doi:10.36849/JDD.6003

In Vitro Clonal Priming Data Suggests Mechanism for Lower Initial Vaccine Dose Yielding Increased Immunity in Astra-Zeneca Vaccine Trial

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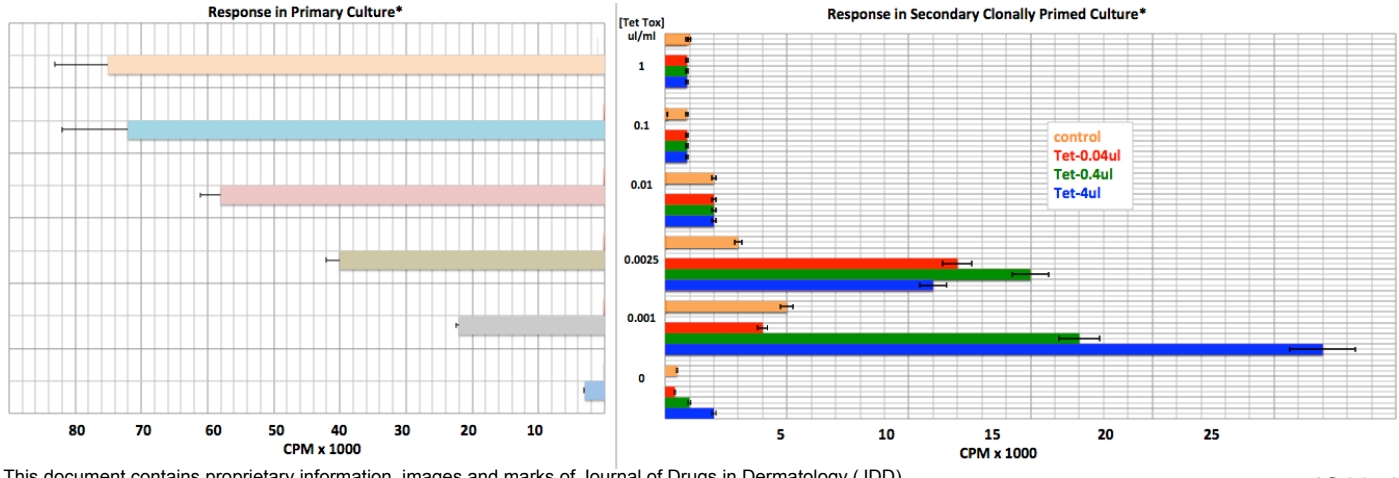
Accidental administration of half the dose of the initial Astra-Zeneca Covid-19 vaccine[1] in an experimental subgroup was surprisingly found, after the second full dose, to confer a higher percent of immunity (90%) than planned full initial dose (62%).[2,3] Side effects after the second dose were reported by Oxford to be milder. Data below obtained 43 years ago at the NIH may help explain the immunologic basis of this observation.[4] It seems ironic that Oxford is apologizing for the unannounced protocol error that yielded better protection.

Studies done on lymphocyte priming and re-stimulation in secondary culture demonstrated a similar but logarithmically greater paradoxical pattern.[1] We found that the optimal antigenic stimulating concentration in the primary culture of leucocytes from a sensitive donor, using tetanus toxin, led to unresponsiveness in secondary culture seven days later. Greater secondary lymphocyte reactivity, measured as blastogenesis by radioactive thymidine incorporation, occurred as we progressively lowered the stimulating concentration to one thousandth the optimal primary stimulating concentration (see Figure 1).[4] Our later studies demonstrated that a feeder layer of irradiated autologous leukocytes could restore the secondary culture response to optimal primary culture antigen levels.[5,6]

One possible explanation is that we saturated the HLA-D antigen presenting and receptor sites so that lymphocytes could not be activated. It is also possible that we induced anti-idiotype immunity. The concept is that with such a large dose of the specific stimulating antigen, a huge number of reactive lymphocytes are induced with the same or similar receptors recognizing that antigen early on. Subsequently, in that same culture, remaining lymphocytes develop receptors against the anti-tetanus toxoid receptor bearing cells in the culture. This possibility is further suggested by our later demonstration of specific suppression of response to microbial antigens by stimulated cells.[7] Work by others has also confirmed this possibility.[8,9] T-cells are involved in Covid-19 immunity directly as evidenced by studies of convalescent Covid-19 patients.

FIGURE 1. Tetanus toxoid in optimal and lesser concentrations was cultured with leukocytes from a highly sensitive donor for 7 days, with counts from aliquots labeled with tritiated thymidine 3 hours shown on Left side, as an index of DNA synthesis as a function of lymphocyte reactivity. On the Right side, radioactivity of 100,000 cells from each primed culture were cultured with 3 different concentrations of tetanus toxoid in secondary culture. Tritiated thymidine uptake was measured after 44 hours of culture, and radioactivity was measured as an index of secondary culture reactivity.



Data on 600 subjects tested blind in the P201 study with two half doses, 50 micrograms of Moderna vaccine, showed production of an equal amount of antibody to the 100-microgram chosen dose, but no clinical studies were done to show relative clinical efficacy. Notably, in the over 55-year-old group, there was a slight decrease in the bAB response in those given a higher 100 microgram vaccine dose.[10]

There is also a need to look for specific T-reg lymphocytes that suppress Covid-19 immunity in those administered the full initial dose of the Astra Zeneca and Moderna vaccines, and possibly with the other vaccines as well.

Berzofsky's group summarizes T-cell subset and antibody responses to antigen dose in vaccine and shows that lower antigen dose can yield more sensitive T-cell response, higher quality T-cell receptors, and higher quality and affinity antibodies. Antibody production requires T-cell help. High avidity T-cells came from stimulation with low primary antigen concentrations. Low-dose antigen stimulates enhanced protection. T-reg cell, follicular T-helper cells, and subset ratios are all dependent on priming antigen dose. Age, infectious agent involved, timing,[11] and adjuvant also affect response, and sufficiently lowering the dose can increase viral sensitivity and effectiveness of the vaccine, or even lower it, depending on interaction on a variety of other factors. The complexity of these later observations supports lowering the antigen dose, but the myriad of specific interactive factors, including higher antigen dose favors antibody production but not memory B-cell production, might explain why a fifty-percent reduction is more optimal clinically than a still greater dose reduction.

The initial priming vaccine dose followed by a repeat dose of vaccine 28 days later has a distinct resemblance to those priming and re-stimulation studies. The observation we made offers a possible scientific explanation of the reportedly puzzling finding and could account for the greater protection with a smaller dose of antigen and should stimulate further studies on the underlying immunologic mechanism of the phenomenon we observed. Lower dose clinical and in vitro studies are needed for the various vaccines, to see if lower initial and secondary Covid-19 vaccine doses give better immunity after the secondary vaccine priming as in our study.

This data does not prove the need for lower dose vaccine administration. It supports the need for further investigation, including a properly monitored volunteer subgroup given half the vaccine dose, in the current experimental vaccine rollout, while following clinical results in all, as well as laboratory-tested immune parameters on a sample of that group, all compared with clinical results and immune parameters in a sample of those receiving full-dose immunization. This dose reduction could improve vaccine protection, enable more people to be vaccinated with the current output, and reduce second vaccine side effects, as seen with the Oxford half initial dose administration.[12] Since the vaccine rollout is still on an experimental basis, there is no reason to hesitate with a trial of a reduced dose already found to give a higher percentage of protection.

CONCLUSION

In conclusion, this study offers not only a mechanism to explore this apparent low-dose paradox, but also the important possibility that a much smaller dose of vaccine could be effective, extending or even doubling the number of people who could now be immunized by the currently available vaccine. That could greatly speed the ending of this Covid-19 pandemic on a world-wide basis, especially during a race for control against appearance of new, more aggressive genetic variants of SARS-Cov-2.

DISCLOSURES

The authors have no declaration of interests and have no relevant interests to declare.

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