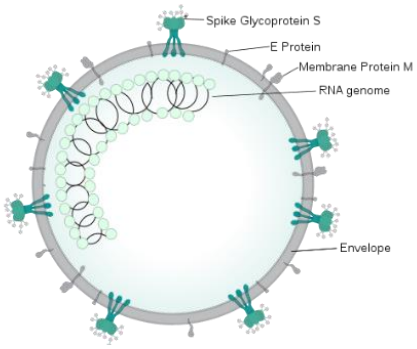
Outline:

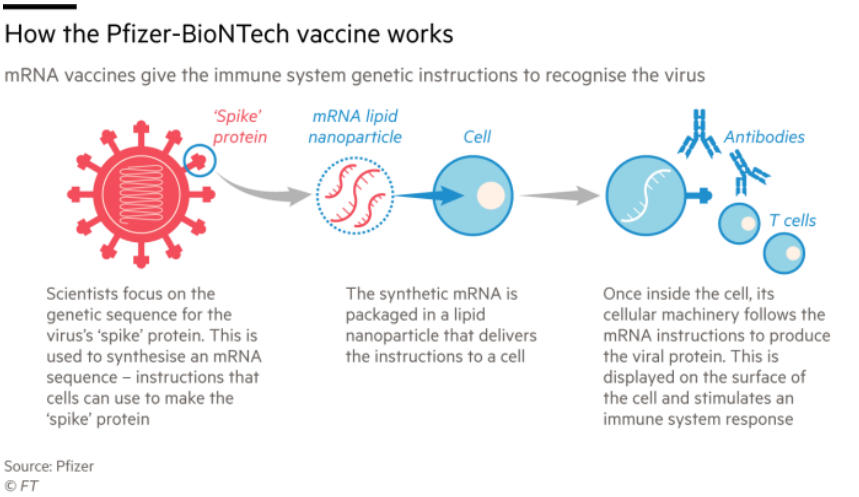
1. **How does the vaccine work?**
2. **Is the vaccine efficacious?**
3. **Is the vaccine safe?**
4. **Conclusions**
5. **FAQ**



Structural Protein	Function of Protein
Nucleocapsid Protein (N)	• Bound to RNA genome to make up nucleocapsid
Spike Protein (S)	• Critical for binding of host cell receptors to facilitate entry of host cell
Envelope Protein (E)	• Interacts with M to form viral envelope
Membrane Protein (M)	• Central organiser of CoV assembly • Determines shape of viral envelope

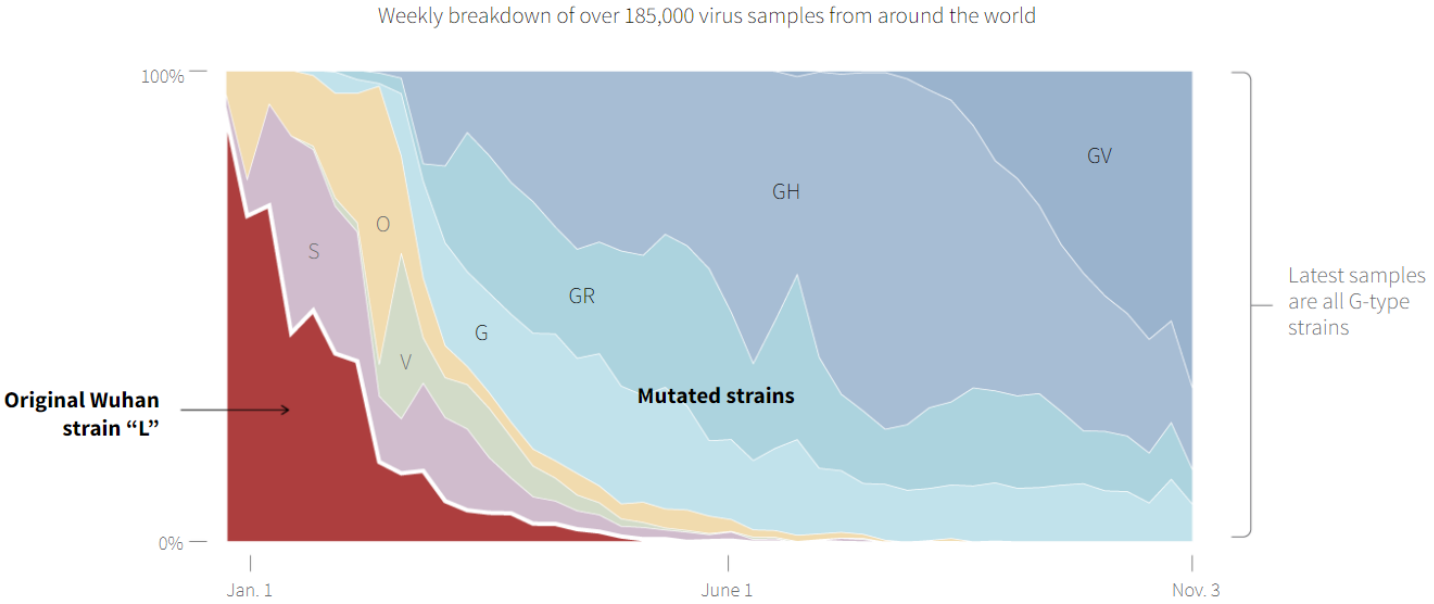
<u>How does the vaccine work?</u>

- Brief review of coronavirus structure and function: Enveloped +ssRNA viruses. Spike protein functions in receptor binding and cell entry. The host receptor for SARS-CoV-2 cell entry is angiotensin-converting enzyme 2 (ACE2).
- The Pfizer vaccine (BNT162b2) is an mRNA vaccine that expresses the full-length spike protein and thus stimulates adaptive humoral and cell-mediated immune response.

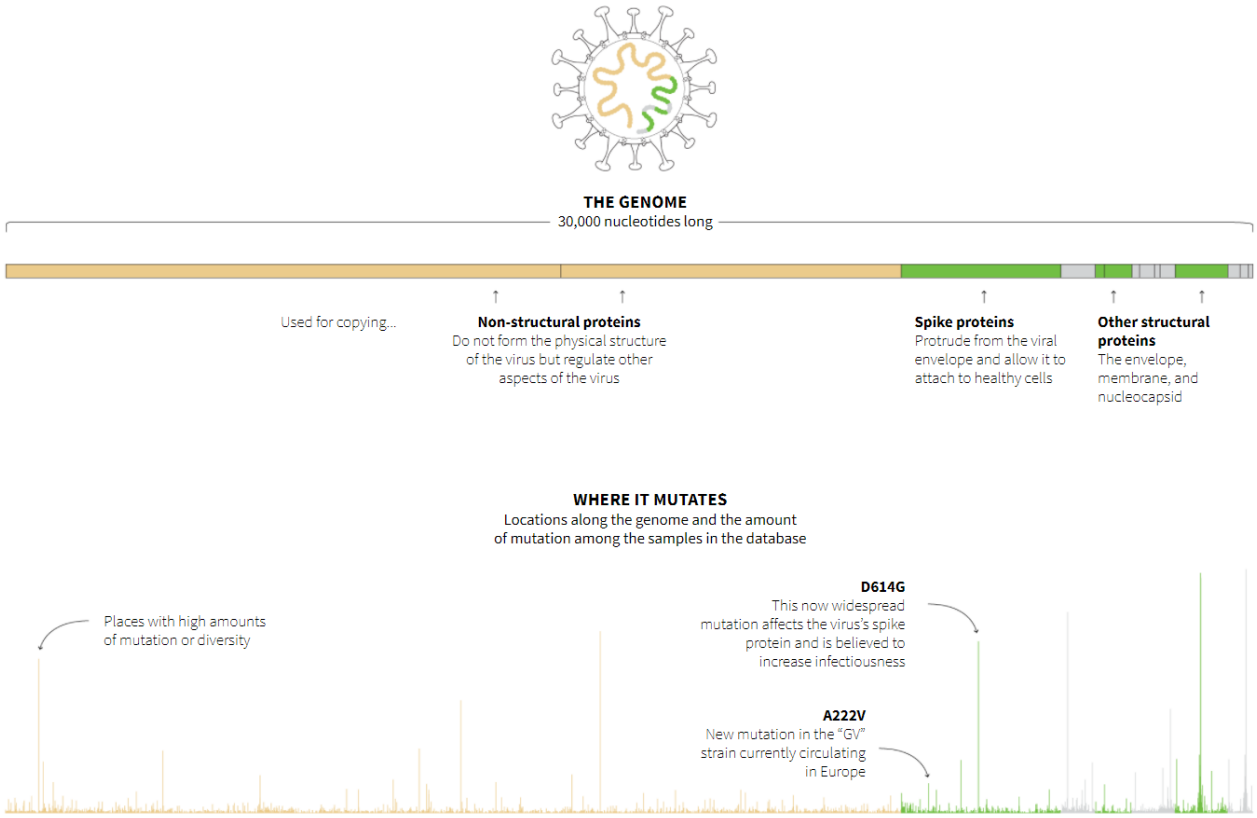


<u>Is the vaccine efficacious?</u>

1. **Yes**. To answer this question, we must first address the various mutations that have resulted in the five predominant strains of SARS-CoV-2. (I'm sure some virologists will argue that clade is more accurate term than strain for these variants, but let's just keep it simple).



2. In brief, the original virus from Wuhan called the L strain (for the amino acid aspartic acid at position D614) mutated into several new strains, most notable of which are the G strains (containing glutamic acid at position G614).[1] There are various plausible theories as to which strains are more infectious or virulent, but that is beyond the scope of this article. Since 6/1/2020, G strains have been the predominant variant causing COVID-19. This is relevant because the Pfizer trial ran during the months of August through November, and thus



efficacy should most accurately be interpreted in response to G strain variants. Of note, although the D614G mutation occurred within the spike protein domain, as illustrated above, this mutation does not appear to impinge on the receptor binding domain. In other words, the Pfizer vaccine is likely equally efficacious against all strains of the virus.

3. Summary of Pfizer's Phase III trial for the age 18-55 demographic:
    a. Approximately 44,000 subjects were enrolled in an observer blinded RTC and divided into a vaccination arm and placebo arm.[2] In brief, the primary end point of the study was development of COVID-19 infection starting 7d after the 2nd dose of vaccine in subjects who previously were negative by RT-PCR testing. The secondary end point was development of COVID-19 infection 7d after the 2nd dose of vaccine in subjects who never had symptoms.
    b. Both end points demonstrated **95% efficacy**.
        i. For the primary end point, 8 subjects in the vaccinated arm later contracted COVID-19 compared to 162 subjects in the placebo arm.
        ii. For the secondary end point, 9 subjects in the vaccinated arm later contracted COVID-19 compared to 169 subjects in the placebo arm.
        iii. One likely explanation for the greater number of subjects who met criteria by secondary end point is because of false negative RT-PCR test results.
    c. Out of about 1,300 subjects with known prior COVID-19 infection, only 1 subject in the vaccinated arm got reinfected compared to 10 subjects in the unvaccinated arm.

<u>Is the vaccine safe?</u>

1. **Yes**. Data was collected for about 2mo after administration of the 2nd dose and analyzed for side effects, serious adverse events, and death. In the 18-55 age group:
    a. There were **zero vaccine related deaths**.
    b. There was practically **only one serious adverse event related to vaccination**. This was notable lymphadenopathy in the axilla contralateral to the side of injection and considered related by the FDA because of the timing of the event and a plausible mechanism.[3] The other "serious adverse event" related to vaccination was a shoulder injury likely from the needle itself.

c. Solicited side effects include fatigue, headache, myalgia, arthralgia, fever, chills, n/v/d all of which were found to be present in about 3% more subjects in the vaccination arm than the placebo arm. However, the median duration of these side effects was one day. So, it's pretty much the same as a regular flu shot and a moot point.
d. The only unsolicited side effects (arguably more important than solicited) that occurred more frequently in the vaccination group was mild lymphadenopathy. There were 54 subjects in the vaccine arm compared to 6 subjects in the placebo arm who experienced this. The median duration of this side effect was 10d. So again, kind of a moot point.
e. Of note, 4 subjects in the vaccination arm developed Bell's palsy compared to none in the placebo arm. However, 4 out of 22,000 subjects is equal to the baseline incidence of Bell's palsy in the general population. One of the subjects had symptoms resolve within 3 days. The remaining three subjects still had ongoing symptoms when the trial results were analyzed. As you know, with glucocorticoid treatment, Bell's palsy has an excellent prognosis with 85% of patients achieving complete recovery in 3-6mo. It is unclear if vaccination has any causational relationship with Bell's palsy at this time, though it seems less likely and fortunately this is a treatable condition.

FAQ

1. Does true reinfection occur?
    a. **Yes**. For example, in one well documented case, a 33yo M was symptomatic and had confirmed infection by RT-PCR testing on 3/26/2020. After a 2wk hospital course he was d/c'd w/ 2 neg RT-PCR tests drawn 24hrs apart from nasopharynx and throat swab. About 5mo later on 8/15/2020 he was asymptomatic but tested positive during airport screening by RT-PCR and sent directly to the hospital where he had an unremarkable course. Whole genome sequencing was conducted on samples from both hospitalizations. The first infection was due to a V strain of the virus and the second infection was due to a G strain of the virus. There is further evidence supporting this event as true reinfection such as seroconversion of IgG during the second episode, however this is beyond the scope of this article.[4]
    b. Several other case reports document similar instances of reinfection with a genetically distinct strain of virus. In one case, a healthy 25yo M was asymptomatic during the first infection and required hospitalization for severe symptoms during the second infection.[5] In another case, an immunocompromised 89yo F was hospitalized during the initial infection and died from the second.[6] Again, convincing data including IgM and IgG titers as well as negative RT-PCR tests support the conclusion of true reinfection but are beyond the scope of this article.
2. Does the vaccine offer protection if I was previously infected?
    a. **Yes**. As described above, there was lower incidence of reinfection in the vaccinated group than the placebo group. Furthermore, the ever-mutating strains of virus offer a logical mechanism which by which this may occur.
3. Does the vaccine confer long-term protection?
    a. **Most likely**. To answer this question, we must first address if an infection confers long-term protection. Several studies have shown variable adaptive immunity (humoral and cell-mediated) responses among patients.[7,8] In addition, there appears to be significant waning antibody response over several months after infection.[9,10] Thus far, reinfection with the exact same strain of virus has not yet been demonstrated, but this is more likely a reflection of insufficient resources for whole genome sequencing of every patient than a commentary on lasting immunity. If infection by the virus provides lasting immunity against that exact same strain, then most likely a vaccine would provide the same immunity. There is as yet insufficient data for a meaningful answer.
4. Can you get COVID-19 from the vaccine?
    a. **No**. The Pfizer vaccine is not a live attenuated vaccine.

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Link to NEJM paper for the Pfizer trial: https://www.nejm.org/doi/full/10.1056/NEJMoa2034577

Link to FDA paper: https://www.fda.gov/media/144245/download

Link to Reuter's graphic: https://graphics.reuters.com/HEALTH-CORONAVIRUS/EVOLUTION/yxmpjqkdzvr/

Disclosures: None