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COVID-19: Vaccines on Their Marks

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Vaccine-derived immunity is being optimistically heralded as the exit strategy to the pandemic, thereby enabling everyone to return to the much-awaited normal patterns of working, schooling, and socialising. The SARS-COV-2 (COVID-19) respiratory virus was first identified in December 2019 in Wuhan, China. Owing to the rampant spread of the virus there was an exigency that called for the development of a vaccine. In this review, we discuss what is currently known about the mechanism of action, efficacy, safety profile, clinical trials, and distribution of three of the most promising vaccine candidates; mRNA-1273 (Moderna), BNT162b2 (Pfizer/BioNtech), ChAdOx1 nCoV-19 (AstraZeneca/Oxford). In the race to come up with a safe and effective vaccine against the novel coronavirus, there are a myriad of factors that play a critical role throughout the development, clinical trials, manufacturing, distribution phases. An in-depth insight is given into the expected scope and the speculated limitations of the aforementioned vaccines.

Keywords: SARS-CoV-2; immunity; vaccines; safety profile; clinical trials; efficacy; Oxford; Pfizer; Moderna

1. Introduction

Immunity in simple words is the ability of the body to discriminate between foreign particles and its cells. These foreign substances are called antigens and to counter these antigens, the protein molecules called antibodies (immunoglobulins) are developed by B lymphocytes. There are usually specific antibodies developed for each antigen. The recognition of the antigen by the antibody followed by binding, cascades the immune response. There are two ways of developing immunity, active and passive. Active immunity is developed by the person's immune system and it usually lasts for a lifetime. Passive immunity is acquired when the antibodies are directly transferred to the person which means that it is not the person's immune system that is involved in producing the antibodies. Usually, passive immunity disappears with time. Vaccines confer active immunity by interacting with the person's immune system without actually causing the disease or any complications. The immune response or the antibodies developed are similar to the ones that would be produced if the infection occurred naturally [1-7]. The different types of vaccines are as illustrated in Fig. 1.

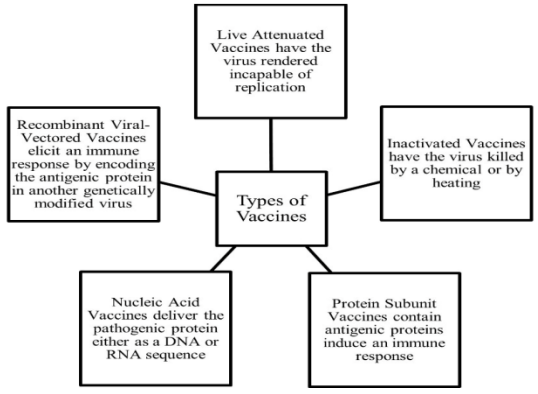

Fig. 1 Flow Diagram summarizing the types of vaccines

2. Vaccine Development

During the procedure of the various stages of vaccine development, the primary goals that have to be achieved are Safety and Efficacy. Safety is at the utmost priority in the development of a vaccine to ensure that the patients do not face any serious or deadly side effects due to its intake.

[8] The efficacy of a vaccine refers to its ability to prevent disease or infection. Efficacy portrays whether the vaccine is protective against the disease.

It was of paramount importance to establish this distinction in the case of COVID19 as the virus affects different people in different ways; it could cause anything from symptoms that require hospitalisation with ventilators or asymptomatic manifestation.

There are particular testing phases that a vaccine has to undergo to meet these goals of Safety and Efficacy.

(i) Pre-clinical phase- It comprises Animal Testing and checks whether the vaccine is safe and effective to move on to the Human Trial phase. In this phase, they give the vaccine to the animals (in this case, mice) and monitor them for any side effects. Skin irritation, fatigue, fever, death is looked out for. After inoculating the mice with the vaccine, the mice are exposed to the virus. Here, the efficacy is checked, based on the production of antibodies and their effectiveness in combating the virus, thereby leading to the prevention of the disease.[9]

(ii) Phase 1- Moving on, we test the vaccine on humans but only on a small sample size, consisting of less than 100 participants. It has to be made sure that the patients do not have any previous underlying illness to differentiate between the symptoms of the vaccine and previous illness. Then, it is checked whether there are still any side effects. Phase 1 trials are also used in finding out the upper and lower limit of the dose of the vaccine. Safety aspects are accentuated in this study.

(iii) Phase 2- In Phase 2, as well, the vaccine is given to humans but the sample size is bigger than the previous phase. The sample size is moderate; ranging from 100-1000 participants, in this phase, the target is to match the demographics of the population such as age, race, gender, and comorbidities. [10] Similar to the previous trial, the side effects are monitored again and the efficacy of the dosage is looked at more closely.

(iv) Phase 3- At this stage, the vaccine is tested on a large sample size- 1,000 to 10,000 along with checking of symptoms and effectiveness after which it goes for Emergency Use Authorization.

3. Pfizer/BioNtech Vaccine

3.1. Mechanism

The Pfizer/BioNtech vaccines are both delivered by lipid nanoparticles. [11] They are phospholipid membranes or bilayers that are wrapping around the mRNA essentially acting as a vehicle or transport mechanism for the SARS CoV-2 virus into the host cell.[12] The mRNA surrounded by this lipid nanoparticle was derived from the SARS CoV-2 virus.[13] Different kinds of proteins come off of the virus. The protein that's mostly involved with the pathogenicity is the S protein [14] and hence the mRNA codes for the S protein of the COVID-19 virus. [15] The S proteins work their way backwards to find the mRNA that is being translated or coded for that protein. The S protein then takes the RNA and incorporates it into the actual Lipid Nanoparticle. [16] The phospholipid membrane of the nanoparticle invades the host cells, fuses with the host membrane [17], and releases the mRNA into the cytoplasm of the target cell [18-21]. Once the mRNA is in this host cell, [22] it does not enter the nucleus or doesn't incorporate into the DNA which is important from the safety viewpoint. [23] The mRNA is translated using the host cell ribosomes and the rough endoplasmic reticulum producing the S protein[24-26]within the cytoplasm.[27-28] The protein is modified and gets expressed on the cell membrane by Major Histocompatibility Complex I (MHC I) and II (MHC II). MHC II protein is only found on antigen-presenting immune cells such as B-cells, macrophages, and dendritic cells. MHC I proteins are found on all nucleated cells in the body (cells having a nucleus). When this viral protein shape, the S-protein, is expressed on the actual complexes, it attracts immune system cells, one of which is called a T helper cell. [29].

This T helper cell has a particular type of membrane protein called T-cell receptor(TCR)[30] that interacts with the pathogenic antigen[31] and another CD4 protein that interacts with the MHC II complex.[32] Once the T cell or T helper cell is activated, it releases cytokines.[33-34] These plenty of cytokines, in turn, release interleukins (Interleukin 2, interleukin 4, interleukin 5) which cause B cells [35] to proliferate and differentiate into very special cells called plasma cells. Once these plasma cells are

developed and stimulated, they make specific antibodies directed against the S protein fragment on the SARS CoV-2 virus.[36] These antibodies, on binding the protein on the virus, begin to neutralize[37] the virus leading to its destruction.[38] These cytokines, cause the original T-Helper cells[39] to proliferate, forming T-Helper memory cells and Effector T cells.[40] These are all immune cells that help to generate an immune response.[41]

Another kind of cells known as the Cytotoxic T cells plays a part by binding to S protein fragments [42-43] that are expressed by non-immune cells through the MHC I complex. The CD8 molecule binds to MHC I while the cytotoxic T cell receptor (TCR) interacts with the S protein fragment.[44]Cytokines are then released by these cytotoxic T cells which amplify the T-Helper cells[45] stimulate B cells, amplifying the immune response and killing infected cells present with the S protein of COVID-19, as depicted in Fig.2.

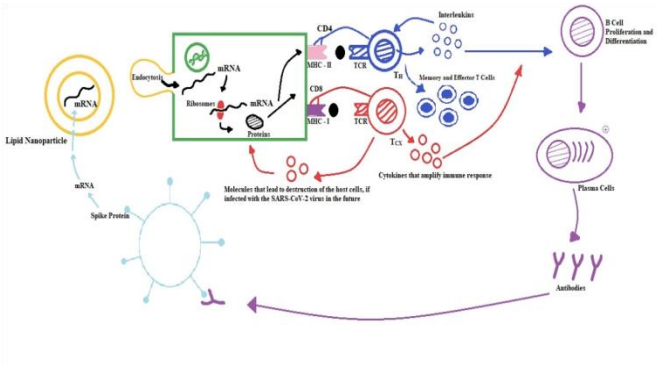

Fig. 2 Schematic Diagram illustrating the mechanism of mRNA vaccines (Pfizer and Moderna)

3.2. Efficacy

3.2. a. Case Studies and Trials

43000 individuals were divided into placebo and vaccinated groups and the Pfizer/BioNtech vaccine injections were given on day 0 and day 21. Then, seven days before the second dosage, the people who faced clinical symptoms were put in a particular category. 162 and 8 individuals were recognized showing clinical symptoms in the placebo and vaccinated group respectively.

This resulted in a 95% efficacy against the clinical symptoms.[46] Furthermore, out of the 162 patients showing symptoms from the Placebo group, 9 faced severe disease and 1 person in the vaccinated group exhibited a severe disease.[47] This concluded an efficacy of 87% against those who displayed clinical symptoms.[48]

3.2. b. Side Effects

The most common side effects were pain, chills, swelling, tiredness, redness, headache, and flu-like symptoms, and their occurrence was witnessed within a day or two of taking the vaccine. To study the side effects faced by the population, they were divided into two groups- age 16-55 and 55+.[49] During the clinical trials,[50] the side effects that occur within 7 days of getting the vaccine, or reactogenicity symptoms, were mild to moderate which later turned into fever, chills, tiredness commonly after the second dosage. In the first group (age 16-55), 42% headache, 4% fever, 33% muscle/joint pain, and 47% fatigue were noted. In the second group, (age 55+), the statistics were: 39% headache, 11% fever, 48% muscle/joint pain and 51% fatigue. [51]

Unfortunately, 0.63% of those who were injected with the vaccine also faced rare anaphylaxis. However, 0.51% of those who did not have the vaccine also experienced an allergic reaction indicating that most of the allergic reactions were not associated with the vaccine. So, we can safely assume that only 0.12% of the people had allergic reactions directly due to the vaccine. Though few people in the clinical trials were hospitalized or died,[55] data suggest that people who got the Pfizer-BioNTech vaccine were less likely to have these more serious outcomes compared to people who got the saline placebo.

3.3. Storage and Distribution

The Pfizer/BioNtech vaccine has to be stored at -94°F (-70°C). This is one of the major drawbacks of the vaccine when it comes to distribution. The requirement of well-established cold chain networks and the transportation of the vaccine at such a low temperature does not make it

suitable for low and middle-income countries. Pfizer has assured the availability of the vaccine to high-risk populations in the US by the end of December 2021. The UK government has also signed a deal to receive 40 million doses (enough for 20 million people). The EU has secured a deal for 200 million doses, with an optional 100 million extra doses. By the end of 2021, 1.3 billion doses are predicted to be sent out globally. The companies have started submission processes in Australia, Canada, Europe, and Japan. [52] The vaccine is estimated to cost around £15 per dose—much higher than the Oxford-AstraZeneca vaccine. [53]

4. Moderna Vaccine

4.1. Mechanism

The US biotech company developed the vaccine known as mRNA-1273 vaccine in partnership with the US National Institutes of Health. The mRNA- 1273 vaccine is based on the same mRNA mechanism as the Pfizer-BioNTech vaccine.

4.2. Efficacy

4.2. a. Case Studies and Trials

Around 30,000 individuals enrolled for the Moderna vaccine trial, being divided into placebo and non-placebo groups. Out of these 30,000 participants, 7000 were aged over 65 and 5000 were under 65 with a high risk of chronic diseases. The injections to the two groups were given on day 0 and the 28th day. Evaluation for clinical symptoms took place 14 days after the second injection was given. In the non-placebo group, 185 individuals showed clinical symptoms while among the vaccinated group 11 individuals showed clinical symptoms. Of the 185 individuals in the placebo group there were 30 severe cases while of those who received the vaccine there were 0 severe cases. [54, 55]. Maximum efficacy of 94.5% culminated against the development of clinical symptoms and 100% against severe disease. [55]

4.2. b. Side Effects

The most common side effects were chills, tiredness, headache and flu-like symptoms a day or two after getting the vaccine. The side effects due to the Moderna vaccine were potentially skewed upwards as all the participants were over the age of 56. [54] The classification of the side effects was also done on the basis of their respective dosages of 25 μg and 100 μg. The number of side effects after the second dose were reported at the low and high level of disease being 40% 84% headaches; 18% 20% fever; 60% 84% muscle/joint pain and 50% 83% for fatigue. No serious adverse side effects were reported. [52]

4.3. Storage and Distribution

Moderna's vaccine can be stored in a household fridge for 30 days, at room temperature for up to 12 hours, and at −20°C for up to six months. The USA signed an agreement for 100 million doses, while the UK government has secured five million doses of the vaccine candidate. This vaccine is much more costly than Oxford-AstraZeneca and Pfizer vaccines at approximately £25 per dose. [56]

5. Oxford Vaccine- AstraZeneca

The abstruse question that has left everyone awestruck is how the vaccine developed in just 10 months.

After the Ebola outbreak, Professor Sarah Gilbert at Oxford University thought that the response of the world to the pandemic should have been better. This is when the Jenner Institute at the University of Oxford contemplated that they should start preparing themselves to combat an unknown "Disease-X".

Vaccines that have live-attenuated or killed viruses of the infection are comparatively slower to develop. Using the concepts of genetic engineering, a revolutionary style of vaccination was visualised. The scientists modified a common cold adenovirus that infects the Chimpanzees and engineered it such that it was rendered incapable of causing infections in humans. Now, the beautiful part is that this virus can be made to express any desired antigen to which you want the body to develop an immune response.

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Before COVID-19 the Chimpanzee Adenovirus Oxford – 1, abbreviated as ChAdOx-1 based vaccine had been given for diseases ranging from flu to Zika virus, and prostate cancer to tropical disease chikungunya.

There is one more serendipitous thing that fostered the process of vaccine development. There had been coronavirus pandemics that had occurred earlier; SARS in 2002 and MERS in 2012. The researchers already were aware of the biology of the virus, and more substantially, they were aware of its Achilles heel which is the spike protein.

So when the perturbations associated with the infectivity of SARS-CoV-2 arose in January, Oxford was on its marks already, ready to get going and lead the vaccine development programme [57-60].

5.1. Mechanism

The Oxford vaccine has a DNA fragment that encodes for the S protein. This DNA fragment is composed of the Chimpanzee adenovirus whose replication machinery has been arrested. The DNA fragment goes to the nucleus, and now uses the replication proteins of the host cell to convert DNA to mRNA [57-60]. This mRNA is translated to the S protein at the rough endoplasmic reticulum in the cytoplasm. The S protein is now processed and can be presented by both MHC I and MHC II complexes, thereby triggering an immune response, as shown in Fig.3 [29-34].

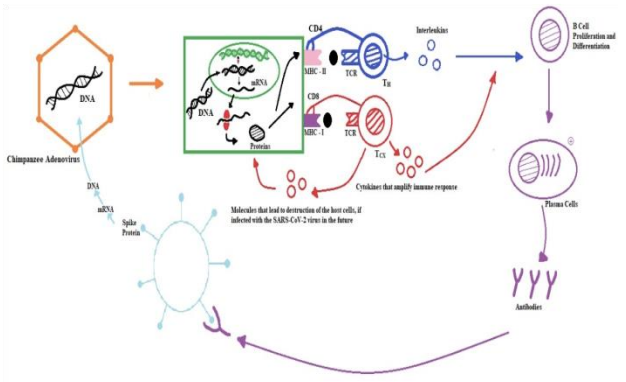

Fig. 3 Schematic Diagram illustrating the mechanism of DNA vaccine (Oxford)

5.2. Efficacy

5.2. a. Case Studies and Trials

As compared to the trials of other vaccine groups, Oxford did not use saline as a placebo but instead used a licensed vaccine against the A, C, W, and Y meningococcus (MenACWY) groups. They said that saline did not cause the minor side effects of fever, headache, and sore arm like ChAdOx-1 nCo-19. They wanted the participants to remain blinded to whether or not they had received the vaccine and not make speculations based on the side effects, thereby eliminating any scope of bias in their study.

There was a very interesting thing that happened in the Phase III AstraZeneca Oxford trials. In the Brazil study, they had 9000 participants and the UK had 3000 participants. In Brazil, they gave a full dose on Day 0 and a full dose on Day 28 whereas, in the UK, they gave half a dose on Day 0 and a full dose on Day 28. The reported efficacy in the former was 62% whereas in the latter it turned out to be a surprising 90%. The combined analysis portrayed an efficacy of 70.4% to prevent infection and 100% to prevent severe disease. [61]Of the 131 cases that tested positive for the virus, none had developed severe symptoms of the disease.

5.2. b. Side Effects

The side effects of the AstraZeneca/BioNtech vaccine were evaluated with and without the administration of Tylenol. Tylenol is acetaminophen used to treat mild to moderate pain and is also used to reduce fever. In the group that was not given Tylenol; headaches were 42%, fever 51%, muscle/joint pain 60%, and fatigue 70%. Severe adverse events were at 0.3% and were linked to a case of hemolytic anaemia [62-73].

5.3. Storage and Distribution

The vaccine can be stored at 2.2°C to 7.8°C. This implies convenient storage and distribution as it does not require a negative temperature. Normal refrigeration can be used which will also help optimize the better economics of the vaccine. AstraZeneca estimates that by the end of 2021, they could generate 3 billion units of the vaccine. And, if

the further trials also second the half dosage regime, they could manufacture up to 4.5 billion units. [55]

6. Conclusion

It is remarkable how a vaccine that otherwise would have taken ten long years, was ready to be rolled out in just 10 months. The cohesive efforts of the governments, researchers, investors, and pharma companies made this possible. A succinct analysis of the vaccination development followed during this pandemic is of cardinal importance. Ultimately, it is the vaccines that shall extricate us from this pandemic. It is imperative and substantial that we be far-sighted to start preparing for such diseases already as a pandemic of this scale jeopardizes the entire normal functioning of the whole world.

7. References

[1] Siegrist, C. A. *"Vaccine Immunology In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. Philadelphia."***2008**, 17.

[2] Plotkin, Stanley A. *The Journal of infectious diseases.***2003**, 187(9), 1349.

[3] Plotkin, Stanley A., and Stanley A. Plotkin. *Clinical infectious diseases*, **2008**, 47(3), 401.

[4] Corum, Jonathan, et al. *The New York Times* 5 **2020**.

[5] Sharpe, Hannah R., Ciaran Gilbride, Elizabeth Allen, Sandra Belij-Rammerstorfer, Cameron Bissett, Katie Ewer and Teresa Lambe.*Immunology* **2020**, 160(3), 223.

[6] Lurie, Nicole, Melanie Saville, Richard Hatchett, and Jane Halton.*N EnglJ Med.* **2020,** 3829(21), 1969.

[7] Speiser, Daniel E., and Martin F. Bachmann. *Vaccines*.**2020**, 8(3), 404.

[8] Poland GA, Ovsyannikova IG, Kennedy RB. *Lancet.***2020**, 396, 1595.

[9] Jiang S. *Nature.* **2020**,579,321.

[10] Li Q, Cao, Rahman P. *Mol Genet Genomic Med.***2020**, 8(8), 1344.

[11] Hassett, K.J., Benenato, K.E., Jacquinet, E., Lee, A., Woods, A., Yuzhakov, O., Himansu, S., Deterling, J., Geilich, B.M., Ketova, T. and Mihai, C. *Mol Ther Nucleic Acids.* **2019,**15, 1.

[12] https://www.nih.gov/newsevents/news-releases/nih-clinical-trial-investigational-vaccinecovid-19-begins. *NIH*. **2020**

[13] https://investors.modernatx.com/newsreleases/news-releasedetails/modernaadvances-late-stage-development-its-vaccine-mrna-1273. *Moderna*. **2020**.

[14] Wu S, Tian C, Liu P, Guo D, Zheng W et al.*J Med Virol.***2020.**

[15] Yang Z-Y, Kong W-P, Huang Y, Roberts A, Murphy BR, Subbarao K, Nabel GJ. *Nature.***2004**, 428(6982), 561.

[16] Amanat F, Krammer F. *Immunity.***2020**, 52, 583.

[17] Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T.S., Herrler, G., Wu, N.H., Nitsche, A. and Müller, M.A., *Cell* **2020**,181(2),271.

[18] Mulligan, M.J., Lyke, K.E., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Neuzil, K., Raabe, V., Bailey, R., Swanson, K.A. and Li, P., *Phase 1/2 study to describe the safety and immunogenicity of a COVID-19 RNA vaccine candidate (BNT162b1) in adults 18 to 55 years of age: interim report.***2020** https://www.medrxiv.org/ content/10.1101/2020.06.30.20142570v1.

[19] Kizzmekia S. Corbett, Darin Edwards, Sarah R. Leist, Olubukola M. Abiona, Seyhan Boyoglu-Barnum, Rebecca A. Gillespie, Sunny Himansu, Alexandra Schäfer, Cynthia T. Ziwawo, Anthony T. DiPiazza, Kenneth H. Dinnon, Sayda M. Elbashir, Christine A. Shaw, Angela Woods, Ethan J. Fritch, David R. Martinez, Kevin W. Bock, Mahnaz Minai, Bianca M. Nagata, Geoffrey B. Hutchinson, Kapil Bahl, Dario Garcia-Dominguez, LingZhi Ma, Isabella Renzi, Wing-Pui Kong, Stephen D. Schmidt, Lingshu Wang, Yi Zhang, Laura J. Stevens, Emily Phung, Lauren A. Chang, Rebecca J. Loomis, Nedim Emil Altaras, Elisabeth Narayanan, Mihir Metkar, Vlad Presnyak, Catherine Liu, Mark K. Louder, Wei Shi, Kwanyee Leung, Eun Sung Yang, Ande West, Kendra L. Gully, Nianshuang Wang, Daniel Wrapp, Nicole A. Doria-Rose, Guillaume Stewart-Jones, Hamilton Bennett, Martha C. Nason, Tracy J. Ruckwardt, Jason S.

McLellan, Mark R. Denison, James D. Chappell, Ian N. Moore, Kaitlyn M. Morabito, John R. Mascola, Ralph S. Baric, Andrea Carfi, View ORCID ProfileBarney S. Graham *SARS-CoV-2 mRNA vaccine development enabled by prototype pathogen preparedness.* **2020.** https://www.biorxiv.org/content/10.1101/2020.06.11.145920v1.

[20] Yu, J., Tostanoski, L.H., Peter, L., Mercado, N.B., McMahan, K., Mahrokhian, S.H., Nkolola, J.P., Liu, J., Li, Z., Chandrashekar, A. and Martinez, D.R., *Science***. 2020**, 369(6505), 806

[21] Smith, T.R., Patel, A., Ramos, S., Elwood, D., Zhu, X., Yan, J., Gary, E.N., Walker, S.N., Schultheis, K., Purwar, M. and Xu, Z. *Immunogenicity of a DNA vaccine candidate for COVID-19. Nat Commun.***2020**,11,2601.

[22] Anderson EJ, Rouphael NJ, Widge AT, Jackson LA, Roberts PC et al. *N Engl J Med.***2020.**

[23] Yu, J., Tostanoski, L.H., Peter, L., Mercado, N.B., McMahan, K., Mahrokhian, S.H., Nkolola, J.P., Liu, J., Li, Z., Chandrashekar, A. and Martinez, D.R., et .*Science*. **2020**, 369(6505), 806.

[24] Gao, Q., Bao, L., Mao, H., Wang, L., Xu, K., Yang, M., Li, Y., Zhu, L., Wang, N., Lv, Z. and Gao, H. *Science* **2020**, 369, 77.

[25] Wang, H., Zhang, Y., Huang, B., Deng, W., Quan, Y., Wang, W., Xu, W., Zhao, Y., Li, N., Zhang, J. and Liang, H. *Cell.***2020,** 182(3), 713.

[26] Chen W-H, Strych U, Hotez PJ, Bottazzi ME. *Curr Trop Med Rep.***2020,** 5.

[27] Zhu, F.C., Li, Y.H., Guan, X.H., Hou, L.H., Wang, W.J., Li, J.X., Wu, S.P., Wang, B.S., Wang, Z., Wang, L. and Jia, S.Y., *Lancet* **2020**,395, 1845.

[28] Neeltje van Doremalen, Teresa Lambe, Alexandra Spencer, Sandra Belij-Rammerstorfer, Jyothi N. Purushotham, Julia R. Port, Victoria Avanzato, Trenton Bushmaker, Amy Flaxman, Marta Ulaszewska, Friederike Feldmann, Elizabeth R. Allen, Hannah Sharpe, Jonathan Schulz, Myndi Holbrook, Atsushi Okumura, Kimberly Meade-White, Lizzette Pérez-Pérez, Cameron Bissett, Ciaran Gilbride, Brandi N. Williamson, Rebecca Rosenke, Dan Long, Alka Ishwarbhai, Reshma Kailath, Louisa Rose, Susan Morris, Claire Powers, Jamie Lovaglio, Patrick W. Hanley, Dana Scott, Greg Saturday, Emmie de Wit, View ORCID ProfileSarah C. Gilbert, View ORCID ProfileVincent J. Munster *ChAdOx1 nCoV-19 vaccination prevents SARS-CoV-2 pneumonia in rhesus macaques.***2020.** https://www.biorxiv.org/content/10.1101/2020.05.13.093195v1.

[29] Yadav, T., Srivastava, N., Mishra, G., Dhama, K., Kumar, S., Puri, B., & Saxena, S. K. *Recombinant vaccines for COVID-19.* **2020**.

[30] Grifoni, A., Weiskopf, D., Ramirez, S.I., Mateus, J., Dan, J.M., Moderbacher, C.R., Rawlings, S.A., Sutherland, A., Premkumar, L., Jadi, R.S. and Marrama, D.. *Cell***. 2020**,181(7), 1489.

[31] Peng, Y., Mentzer, A.J., Liu, G., Yao, X., Yin, Z., Dong, D., Dejnirattisai, W., Rostron, T., Supasa, P., Liu, C. and Lopez-Camacho, C., *Nat Immunol*. **2020,** 21(11), 1336.

[32] Smith, T.R., Patel, A., Ramos, S., Elwood, D., Zhu, X., Yan, J., Gary, E.N., Walker, S.N., Schultheis, K., Purwar, M. and Xu, Z. *Nat Commun.* **2020**, 11(1), 1.

[33] Donaldson MM, Kao S-F, Foulds KE. *Cytometry A***. 2019**,95, 261.

[34] Finak, G., McDavid, A., Chattopadhyay, P., Dominguez, M., De Rosa, S., Roederer, M. and Gottardo, R., *Biostatistics*. **2014**,15, 87.

[35] Munster, Friederike Feldmann, Brandi N. Williamson, Neeltje van Doremalen, Lizzette Pérez-Pérez, Jonathan Schulz, Kimberly Meade-White, Atsushi Okumura, Julie Callison, Beniah Brumbaugh, Victoria A. Avanzato, Rebecca Rosenke, Patrick W. Hanley, Greg Saturday, Dana Scott, Elizabeth R. Fischer, Emmie de Wit *Respiratory disease and virus shedding in rhesus macaques inoculated with SARS-CoV-2.* **2020.** https://www.biorxiv.org/content/10.1101/2020.03.21.001628v1

[36] Pallesen, J., Wang, N., Corbett, K.S., Wrapp, D., Kirchdoerfer, R.N., Turner, H.L., Cottrell, C.A., Becker, M.M., Wang, L., Shi, W. and Kong, W.P., *Proc Natl Acad Sci U S A.* **2017,** 114.

[37] Wang W, Wang H, Deng Y, et al. *Emerg Microbes Infect.***2016**,5(11),113.

[38] Widjaja, I., Wang, C., van Haperen, R., Gutiérrez-Álvarez, J., van Dieren, B., Okba, N.M., Raj, V.S., Li, W., Fernandez-Delgado, R., Grosveld, F. and van Kuppeveld, F.J. *Emerg Microbes Infect*. **2019**,8, 516.

[39] Weiskopf D, Schmitz KS, Raadsen MP, et al. *Sci Immunol*.**2020**, 5, 2071.

[40] Wrapp, D., Wang, N., Corbett, K.S., Goldsmith, J.A., Hsieh, C.L., Abiona, O., Graham, B.S. and McLellan, J.S. *Science* **2020**,367, 1260.

[41] Neidleman, J., Luo, X., Frouard, J., Xie, G., Gill, G., Stein, E.S., McGregor, M., Ma, T., George, A.F., Kosters, A. and Greene, W.C. *bioRxiv*. **2020**

[42] Wang, L., Shi, W., Chappell, J.D., Joyce, M.G., Zhang, Y., Kanekiyo, M., Becker, M.M., van Doremalen, N., Fischer, R., Wang, N. and Corbett, K.S. *J Virol.* **2018**,92(10), 2002.

[43] Wang, N., Rosen, O., Wang, L., Turner, H.L., Stevens, L.J., Corbett, K.S., Bowman, C.A., Pallesen, J., Shi, W., Zhang, Y. and Leung, K., *Cell Rep*.**2019**,28(13),3395.

[44] Sekine, T., Perez-Potti, A., Rivera-Ballesteros, O., Strålin, K., Gorin, J.B., Olsson, A., Llewellyn-Lacey, S., Kamal, H., Bogdanovic, G., Muschiol, S. and Wullimann, D.J. **2020,** 183(1), 158.

[45] Meckiff, B.J., Ramírez-Suástegui, C., Fajardo, V., Chee, S.J., Kusnadi, A., Simon, H., Grifoni, A., Pelosi, E., Weiskopf, D., Sette, A. and Ay, F., *Single-cell transcriptomic analysis of SARS-CoV-2 reactive CD4 + T cells*. **2020** Available at SSRN 3641939.

[46] Polack, F.P., Thomas, S.J., Kitchin, N., Absalon, J., Gurtman, A., Lockhart, S., Perez, J.L., Pérez Marc, G., Moreira, E.D., Zerbini, C. and Bailey, R. *N Engl J Med*. **2020**, 383(27), 2603

[47] Liu MA. *Vaccines (Basel).***2019**, 7(2), 37.

[48] Jackson, L.A., Anderson, E.J., Rouphael, N.G., Roberts, P.C., Makhene, M., Coler, R.N., McCullough, M.P., Chappell, J.D., Denison, M.R., Stevens, L.J. and Pruijssers, A.J. *N Engl J Med.***2020.**

[49] BMJ **2020**, 371, 4826.http://dx.doi.org/10.1136/bmj.m4826. 11 December **2020**

[50] Bahl, K., Senn, J.J., Yuzhakov, O., Bulychev, A., Brito, L.A., Hassett, K.J., Laska, M.E., Smith, M., Almarsson, Ö., Thompson, J. and Ribeiro, A.M., *Mol Ther*. **2017**,25, 1316.

[51] Morais, I.J., Polveiro, R.C., Souza, G.M., Bortolin, D.I., Sassaki, F.T. and Lima, A.T.M., *Nature Research.* **2020**, 10(1), 1.

[52] Mishra SK, Tripathi Y.Acta *Trop.* **2021.**

[53] Jackson, L. A., Anderson, E. J., Rouphael, N. G., Roberts, P. C., Makhene, M., Coler, R. N., Beigel, J. H. *N Engl J Med*. **2020.**

[54] Folegatti, P.M., Ewer, K.J., Aley, P.K., Angus, B., Becker, S., Belij-Rammerstorfer, S., Bellamy, D., Bibi, S., Bittaye, M., Clutterbuck, E.A. and Dold, C. *Lancet.***2020,** 396(10249), 467.

[55] *Evaluation of the Moderna, Pfizer/BioNtech, Astrazeneca/Oxford and Sputnik V Vaccines for COVID-19-Joseph Angel de Soto1-School of Science, Technology, Engineering and Math, Dine College, Tsaile AZ* 86566.

[56] Ardo N., et al. *Nature Reviews drug discovery* **2018,** 17, 264**.**

[57] https://www.bbc.com/news/health-55041371

[58] Mullard, Asher. *Lancet.***2020**, 395(10239), 1751.

[59] https://www.ox.ac.uk/news/**2020**-11-23-oxford-university-breakthrough-global-covid-19-vaccine

[60] Mahase, Elisabeth.*Bmj.* **2021**,372.

[61] Destefano F, Offit PA, Fisher A. *Vaccine Safety. Plotkin's Vaccines.***2018,** 1584.

[62] Mahase, Elisabeth.*Bmj.* **2021**,372.

[63] Folegatti, P.M., Ewer, K.J., Aley, P.K., Angus, B., Becker, S., Belij-Rammerstorfer, S., Bellamy, D., Bibi, S., Bittaye, M., Clutterbuck, E.A. and Dold, C., *The Lancet*, 396(10249) **2020**, 467.

[64] https://www.ox.ac.uk/news/**2020**-12-08-first-peer-reviewed-results-phase-3-human-trials-oxford-coronavirus-vaccine

[65] https://www.ox.ac.uk/news/**2020**-11-19-oxford-coronavirus-vaccine-produces-strong-immune-response-older-adults

[66] Mahase, Elisabeth. *"Covid-19: UK approves Oxford vaccine as cases of new variant surge."***2020**.

[67] Mahase, Elisabeth. *"Covid-19: Oxford team begins vaccine trials in Brazil and South Africa to determine efficacy."***2020**.

[68] Mahase, Elisabeth. *"Covid-19: Oxford vaccine could be 59% effective against asymptomatic infections, analysis shows."* **2020**.

[69] Mahase, Elisabeth. *"Covid-19: Oxford vaccine is up to 90% effective, interim analysis indicates."* **2020**.

[70] Mahase, Elisabeth. *"Covid-19: Oxford researchers halt vaccine trial while adverse reaction is investigated."* **2020**.

[71] Freeman, D., Waite, F., Rosebrock, L., Petit, A., Causier, C., East, A., Jenner, L., Teale, A.L., Carr, L., Mulhall, S. and Bold, E. *Psychological medicine*. **2020**, 1.

[72] Bordon, Yvonne. *Nature Reviews Immunology*. **2021**.

[73] Iacobucci, Gareth, and Elisabeth Mahase. "*Covid-19 vaccination: What's the evidence for extending the dosing interval?."* **2021**.