COMMENTARY **February 26, 2022**

A smarter pandemic response

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KEY POINTS

- Pandemic RNA viruses naturally evolve to higher transmission and lower pathogenesis to reach 'endemic status'. However, the introduction of selective pressures such as neutralizing and RBD antibodies to SARS-CoV-2 spike protein, may select for immune escape variants with higher transmission and with higher pathogenesis. In part this may be due to antibody dependent enhancement (ADE) of SARS-COV-2 infection in foamy macrophages which aborts trained (innate) immunity (TI) protection and induces immunosenescence, both contributing to COVID-19 severity.
- Accumulating evidence has shown sterilizing immunity to SARS-COV-2 and herd immunity, is difficult to achieve and maintain with adaptive immunity (AI) vaccines related to the selection of variants over time. In Ontario and elsewhere in the world, the delta variant became dominant subsequent to 50 % or more of the population over 59 having received the second dose of two dose AI COVID-19 vaccines. Based on Ontario data, the delta variant had higher risk of hospitalization and deaths than the alpha variant which was higher than the

original Wuhan strain. Thus, selection of these variants was associated with increased pathogenesis in Ontario.

- Consistent with ADE, in the UK following the emergence of the delta variant, elevated case rates per 100,000 in the double vaccinated over the unvaccinated have been increasing and in younger populations associated with the administration of the second dose. Preliminary evidence from the UK also suggests increasing pathogenesis for the delta variant with time. Moreover, hospitalizations and mortality were lowest for one dose (TI) versus two doses (AI) of COVID-19 vaccine when the UK data concerning the delta variant were stratified by age (<50 and >49 years of age). Researchers in California have reported increased selection of variants of concern (VoCs) and/or immune escape variants for the fully vaccinated over the unvaccinated whereas the lowest levels of selection were found for one dose of vaccines. These results support the notion that TI (one dose) protects better and more consistently against pandemic RNA viruses over AI (two doses).
- Finally, boosting TI may provide consistent and durable sterilizing immunity to SARS-CoV-2 VoCs importantly including the delta variant. Remarkably, TI vaccines by counteracting immunosenescence and providing protection against other pathogens as well as tumors, may additionally improve non-COVID-19 all-cause mortality. Thus, a smarter pandemic vaccination response to achieve herd immunity and the taming of *any* pandemic might employ exclusively TI vaccines.

In a recent editorial,[1] Kirsten Patrick, the interim editor-in-chief at the Canadian Medical Association Journal suggested countering the sequentially emerging more virulent variants will require a smarter pandemic response. There was also mention of the commonly held belief that vaccine hesitancy is "jeopardizing efforts to reach SARS-CoV-2 herd immunity". However, a closer examination reveals that it is not the unvaccinated but the adaptive immunity (AI) COVID-19 vaccines themselves which appear to be contributing to this failure as explained below.

BACKGROUND

Pandemic RNA viruses differ from traditional viruses in that they are recently emerged and have not yet had the time to reach 'endemic status'. As explained by Lythgoe et al.,[2] if there are no selective pressures put on the pandemic RNA virus, the virus will naturally evolve to one with higher transmission and less pathogenesis. Eventually, the virus will reach a state of balance referred to as endemic status (taming). However, if there are selective pressures such as neutralizing antibodies (NAbs), these antibodies will select for more transmissible variants (no longer neutralized by the NAbs, thus escape mutants) with higher virulence.

The Concept of ADE with SARS-CoV-2

The higher virulence may in fact be associated in part with antibody dependent enhancement (ADE) which may potentiate entry of SARS-COV-2 into sebocytes (specialized foamy macrophages) in the sebaceous glands of the oral mucosa[3] and into foamy macrophages such as in the lungs of COVID-19 patients with severe disease.[4] While these cells do not express ACE2 nor TMPRSS2, they bear the FC gamma receptors FCGR1A, FCGR2A, and FCGR3A [5,6] the latter two implicated in ADE.[7] These innate immunity foam cells also express basigin (BSG

/CD147) [5,6] a marker and master regulator of foam cells[8] and ERVK-7 (human endogenous retrovirus K102, HERV-K102).[5,6]

HERV-K102 Innate Immunity Protector System Against Pandemic RNA Viruses

HERV-K102 is a protector foamy virus of humans wherein particle production generates foam in macrophages.[9,10] HERV-K102 putatively is a critical component of trained innate immunity that may confer sterilizing immunity against pandemic RNA viruses such as HIV-1.[10] It is noteworthy that the increased genomic DNA HERV-K102 proviral copy number (five-fold) over healthy controls was demonstrated in an HIV exposed seronegative cohort that had been shown to be resistant to HIV-1 acquisition. In other words, sterilizing immunity against pandemic RNA viruses associated with HERV-K102 replicative activity occurs in the absence of adaptive immunity antibodies. Of relevance to trained innate immunity, the HERV-K102 protection system also includes the activation of innate T cells and B cells recognizing HERV-K102 envelope (reviewed in ref.11). Accumulating data shows HERV-K102 envelope becomes expressed at the surface of virus infected or tumor transformed cells but not normal cells where it behaves as an autoantigen targeting cells for destruction by these innate T cells and by the antibody to HERV-K102 envelope. Antibodies to HERV-K102 envelope peptide sequences were detected at higher prevalence in HIV-1 patients (70-80%) than

those with herpes virus infections (18%) while only marginal activity was shown in 2% of normal healthy controls.[9] Although the levels of HERV-K102 particles in plasma for HIV-1 patients estimated at an average of 8,600 per ml of plasma (72 % positive) never reached the maximal levels found with other bloodborne pathogens (about 3 x 10^{12} per ml of plasma), it is noteworthy that antibody to HERV-K102 envelope and/or the presence of low levels of particles were demonstrated in 96 % of HIV-1 patients. Thus, these data showed the HERV-K102 innate protection system was universally activated by a pandemic RNA virus.

Single Cell Transcriptome Analysis of BALF in Severe COVID-19 Patients Supports the Notion of ADE Mediating Severity

In the bronchoalveolar lavage fluids (BALF) of severe COVID-19 patients but not in their peripheral blood mononuclear cells (PBMCs) nor in BALF or PBMCs from moderate COVID-19 patients, the macrophages (and neutrophils) not only have SARS-CoV-2 RNA present but both positive and negative strands are detectable. This indicated SARS-CoV-2 was replicating within these cells[4] and that infection/replication in macrophages only occurred in severe cases. Moreover, the levels of SARS-CoV-2 co-receptors, BSG and the transferrin receptor (TFRC) in the macrophages in severe BALF strongly correlated with viral loads within these cells,[4] implying these co-receptors were used for viral entry and/or upregulated upon SARS-CoV-2 infection/replication. It is extremely

relevant to the notion of ADE correlating with pathogenesis that COVID-19 severity was strongly correlated with enrichment of the B_C05-MZB1-XBP1 plasma B cell subset which produced primarily IgA1 and IgG1 antibodies and contained sequences known to be common to SARS-CoV-2 neutralizing antibodies (NAbs). With convalescence in the severe COVID-19 patients, this plasma B cell subset diminished. On the other hand, moderate COVID-19 was associated with an increase in the numbers of innate immunity T cells in PBMCs, the γ/δ2 T cells and mucosal-associated invariant T cells (MAIT cells), but their depletion correlated with COVID-19 severity.[4] Taken all together, these findings are consistent with the notion that NAbs and/or receptor binding domain (RBD) antibodies may have mediated entry of SARS-CoV-2 into the protector macrophages by ADE which abolished the innate immunity protector system as evidenced by the loss of innate T cells.

ADE More Likely in the Aged Potentially Associated with Immunosenescence

As Lee *et al.* (2020) aptly pointed out,[12] you know you are going to have a problem with ADE with a virus when seroconversion and the development of neutralizing antibodies *correlate with clinical severity rather than protection* as was observed for SARS-CoV-1 and now SARS-CoV-2.[13] Older patients, who are at increased risk of immunosenescence which results in failed lytic release of HERV-K102 particles from foamy macrophages,[14] are more likely to develop

ADE.[15] In the latter paper, for the first time, as shown in a human macrophage based model of ADE, the antibody dependent infection and *replication* of SARS-CoV-2 was associated with elevated IL-6 production at 3 days and where IL-6 levels are known to correlate with COVID-19 severity. It is important to note that the claim by Maemura and colleagues that monocyte derived macrophages infected by SARS-COV-2 by ADE did not contribute to aberrant cytokine secretion[7] may have been in part because the RPMI media they used for their cultures blocks foam cell formation and thus, they did not assess ADE effects in pro-inflammatory foamy macrophages. As well, they did not employ GM-CSF to drive development towards the M1 pro-inflammatory phenotype of macrophages.

Animal Models Show SARS-CoV-2 Associated Cytokine Storm Mediated by BSG Positive Cells

A monoclonal antibody to BSG has been shown to partially inhibit entry of SARS-COV-2 into cells *in vitro* including VeroE6 cells, and *in vivo:* to partially reduce tissue viral loads, to resolve pneumonia at 6 dpi, and to prevent cytokine storm in human BSG transgenic mice.[16] Thus, BSG positive foam cells once hijacked by SARS-COV-2 appear to mediate key aspects of COVID-19 pathogenesis.

Trained Innate Immunity and Heterologous Protection by HERV-K102

The pro-inflammatory memory response for innate immunity is called 'trained (innate) immunity (TI)[17] and provides heterologous protection (non-pathogen specific) against wide variety of pathogens. It can be induced by live vaccines including the mycobacterium Bacillus Calmette-Guérin (BCG) vaccine and is an important host-directed approach in COVID-19 patients, which might lead to improved anti-viral host defense as well as decreased systemic inflammation.[18] TI involves foam cell formation in macrophages along with increased cytokine production.[19] The mevalonate (cholesterol) pathway is essential for the induction of TI[20] and it is notable that SARS-COV-2 infection blocks the mevalonate pathway[21] indicating it antagonizes TI and the formation of HERV-K102 particles. Furthermore, live *Mycobacterium tuberculosis* strongly induces foamy macrophages in cultured peripheral blood mononuclear cells even when cultured in RPMI media[22] substantiating the notion that the BCG vaccine would be most effective in inducing or boosting the pro-inflammatory foamy macrophages (producing HERV-K102 particles) and TI.

SARS-CoV-2 ADE Mediated Immunosenescence

Once SARS-COV-2 enters these foam cells (sebocytes in the oral mucosa[3] or foamy macrophages in the lungs[4]), these foamy macrophages can no longer release the protective HERV-K102 particles by lysis due to apoptosis resistance,[23] which aborts TI protection. Moreover, the failed lytic release of HERV-K102 from foamy macrophages has been proposed to define immunosenescence[14] which involves immunosuppression and paradoxically a proinflammatory response in the dysfunctional foamy cells. Thus, this process helps to explain how ADE of infectivity into innate foamy cells could be associated with increased pathogenesis by emerging RNA viruses by both aborting TI and through induction of immunosenescence.

Immunosenescence is causally related to the initiation and progression of chronic diseases[14] and is the major risk factor for COVID-19 severity [24,25] and COVID-19 vaccine failure.[25]

Evidence for Delta Selection by the Second Dose of the COVID-19 mRNA Vaccines and Increased Pathogenesis

Evidence from the UK,[26] Quebec[27] and Ontario [28,29] has linked the dominance of the delta variant coincident with a period within 2 weeks after the administration of the 2nd COVID-19 vaccine dose in roughly half of the people over the age of 59. This was further substantiated by phylogenetic analysis of the expansion of the delta variant subtypes in Ontario.[28] Indeed, Servellita et al.[30] have shown that in the category of the fully vaccinated, there were higher levels of SARS-COV-2 variants of concern (VoCs) and/or mutations associated with immune escape over the unvaccinated. Most strikingly, however, in individuals who had only received one dose, escape mutants were the least prevalent.[30]

It should be noted that one dose of COVID-19 mRNA SARS-COV-2 spike vaccines does not elicit high levels of spike antibodies and NAbs whereas the second dose does.[31,32] This indicates one dose of the COVID-19 vaccines stimulates innate immunity, whereas two doses stimulate adaptive immunity.

Fisman and Tuite[33] have shown increased pathogenesis of the delta variant over the alpha variant, and both over the wildtype SARS-COV-2 strain in Ontario based on significantly increased odds ratios (ORs) for: hospitalization 2.08, ICU admission 3.35 and deaths 2.33 [and for the grouped alpha, beta and gamma

variants at 1.52, 1.89 and 1.51, respectively]. Moreover, there were no significant differences between the ORs for partially vaccinated versus fully vaccinated for hospitalization or for ICU admission suggesting the protection may have been mediated mostly by TI rather than AI. However, there may have been a difference in ORs where partial vaccination (TI) showed better protection against death in patients with COVID-19 than full vaccination (AI) [0.09 (95% CI 0.07 to 0.10) versus 0.21 (95% CI 0.10 to 0.35) respectively]. Thus, the data appears to be consistent with the notion that not only did the two dose vaccines select for the more transmissible delta variants, but as predicted by Lythgoe *et al.*, it selected for more pathogenic variants as well.

In the UK, the pathogenesis of the delta variant also increased with time based on preliminary data both for case fatality rates and case hospitalization rates where these infections involved the delta variant (extracted UK data compiled in Tables 1 and 2 **in Image 1)**.[34] Moreover, there were lower death and hospitalization rates associated with one dose of COVID-19 vaccines over two doses. This is in keeping with the notion of superior protection against hospitalization and death by TI over AI against pandemic variants of concern.

Reduced VE Against Symptomatic Infection Associated with Two or More Doses of COVID-19 Vaccines

ADE is expected to increase pandemic RNA virus transmission rates by promoting the infection of sebocytes in the oral mucosa (infection of sebocytes was shown[3]) and blocking trained innate immunity related to the failed lytic release of HERV-K102 particles. This may not only also increase infection rates per se but could promote increased cases of symptomatic to asymptomatic infections.

Public Health England/UK Health Security Agency has been reporting increasingly, higher case numbers per 100,000 in the fully (2 dose) vaccinated over the unvaccinated following the emergence of the delta variant, where for example by week 2 of 2022, the 18 to 69 years of age had at least a 2 fold increased risk of SARS-CoV-2 symptomatic infection.[35] The newest data for week 8 of 2022 with the omicron variant[36] and where data was only provided for those with 3 doses of vaccine, showed all age groups except the under 18 had elevated symptomatic infection per 100,000 over the unvaccinated with a more than 2.90 fold increased risk in the ages 30 to 69. This demonstrated a loss in vaccine effectiveness (VE) worsened in the UK against symptomatic infection with time.

Data from Southern California has provided a unique window into the concept of boosting TI.[37] In their Appendix 5c, they provided data on SARS-

COV-2 cases by 100,000 per year that occurred at <7 days after the second Pfizer dose was administered (TI boosting) and compared with >6 days after the second Pfizer dose was administered (AI boosting) in the >64 years of age category. This data is compiled in **Image 2.** This data strongly implies the boosting of trained innate immunity in those over 64 years of age is associated with sterilizing immunity and was stable even with the emergence of the alpha then delta variants. In contrast, VE dropped for adaptive immunity over the same time frame. These findings are consistent with the notion that the protection offered by boosted trained innate immunity is counteracted when ADE promoted by the NAbs and RBD Ab produced by the second dose of vaccine, allow SARS-CoV-2 to infect the sebocytes and block the release of the protective HERV-K102 particles.

Along these lines, anecdotal evidence provided in the **Appendix** discusses increased lysis of sebocytes (Fordyce spots) at 6 *days* following the first Pfizer COVID-19 vaccination and at 6 *hours* following the second Pfizer dose. This implies there may have been induction of antibodies to HERV-K102 envelope[9] elicited after the first vaccine dose. It has been established that triggering HERV-K102 envelope itself such as expressed on tumor cells with an antibody to HERV-K102 envelope directly mediates apoptosis (lysis) involving caspase 3 activation.[38] This seems to imply that unlike other normal cells within the body including foamy macrophages which do not express HERV-K102 envelope (unpublished data), that

sebocytes possibly due to its immunoprivileged niche, do express HERV-K102 envelope at their cell surface. This is an easily testable hypothesis.

While the loss in VE against infection for COVID-19 vaccination is widely and consistently found, what is relevant to those who question vaccine mandates is the notion of natural immunity and how the risk of re-infection compares in those previously infected with those doubly vaccinated. This was recently addressed in a report of the UK SIREN study covering the period of vaccination from March 20, 2020 to September 2021 and which reported on both asymptomatic and symptomatic infection together. [39] Those with a previous infection had a crude incidence rate of 2.25 per 10,000 person-days at risk, while the unvaccinated with no previous infection had a rate of 15.98. When compared with those who received the Pfizer-BioNTech BNT162b2 vaccine, natural immunity from a previous infection was as good as or better than two doses of BNT162b2 except during the 14-73 days post vaccination period. Against the one dose of the same vaccine, the vaccination protection was suboptimal for the period 21 to 41 days post vaccination (5.05 or 2.98 infections per 10,000 person-days), but at 42 to 280 days the one dose vaccinated fared slightly better than natural immunity at 1.4 to 1.55 infections per 10,000 person-days. The best protection was evidenced in people who had a previous infection more than a year prior followed by two doses with a crude incidence rate of 0.9 to 1.31 infections per 10,000 person-days from day 14

to 262 days. Thus, as suspected by many, for all intents and purposes, natural immunity was as good as or better than two dose vaccination.

The Heterologous Protection by Trained Innate Immunity

Other benefits of TI vaccination would include protection against all-cause mortality; as TI/HERV-K102 protects against heterologous pathogens, tumors and by reversing immunosenescence, would ameliorate chronic disease.[14] Along these lines in an effort to establish that the COVID-19 vaccines were not inducing non-COVID-19 disease (such as vaccine associated death), Xu et al.,[40] demonstrated for the adjusted relative mortality risks that those of the ages 45 to 85 + received the most benefits for the mRNA vaccines against non-COVID-19 causes of death. Once again and in agreement with the findings of Fisman and Tuite but for COVID-19 related deaths,[33] there was no significant difference between one dose and two doses vaccination overall, showing the benefit as expected, either for non-COVID-19 and COVID-19 related deaths was due to innate immunity and not adaptive immunity.

DISCUSSION

The important question arises, could have public health authorities known in advance that AI vaccines might select for more pathogenic variants and/or that sterilizing immunity needed for herd immunity was unlikely to be achievable by AI vaccines. The answer may be yes. As observed from the very beginning, and as reported in a meta-analysis, during natural infection with SARS-COV-2, antibodies (Abs) and NAbs to SARS-COV-2 did not correlate with protection, but instead correlated with COVID-19 severity[41] implying a potentiating role in pathogenesis. Insight into this paradox was derived from a more recent paper which showed high viral loads in the nasopharyngeal swabs correlated with the presence of SARS-CoV-2 spike protein specific Abs/NAbs in serum while low viral loads were correlated with the absence of antibody.[42] Indeed, during natural infection with SARS-COV-2 , Wu et al.,[43] provided direct evidence that ADE as assessed from convalescent plasma, correlated with disease severity, higher ages, longer days of hospitalization and longer duration of disease. Altogether these findings pointed to the conclusion that antibodies and NAbs to SARS-COV-2 were not protective but harmful. Thus, it could have been surmised early in the pandemic that adaptive immunity vaccination against SARS-CoV-2 would have problems with ADE. This would likely entail the selection of variants with time rendering herd immunity unattainable.

CONCLUSION

Accordingly, the writing was on the wall from early in the pandemic that AI vaccines were unlikely to provide herd immunity because these NAbs and RBD binding antibodies correlated with severity and not protection. Moreover, as demonstrated here, ADE interfered with trained innate immunity needed to establish herd immunity and in fact lead to higher infection rates in the fully vaccinated over the unvaccinated. Finally, these adaptive vaccines by selecting for variants, only served to prolong the pandemic and may have worsened outcomes as these variants became more pathogenic over time.

In conclusion, the unvaccinated cannot be blamed for the failure to achieve herd immunity, but rests with the AI vaccines themselves.

Table 1. Trends in Case Fatality Rates[a] Involving SARS-CoV-2 Delta Variant in England from June 21 to September 12, 2021 by Vaccination Status and Stratified by Age (Delta Variant Cumulative Cases Since February 1, 2021)

AGE Category (years)	TB # * (issue date in 2021)	Unvaccinated	Two Doses (>13 days)	One Dose (>20 days)	n one dose/two doses
>/= 50	23 (Sept 17)	6.90 %	2.17 %	1.90 %	7129/71991
	20 (Aug 6)	5.96 %	1.81 %	1.15 %	5640/21472
	18 (July 9) +	5.60 %	2.22 % +	0.90 %	4542/5234
	17(Jun 25) +	3.89 %	1.41 %	0.43 %	3865/3546
< 50	23 (Sept 17)	0.053 %	0.056 %	0.0130 %	83009/85407
	20 (Aug 6)	0.033 %	0.051 %	0.0099 %	40449/25536
	18 (July 9) +	0.030 %	0.036 %	0.0022 %	13391/5600
	17(Jun 25) +	0.011 %	0	0.0020 %	9850/3689

a) Death within 28 days of the first positive specimen (hospitalized or not).
* TB # = Technical Briefing Number. SARS-CoV-2 variants of concern and variants under investigation in England: Technical Briefings. https://www.gov.uk/government/publications/investigation-of-novel-sars-cov-2-variant-variant-of-concern-20201201
+ Both the TB #17 and #18 reported on cases up to June 21, 2021,. The extra data in the July 9 2021 report might potentially explain the increased CFR for two doses at 2.22% for the over or equal to 50 years of age.

Table 2. Trends in Hospitalizations[a] Involving SARS-CoV-2 Delta Variant in England from June 21 to September 12, 2021 by Vaccination Status and Stratified by Age (Delta Variant Cumulative Cases Since February 1, 2021)

AGE Category (years)	TB # * (issue date in 2021)	Unvaccinated	Two Doses (>13 days)	One Dose (>20 days)	Proportion of Hospitalized Cases by Age Category
>/= 50	23 (Sept 17)	20.9 %	5.43 %	5.51 %	49.7 %
	20 (Aug 6)	19.5 %	5.27 %	4.08 %	40.2 %
	18 (July 9) +	15.4 %	5.06 %	3.08 %	32.3 %
	17(Jun 25) +	13.9 %	4.60 %	2.69 %	31.6 %
< 50	23 (Sept 17)	1.82 %	0.84 %	0.68 %	50.2 %
	20 (Aug 6)	1.55 %	0.88 %	0.74 %	60.0 %
	18 (July 9) +	1.40 %	0.86 %	0.88 % +	67.4 %
	17(Jun 25) +	1.32 %	0.73 %	0.86 %	68.3 %

a) Hospitalized even with a positive PCR result on the day of admission ie., includes those hospitalized for some other reason than the classical signs and symptoms of COVID-19 but positive for SARS-CoV-2.
* TB # = Technical Briefing Number. SARS-CoV-2 variants of concern and variants under investigation in England: Technical Briefings. https://www.gov.uk/government/publications/investigation-of-novel-sars-cov-2-variant-variant-of-concern-20201201
+ Both the TB #17 and #18 reported on cases up to June 21, 2021. The extra data in the July 9 2021 report might potentially explain the increased hospitalizations for one dose at 0.88 % for the < 50 years of age.

Image 1. Data Extracted and Compiled from Technical Briefings on SARS-CoV-2 Variants of Concern and Variants Under Investigation in England[34] Suggested Increased Pathogenesis of the Delta Variant with Time for Case Fatality Rates (Table 1) or for Case Hospitalization Rates (Table 2)

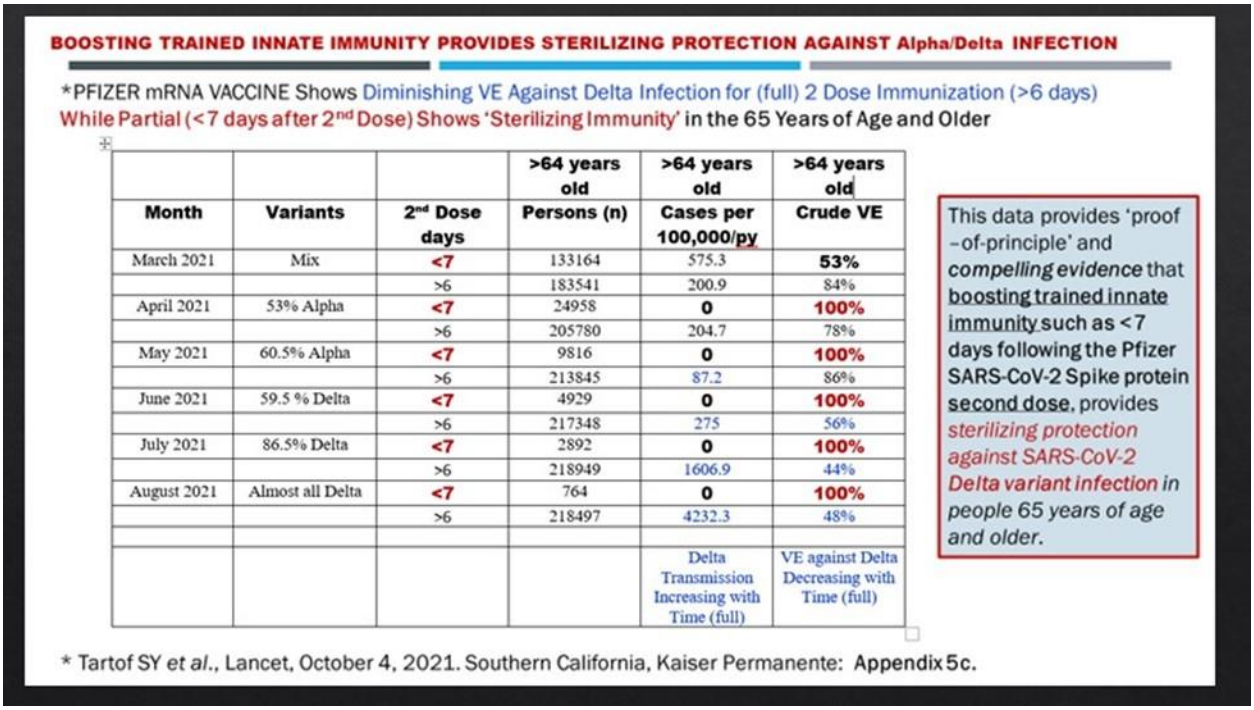

Image 2. Data Extracted and Compiled from Appendix 5c From Tartof et al., 2021[37] Shows For the First 6 Days Following the Second Dose of Vaccine That Sterilizing Immunity is Achieved and is Stable with the Emergence of the Alpha and Delta Variants Whereas the VE Against Symptomatic Infection for Two Doses Substantially Drops

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Affiliations: None, recently retired. Dr. Laderoute led the discovery of HERV-K102 as a protector foamy virus of humans putatively against pandemic RNA viruses such as HIV-1 at the Public Health Agency of Canada, Ottawa, Ont. She authored the new immunosenescence paradigm published in Discovery Medicine in 2015 associated with her work at Immune System Management Clinic & Lab, Ottawa, Ont.

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Appendix

Fordyce spots are creamy 'visible' enlarged sebaceous glands under the upper lip where sebocytes are believed to be producing HERV-K102 particles.

In this individual (67 years old), 6 days after the first vaccination with the Pfizer SARS-CoV-2 mRNA vaccine, the Fordyce spots blistered. After the second Pfizer dose at 111 days, blistering occurred at 6 hours.

This provides *anecdotal evidence* that:

i) mRNA vaccines may enhance HERV-K102 production/release from foamy sebocytes,

ii) HERV-K102 may exhibit a memory response contributing to 'trained (innate) immunity'.

Clearly this phenomenon needs to be studied further and validated in randomized clinical trials (RCT). Whether the memory response relates to the generation of antibodies to HERV-K102 envelope (Laderoute M *et al.*, 2007) by mRNA vaccines, remains to be investigated.

Fordyce spots under the upper lip.