UJEMI PERSPECTIVES

Effectiveness of currently authorized vaccines against SARS-CoV-2 variants of concern and the future of COVID-19 vaccines

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SUMMARY Knowledge is still limited on the effectiveness of currently authorized COVID-19 vaccines against the numerous variants of SARS-CoV-2. Authorized vaccines are still showing high levels of effectiveness in preventing severe disease symptoms of COVID-19. However, there are several limitations to the highly effective mRNA vaccines, and the existing vaccine supply is still falling short of the global demand. Furthermore, the rapidly spreading Omicron variant has clustered mutations at the ACE2 receptor binding sites as well as at antibody sites, which happen to be the targets of widely used COVID-19 vaccines. The effectiveness of authorized vaccines on emergent variants continues to be an important point of clinical research, as well as the need to find other vaccine technology that could provide more comprehensive protection against emerging variants. This article will address current knowledge on the effectiveness of authorized vaccines and discuss other vaccine technology that could become important prevention tools in the near future against circulating SARS-CoV-2 variants of concern. This article will outline studies that suggest that vaccines focusing more on stimulating T cell response and on conserved peptides could become important in providing immunity against emergent variants of concern. Nanocarriers also continue to be an immensely promising area of vaccine development. Among nanocarrier vaccine technology, subunit adjuvant vaccines are especially gaining traction. This article will also introduce recent research that suggests that adjuvant vaccines could become important second and third generation COVID-19 vaccines. As the pandemic progresses, many considerations must be made including vaccine affordability, distribution and access. From a Canadian perspective, it will become increasingly important to put vaccine development and biomanufacturing technology in place within Canada rather than relying heavily on biotechnology companies outside of the country.

INTRODUCTION

As of February 2022, over 60% of the global population have received at least one dose of a COVID-19 vaccine, with over 22 million doses being administered every day (1). Though these statistics seem promising, the global vaccine supply still remains below global demand, with only around 10% of people in low-income countries having received at least one COVID-19 vaccine dose (1). Over 80% of the Canadian population are currently considered fully vaccinated, with over 45% of the population receiving a booster dose (1).

Over time SARS-CoV-2 mutated, as viruses tend to do, in order to gain a competitive edge against protective measures. Variants of concern include the Alpha, Beta, Gamma, Delta, and Omicron variants which are each characterized by amino acid substitutions in their receptor binding domains (2). The variants of concern are also characterized by high rates of infectivity and transmissibility (3). Though the highly transmissible Omicron variant was shown to be unable to increase the risk of primary infection in a population, it seems to be able to increase the risk of reinfection (3).

Vaccines for COVID-19 were available within a year of the beginning of the pandemic (4). Six vaccines are authorized by Health Canada as of February 2022, as indicated by the

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Public Health Agency of Canada (4). This includes the mRNA vaccines from Pfizer-BioNTech and Moderna, as well the viral vector vaccines from AstraZeneca and Johnson & Johnson (4). Recently, the Novavax Nuvaxovid vaccine and the Medicago Covifenz vaccine, both of which are protein subunit vaccines, were approved by Health Canada (4).

The Novavax vaccine, which uses matrix-M as an adjuvant, was recently approved for Canadians aged 18 and older, with trial data indicating the vaccine to be 90 % effective in preventing severe COVID-19 symptoms (5). It was eventually decided that Novavax would produce the vaccine supply at the National Research Council in Quebec (5). Medicago's Covifenz is a plant-based COVID-19 vaccine developed here in Canada (6). Shortly following Novavax, it became the 6th vaccine to be approved by Health Canada (6). Some Canadians may prefer, or be less hesitant, about this plant-based nationally developed option over mRNA vaccines (6). Clinical trials have shown the Covifenz vaccine to be 71% effective in protecting trial participants, as well as being essentially 100% effective against severe disease (7).

PROPOSED RESEARCH QUESTIONS

Effectiveness of vaccines is important to continue to study, as well as the exploration of other vaccine technologies that hold high potential as future COVID-19 vaccines. Longevity and distribution are some disadvantages of mRNA vaccines, and the challenge to find broad spectrum universal vaccine technology against SARS-CoV-2 is still a rapidly developing area of knowledge. This article will therefore focus on the following research questions:

1. What is the effectiveness of current authorized vaccines against SARS-CoV-2 variants of concern?
2. What are other vaccine technologies that show potential in future Covid-19 vaccine development?

PROPOSED PROJECT NARRATIVE

All authorized COVID-19 vaccines have shown ≥ 89% efficacy against hospitalization, and have demonstrated 65% - 95% efficacy against laboratory confirmed symptomatic COVID-19 in adults (8). Research is ongoing on the effectiveness of authorized vaccines against COVID-19 variants, though it seems authorized vaccines are still showing high effectiveness against several circulating variants of concern (See TABLE 1). The wide usage of mRNA vaccines especially include advantages such as low risk of virulence reversion or insertional mutagenesis (12). However, studies with real-world high quality safety data for mRNA vaccines remain scarce and researchers are still looking for a more long-term vaccine solution to COVID-19 as variants of concern continue to circulate (12).

First detected in November 2021, the Omicron variant has 26-32 amino acid changes in the spike protein (2). This is especially concerning as this is the primary target of authorized COVID-19 vaccines (8). Preliminary data from Pfizer-BioNTech put forward that three doses seems to neutralize the Omicron variant, while two doses seem to stimulate a significantly decreased neutralization titer (2). In findings that are yet to be peer reviewed, Omicron was better than Delta at breaking through vaccine immunity, though a third dose booster shot still lowered the risk of infection by Omicron by 50% (13). Omicron also showed lower lung infectivity and pathogenicity in a hamster model than the Delta variant (14). Researchers are recently tracking the BA.2 lineage of Omicron, which seems to have a growth advantage over other variants and has new mutations that have not yet been tested (15).

Though vaccination is anticipated to continue to protect against severe symptoms, the question remains regarding how often COVID-19 vaccines need to be updated to keep SARS-CoV-2 under control (2, 8). It is unclear how long boosters can last, and emerging data from Israel suggests that the fourth dose does not provide particularly effective protection (16). Early studies are also indicating that Omicron customized booster vaccines have been providing little advantage over standard vaccine doses in animal models (17). Experts have put forward that COVID-19 seems to be headed towards becoming an endemic disease (18). It is hence very important to recognize common themes in vaccine technology research before going forward into the next stages of this global pandemic.

TABLE 1. Efficacy of authorized SARS-CoV-2 vaccines against several circulating variants of concern. Summary of trial data on the effectiveness of four out of the six vaccines authorized by Health Canada against circulating SARS-CoV-2 variants of concern. Adapted from (3, 9, 10, 11).

SARS-CoV -2 Variant of Concern	Pfizer-BioTech vaccine mediated protection	Moderna vaccine mediated protection	AstraZeneca vaccine mediated protection	Johnson & Johnson vaccine mediated protection
Wuhan Strain	➢ 95% (9) ➢ Overall humoral immunity (3)	➢ 94.1% (9) ➢ Overall humoral and cellular immunity (3)	➢ 55-81% (9) ➢ 62.1 -79% (3) ➢ Overall cellular immunity (3)	➢ 66% (9)
Alpha (B.1.1.7)	➢ 90% (9)	➢ 89% (3) ➢ 2.3-6.4 in titers of neutralizing antibodies (9)	➢ 75% (9) ➢ 74.5 % (3)	➢ 70% (9)
Beta (B.1.351)	➢ 75- 100% (9)	➢ 85% (3) ➢ Reduced levels of neutralizing antibodies	➢ 61.1%, 10.4% for Beta, HIV negative (3) ➢ 10% (9)	➢ 72% in USA, 57% in South Africa (9)
Gamma (P.1)	➢ No evidence of reduced protection (9)	➢ 85% (3) ➢ Reduced levels of neutralizing antibodies (9)	➢ Unknown (9)	➢ 68% (9)
Delta (B.1.617.2)	➢ One dose is 88% effective (9) ➢ Varying efficacy against symptomatic infection documented by Patel et al: From 41% - 88%. Efficacy against severe infection in the range of (89 % - 93%) (11) ➢ In Canada, 78% effectiveness against hospitalization over 21 days after first dose, when Delta was the dominant variant when the survey was conducted (10)	➢ 50.6% (3) ➢ Neutralization titer 6.8-1 (9) ➢ In Canada, 95% effectiveness against hospitalization over 21 days after first dose, when Delta was the dominant variant when the survey was conducted (10)	➢ 92% effective against hospitalization (9) ➢ 67% (3)	➢ Reports of 60% effectiveness (9) ➢ ~66% effective in preventing moderate infection 2-3 weeks post injection (11) ➢ 80% effective in preventing severe infection 2-3 weeks post injection (11)
Omicron (B.1.1.529)	➢ 22.5% (3) ➢ 89-96% for pregnant women (3)	Ongoing discovery	Ongoing discovery	Ongoing discovery

What are other vaccine technologies that show potential in future Covid-19 vaccine development?

Several recent papers have focused on inducing T cell immunity mediated vaccine protection (See TABLE 2 Part A). T cell mediated pathways provide broad spectrum protection, which is less affected by evolving variants (19). Hence, despite the extensive mutations that exist with the Omicron variant, it seems that T cell responses induced by vaccination and/or induced by previous infection can cross-recognize the variant (20). However, it is still to be determined whether the T cell immunity to Omicron can be protective in cases of severe COVID-19 (20). CoVac-1 is an example of a peptide-based vaccine candidate that aimed to and was able to induce SARS-CoV-2 specific T cell response in an adult sample (19). Other examples of T cell immunity focused vaccines include both spike and nucleocapsid proteins of SARS-CoV-2, with explored delivery methods including

TABLE 2. Recent literature on vaccine technology with high potential for the near future. Part A) Recent studies (as of February 2022) covering T cell focused vaccine immunity against COVID-19. Part B) Recent studies (as of February 2022) covering nanoparticle, subunit adjuvant vaccine technology against COVID-19.

Part A – T cell mediated immunity and peptide vaccines	**Source**
A COVID-19 peptide vaccine for the induction of SARS-CoV-2 T cell immunity	Heitmann et al., 2021, *Nature*
Intranasal plus subcutaneous prime vaccination with a dual antigen COVID-19 vaccine elicits T-cell and antibody responses in mice	Rice et al., 2021, *Scientific Reports*
T cell responses to SARS-CoV-2 spike cross-recognize Omicron	Keeton et al., 2022, *Nature*
Induction of Th1 and Th2 in the protection against SARS-CoV-2 through mucosal delivery of an adenovirus vaccine expressing an engineered spike protein	Chung et al., 2022, *Vaccine*
Design of a multi-epitope-based-based peptide vaccine against the S and N proteins of SARS-COV-2 using immunoinformatics approach	Rouzbahani et al., 2022, *Egyptian Journal of Medical Human Genetics*
Part B – Nanoparticles, subunit vaccine adjuvants	**Source**
SARS-CoV-2 subunit vaccine adjuvants and their signaling pathways	Mekonnen et al., 2021, *Expert Rev Vaccines*
Nanocarrier vaccines for SARS-CoV-2	Macchi et al., 2021, *Advanced Drug Delivery Reviews*
Nanoparticle and virus-like particle vaccine approaches against SARS-CoV-2	Kim et al., 2022, *Journal of Microbiology*
Design and Immunological Properties of the Novel Subunit Virus-like Vaccine against SARS-CoV-2	Krasilnikov et al., 2022, *Vaccines (Basel)*
Oral subunit SARS-CoV-2 vaccine induces systemic neutralizing IgG, IgA and cellular immune responses and can boost neutralizing antibody responses primed by an injected vaccine	Pitcovski et al., 2022, *Vaccine*

intranasal and subcutaneous (21, 22, 23). Challenges to vaccine technology development include the limited knowledge on the pathophysiology of the SARS-CoV-2 virus and inducing robust humoral and cellular immunity (24).

Nanocarrier delivery has become an important part of SARS-CoV-2 vaccine development, as nanoparticles are similar in size to viruses and are especially capable of penetrating membranes (25). Adjuvant subunit vaccine technology seems particularly promising, and experts suggest that nanoparticle subunit adjuvant vaccines could become important second and third generation COVID-19 vaccines (25, 26, 27). Defensin, alum, matrix-M and CpG were found to be the most utilized adjuvants in current subunit vaccine development research (27). Several recent papers have explored this vaccine strategy for combating SARS-CoV-2 (See TABLE 2 Part B).

There are even more vaccine technologies that are certainly far from losing traction. These vaccine strategies include inactivated vaccines, as well the option of mixing-and-matching vaccines. An example of an inactivated vaccine in recent development is the whole-virion inactivated SARS-CoV-2 vaccine candidate TURKOVAC (30). Additionally, mixing the same vaccine platform or two different vaccine platforms may provide another great strategy, with research suggesting that combining two different vaccines provides protection on par with mRNA vaccines (31, 32).

POTENTIAL IMPACT/CONCLUSIONS

Overall, there is evidence of high effectiveness of authorized vaccines against circulating SARS-CoV-2 variants of concern. Among emerging themes in future SARS-CoV-2 vaccine development, important vaccine technology focuses include the induction of a robust T cell immunity and the use of nanocarriers. Among nanocarrier vaccines, adjuvant subunit vaccine technology has been showing particular potential. Nevertheless, the state of knowledge on SARS-CoV-2 variants and the ability of vaccines to keep up protection against symptomatic COVID-19 is adjusting daily. Essential considerations for vaccine development include safety, affordability, and access. Trying to optimize these factors is an ongoing challenge for vaccine development for COVID-19. Future research on emerging vaccine technology within this rapidly developing field will continue to be of great interest.

Canada must keep looking towards key themes in developing SARS-CoV–2 vaccine options, such as those highlighted within this article, as we enter the next stage of this global pandemic. It was a huge step for Health Canada to have authorized the Medicago Covifenz vaccine. Considering the potential of an endemic SARS-CoV-2 presence, it is critical to build stronger biomanufacturing capacity within Canada rather than relying heavily on products from biotechnology companies from outside the country.

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REFERENCES

1. **Ritchie H, Mathieu E, Rodés-Guirao L, Appel C, Giattino C, Ortiz-Ospina E, Hasell J, Macdonald B, Beltekian D, Roser M.** 2020. Coronavirus Pandemic (COVID-19). Our World Data.
2. **Mistry P, Barmania F, Mellet J, Peta K, Strydom A, Viljoen IM, James W, Gordon S, Pepper MS.** 2022. SARS-CoV-2 Variants, Vaccines, and Host Immunity. *Front Immunol* **12**:809244.
3. **Jiang Y, Wu Q, Song P, You C.** 2022. The Variation of SARS-CoV-2 and Advanced Research on Current Vaccines. *Front Med* **8**:806641.
4. **Public Health Agency of Canada**. 2020. Vaccines for COVID-19. navigation page - topic page. https://www.canada.ca/en/public-health/services/diseases/coronavirus-disease-covid-19/v accines.html. Retrieved 1 February 2022.
5. **CBC News**. 2022. Novavax's COVID-19 vaccine approved for Canadians 18 and older | CBC News. CBC. https://www.cbc.ca/news/health/novavax-health-canada-approval-1.6355106. Retrieved 24 February 2022.
6. **Pelley L**. 2022. Medicago's homegrown, plant-based COVID-19 vaccine approved by Health Canada | CBC News. CBC. https://www.cbc.ca/news/health/medicago-s-homegrown-plant-based-covid-19-vaccine-a pproved-by-health-canada-1.6362745. Retrieved 24 February 2022.
7. **Lavery I**. 2022. Medicago's Canada-made COVID-19 vaccine approved by Health Canada | Globalnews.ca. Global News. https://globalnews.ca/news/8642643/covid-vaccine-canadian-approved/. Retrieved 24 February 2022.
8. **CDC**. 2020. Coronavirus Disease 2019 (COVID-19). Cent Dis Control Prev. https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/fully-vaccinated-peop le.html. Retrieved 28 January 2022.
9. **Singh DD, Parveen A, Yadav DK.** 2021. SARS-CoV-2: Emergence of New Variants and Effectiveness of Vaccines. *Front Cell Infect Microbiol* **11**:777212.
10. **Jin Y, Hou C, Li Y, Zheng K, Wang C** . 2022. mRNA Vaccine: How to Meet the Challenge of SARS-CoV-2. *Front Immunol* **12**:821538.
11. **Gohda E**. 2022. Effectiveness of and Immune Responses to SARS-CoV-2 mRNA Vaccines and Their Mechanisms. *J Disaster Res* **17**:7–20.
12. **Patel R, Kaki M, Potluri VS, Kahar P, Khanna D**. 2022. A comprehensive review of SARS-CoV-2 vaccines: Pfizer, Moderna & Johnson & Johnson. *Hum Vaccines Immunother* **0**:1–12.

13. **Reardon S.** 2022. How well can Omicron evade immunity from COVID vaccines? *Nature* https://doi.org/10.1038/d41586-022-00283-4.
14. **Suzuki R, Yamasoba D, Kimura I, Wang L, Kishimoto M, Ito J, Morioka Y, Nao N, Nasser H, Uriu K, Kosugi Y, Tsuda M, Orba Y, Sasaki M, Shimizu R, Kawabata R, Yoshimatsu K, Asakura H, Nagashima M, Sadamasu K, Yoshimura K, Sawa H, Ikeda T, Irie T, Matsuno K, Tanaka S, Fukuhara T, Sato K**. 2022. Attenuated fusogenicity and pathogenicity of SARS-CoV-2 Omicron variant. *Nature* **1**–1.
15. **Callaway E**. 2022. Why does the Omicron sub-variant spread faster than the original? *Nature* **602**:556–557.
16. **Willyard C**. 2022. What the Omicron wave is revealing about human immunity. *Nature* **602**:22–25.
17. **Waltz E**. 2022. Omicron-targeted vaccines do no better than original jabs in early tests. *Nature* https://doi.org/10.1038/d41586-022-00003-y.
18. **Adam D**. 2022. Will Omicron end the pandemic? Here's what experts say. *Nature* **602**:20–21.
19. **Heitmann JS, Bilich T, Tandler C, Nelde A, Maringer Y, Marconato M, Reusch J, Jäger S, Denk M, Richter M, Anton L, Weber LM, Roerden M, Bauer J, Rieth J, Wacker M, Hörber S, Peter A, Meisner C, Fischer I, Löffler MW, Karbach J, Jäger E, Klein R, Rammensee H-G, Salih HR, Walz JS.** 2022. A COVID-19 peptide vaccine for the induction of SARS-CoV-2 cell immunity. 7894. *Nature* **601**:617–622.
20. **Keeton R, Tincho MB, Ngomti A, Baguma R, Benede N, Suzuki A, Khan K, Cele S, Bernstein M, Karim F, Madzorera SV, Moyo-Gwete T, Mennen M, Skelem S, Adriaanse M, Mutithu D, Aremu O, Stek C, du Bruyn E, Van Der Mescht MA, de Beer Z, de Villiers TR, Bodenstein A, van den Berg G, Mendes A, Strydom A, Venter M, Giandhari J, Naidoo Y, Pillay S, Tegally H, Grifoni A, Weiskopf D, Sette A, Wilkinson RJ, de Oliveira T, Bekker L-G, Gray G, Ueckermann V, Rossouw T, Boswell MT, Bihman J, Moore PL, Sigal A, Ntusi NAB, Burgers WA, Riou C**. 2022. T cell responses to SARS-CoV-2 spike cross-recognize Omicron. *Nature* **1**–5.
21. **Rice A, Verma M, Shin A, Zakin L, Sieling P, Tanaka S, Balint J, Dinkins K, Adisetiyo H, Morimoto B, Higashide W, Anders Olson C, Mody S, Spilman P, Gabitzsch E, Safrit JT, Rabizadeh S, Niazi K, Soon-Shiong P.** 2021. Intranasal plus subcutaneous prime vaccination with a dual antigen COVID-19 vaccine elicits T-cell and antibody responses in mice. 1. *Sci Rep* **11**:14917.
22. **Rouzbahani AK, Kheirandish F, Hosseini SZ.** 2022. Design of a multi-epitope-based peptide vaccine against the S and N proteins of SARS-COV-2 using immunoinformatics approach. *Egypt J Med Hum Genet* **23**:16.
23. **Chung N-H, Chen Y-C, Yang S-J, Lin Y-C, Dou H-Y, Hui-Ching Wang L, Liao C-L, Chow Y-H.** 2022. Induction of Th1 and Th2 in the protection against SARS-CoV-2 through mucosal delivery of an adenovirus vaccine expressing an engineered spike protein. *Vaccine* **40**:574–586.
24. **Hosseini SA, Zahedipour F, Mirzaei H, Kazemi Oskuee R**. 2021. Potential SARS-CoV-2 vaccines: Concept, progress, and challenges. *Int Immunopharmacol* **97**:107622.
25. **Machhi J, Shahjin F, Das S, Patel M, Abdelmoaty MM, Cohen JD, Singh PA, Baldi A, Bajwa N, Kumar R, Vora LK, Patel TA, Oleynikov MD, Soni D, Yeapuri P, Mukadam I, Chakraborty R, Saksena CG, Herskovitz J, Hasan M, Oupicky D, Das S, Donnelly RF, Hettie KS, Chang L, Gendelman HE, Kevadiya BD**. 2021. Nanocarrier vaccines for SARS-CoV-2. *Adv Drug Deliv Rev* **171**:215–239.
26. **Kim C, Kim J-D, Seo S-U**. 2022. Nanoparticle and virus-like particle vaccine approaches against SARS-CoV-2. *J Microbiol* https://doi.org/10.1007/s12275-022-1608-z.
27. **Mekonnen D, Mengist HM, Jin T.** SARS-CoV-2 subunit vaccine adjuvants and their signaling pathways. *Expert Rev Vaccines* **1**–13.
28. **Krasilnikov IV, Kudriavtsev AV, Vakhrusheva AV, Frolova ME, Ivanov AV, Stukova MA, Romanovskaya-Romanko EA, Vasilyev KA, Mushenkova NV, Isaev AA.** 2022. Design and Immunological Properties of the Novel Subunit Virus-like Vaccine against SARS-CoV-2. *Vaccines* **10**:69.
29. **Pitcovski J, Gruzdev N, Abzach A, Katz C, Ben-Adiva R, Brand-Shwartz M, Yadid I, Ratzon-Ashkenazi E, Emquies K, Israeli H, Haviv H, Rapoport I, Bloch I, Shadmon R, Eitan Z, Eliahu D, Hilel T, Laster M, Kremer-Tal S, Byk-Tennenbaum T, Shahar E.** 2022. Oral subunit SARS-CoV-2 vaccine induces systemic neutralizing IgG, IgA and cellular immune responses and can boost neutralizing antibody responses primed by an injected vaccine. *Vaccine* **40**:1098–1107.
30. **Pavel STI, Yetiskin H, Uygut MA, Aslan AF, Aydın G, İnan Ö, Kaplan B, Ozdarendeli A**. 2021. Development of an Inactivated Vaccine against SARS CoV-2. *Vaccines* **9**:1266.
31. **Chatterjee B, Thakur SS.** Diverse vaccine platforms safeguarding against SARS-CoV-2 and its variants. *Expert Rev Vaccines* **21**:47–67.
32. **Callaway E**. 2021. Mix-and-match COVID vaccines ace the effectiveness test. *Nature* https://doi.org/10.1038/d41586-021-02853-4.