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Theoretical novel COVID-19 vaccination risk of rare and severe adverse events versus COVID-19 mortality

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ABSTRACT
COVID-19 continues pandemic and researchers and companies are racing to develop effective vaccines with currently (September 2020) over 320 vaccine candidates, 32 of which are in clinical trials that plan to enroll >280,000 volunteers from >470 sites in 34 different countries. Vaccines are given to healthy multitudes and for this reason, they must adhere to high safety standards. Many question the safety of vaccines developed with the current alacrity, commonly citing potential hypothetical and unknown (and indeed unknowable) side effects. This brief paper will outline the risk of such hypothetical events after a vaccine has gone through the appropriate testing phases and will compare this to estimated death rate from COVID-19 after factoring in asymptomatic cases, using a variety of scenarios and working with estimates of population, case and infection fatality ratios (analysed as Population Fatality Rate, Infection Fatality Ratio and Case Fatality Ratio). Even after factoring in up to 80% of individuals testing positive COVID-19 being asymptomatic, an effective vaccine that completes phase 3 trials having been administered to 20,000 individuals with very few (<2) or no serious effects is well worth taking.

1. Introduction

The world remains in thrall to COVID-19 and is likely to remain so until the availability of an effective vaccine and/or treatment. Researchers and companies are racing to develop effective vaccines with currently (September 2020) over 320 vaccine candidates, 32 of which are in clinical trials that plan to enroll >280,000 volunteers from >470 sites in 34 different countries [1]. These vaccines are of various types, including attenuated or inactivated forms, nucleic-acid, viral-vector (replicating or non-replicating) and protein-based vaccines (protein subunits or virus-like particles) [2].

Vaccines are given to healthy multitudes and for this reason, their development usually takes years of testing since they must adhere to higher safety standards than other pharmaceuticals [1]. However, due to the potential for large scale pandemic morbidity and mortality, successful COVID-19 vaccines are likely to be widely available within 12 to 18 months of the initial onset of this pandemic, i.e. mid-2021 [3]. Many question the safety of vaccines developed with such alacrity, commonly citing potential hypothetical and unknown (and indeed unknowable) side effects, including rare and serious adverse events up to and including death – a possibility especially if vaccines are not tested rigorously [4]. This brief paper will outline the risk of such hypothetical events after a vaccine has gone through the appropriate testing phases and will compare this to estimated death rate from COVID-19 after factoring in asymptomatic cases, using a variety of scenarios and working with estimates of population, case and infection fatality ratios.

2. Vaccine testing phases

It is salutary to briefly describe vaccine testing phases: [5].

- Pre-clinical stage: animals are tested with a vaccine candidates to check for the elicitation of an immune response. This is followed by three phases of clinical tests.
- Phase 1: A small group of volunteers are vaccinated in order to determine safety and the nature of the immune response provoked.
- Phase 2: Several hundred volunteers are vaccinated to confirm safety and determine optimum dosages.
- Phase 3: Thousands of volunteers are enrolled to further confirm vaccine safety including the potential to elicit rare side effects and further delineate vaccine effectiveness. These trials include a control group which is administered a placebo. Volunteers are not deliberately or intentionally exposed to the disease but the vaccine is administered to cohorts from locations with a high incidence of the disease, allowing an eventual comparison between infection frequency rates and disease severity in the vaccine and placebo groups.

3. AstraZeneca’s AZD1222 Phase 3

For example, phase 3 of AstraZeneca’s COVID-19 vaccine candidate (AZD1222) has commenced in the United States. This is a multi-site clinical trial that will enroll approximately 30,000 adult volunteers at 80 sites as part of a multi-agency collaboration led by the United States Department of Health & Human Services. This endeavor aims to accelerate the

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development, manufacturing and distribution of COVID-19 medical countermeasures [6]. AZD1222 utilises a non-replicating chimpanzee adenovirus to deliver a SARS-CoV-2 spike protein in order to induce an immune response, and is administered as two injections four weeks apart. The ratio of placebo to vaccine is 1:2 such that 20,000 volunteers will receive the investigational vaccine and 10,000 will receive a placebo [7].

The trial is designed to determine whether two doses of AZD1222 can prevent symptomatic COVID-19, prevent severe COVID-19 and reduce COVID-19-related incidence of emergency department visits [7]. The volunteers will be monitored for safety and reactogenicity i.e. typical short-term side effects such as fever, soreness at the site of the vaccine etc. Participants will be asked to record any symptoms and an independent Data and Safety Monitoring Board will provide oversight to ensure the safe and ethical conduct of the study. It is also planned that participants will continue to be followed for two years post vaccination and will be asked to provide blood samples periodically to further determine immune responses [7].

4. Risk of rare and serious side effects

It may be argued that a rare and serious side effect might potentially be missed if “only” 20,000 volunteers are vaccinated with 40,000 doses. This implies a negative individual rate of 0/20,000, a zero numerator. A rate like this cannot have a lower confidence interval but an upper confidence interval can be quite simply calculated using the formula $\frac{3}{n}$, the Poisson approximation [8], as previously described and set up in Microsoft Excel in this journal [9]. For very small proportions, confidence intervals can be calculated using the equations of Fliess as shown in Fig. 1 [10]. Table 1 shows the rate, percentage and upper 95% confidence intervals where 0, 1 or 2 hypothetical, rare and serious events were to occur (e.g. transverse myelitis).

5. Estimated COVID-19 mortality

The estimates in this analysis only consider risk of death and do not include the potentially important consequences of COVID-19 sequela such as “long COVID” or the complications related to treatment [11,12]. Risk of death from COVID can be estimated as Population Fatality Rate, Infection Fatality Ratio and Case Fatality Ratio [11].

5.1. Population Fatality Rate

PFR is the risk of death from COVID-19 in the general and uninfected population. This is influenced by public health measures (and adherence thereto) and duration of potential exposure.

For Italy, as of May 92,020, it was estimated that PFR had reached 0.26% in the most affected region of Lombardy and 0.58% in the most affected province of Bergamo [13]. For the United Kingdom, for the five weeks leading up to 1st May 2020, the overall PFR was 0.06 (Table 2) [11]. The following table has been slightly modified from source with an additional second part wherein excess deaths (i.e. deaths over and above the expected number of deaths expected per week based on mortality in previous years) are included in the calculation instead of only COVID deaths, to circumvent any potential bias that may have been introduced through the labelling of deaths as being COVID deaths [14]. Indeed, this percentage of deaths is higher than that identified by Spiegelhalter using COVID-certified deaths [11].

5.2. Case Fatality Ratio

CFR estimates the proportion of deaths in total diagnosed cases. This value is naturally dependent on the swabbing rate and varies widely between countries, ranging from an average of 0.2% in Germany to 7.7% in Italy, and this also varies with age, a factor which will not be entertained in these estimates [15]. These CFRs are not necessarily accurate comparisons of the true likelihood of death following infection with COVID-19 as asymptomatic and undiagnosed cases naturally not included. Indeed, it was initially recognized that anything between 5%–80% of individuals testing positive COVID-19 may be asymptomatic [16], and while the exact value remains uncertain, for the purposes of this paper and the calculations hereunder, asymptomatic cases are individually estimated at rates of 50, 60, 70 and 80%.

5.3. Infection Fatality Ratio

IFR estimates the proportion of deaths in all infected individuals. Table 3 calculates percentage of deaths from all infections with 50, 60, 70 and 80 (%) asymptomatic cases, assuming all symptomatic are diagnosed and with CFR as noted above at

$$\text{Upper CI} = \frac{(2np + z^2 + 1) + z\sqrt{z^2 + (2 - \frac{1}{n}) + 4p(nq - 1)}}{2(n + z^2)}$$

$$\text{Lower CI} = \frac{(2np + z^2 - 1) - z\sqrt{z^2 - (2 + \frac{1}{n}) + 4p(nq + 1)}}{2(n + z^2)}$$

Fig. 1. Calculation of upper and lower confidence intervals for a very small or very large proportion [10].

| Age | COVID deaths | Population | COVID death rate per 100,000 | COVID death rate as % |
|-----|--------------|------------|-----------------------------|----------------------|
| 0–14 | 2 | 10,674,532 | 0 | 0 |
| 15–24 | 25 | 6,988,755 | 0.4 | 0.0054 |
| 25–44 | 348 | 15,459,158 | 2.3 | 0.015 |
| 45–64 | 3455 | 15,162,118 | 22.8 | 0.154 |
| 65–74 | 5166 | 5,906,928 | 87.5 | 0.77 |
| 75–90 | 17,218 | 3,995,259 | 391.7 | 3.91 |
| 90– | 6504 | 528,959 | 1229.6 | 12.29 |
| All | 32,718 | 59,115,809 | 55.3 | 0.55 |
| All ages | COVID deaths | Population | COVID death rate per 100,000 | COVID death rate as % |
| England and Wales | 51,501 | 59,115,809 | 87.1 | 0.87 |
| Britain | 56,577 | 66,796,807 | 84.7 | 0.85 |
| Rate/1000 | % Upper CI/1000 | % |
| 0 | 20,000 | 0 | 0 | 0.00015 | 0.015 |
| 1 | 20,000 | 0.05 | 0.005 | 0.32 | 0.032 |
| 2 | 20,000 | 0.10 | 0.01 | 0.40 | 0.040 |

Table 1

Rate, percentage and upper 95% confidence intervals where 0, 1 or 2 hypothetical, rare and serious events were to occur.

Table 2

Top half: deaths registered in the five weeks of the peak of the epidemic. Modified from Spiegelhalter [11]. Bottom part of table: same calculations based on excess deaths obtained from the Economist github data [14].

| Age | COVID deaths | Population | COVID death rate per 100,000 | COVID death rate as % |
|-----|--------------|------------|-----------------------------|----------------------|
| 0–14 | 2 | 10,674,532 | 0 | 0 |
| 15–24 | 25 | 6,988,755 | 0.4 | 0.0054 |
| 25–44 | 348 | 15,459,158 | 2.3 | 0.015 |
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| Rate/1000 | % Upper CI/1000 | % |
| 0 | 20,000 | 0 | 0 | 0.00015 | 0.015 |
| 1 | 20,000 | 0.05 | 0.005 | 0.32 | 0.032 |
| 2 | 20,000 | 0.10 | 0.01 | 0.40 | 0.040 |
0.2 and 7.7% as well as the midpoint value of 3.95%. The best case scenario is 0.04% mortality.

6. Discussion

PFR in localities which suffered a high infection rate (0.58% for Bergamo) or even lower but important levels of infection rates (0.06% for the UK) clearly had deaths well in excess of the estimated 0.015% estimated risk of severe (potentially even fatal) rare events that might arise from a novel vaccine based on a zero rate of such events after vaccinating 20,000 volunteers in phase 3 trials. Even if two hypothetical rare and serious side effects were to occur, the upper 95% confidence interval for this estimate is still favourable at 0.04%.

CPR ranges of 0.2% (Germany) to 7.7% (Italy) also greatly exceed 0.015%. With regard to IFR, even an estimated theoretical best case scenario of 0.04% mortality, factoring in an 80% asymptomatic rate, is 2.7 times the vaccination value. This is equivalent to the upper 95% confidence interval value in the case were there occur two hypothetical rare and serious side effects at 0.04%.

This study has not factored in two further crucial issues. The first is in that the longer the virus circulates, in the absence of herd immunity, despite precautions, it will continue to inflict morbidity and mortality. The American epidemiologist Michael Osterholm stated this quite simply: “We weren’t sure what this coronavirus would do because we’ve never witnessed a pandemic of a coronavirus before. Now we know it’s kind of a super forest fire. It just keeps burning and burning and burning wherever there is human wood.” [17]

The second important issue is that of the disease sequelae, most notably “long/longhaul COVID”, a novel term that describes lasting illness in patients who have either recovered from COVID-19 but still experience chronic symptoms or who have had symptoms for longer than expected. Up to 90% of symptomatic patients may go through this, with 90%, 32% and 55% still experiencing at least one, two, or three or more symptoms respectively 60 days after onset. These symptoms include fatigue (53%), dyspnoea (43%), joint pains (27%), and chest pains (22%) [18]. It has been estimated that the healthcare financial impact for these patients is equivalent to that of elderly patients with severe chronic diseases [19], with enormous public health implications particularly pertaining to younger and previously health individuals who, despite lacking significant comorbidities, fail to return to their baseline functional status [20].

7. Conclusion

“The public health community wants a safe and effective [COVID-19] vaccine as much as anybody could want it. But the data have to be clear and compelling.” [21] An effective vaccine that completes phase 3 trials having been administered to 20,000 individuals with very few or no serious effects is well worth taking.

Declaration of competing interest

The authors have no conflict of interest to declare.

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