



Improving COVID-19 Vaccine Efficacy and Safety with Intradermal and Reduced-Dose Approaches

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Abstract

As SARS-CoV-2 continues to impact healthcare and new variants continue to spread, vaccination remains a key element in mitigating its effects. The Oxford-AstraZeneca vaccine (ChAdOx1-S/nCov-19 recombinant) has great global reach. Optimizing its administration can have lasting effects on our efforts towards limiting the spread of SARS-CoV-2, reducing the disease severity associated with COVID-19, slowing the speed of variant evolution, and significantly reducing the associated burdens on health systems and the economy. This review investigates two strategies with potential for improving the safety and efficacy of this vaccine: 1) using intradermal route of vaccination and 2) utilizing a reduced dose for intramuscular administration. The current literature indicates that there may be a stronger immune response and reduced incidence of adverse reactions when implementing these strategies, highlighting the need for further research. This research can be specific to vaccine strategy that produces a superior- if not equivalent- immunogenic response across all age groups, expands our available global vaccine supply, improves overall patient safety, and provides longer-lasting protection against SARS-CoV-2.

Key Words: Vaccine, Efficacy, Dosage, Administration, Immune Response

Introduction

Covid and vaccination

From November 2019 to March 2022 there have been approximately 476 million confirmed cases and over 6 million deaths from the SARS-CoV-2 virus [1]. COVID-19 is the disease resulting from the viral respiratory infection that has been associated with many serious complications from cytokine storms including acute respiratory distress syndrome, major depressive disorder, thromboembolism, hypercalcemia, and persisting fatigue often referred to as "long Covid" [2-4]. Many different measures have been implemented to reduce its impact on public health, including lockdowns, face masks, social distancing, and vaccination. Despite the many public health measures and the current vaccination efforts, Covid continues to spread and new variants continue to develop, and it will likely continue to present a public health challenge for years into the future [5, 6].

Vaccines have been critical in mitigating the spread and severity of COVID 19, as well as many other diseases throughout history. Vaccination has been shown to reduce both the severity of COVID 19 infections and its transmissibility, demonstrating its importance both to protect individuals from severe infections and to reduce its spread throughout the population [7]. Currently, 56% of the global population has been fully vaccinated by the Pfizer/BioNTech, Moderna, Johnson & Johnson, Oxford/AstraZeneca, Sinovac, Sinopharm, and Sputnik V COVID-19 vaccine [8]. The vaccines differ in their mechanism of action, efficacy, contraindications, global availability, cold chain requirements, and ease of transportability [7-9].

Globally, it is estimated that 3.49 billion people, a significant portion of the global population, remain unvaccinated [8]. Given that the efficacy of the COVID-19 vaccines varies greatly, and that COVID-19 vaccine efficacy has been shown to decrease by 20-

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30% by 6 months post vaccination [10], our vaccination efforts require further development with respect to scale of distribution, maximizing efficacy, and improving duration of protection associated with the available COVID-19 vaccines. The Coalition for Epidemic Preparedness Innovations (CEPI) estimates the global vaccine manufacturing capacity to be 2-4 billion doses per year. At this production rate, the manufacturing speed of these vaccines may not meet the estimated demand for the global population until 2023-2024 [7]. Considering the increased risk of transmissibility of SARS-CoV-2 amongst vulnerable unvaccinated populations [11], the recent surges in COVID-19 cases due to the spread of the SARS-CoV-2's delta and omicron variants [5, 6], and the recent relaxation of several country-level COVID-19 public health guidelines [12], there is a strong need for a new vaccination strategy that optimizes our ability to fully vaccinate the remaining unvaccinated populations around the world at a faster rate and accounts for new data on vaccine efficacy, vaccine safety, and cost-effectiveness. By determining the most effective and efficient vaccination approaches, the effects of COVID 19 on both individual and public health can be mitigated even further. If found to be clinically effective, safe, and cost-efficient, these vaccination techniques may be applied toward other infectious diseases in the future.

Though vaccines are a potent way of combating the effects of SARS-CoV-2 and its variants (delta, omicron, omicron BA. 2) [15, 16], they have been associated with side effects and adverse reactions. The vaccine side effects include redness and soreness at the injection site and may mimic symptoms of COVID-19 infection ranging from fever and myalgia to more serious complications. Some serious complications include cytokine storm induced thrombotic events, like thrombotic microangiopathy which can lead to pure sensory stroke [13]. Others include cytokine storm induced encephalopathy [14], Guillain-Barre syndrome, and thrombosis with thrombocytopenia syndrome [15, 16]. By improving the safety of the COVID-19 vaccines, we can reduce the rates of adverse events in individuals and the fears of vaccine-hesitant groups. Further, some patient populations have contraindications or precautions to receiving the vaccines, including those with previous anaphylactic reaction to the vaccine or its components, multisystem inflammatory syndrome, or other acute illnesses [7, 15, 16]. If the vaccine can be delivered in a way that reduces systemic adverse reactions, then it may become safe enough to be used in these patients, further expanding the number of people who can be vaccinated.

Oxford-AstraZeneca vaccine

With an estimated efficacy of 61-81% in clinical trials and features that make it amenable to global use, the Oxford-AstraZeneca COVID-19 vaccine has potential for global reach and is currently being used in over 170 countries and territories since its approval in December 2020 [17]. One full dose (0.5 ml) of the AstraZeneca vaccine contains 5×10^{10} viral particles. The ChAdOx1-S/nCoV-19 recombinant vaccine is a chimpanzee adenoviral vector vaccine, which carries a gene that encodes the SARS-CoV-2 spike glycoprotein. The host cell creates the encoded protein, and the immune system creates antibodies against this spike protein, preparing the immune system to mount a rapid, robust response to future encounters with this same antigen during active SARS-CoV-2 infections [16].

It can be stored at refrigerator temperatures, making it easier to store and transport than other vaccines and facilitating its global reach. Its efficacy is estimated to be 61-81% in clinical trials, varying based on multiple factors including the specific COVID 19 variant, number of doses, and time since administration [18]. Though it can be safely recommended to most patients, and it is a powerful tool against the spread of COVID 19, it has been associated with adverse effects like other COVID 19 vaccines. One serious complication includes thrombotic microangiopathy,

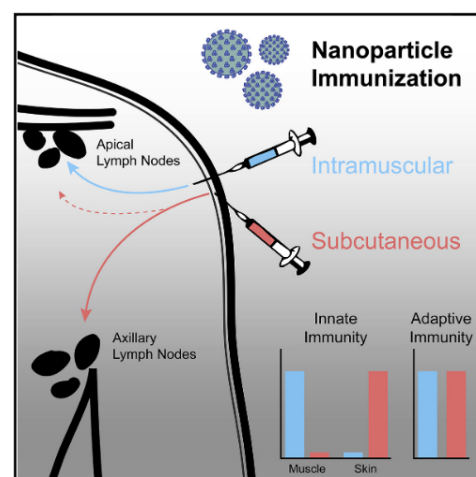
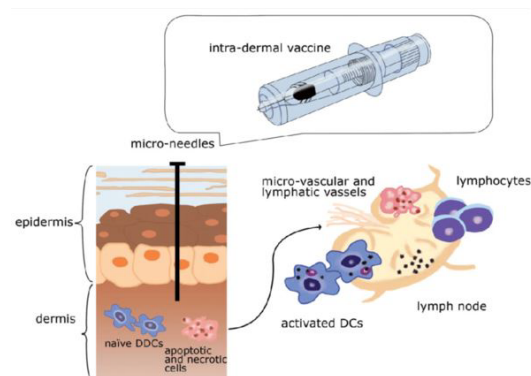


Figure 1A: Visual representation of IM vs subcutaneous vaccine administration, which has a very similar mechanism to ID vaccination [19]. The subcutaneous route is associated with axillary lymph node activation and different types of innate immune response, but a very similar adaptive immune response.



A pictorial scheme of the different mechanism at the basis of the action of intradermal vaccines.

DCs: Dendritic Cells

DDCs: Dermal Dendritic Cells

Figure 1B: Visual representation of intradermal vaccination [21].

potentially leading to pure sensory stroke [13]. Others include cytokine storm and encephalopathy [14], as well as complications shared with the other vaccines like thrombosis, thrombocytopenia, and allergic reactions like anaphylaxis [15, 16].

Overall, the Oxford-AstraZeneca vaccine has demonstrated its value as an effective vaccine against SARS-CoV-2 and its variants including delta, omicron, and newly reported BA. 2 [15, 16]. Given its significant global reach, optimizing its administration can amplify its impact in reducing the spread and complications associated with COVID 19.

Intradermal vaccines and reduced doses

Though most vaccines are typically administered via the intramuscular (IM) route, research on intradermal (ID) administration has been shown to elicit similar or even stronger immune responses. These findings hold true for many different contexts, including different animal models, vaccine mechanisms, and infectious diseases [19]. Because the dermis and epidermis

of human skin are rich in dendritic antigen-presenting cells, it is hypothesized that stronger cellular and humoral immune responses can be induced more efficiently through ID vaccination relative to IM vaccination [20]. ID vaccines then induce signaling in axillary lymph nodes and are associated with more direct activation of the adaptive immune system. This contrasts with IM vaccines, which are associated with activity in the apical lymph nodes and activate the innate immune response first. Despite the different pathway for activation, ID administration has consistently demonstrated similar or greater long-term immune response compared to IM vaccines (Figure 1A and 1B).

Further, there is historical evidence that ID administration can be a safe and effective route. ID vaccine administration with reduced doses was demonstrated as a viable strategy in a randomized open-label trial in 2004, when it was implemented as a response to limited supply of the influenza vaccine at the time [22]. As discussed later, this demonstrated an immune response that was similar or even more robust than the IM route. Later studies continued to confirm its efficacy and safety in other contexts, such as with other infectious diseases and with more measures of efficacy, and there are active clinical trials that continue to investigate its effectiveness and the optimal approach.

However, more research is needed before ID vaccination can be used as widely as IM. Specifically, changing the route would necessitate further research on different dosages, formulations, mechanisms of action, safety outcomes, and regulations before it could be widely used. If these challenges can be overcome, ID vaccines with reduced doses show potential to improve the safety and efficacy of our current vaccines, reducing the serious consequences of infectious diseases like COVID 19 and alleviating some of the burden that such diseases have placed on public health.

Main Analysis

Early Application of Intradermal and Reduced Dose Approaches

The use of ID vaccination, though not widely used in practice, has been the subject of a significant body of research. Due to

the previously mentioned vaccine supply shortage, alternate approaches had to be investigated and implemented. One study on vaccines against influenza from 2004 investigated the immunogenic responses to the H3N2, H1N1, and B strains in a randomized open-label clinical trial outside the influenza season [22]. Participants were randomly assigned to either the IM vaccination group using a 0.5 mL dose or ID vaccination group with a reduced 0.1 mL dose, and they compared the immune response, rates of local adverse reactions, and rates of systemic adverse reactions. Significant differences observed between the groups are reported below in Table 1.

The results of this early study by Kenney et al. [22] show that ID vaccination led either no statistically significant difference or, in some cases, greater mean titers, such as in the H3N2 and B/Hong Kong groups at 42 days. Regarding adverse events, the intradermal approach did lead to a significant increase in local reactions (most often erythema, swelling, pruritis, and induration), though there was no significant difference in systemic reactions.

Although the results are promising, there were many limitations to this study. At the time of publication, it was unclear if the antibody titer was closely correlated to protection in a practical context, but later studies have shown that this is less controversial and it's a well-accepted correlate of protection [23]. Finally, this study only included 100 healthy participants aged 18-40, introducing concerns about generalizability. Future publication that demonstrated similar findings within even broader populations [24-31] have addressed these concerns. While intradermal vaccinations may not be ideal for every disease and have limitations [20], recent studies have continued to investigate its use for diseases like COVID 19.

The relationship between reduced doses and ID vaccine administration was further investigated over time, including a systematic review published in 2020 by Egunsola et al. [32]. It included 29 randomized controlled trials, with a total of 13,659 patients, as well as a cohort study with 164,021 patients, and focused on seroconversion and sero protection rates after

Variable	A/New Caledonia (H1N1)			A/Panama (H3N2)			B/Hong Kong		
	Day 0	Day 21	Day 42	Day 0	Day 21	Day 42	Day 0	Day 21	Day 42
Geometric mean titer									
Value (95% CI)									
Intramuscular group	10 (8 to 14)	153 (106 to 221)	131 (91 to 188)	28 (19 to 43)	201 (143 to 282)	171 (123 to 238)	19 (14 to 27)	297 (215 to 409)	253 (181 to 353)
Intradermal group	8 (7 to 10)	126 (85 to 189)	112 (73 to 170)	23 (15 to 33)	431 (291 to 640)†	373 (256 to 544)†	14 (10 to 19)	175 (130 to 236)	147 (113 to 192)‡
95% CI for ratio of geometric mean — %	85 to 180	70 to 210	67 to 205	71 to 221	28 to 79	28 to 76	86 to 217	109 to 264	112 to 264
Fold increase in geometric mean titer									
Value (95% CI)									
Intramuscular group		14.9 (9.5 to 23.5)	12.7 (8.2 to 19.8)		7.1 (4.8 to 10.3)	6.0 (4.3 to 8.5)		15.3 (10.0 to 23.5)	13.1 (8.5 to 20.2)
Intradermal group		15.2 (10.3 to 22.5)	13.4 (9.0 to 20.1)		19.0 (11.4 to 31.8)†	16.4 (10.1 to 26.7)†		12.4 (8.2 to 18.6)	10.4 (7.2 to 15.1)‡
95% CI for ratio of fold increase — %		53 to 179	52 to 173		19 to 71	20 to 67		68 to 225	70 to 224
Seroconversion rate (%)									
Intramuscular group		78	74		66	60		82	78
Intradermal group		82	84		78	78		82	72
Difference between groups (95% CI)		-4 (-20 to 12)	-10 (-26 to 7)		-12 (-30 to 7)	-18 (-36 to 1)		0 (-16 to 16)	6 (-11 to 23)
Seroprotection rate (%)									
Intramuscular group	24	94	90	50	98	94	38	100	100
Intradermal group	10	84	86	42	96	96	28	100	92
Difference between groups (95% CI)	14 (-1 to 30)	10 (-3 to 24)	4 (-10 to 18)	8 (-12 to 28)	2 (-7 to 12)	2 (-13 to 8)	10 (-9 to 26)	0	8 (0 to 19)

*CI denotes confidence interval

† P<0.001 for the comparison with the intramuscular group with the use of a generalized linear model.

‡ P<0.04 for the comparison with the intramuscular group with the use of a generalized linear model.

Table 1: Data Summary Adapted from Kenney et al. [22] 2004.

	Total number of cases	ChAdOx1 nCoV-19		Control		Vaccine efficacy (CI*)
		n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	n/N (%)	Incidence rate per 1000 person-years (person-days of follow-up)	
All LD/SD and SD/SD recipients	131	30/5807 (0.5%)	44.1 (248 299)	101/5829 (1.7%)	149.2 (247 228)	70.4% (54.8 to 80.6)†
COV002 (UK)	86	18/3744 (0.5%)	38.6 (170 369)	68/3804 (1.8%)	145.7 (170 448)	73.5% (55.5 to 84.2)
LD/SD recipients	33	3/1367 (0.2%)	14.9 (73 313)	30/1374 (2.2%)	150.2 (72 949)	90.0% (67.4 to 97.0)‡§
SD/SD recipients	53	15/2377 (0.6%)	56.4 (97 056)	38/2430 (1.6%)	142.4 (97 499)	60.3% (28.0 to 78.2)
COV003 (Brazil; all SD/SD)	45	12/2063 (0.6%)	56.2 (77 930)	33/2025 (1.6%)	157.0 (76 780)	64.2% (30.7 to 81.5)‡
All SD/SD recipients	98	27/4440 (0.6%)	56.4 (174 986)	71/4455 (1.6%)	148.8 (174 279)	62.1% (41.0 to 75.7)

Figure 2: This data demonstrates the relative efficacy of those who received the LD/SD protocol compared to those receiving the SD/SD protocol [33].

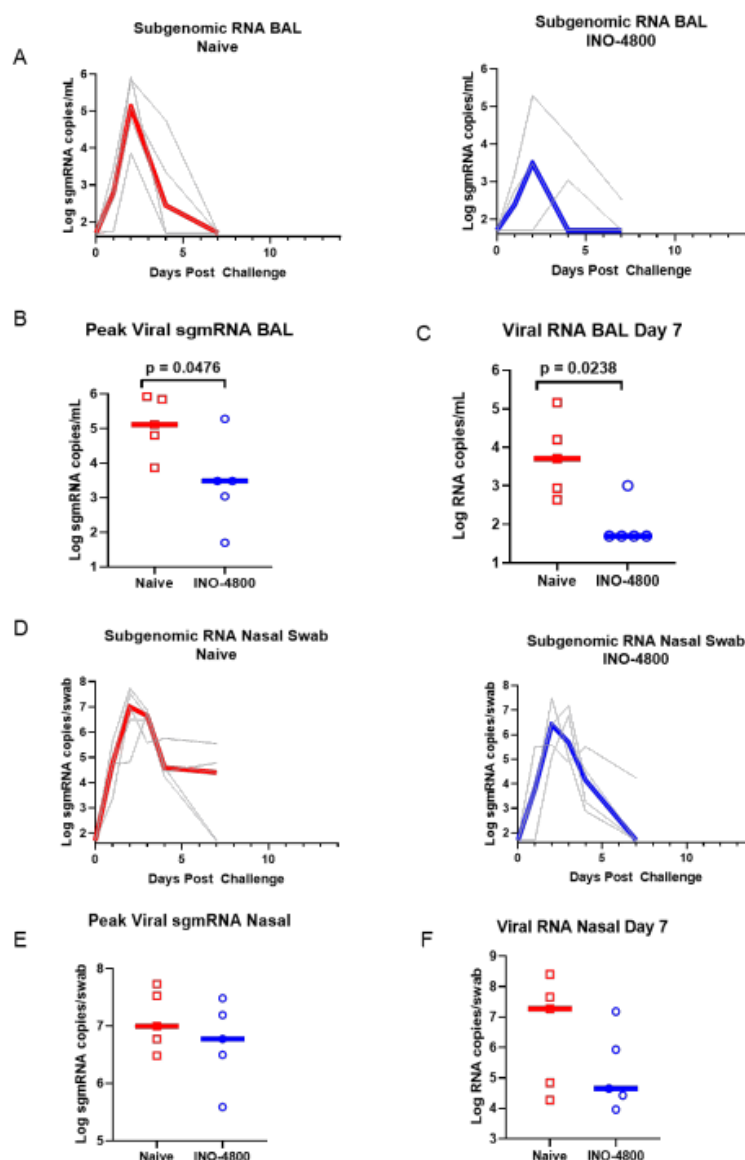


Figure 3: This data from the referenced study shows the viral load (sgmRNA) at different time frames after the subjects were challenged with the SARS-CoV-2 virus. There is a significant decrease in viral load for those vaccinated with the INO-4800 DNA vaccine both at their peak and after 7 days [42].

vaccination against H1N1, H3N2, and B strains of influenza, as well as the safety profile. Further, they compared results among multiple different doses and between ID and IM routes and grouped the results from the studies into four categories: seroconversion, sero protection, geometric mean titer of antibodies, and safety profile.

Regarding seroconversion, there was no significant difference between the 15µg IM group compared to the 3µg, 5µg, 7.5µg, and 9µg ID groups for any of the three strains, and the H1N1 strain saw increased sero conversion with the 15µg group. Relative to the 15µg IM dose, sero protection against the H1N1 strain was significantly increased with the 15µg ID dose and significantly decreased for the 6µg ID dose. The remaining groups showed no significant difference in seroprotection. The geometric mean titer was also generally similar among all ID doses compared to IM administration, though with significant increases for the 9µg ID dose against H3N2, increases for the 15µg ID dose against B strain, and decreases for the 3µg and 6µg ID doses against H1N1. In older adults, there again were very few significant differences observed except for increased seroconversion with the 15µg ID dose. Additionally, the risk of influenza or influenza-like illnesses was significantly lower with ID administration overall, though it was not always consistent across different ID doses [32].

Local adverse events, as seen in most studies on ID vaccines, were more common, and occurred at a similar rate in all dosages except the 3µg group where they were least common. Systemic adverse events were similar in all groups except for an increase in fever and chills in the 9µg and 15µg ID administrations [32].

There was significant heterogeneity across the studies, including demographics, comorbidities, and methods. In summary, this study showed that implementing ID approaches and reduced doses could lead to immune protection that is comparable or even more potent than through IM approaches with very similar safety profiles. It also demonstrates which factors may be dose-dependent and which factors are most significantly affected by reducing the dosage, paving the way for more research on how to best apply this knowledge and inform our vaccination practices [32].

Reduced doses in covid vaccines

Due to an error in dose quantification of the AstraZeneca ChAdOx1 nCoV-19 vaccine, batches of low dose vaccines containing 2.2×10^{10} viral particles instead of the standard dose that contained 5×10^{10} viral particles were distributed amongst several vaccination sites in the United Kingdom between May 13th and June 10, 2020 [33]. Ultimately, this created an interesting study that analyzed the differences in efficacy and vaccine safety when using Low Dose (LD) and Standard Dose (SD) protocols.

Using the data from the randomized clinical trials titled COV001 (Phase I/II; UK), COV002 (Phase II/III; UK), COV003 (Phase III; Brazil), and COV005 (Phase I/II; South Africa), the interim analysis on efficacy was assessed by a prespecified global pooled analysis combining data from COV002 and COV003, and the safety of the vaccine was assessed from all four studies. In the COV002 and COV003 trials, two dosage groups were included: an LD/SD group and an SD/SD group.

As shown in Figure 3, the findings show a significant increase in the efficacy of the vaccine when receiving the LD/SD protocol (62%, 95% CI 41. 0–75. 7) compared to the SD/SD protocol (90.0%, 95% CI 67. 4–97. 0; $p < 0. 01$). Further, both dosage patterns had an acceptable safety profile similar to ones profiles reported in other studies. It also showed a decrease in the number of asymptomatic cases, but the number of cases in both the study groups and control groups was too small to generate statistical significance. By using a larger sample size, future studies can help strengthen the power of the study and the generalizability of the observed results in this regard (Figure 2).

This study helps build our understanding of using substantial sample size that helps build practical consideration of using reduced doses. With a significant sample size (11636 patients included in analysis) and focus on clinical outcomes rather than immune markers, it helps confirm that the theorized benefits of reduced dose approaches likely hold true when applied practically.

The major limitations of this study are based on the demographics of each group. There appear to be strong differences in baseline covariates between the UK cohort and Brazilian cohorts being compared against each other when considering age, ethnic heterogeneity, and percentage of non-healthcare workers. The LD/SD cohort- based in the UK- consisted of 60. 6% healthcare workers and proved to be less ethnically diverse (92% white) and younger. The pooled SD/SD cohort consisted of 88. 9% healthcare workers and proved to be more ethnically diverse and older. While immunogenic responses between healthcare workers and non-healthcare workers should be similar, generalizability concerns exist for older individuals and vulnerable populations of higher risk (including but not limited to the immunocompromised, people with chronic conditions, older people, and the pediatric population). The limitations regarding the differences in age group have been acknowledged by the authors of the original study [33] and other commentaries on this study [34-37]. Secondly, a few methodological issues make it harder to attribute the reported efficacies solely to the LD/SD dosing approach. Between the LD/SD and SD/SD groups, there are large differences in the time intervals between which participants received their 1st and 2nd doses. Based on current literature studying the time-interval between AstraZeneca vaccination doses, it is known that higher time intervals between doses are associated with higher efficacies [38, 39]. This serves as a potential confounder between the LD/SD dosing strategy and the observed improvement in vaccine efficacies. While efforts were made to balance out these differences through randomization, blinding, and large sample sizes, these differences between the groups make it harder to isolate whether the improved efficacy is solely attributable to the LD/SD dosing regimen.

A different study, which investigated reduced dosages of mRNA COVID-19 vaccines, was conducted by Chu et al. [40] in 2021. Using the Moderna mRNA-1273 vaccine at either 50µg or 100µg, given IM, they again investigated the immune response and rate of adverse effects. Across eight vaccination sites, 600 otherwise healthy adult participants were divided into two cohorts (18-55 years old, and >55 years old; 300 patients each) and randomly assigned equally into a placebo, 50 µg, or 100 µg vaccine treatment groups. The participants in the experimental groups received two doses 28 days apart. Data from the trial demonstrated how, even with an IM vaccination, giving half the dose of the mRNA vaccine resulted in highly comparable immune responses and an overall improvement in certain safety measures [40].

The results from this study show that the reduced dose led to similar immune response and had an acceptable safety profile. The safety analysis showed comparable rates of adverse reactions compared to other trials and across both age groups. Though the frequency of certain reactions was slightly higher in the 100µg group, there was overall no dose-dependent effect on reactions, though they were generally less often reported in the cohort with patients >55 years old [40].

This publication expands our knowledge of the vaccines in multiple ways, but still leaves much area for research. The population utilized included add older individuals (>55 years old) and included 600 total participants, creating a more substantial sample size. Additionally, this study used preliminary data as

part of a larger investigation, the Phase III COVE trial, further statistical analysis with more study groups can gather greater insights. However, it only explored two dosages and one route of administration, further studies are needed to obtain a more complete picture.

Intradermal administration of covid vaccines

There is limited data regarding ID and reduced dose approaches for the AstraZeneca vaccine, data from other COVID 19 vaccines show promising results. A 2021 randomized controlled trial by Yadav et al. [41] studied the immune response using a receptor-binding protein immunogen in mice models who were given two doses with a 3-week interval. This study used a different animal model and small sample size (20 mice total), the findings continue to confirm a potent immune response. The authors noted a very similar production of IgG1 antibodies after both the first and second administration, but significantly greater levels of many other markers of immune response, including CD-8+ cells producing IL-2 and IFN- γ [41]. Future studies should investigate whether the Th1 vs Th2 polarization difference observed between the ID and IM vaccination groups could be observed in humans and how closely this difference correlates to protection against infection. If so, it may be associated with decreased risk of systemic adverse reactions like cytokine storm, which is associated with the overproduction of IL-6, through ID vaccination.

The evidence from this study helps bolster our understanding of the ID vaccines, the study has many factors that limit its applications in other contexts. They used a small sample size in a mice model using a protein immunogen, which theoretically may not correlate to human trials with other vaccine mechanisms like mRNA or viral vector vaccines. However, when considering the evidence in context from surrounding literature, it becomes apparent that these results may be generalizable to other contexts.

A 2020 study by Patel et al. [42] studied the immunogenicity of intradermal administration of the INO-4800 DNA COVID-19 vaccine, which encodes the SARS-CoV-2 spike protein. Two doses at weeks 0 and 4 were delivered through the ID route to a population of 5 rhesus macaques alongside 5 control macaques who received no vaccine. To measure the efficacy, they recorded the T cell response after immunization as well as the viral load after exposure to the virus 13 weeks after the initial vaccination, effectively measuring both the initial immune response and its ability to suppress the virus in a more practical context [42].

The results showed appropriate seroconversion with IgG detected at appropriate levels throughout the 15 weeks after vaccination as well as in sputum obtained via a broncho-alveolar lavage after 8 weeks. Additionally, they tested the immune response to a mutated spike protein to simulate the response to different potential variants of COVID 19 (utilizing both the D614 and G614 spike variants), and obtained appropriate immune responses to both variants, indicating some level of protection against future variants. When the subjects were challenged with SARS-CoV-2 13 weeks after vaccination via intranasal and intratracheal inoculation, the vaccinated macaques demonstrated increased antibody titers at both 7 and 14 days after exposure. Viral load was measured with sub-genomic RNA (sgmRNA) levels and were found to be significantly lower in the vaccinated group at 7 days post-challenge and when comparing peak values [42] (Figure 3).

This study [42] helps build support for ID vaccines, with some limitations. The use of an animal model and a small sample size limits external generalizability to humans. Additionally, compared to other studies under identical conditions the control

group here experienced substantially higher viral load after the viral challenge, though the vaccine still demonstrated a significant decrease in viral load and durable immune response in every measured way. Overall, this study helps provide support for ID administration with a DNA vaccine as a means of generating a strong immune response and reducing the viral load when fighting an active COVID 19 infection and even against certain variants of the targeted spike protein.

A recent non-inferiority randomized controlled trial conducted by Tawinprai et al. [43] found that an intradermal fractional third dose of the AstraZeneca COVID-19 vaccine (AZD1222) proved to be non-inferior to the standard IM third dose amongst individuals previously vaccinated with the CoronaVac COVID-19 vaccine and older than 18 years of age (IQR: 35-52 years of age). A total of 125 participants were randomized into one of three groups: a standard group, an ID1 group, and an ID2 group. The standard group received the standard AstraZeneca booster dose that was administered intramuscularly. The ID1 group received an intradermal vaccination containing 20% of the standard dose of AZD1222. The ID2 group received an intradermal vaccination containing 40% of the standard dose of AZD1222. The authors assessed immunogenicity by comparing the surrogate neutralizing antibody levels, the anti-RBD antibody levels, and the geometric mean ratio of anti-receptor binding domain antibodies amongst the three groups fourteen days post-vaccination. When comparing the safety of the three groups, it was ultimately found that the intradermal administration technique was associated with lower systemic adverse events relative to the standard intramuscular administration technique [43]. A summary of the study's results is reported in Table 2 below.

With limitations regarding external generalizability, this study demonstrates promising results for an intradermal approach. First, it is possible that the results observed from the participants in this study might not be generalizable to people belonging to different ethnic groups (all participants were Thai decent) and age ranges (pediatric and elderly populations [age>66] not represented). Second, the intramuscular group, unintentionally, had a higher number of subjects with comorbidities (hypertension and diabetes). It is possible that the observed differences in the higher rate of severe adverse events may have resulted from this difference between the two groups. Third, according to Tawinprai et al. [43], it is possible that observer bias played a role in the assessment of the vaccination safety profiles as the participants and investigators were not blinded during the study period. Finally, this study cannot answer whether ID fractional doses can be applied to primary vaccinations [43].

Combining ID and reduced dose methods

Other studies have been able to combine both ID and reduced dosage approaches with COVID 19 vaccination. This study, conducted by Roozen et al. [44], was a Phase II trial investigating ID vs IM administration of the Moderna mRNA-1273 vaccine against COVID 19. It included 38 participants of healthy individuals aged 18-30 and compared in three study groups who received 2 doses with a 29-day interval through the following methods: 10 μ g ID, 20 μ g ID, or 20 μ g IM. These groups were then compared with patients from other trials like the PIENTER-Corona study, which used 100 μ g IM vaccination. Compared to both the 20 μ g and 100 μ g IM approach, the results showed very similar levels of IgG antibodies against both the spike protein and its receptor-binding domain by using the either 10 μ g or 20 μ g ID approach, though the 20 μ g ID group showed the greatest levels of IgG. Figure 2 is a graphical interpretation of this data from the study. Regarding safety, the results were consistent with previously discussed studies; ID approaches led to more frequent local adverse events but very similar incidence of systemic or

severe adverse events. Additionally, it was noted that there were fewer local adverse events with the second dose and with smaller doses [44] (Figure 4).

Though the study illustrates the relationship between vaccination route and reduced doses, multiple limitations must still be considered. Like the previously mentioned studies, they used a small sample size of healthy individuals with a relatively narrow range of ages. These factors limit the ability to study how well it is tolerated in younger or older populations, or those with immunodeficiencies or comorbidities. Finally, there are concerns that the results observed in this study might only be specific to this mRNA-1273 vaccine. However, the promising results from Tawinprai et al. [43], Patel et al. [42], Yadav et al. [41], and surrounding literature suggest that the intradermal approach for COVID-19 vaccines can be successful across adenovirus, DNA, mRNA, and peptide-based immunogen vaccine vectors. Despite the limitations of this individual study, this publication still helps build our understanding of ID vaccines and reduced doses by comparing the safety and effectiveness of the different vaccination approaches (reduced dose IM and ID, higher dose ID, and full dose IM).

Other benefits of ID vaccines

In addition to the evidence around the immune response and protection against active infections, there are other practical benefits of ID vaccines and using reduced doses. One example is easier distribution and management of vaccine supplies, since reduced doses lower the needed quantity of vaccines and could allow more people to receive the vaccine. This is especially powerful at times when vaccine supply is reduced, like the example from 2004 with influenza vaccines discussed earlier. COVID 19 also created significant demand for vaccines in a short amount of time, and there is still substantial need for more vaccination efforts around the world, optimizing supply will continue to be essential.

Unlike intramuscular vaccinations that typically require hypodermic needles and syringes, intradermal vaccinations can also be delivered through a disposable-syringe jet injectors, a standard intradermal needle and syringe, or by a self-applicable intradermal microneedle patch [20, 45]. The expanded delivery

options might help us vaccinate some individuals that are vaccine hesitant, as some often cite their “needle-phobia” as a deterrent from seeking vaccinations [46]. To implement these methods at a large scale, further testing on each method’s efficacy and safety would be essential for guiding public policy and vaccination strategy.

Limitations and future research directions

The promising results in favor of an intradermal vaccination or an alternative dose-sparing approach are not without its limitations. Although neutralizing antibody titers are a frequently used measure of immune response, their use as correlates of protection for COVID-19 is currently under debate [36, 47-50]. However, different studies featured in this review used various other measures of immune response, including viral load, relative risk reduction against infection, and other cellular markers. Through these different measures, it is evident that there is a significant and robust immune response from standard intramuscular, reduced-dose intramuscular, and intradermal COVID-19 vaccination strategies.

The populations studied across all the reviewed studies did not necessarily capture the higher risk populations who are especially vulnerable to complications from both COVID 19 and the vaccines. These studies often focused on younger and otherwise healthy adults and had small sample sizes that prevented further causal inferences from being made. Future randomized control trials could examine the differences in vaccine safety and efficacy amongst higher risk populations and other age groups not included in the above studies.

Additionally, the serious adverse reactions noted in the studies were typically infrequent and varied, making analysis and comparison of safety profiles often difficult because of the low statistical power. Regardless, it is important to find vaccine administration techniques and dosage volumes that significantly reduce the prevalence of Oxford-AstraZeneca vaccine-induced adverse events given the case reports and studies demonstrating their association with cytokine storms that cause deep vein thrombosis, thrombotic microangiopathies and post-secondary stroke, hypercalcemia, depression, and encephalopathy [2, 3, 13, 14, 51].

Group	N = 125 (1 participant lost to follow-up)	Geometric mean concentration of anti-SARS-CoV-2 spike protein antibodies (95% CI)	Geometric mean ratio (95% CI)	Systemic Adverse Events (Day 1)	Rate of Local Adverse Events (Day 1)	Severe Adverse Events (Severe made up 7.8% of all AEs)
Intramuscular (Standard)	41	6414.62 (5107.56-8056.17)	Reference	Myalgia (69%) Fatigue (64%) Fever (61%)	44%	79.17%
ID1	40	5669.49 (4560.30-7048.45)	0.94 (0.8-1.09)	Myalgia (14%) Drowsiness (14%) Fever (11%) Headache (11%)	20.6%	0
ID2	43	8230.37 (6697.04-10114.8)	1.28 (0.95-1.74)	Myalgia (40%) Drowsiness (40%) Fever (43%) Headache (40%)	51.4%	20.83%

Table 2: Results Summary: A stronger, yet non-significant, immune response was associated with the intradermal vaccination approach using 40% of the standard intramuscular dose. Ultimately, both intradermal administration techniques for the AZD1222 COVID-19 vaccine proved to be non-inferior. A higher rate of local adverse events (mild-moderate in severity) was associated with the intradermal approaches. The group given an intramuscular administration of AZD1222 reported a higher rate of severe adverse events and a higher rate of systemic adverse events relative to the groups receiving an intradermal AZD1222 COVID-19 vaccination [43].

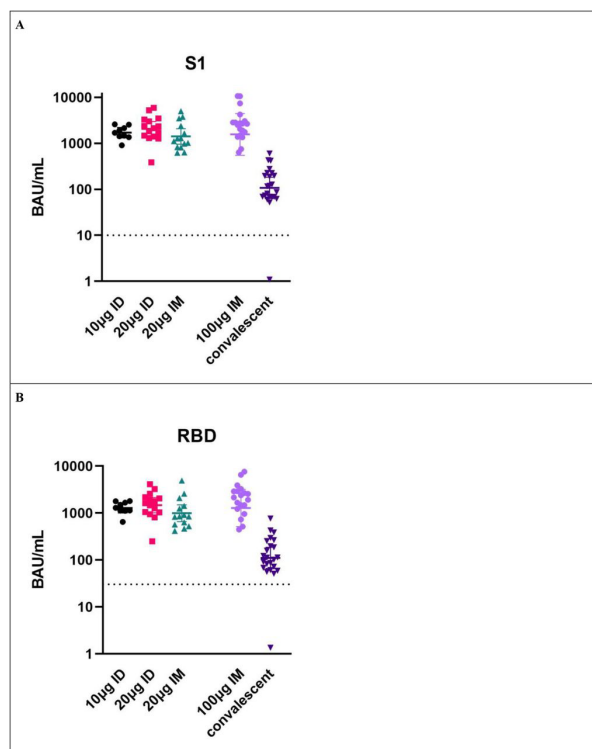


Figure 4: This figure shows the concentration of IgG antibodies (measured as Binding Antibody Units (BAU)/mL) for each participant in the study for both the S1 spike glycoprotein and the Receptor Binding Domain. Similar immune responses were observed for the reduced dose groups and ID administration groups compared to the data from other studies with the standard 100µg IM dose [44].

There is a paucity of clinical trials on the varied doses with the intradermal approach relative to the intramuscular approach for the SARS-CoV-2 vaccines. In some of the prior literature studying intradermal vaccination, it is often hard to determine whether the improvements in efficacy are due to the difference in dosages between the two groups or the improvements are due to the route of administration. While clinical trials studying intradermal vaccination typically report that reduced intradermal doses induce a comparable or non-inferior immune response compared with the standard regimen [20], there is a need for additional large-scale trials that compare efficacy between equivalent amounts of antigen delivered across intramuscular and intradermal administration routes. This will help us better isolate, understand the factors behind the higher efficacy of intradermal vaccinations relative to intramuscular vaccinations, and help us identify the best dose-sparing technique.

There are ongoing studies investigating the comparative effectiveness and non-inferiority of intradermal vaccination relative to intramuscular vaccination for the mRNA-1273 vaccine such as the follow study to Voysey et al. [33] and a new efficacy study by Dr Subhai Kongsangdao titled, "IntraDermal Versus Intramuscular Comirnaty® Efficacy Study" (clinicaltrials.gov Identifier: NCT05029245). Additional research investigating the optimal dosing strategies and comparative effectiveness of ID Oxford-AstraZeneca vaccine relative to the IM Oxford-AstraZeneca vaccine is needed [43]. Insights from these studies and future research will be important for determining the optimal vaccine administration and dosing strategies, allowing for more efficient and effective vaccines, and helping ease the burden that COVID 19 and other infectious diseases place on individuals and

public health.

Conclusion

Based on the evidence presented, it becomes clear that using reduced doses of the COVID-19 vaccines shows great promise for the future of COVID-19 vaccine administration. Similar results have been achieved through intradermal administration of the vaccine. Both approaches have been shown in multiple studies to elicit an equal or stronger immune response with potentially lower risk of systemic side effects. Further, these approaches would facilitate vaccine distribution and potentially improve access to patients who currently have contraindications to receiving it. The limitations present in the current literature highlights the need for further investigations, such as increased sample size, more standardization, and trials in populations with higher risk of adverse reactions. With increased evidence from current clinical trials and future studies, the optimal dosing strategy for the Oxford-AstraZeneca vaccine implemented and the vaccine can be administered with the safest and most effective approach.

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