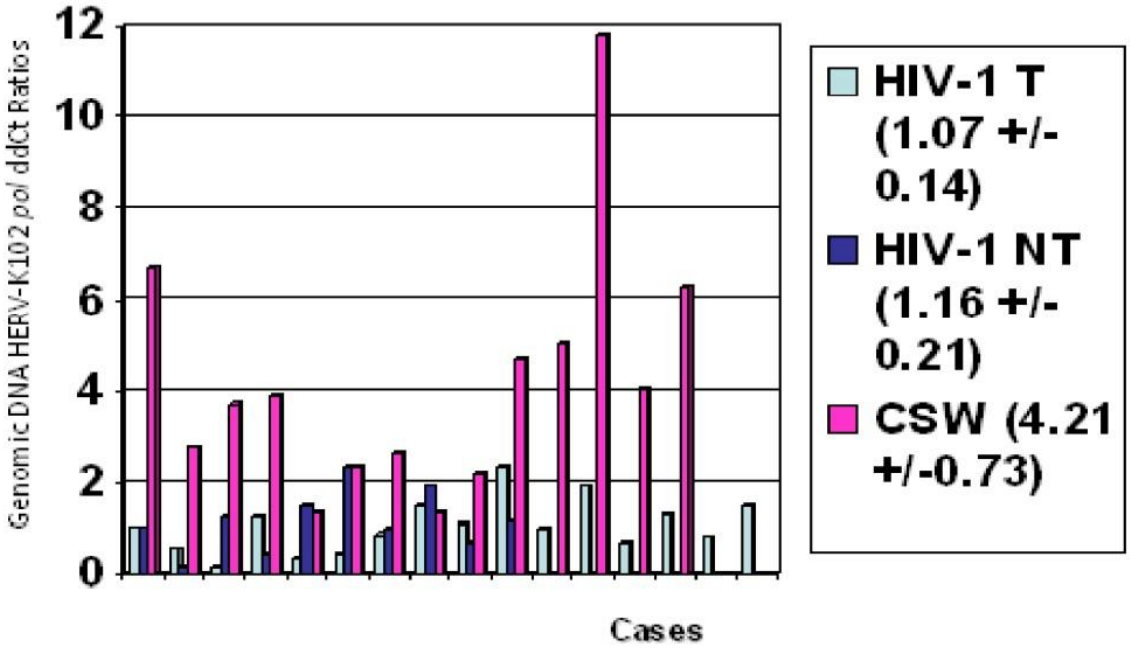

Figure 3. The HIV Exposed Seronegative (HESN) Cohort of Fowke et al, 1996[6] Consisting of Female Commercial Sex Workers (CSW) Resistant to HIV-1 Acquisition for at Least 3 years, Display a 5-fold Increased Gene Copy Number for HERV-K102 *pol* Over Healthy Normal Controls (0.88 +/- 0/37; p< 0.0005) By ddCt Real Time PCR on DNA Purified from Plasma (Treated with Uracil-N-Glycosylase to Digest HERV-K102 Particle Associated cDNA)[3]

[5] Laderoute MP. **Controversies Concerning the Immunology of the COVID-19 Adaptive Immunity Vaccines (submitted)**

[6] Fowke KR, Nagelkerke NJ, Kimani J, et al. Resistance to HIV-1 infection among persistently seronegative prostitutes in Nairobi, Kenya. Lancet. 1996 Nov 16;348(9038):1347-51. doi: 10.1016/S0140-6736(95)12269-2.

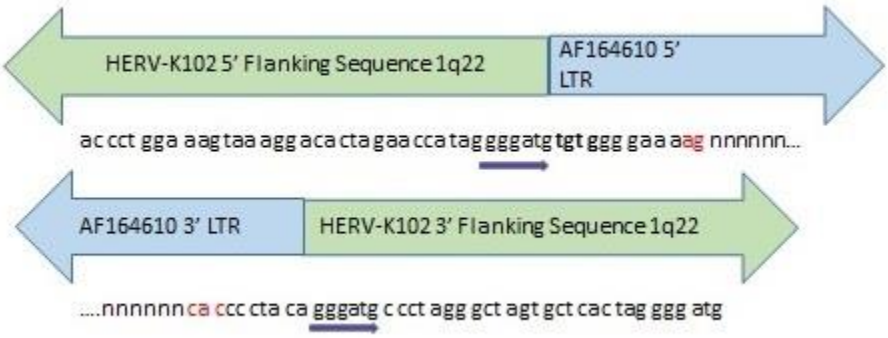

Figure 4.

Figure 4. Evidence for Past Integration and Excision of HERV-K102 at Orthologous Positions (1q22) in the Neanderthal and Denisovan Genomes.

Direct repeats (gggatg) flank the orthologous HERV-K102 sequence in the human and extinct hominin genomes. The nucleotides marked in red were missing from the Denisovan orthologous position but present in the Neanderthal genome. Most of the HERV-K102 provirus was missing in both extinct hominins with only a few nucleotides corresponding to the ends of the LTRs remaining intact. "n" stands for missing nucleotides. Inquiry was made of the Altai Neanderthal or Denisovan genome at http://bioinf.eva.mpg.de/fetchseq/ on chromosome 1 strand at 155,596,423 to 155,605,644. AF164610 GenBank LTR flanking sequences used: 5' LTR sequence = AF095801 and 3' LTR sequence = AF095802.

From the Key Points of this book chapter,[5] I would like to quote the following:

"**As was expected, the strategy of generating adaptive IgG antibodies to spike protein as a means to protect citizens and contain an RNA virus pandemic has been proven to be ineffective, as well as the use of the mRNA and virus vector vaccines due to their toxicity. On the other hand, a new pandemic preparedness paradigm based on the stimulation of trained (INNATE) immunity involving human endogenous retrovirus - K102 (HERV-K102) particle production in WDR74 positive, lipid body negative foamy macrophages (LB- FMs see Figure 1), has been validated as the sole strategy for taming RNA virus pandemics, since there is no possibility for selection of immune escape variants.**

Incidentally, the INNATE HERV-K102 trained immunity protector system is favored by optimal vitamin D3 levels and supported by the early COVID-19 treatment protocols {*involving alpha-fetoprotein antagonists, such as zinc, flavonoids, ivermectin*[7]} . There is some additional direct evidence that trained immunity and/or HERV-K102 replication might provide sterilizing immunity against the RNA enveloped pandemic viruses, SARS-CoV-2[8] and/or HIV-1."

I would just like to make the following comments:

1) It was extremely unexpected that the FDA would provide EUA for an intervention (gene therapy: mRNA and/or viral vector vaccines) involving the induction of IgG antibodies especially neutralizing antibodies with specificity for SARS-CoV-2 spike protein when by the time of the submissions to the FDA, **it was well established in the literature that these antibodies were not protective but caused progression to more severe disease including DEATH**[9] (and see references 61-73 in reference

[7] Laderoute M. Ivermectin may prevent and reverse immunosenescence by antagonizing alpha-fetoprotein and downmodulating PI3K/Akt/mTOR hyperactivity. Open Heart, April 29, 2021. https://openheart.bmj.com/content/8/1/e001655.responses#ivermectin-may-prevent-and-reverse-immunosenescence-by-antagonizing-alpha-fetoprotein-and-downmodulating-pi3k-akt-mtor-hyperactivity.

[8] Tartof SY, Slezak JM, Fischer H, et al. Effectiveness of mRNA BNT162b2 COVID-19 vaccine up to 6 months in a large integrated health system in the USA: a retrospective cohort study. Lancet. 2021 Oct 16;398(10309):1407-1416. doi: 10.1016/S0140-6736(21)02183-8. (please see Supplemental Table 5)

[9] Huang AT, Garcia-Carreras B, Hitchings MDT, et al. A systematic review of antibody mediated immunity to coronaviruses: kinetics, correlates of protection, and association with severity. Nat Commun. 2020 Sep 17;11(1):4704. doi: 10.1038/s41467-020-18450-4.

5). This issue concerning ADE of infection leading to more severe disease and death, was often associated with early IgG responses (see refs. 44, 72, 81-86 in reference 5) in the upper respiratory tract (URT) that occurred before innate immunity could eliminate live infectious SARS-CoV-2 virions, and where in fact the IgG antibodies through ADE mediated infection of the protector LB-FMs which resulted in the loss of trained innate immunity in both the upper[10] and lower[11] respiratory tracts (URT) (reviewed in ref. 5).

2) The FDA appears to have overlooked the issue that the second dose of the mRNA and adenovirus vaccines strongly induces IgG against spike protein in the URT (saliva, NPS etc) whereas during natural infection the appearance of IgG to spike protein only occurs with severe or critical COVID-19 disease.[12] While ADE occurs both in the URT and LRT, only the URT involves the selection of variants via the classical FCGR2A (for IgG1/IgG3 isotypes).[5,10] On the other hand, the LRT involves a novel mechanism of switch from primary receptor interaction (spike:ACE2) to secondary receptor interaction (spike:BSG) but where antibody isotypes are completely irrelevant.[11] Thus, prior to mass vaccination there was little selection pressure for the emergence of the alpha/delta variants (see Our World in DATA)[13] since there were few cases of IgG to spike protein in the URT. However, following the widespread introduction of the COVID-19 second dose which generates most of the spike-specific IgG in the URT, it selected for immune escape variants as witnessed in the UK and Canada.[5] Indeed based on a comprehensive study of mutations, it has been suggested the SARS-CoV-2 pandemic was destined to end by May 2021,[14] except the selection of variants by the

[10] Ziegler CGK, Miao VN, Owings AH, et al. Impaired local intrinsic immunity to SARS-CoV-2 infection in severe COVID-19. Cell. 2021 Sep 2;184(18):4713-4733.e22. doi: 10.1016/j.cell.2021.07.023.

[11] Ren X, Wen W, Fan X, et al. COVID-19 immune features revealed by a large-scale single-cell transcriptome atlas. Cell. 2021 Apr 1;184(7):1895-1913.e19. doi: 10.1016/j.cell.2021.01.053.

[12] Guerrieri M, Francavilla B, Fiorelli D, et al. Nasal and salivary mucosal humoral immune response elicited by mRNA BNT162b2 COVID-19 vaccine compared to SARS-CoV-2 natural infection. Vaccines (Basel). 2021 Dec 18;9(12):1499. doi: 10.3390/vaccines9121499. **and** Aksyuk AA, Bansal H, Wilkins D, et al. AZD1222-induced nasal antibody responses are shaped by prior SARS-CoV-2 infection and correlate with virologic outcomes in breakthrough infection. Cell Rep Med. 2022 Dec 15:100882. doi: 10.1016/j.xcrm.2022.100882.

[13] Mathieu E, Ritchie H, Rodes-Guirao L et al., Coronavirus Pandemic (COVID-19). Published on-line at OurWorldInData.org. 2020, Retrieved from: https://ourworldindata.org/coronavirus.

[14] Kistler KE, Huddleston J, Bedford T. Rapid and parallel adaptive mutations in spike S1 drive clade success in SARS-CoV-2. Cell Host Microbe. 2022 Apr 13;30(4):545-555.e4. doi: 10.1016/j.chom.2022.03.018.

second dose of the vaccines kept it going.[15] By this time most nations were just starting to roll out the second doses, and should have been stopped.

3) Unexpectantly, the FDA did not consider the quintessential **risk-benefit analysis** which requires an assessment of the relative ratios (relative risk) of death rates per 100,000 person years for ever vaccinated over never vaccinated for **all-cause mortality**. From the UK office for National Statistics published July 6, 2022 (**Table 1**),[16] and as summarized in **Table 2,** the COVID-19 vaccines failed this test miserably . Even the randomized clinical trial data shown in **Table 4** from a systematic review[17] showed a complete failure to pass this test of risk-benefit except for the Janssen one dose vaccine but where for the latter, data manipulation and exclusion of deaths occurring during the first 28 days following the vaccine administration[18] cannot be ruled out. [5]

[15] Servellita V, Morris MK, Sotomayor-Gonzalez A, et al. Predominance of antibody-resistant SARS-CoV-2 variants in vaccine breakthrough cases from the San Francisco Bay Area, California. Nat Microbiol. 2022 Feb;7(2):277-288. doi: 10.1038/s41564-021-01041-4.

[16] Office for National Statistics (UK). Deaths involving COVID-19 by vaccination status, England: Deaths occurring between 1 January 2021 and 31 May 2022. Age-standardised mortality rates and raw death numbers for deaths involving COVID-19 by vaccination status, broken down by age and /or sex group. https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsinvolvingcovid19byvaccinationstatusengland/deathsoccurringbetween1january2021and31may2022.

[17] Graña C, Ghosn L, Evrenoglou T, et al. Efficacy and safety of COVID-19 vaccines. Cochrane Database Syst Rev. 2022 Dec 7;12(12):CD015477. doi: 10.1002/14651858.CD015477.

[18] Sadoff J, Le Gars M, Shukarev G, et al. Interim results of a phase 1-2a trial of Ad26.COV2.S Covid-19 vaccine. N Engl J Med. 2021 May 13;384(19):1824-1835. doi: 10.1056/NEJMoa2034201.

Table 1. Office for National Statistics (ONS) UK Mortality Rates Per 100,000 Person-Years: Rate Ratios* of Ever Vaccinated (Ever Vax) over Unvaccinated (Unvax) January 1, 2021 to May 31, 2022[1]

		All-Cause Mortality			COVID-19 Mortality			Non-C19 Mortality		
		RATE Unvax	Actual RATE Ever Vax	Ratio of Vax/ Unvax Rates	RATE Unvax	Actual RATE Ever Vax	Ratio of Vax/ Unvax Rates	RATE Unvax	Actual RATE Ever Vax	Ratio of Vax/ Unvax Rates
2021	Jan	2507.6	3483.5	1.39	1187	1526	1.29	1320	1958	1.48
	Feb	5261.5	3205.4	0.61	2174	456.8	0.21	3087	2689	0.87
	Mar	3307.8	4192.7	1.27	5919	283.9	0.05	2716	3909	1.44
	April	2298.4	5039.7	2.19	145.8	184	1.26	2153	4855	2.25
	May	1718.8	8582.6	4.99	45.5	84.5	1.86	1673	8426	5.04
	June	1589.7	10060	6.33	55.6	87.7	1.58	1534	9916	6.46
	July	1610.7	10307.1	6.40	218.2	224.9	1.03	1392	9960	7.16
	Aug	1711.6	10340.7	6.04	404.2	402.9	1.00	1307	9266	7.09
	Sept	1664.5	8639	5.19	367.8	520.2	1.41	1297	7884	6.08
	Oct	1623.7	12456.3	7.67	322.3	568.6	1.76	1302	11845	9.10
	Nov	1708	15546.6	9.10	421.3	721	1.71	1287	14155	11.00
	Dec	1878.5	16974.3	9.04	520.5	1121.9	2.16	1358	15501	11.41
2022	Jan	1812	19997.9	11.04	584.6	2310.9	3.95	1227	16417	13.38
	Feb	1384.5	12474.4	9.01	258.7	1128.4	4.36	1126	11346	10.08
	Mar	1231.7	10257.2	8.33	183.5	763.6	4.16	1048	9445	9.01
	April	1204.6	12423.2	10.31	204.7	800.8	3.91	1000	11622.4	11.62
	May	872.9	8246	9.45	77.6	261.8	3.37	795	7914	9.95

*Rates are per 100,000 Person-Years

4)

Table 2. Statistics for Table 1.

Office for National Statistics (ONS) UK Mortality Rates Per 100,000 Person-Years: Rate Ratios of Ever Vaccinated (Ever Vax) over Unvaccinated (Unvax) January 1, 2021 to May 31, 2022[56]

Mortality Classification	Relative Risk of Vax/UnVax Rates	P value	NOTES
All-cause	**6.37**	0.0001	Highly Significant
Non-COVID	**7.26**	0.0001	Highly Significant
COVID-19			
Entire period	**2.06**	0.80	Not significant
Jan 1, 2021 to Sept 30, 2021 a)	**0.36**	0.30	Not significant
Oct 1, 2021 to May 31, 2022 b)	**3.17**	0.01	Significant

a) Represents the period of one and two dose outcomes.
b) Represents the period of booster shot outcomes (dose 3).

Table 4. Cochrane Review December 2022:# Randomized Clinical Trial (RCT) Data Provides No Clear Evidence for Benefit Over Risk for COVID-19 Vaccines Based on Relative Risk (RR) for All-Cause Mortality[192]

ID	Manufacturer	Product	n	Duration of Follow-up (in months)	RR (95% CI) [death counts in vaccinated versus unvaccinated]	Reference
1	Pfizer-BioNTech	BNT162b2	43,847	6 m	1.07 (0.52-2.22) [16 vs 16]	Thomas SJ et al, NEJM 2021. [193]
2	Moderna	mRNA-1273	30,415	7 m	0.94 (0.48-1.86) [16 vs 16]	El-Sahly HM et al, NEJM 2021.[194]
3	Astra Zeneca	ChAdOx1	32,451	2 m	0.48 (0.20-1.14) [7 vs 7]	Falsey AR et al, NEJM 2021.[195]
4	Janssen	Ad26.CoV2.S	43,783	1.9 m	0.25 (0.09 – 0.67) [3 vs 16]	Sadoff J et al, NEJM 2021.[196]

Grana C et al, December 2022.[192]

4) Unexpectantly, the FDA did not require NOR examine the relative ratios (relative risk) of death rates per 100,000 person years for ever vaccinated over never vaccinated for **all-cause, COVID-19 and non-COVID-19 mortality for the month of January 2021 from each of the manufacturers and which should have been made openly available by the CDC (overall results for the USA or at least a subset of the States).** If they had and had the results been similar to the UK (Table 1), the COVID-19 vaccine **would have been stopped by the first week in February 2021**, which would have saved hundreds of thousands of people serious morbidity and mortality.[19]

CLOSING COMMENTS:

In short, with the advent of the SARS-CoV-2 pandemic, which may or may not have been created with funding from the NIH, (many scientists believe the pandemic started as an accidental release of SARS-CoV-2 from the Wuhan Institute of Virology), the FDA appears to be derelict in their duties to protect the public from harm from these dangerous gene therapy COVID-19 vaccines (and so called antivirals) and has abandoned the principles of evidence-based medicine and proper and intense review of product safety and efficacy, purity (consistent batches and oversight of chemistry and manufacturing issues), pharmacology, risk vs benefit, and so on.

The FDA is currently unable to perform its duties in a science-based manner and those in charge of making the decisions for the COVID-19 vaccines, should be fired (without pay or benefits) and subject to criminal investigations. Similarly, the current members of the sham advisory committee should be replaced with scientists and clinicians with NO CONFLICT OF INTEREST.

This is my honest opinion and I have no conflict of interest.

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[19] Seneff S, Nigh G, Kyriakopoulos AM, McCullough PA. Innate immune suppression by SARS-CoV-2 mRNA vaccinations: The role of G-quadruplexes, exosomes, and microRNAs. Food Chem Toxicol. 2022 Apr 15;164:113008. doi: 10.1016/j.fct.2022.113008.