Review

Comparative Benefits and Risks Associated with Currently Authorized COVID-19 Vaccines

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Abstract: This article provides a systematic assessment of the efficacy, risks, and methodological quality of evidence from five major publicly available vaccine trials. Results from Pfizer-BioNTech mRNA, Moderna-US NIH mRN-1273, AstraZeneca-Oxford ChAdOx1 nCov-19, Gamaleya GamCovidVac (Sputnik V), and Ad26.COV2.S Johnson & Johnson vaccines were included. Extracted benefits and risks data from each trial were summarized using the GRADE approach denoting the overall certainty of evidence along with relative and absolute effects. Relative risk reduction across all five vaccine trials ranged from 45% to 96%. Absolute risk reduction in symptomatic COVID-19 ranged from 6 to 17 per 1000 across trials. None of the vaccines were associated with a significant increase in serious adverse events compared to placebo. The overall certainty of evidence varied from low to moderate. All five vaccines are effective and safe, but suggest room for improvement in the conduct of large-scale vaccine trials. Certainty of evidence was downrated due to risk of bias, which can be mitigated by improving transparency and thoroughness in conduct and reporting of outcomes.

Keywords: COVID; vaccines; grade; evidence; transparency

1. Introduction

Several public health strategies, such as mask mandates, isolation, social distancing, and contact tracing, aimed at reducing transmission have been insufficient to stop the global rise of COVID-19 [1]. A widely available vaccine has been suggested as the most effective method to prevent the rapid spread of infections. At present, 50 COVID-19 vaccines have reached the final stages of clinical trial testing in humans [2]. First to emerge publicly, the clinical trial results from five major vaccines have been published outlining their efficacy and safety: Pfizer-BioNTech BNT162b2 mRNA vaccine [3], Moderna-US National Institute of Health (NIH) mRN-1273 vaccine [4], Johnson & Johnson (J&J) Ad26.COV2.S vaccines [5], AstraZeneca-Oxford ChAdOx1 nCov-19 vaccine [6], and Gamaleya GamCovidVac (Sputnik V) vaccine [7]; Pfizer, Moderna, J&J, AstraZeneca, Sputnik, respectively. Of these, Pfizer was the first to be granted full FDA approval in the United States [8]. Despite wide dissemination of the benefits of these vaccines, 76% of the United States and less than 63.5% of the global population are currently vaccinated [9–12].

Multiple factors have attributed to low vaccination rates globally. In the United States, vaccine hesitancy remains a major issue despite widespread availability and free access. One contributing factor may be the lack of comparative information related to benefits and risks associated with various vaccines. Specifically, reliable evidence related to the efficacy of all COVID-19 vaccines is critical for all stakeholders, including patients, physicians, healthcare workers, and policymakers. Furthermore, accurate interpretation
of this evidence is required to make effective personal and public health decisions regarding a COVID-19 vaccine. Unfortunately, misinterpretation and misrepresentation of clinical trial data have been a common occurrence [13,14]. It is imperative that the benefits and risks associated with available vaccines be communicated transparently and concisely to allow for informed choices. The goal of this paper is to provide a systematic assessment of the risks, efficacy, and methodological quality of evidence from five major vaccine trials in a format that may be used as a tool to facilitate informed decision making for all stakeholders involved in the COVID-19 vaccination efforts.

2. Materials and Methods

We compiled the interim results of five COVID-19 vaccine studies published in scientific journals and that are currently globally distributed: Pfizer-BioNTech BNT162b2 mRNA vaccine [3], Moderna-US National Institute of Health (NIH) mRN-1273 vaccine [4], AstraZeneca-Oxford ChAdOx1 nCov-19 vaccine [5], Gamaleya GamCovidVac (Sputnik V) vaccine [7], and Johnson & Johnson (J&J) Ad26.COV2.S vaccines [5]. In addition to the published reports, FDA briefing documents were referenced for the Pfizer, Moderna, and J&J vaccines. Metrics of efficacy and adverse events were selected based on saliency and homogeneity of criteria definition across trials. Data on benefits and risks associated with each vaccine were extracted from these reports. The efficacy endpoints were incidence of symptomatic COVID-19 cases, severe COVID-19 cases, mortality due to COVID-19, and all-cause mortality. Adverse events included any serious adverse events due to vaccination and any related unsolicited adverse events due to vaccination defined according to each study’s criteria.

The abstracted benefits and risks data from each trial were summarized using the GRADE approach denoting the relative and absolute effects along with the overall methodological quality of evidence associated with each outcome [15]. All analyses for the desirable outcomes (i.e., benefits) were performed using the intention to treat principle (ITT). All adverse events were analyzed using a per-protocol (PP) approach.

3. Results

The trial and participant characteristics for five vaccines are reported in the supplementary document. Briefly, all five studies were randomized controlled trials (RCT) and enrolled between 15,210 to 44,325 subjects. Further summary of trial characteristics is provided in Appendix A. Vaccine, Trial, and Participant Characteristics

Outcomes:
Sputnik (ITT population = 21,977 participants)
Assessment of COVID-19 Positivity
Symptomatic COVID-19 was defined as a positive PCR test in addition to clinical signs of respiratory infection. Seventy-nine (0.5%) participants in the vaccine arm and ninety-six (1.8%) in the placebo arm reported symptomatic COVID-19 (relative risk [RR] 0.27; 95% confidence intervals [CI] 0.20–0.37; Supplemental Figure S1a). The overall certainty of evidence was moderate (Supplemental Table S1).

Symptomatic COVID-19 After Effective Period
The effective period for the Sputnik vaccine was 21 days after the first immunization. Sixteen cases (0.1%) in the vaccine arm and sixty-two (1.1%) in the placebo arm were reported after the effective period (RR 0.09; 95% CI 0.05–0.15; Supplemental Figure S1b). The overall certainty of evidence was moderate (Supplemental Table S1).

Severe COVID-19 Cases After Effective Period
Severe COVID-19 cases were reported combined with moderate COVID-19 cases for all participants who received both injections. Zero (0.0%) participants in the vaccine arm contracted moderate-severe COVID-19 compared to twenty (0.4%) in the placebo arm (RR 0.01; 95% CI 0.00–0.13; Supplemental Figure S1c). The overall certainty of the evidence was moderate (Supplemental Table S1).

COVID-19-Related Mortality
Two (0.01%) deaths in the vaccine arm and zero (0.0%) deaths in the placebo arm were reported (RR 1.16; 95% CI 0.08–34.56; Supplemental Figure S2a). Both participants who died displayed symptoms within 5 days of their first vaccination and had significant comorbidities. The overall certainty of the evidence was low (Supplemental Table S1).

All-Cause Mortality
Three (0.02%) participants in the vaccine arm and one (0.02%) participant in the placebo arm died throughout the trial (RR 1.00; 95% CI 0.10–9.57; Supplemental Figure S2b). The overall certainty of the evidence was low (Supplemental Table S1).

Any Serious Adverse Events
Serious adverse events were any reaction that required hospital admission. Forty-three (0.3%) of participants in the vaccine arm and twelve (0.2%) in the placebo arm reported serious adverse events (RR 1.19; 95% CI 0.63–2.25; Supplemental Figure S3a). The overall certainty of the evidence was low (Supplemental Table S1).

Related Unsolicited Serious Adverse Events
An independent data monitoring committee (IDMC) determined whether serious adverse events were related to vaccination. The IDMC determined that zero (0.0%) participants in the vaccine arm and one (0.02%) in the placebo arm experienced an unsolicited serious adverse event related to the vaccination (RR 0.11; 95% CI 0.00–2.72; Supplemental Figure S3b). The overall certainty of the evidence was low (Supplemental Table S1).

AstraZeneca (ITT population = 23,848 participants)

Assessment of COVID-19 Positivity
Symptomatic COVID-19 was defined as a positive PCR test in addition to one of the following: Fever ≥ 37.8 °C, cough, shortness of breath, anosmia or ageusia. Sixty-three (0.5%) participants in the vaccine arm and one hundred and fifty (1.3%) participants in the placebo arm developed symptomatic COVID-19 (RR 0.41; 95% CI 0.31–0.55; Supplemental Figure S1a). The overall certainty of the evidence was low (Supplemental Table S2).

Symptomatic COVID-19 after Effective Period
The effective period for the AstraZeneca vaccine was 14 days after the second immunization. Thirtyseven (0.3%) cases in the vaccine arm and one hundred and twelve (1.0%) in the placebo arm were reported (RR 0.32; 95% CI 0.22–0.47; Supplemental Figure S1b). The overall certainty of the evidence was low (Supplemental Table S2).

Severe COVID-19 Cases after Effective Period
Severe COVID-19 was defined as WHO clinical progression score of ≥6. Zero (0.0%) participants in the vaccine arm contracted severe COVID-19 after the effective period compared to one (0.01%) in the placebo arm (RR 0.32; 95% CI 0.01–7.97; Supplemental Figure S1c). The overall certainty of the evidence was very low (Supplemental Table S2).

COVID-19-Related Mortality
COVID-19-related mortality was zero (0.0%) in the vaccine arm and one (0.01%) in the placebo arm (RR 0.33; 95% CI 0.01–7.98; Supplemental Figure S2a). The overall certainty of the evidence was low (Supplemental Table S2).

All-Cause Mortality
One (0.01%) participant in the vaccine arm and four (0.03%) in the placebo arm died (RR 0.24; 95% CI 0.03–2.18; Supplemental Figure S2b). The overall certainty of the evidence was low (Supplemental Table S2).

Any Serious Adverse Events
The definition of serious adverse events was unclear. Seventy-seven (0.6%) participants in the vaccine arm and seventy-eight (0.7%) in the placebo arm reported any serious adverse events (RR of 0.96; 95% CI 0.70–1.32; Supplemental Figure S3a). The overall certainty of the evidence was low (Supplemental Table S2).

Related Unsolicited Serious Adverse Events
Causality of adverse events was determined by a site investigator. One (0.01%) participant in the vaccine arm and one (0.01%) in the placebo arm experienced an unsolicited
serious adverse event related to the vaccination (RR 0.98; 95% CI 0.06–15.59; Supplemental Figure S3b). The overall certainty of the evidence was low (Supplemental Table S2).

Moderna (ITT population = 30,420 participants)

Assessment of COVID-19 Positivity

Symptomatic COVID-19 was defined as a positive PCR test in addition to two of the following: Fever, chills, myalgia, headache, sore throat, loss of taste or smell or one of the following: Respiratory sign or symptom. Nineteen (0.1%) participants in the vaccine arm and two hundred and sixty-nine (1.8%) in the vaccine arm had symptomatic COVID-19 (RR 0.07; 95% CI 0.04–0.11; Supplemental Figure S1a). The overall certainty of the evidence was moderate (Table 1).

Table 1. GRADE evidence profile denoting the benefits and risks associated with the Moderna vaccine for the prevention of COVID-19 in adults. The table includes relative and absolute effects along with the overall certainty of the evidence.

<table>
<thead>
<tr>
<th>Participants (Studies) Follow-Up</th>
<th>Risk of Bias</th>
<th>Inconsistency</th>
<th>Indirectness</th>
<th>Imprecision</th>
<th>Publication Bias</th>
<th>Overall Certainty of Evidence</th>
<th>Study Event Rates (%)</th>
<th>Relative Effect (95% CI)</th>
<th>Risk Difference with Placebo</th>
<th>Risk Difference with Moderna</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any symptomatic cases</td>
<td>Serious a</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>Moderate</td>
<td>269/15,210 (1.8%)</td>
<td>RR 0.07 (0.04 to 0.11)</td>
<td>18 per 1000</td>
<td>16 fewer per 1000 (from 17 fewer to 16 fewer)</td>
</tr>
<tr>
<td>Symptomatic cases after effective period</td>
<td>Serious a</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>Moderate</td>
<td>204/15,210 (1.3%)</td>
<td>RR 0.06 (0.02 to 0.11)</td>
<td>13 per 1000</td>
<td>13 fewer per 1000 (from 13 fewer to 12 fewer)</td>
</tr>
<tr>
<td>Severe cases after effective period</td>
<td>Serious a</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>Moderate</td>
<td>30/15,210 (0.2%)</td>
<td>RR 0.02 (0.00 to 0.27)</td>
<td>2 per 1000</td>
<td>2 fewer per 1000 (from 1 fewer to 0)</td>
</tr>
<tr>
<td>COVID-19 deaths</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>Serious b,c</td>
<td>none</td>
<td>Moderate</td>
<td>1/15,210 (0.0%)</td>
<td>RR 0.33 (0.01 to 0.18)</td>
<td>0 per 1000</td>
<td>0 fewer per 1000 (from 0 fewer to 0 fewer)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>Serious b,c</td>
<td>none</td>
<td>Moderate</td>
<td>4/15,210 (0.0%)</td>
<td>RR 0.50 (0.09 to 2.73)</td>
<td>0 per 1000</td>
<td>0 fewer per 1000 (from 0 fewer to 0 fewer)</td>
</tr>
<tr>
<td>Any serious adverse events</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>Serious b</td>
<td>none</td>
<td>Moderate</td>
<td>153/15,170 (1.0%)</td>
<td>RR 0.96 (0.77 to 1.20)</td>
<td>10 per 1000</td>
<td>0 fewer per 1000 (from 2 fewer to 2 more)</td>
</tr>
</tbody>
</table>

Related unsolicited serious adverse events
Symptomatic COVID-19 After Effective Period
The effective period for the Moderna vaccine was 14 days after the second immunization. Twelve (0.1%) cases in the vaccine arm and two hundred and four (1.3%) in the placebo arm were reported (RR 0.06; 95% CI 0.03–0.11; Supplemental Figure S1b). The overall certainty of the evidence was moderate (Table 1).

Severe COVID-19 Cases After Effective Period
Severe COVID-19 was defined as symptomatic COVID-19 in addition to death, ICU admission or severe respiratory, cardiac, renal, hepatic or neurologic symptoms. Zero (0.0%) participants in the vaccine arm contracted severe COVID-19 after the effective period compared to thirty (0.2%) in the placebo arm (RR 0.02; 95% CI 0.00–0.27; Supplemental Figure S1c). The overall certainty of the evidence was moderate (Table 1).

COVID-19-Related Mortality
Zero (0.0%) deaths in the vaccine arm and one (0.01%) in the placebo arm were reported (RR 0.33; 95% CI 0.01–8.18; Supplemental Figure S2a). The overall certainty of the evidence was moderate (Table 1).

All-Cause Mortality
Two (0.01%) participants in the vaccine arm and four (0.03%) in the placebo arm died throughout the trial (RR 0.50; 95% CI 0.09–2.73; Supplemental Figure S2b). The overall certainty of the evidence was moderate (Table 1).

Any Serious Adverse Events
Serious adverse events were defined as any adverse event that was life-threatening, a medically important event or caused significant incapacity, hospitalization or death. One hundred and forty-seven (1.0%) participants in the vaccine arm and one hundred and fifty-three (1.0%) in the placebo arm reported serious adverse events during the trial (RR 0.96; 95% CI 0.77–1.20; Supplemental Figure S3a). The overall certainty of the evidence was moderate (Table 1).

Related Unsolicited Serious Adverse Events
Unsolicited serious adverse events were any side effects not specifically inquired about. Six (4.0%) participants in the vaccine arm and four (0.03%) in the placebo arm experienced unsolicited adverse events related to the vaccination (RR 1.50; 95% CI 0.42–5.31; Supplemental Figure S3b). The overall certainty of the evidence was moderate (Table 1).

Pfizer (ITT population = 43,448 participants)

Assessment of COVID-19 Positivity
Symptomatic COVID-19 was defined as a positive PCR test in addition to one of the following: Fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea or vomiting. Fifty (0.2%) participants in the vaccine arm and two hundred and seventy-five (1.3%) in the vaccine arm had symptomatic COVID-19 (RR 0.18; 95% CI 0.13–0.25; Supplemental Figure S1a). The overall certainty of the evidence was moderate (Table 2).
Table 2. GRADE evidence profile denoting the benefits and risks associated with Pfizer vaccine for the prevention of COVID-19 in adults. The table includes relative and absolute effects along with the overall certainty of the evidence.

<table>
<thead>
<tr>
<th>Study Event Rates (%)</th>
<th>Relative Effect (95% CI)</th>
<th>Anticipated Absolute Efects</th>
</tr>
</thead>
<tbody>
<tr>
<td>With Placebo</td>
<td>With Pfizer</td>
<td>Risk with Placebo</td>
</tr>
<tr>
<td>any symptomatic cases</td>
<td>RR 0.18 (0.13 to 0.25)</td>
<td>13 per 1000</td>
</tr>
<tr>
<td>symptomatic cases after effective period</td>
<td>RR 0.05 (0.02 to 0.10)</td>
<td>7 per 1000</td>
</tr>
<tr>
<td>severe cases after effective period</td>
<td>RR 0.33 (0.03 to 3.21)</td>
<td>0 per 1000</td>
</tr>
<tr>
<td>COVID-19 deaths</td>
<td>RR not estimable</td>
<td>0 per 1000</td>
</tr>
<tr>
<td>all-cause mortality</td>
<td>RR 0.50 (0.09 to 2.73)</td>
<td>0 per 1000</td>
</tr>
<tr>
<td>any serious adverse events</td>
<td>RR 1.13 (0.88 to 1.46)</td>
<td>6 per 1000</td>
</tr>
<tr>
<td>related unsolicited serious adverse event</td>
<td>RR 8.99 (0.48 to 167.03)</td>
<td>0 per 1000</td>
</tr>
</tbody>
</table>

CI: Confidence interval; RR: Risk ratio. Explanations: a. The primary and secondary outcomes were reported following the per-protocol analysis approach. b. The 95% confidence intervals for this outcome were wide. c. The 95% confidence interval for this outcome includes the possibility of no effect. d. The overall certainty of evidence is visually delineated on a four-point scale.

Symptomatic COVID-19 after Effective Period

The effective period for the Pfizer vaccine was 7 days after the second immunization. Eight (0.04%) cases in the vaccine arm and one hundred and sixty-two (0.7%) in the placebo were reported (RR 0.05; 95% CI 0.02–0.10; Supplemental Figure S1b). The overall certainty of the evidence was moderate (Table 2).

Severe COVID-19 Cases after Effective Period
Severe COVID-19 was defined as symptomatic COVID-19 in addition to death, ICU admission, shock, severe systemic illness or severe respiratory, neurologic, hepatic or renal symptoms. One (0.005%) participant in the vaccine arm and three (0.01%) in the placebo arm contracted severe COVID-19 after the effective period (RR of 0.33; 95% CI 0.03–3.21; Supplemental Figure S1c). The overall certainty of the evidence was low (Table 2).

COVID-19-Related Mortality

Zero (0.0%) deaths in the vaccine and placebo arm were reported (Supplemental Figure S2a). The overall certainty of the evidence was high (Table 2).

All-Cause Mortality

Two (0.01%) participants in the vaccine arm and four (0.02%) in the placebo arm died throughout the trial (RR 0.50; 95% CI 0.09–2.73; Supplemental Figure S2b). The overall certainty of the evidence was moderate (Table 2).

Any Serious Adverse Events

Serious adverse events were defined as any adverse event that was life-threatening, resulted in prolonged disability, required hospital admission or death. One hundred and twenty-six (0.7%) participants in the vaccine arm and one hundred and eleven (0.6%) in the placebo arm reported serious adverse events during the trial (RR 1.13; 95% CI 0.88–1.46; Supplemental Figure S3a). The overall certainty of the evidence was moderate (Table 2).

Related Unsolicited Serious Adverse Events

Four (0.02%) unsolicited serious adverse events in the vaccine arm and zero (0.0%) in the placebo arm were reported (RR 8.99; 95% CI 0.48–167.03; Supplemental Figure S3b). The overall certainty of the evidence was moderate (Table 2).

Johnson & Johnson (ITT population = 44,325 participants)

Assessment of COVID-19 Positivity

Symptomatic COVID-19 was defined as a positive PCR test in addition to one of the following: Fever, sore throat, malaise, headache, myalgia, gastrointestinal symptoms, cough, chest congestion, runny nose, wheezing, skin rash, eye irritation or discharge, chills, new or changing olfactory or taste disorders, red or bruised looking feet or toes or shaking chills or rigors. One hundred and ninety-five (0.9%) participants in the vaccine arm and four hundred and thirty-five (2.0%) in the placebo had symptomatic COVID-19 (RR 0.45; 95% CI 0.38–0.53; Supplemental Figure S1a). The overall certainty of the evidence was moderate (Table 3).

<table>
<thead>
<tr>
<th>Study Event Rates (%)</th>
<th>Anticipated Absolute Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Relative Effect (95% CI)</td>
</tr>
<tr>
<td></td>
<td>With Placebo</td>
</tr>
<tr>
<td>Any symptomatic cases</td>
<td>RR 0.45 (0.38 to 0.53)</td>
</tr>
<tr>
<td>Symptomatic cases after effective period</td>
<td>RR 0.34 (0.26 to 0.45)</td>
</tr>
</tbody>
</table>

Table 3. GRADE evidence profile denoting the benefits and risks associated with Johnson & Johnson vaccine for the prevention of COVID-19 in adults. The table includes relative and absolute effects along with the overall certainty of the evidence.
### Severe cases after effective period

<table>
<thead>
<tr>
<th></th>
<th>Serious</th>
<th>not serious</th>
<th>not serious</th>
<th>Serious</th>
<th>none</th>
<th>RR (95% CI)</th>
<th>1 fewer per 1000</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID-19 deaths</td>
<td>Serious a</td>
<td>not serious</td>
<td>not serious</td>
<td>Serious b</td>
<td>none</td>
<td>RR 0.15 (0.06 to 0.38)</td>
<td>2 per 1000</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>Serious c</td>
<td>not serious</td>
<td>not serious</td>
<td>Serious b</td>
<td>none</td>
<td>RR 0.09 (0.01 to 1.64)</td>
<td>0 per 1000</td>
</tr>
<tr>
<td>Any serious adverse events</td>
<td>Serious c</td>
<td>not serious</td>
<td>not serious</td>
<td>not serious</td>
<td>none</td>
<td>RR 0.86 (0.64 to 1.16)</td>
<td>4 per 1000</td>
</tr>
<tr>
<td>Related unsolicited serious adverse event</td>
<td>Serious c</td>
<td>not serious</td>
<td>not serious</td>
<td>Serious b</td>
<td>none</td>
<td>RR 3.50 (0.73 to 16.84)</td>
<td>0 per 1000</td>
</tr>
</tbody>
</table>

CI: Confidence interval; RR: Risk ratio. Explanations: a. Data for this outcome were not available for all participants randomized. b. The 95% confidence intervals for this outcome were wide. c. Data for this outcome were not available for all participants vaccinated. d. The overall certainty of evidence is visually delineated on a four-point scale.

### Symptomatic COVID-19 after Effective Period

The effective period for the Johnson & Johnson vaccine was 28 days after immunization. The trial recorded sixty-six (0.3%) cases in the vaccine arm and one hundred and ninety-five (0.9%) in the placebo after the effective period (RR 0.34; 95% CI 0.26–0.45; Supplemental Figure S1b). The overall certainty of the evidence was moderate (Table 3).

### Severe COVID-19 Cases after Effective Period

The trial reported severe-critical COVID-19 which we categorized as severe COVID-19 infection for comparison with the other trials. Severe-critical COVID-19 was defined as a positive PCR test in addition to one of the following: Death, ICU admission, shock or severe respiratory, cardiac, renal, hepatic or neurologic symptoms. Five (0.02%) participants in the vaccine arm and thirty-four (0.2%) in the placebo contracted severe-critical COVID-19 after the effective period (RR 0.15; 95% CI 0.06–0.38; Supplemental Figure S1c). The overall certainty of the evidence was low (Table 3).

### COVID-19-Related Mortality

Zero (0.0%) deaths in the vaccine arm and five (0.02%) in the placebo arm were reported (RR 0.09; 95% CI 0.01–1.64; Supplemental Figure S2a). The overall certainty of the evidence was low (Table 3).

### All-Cause Mortality

Three (0.01%) participants in the vaccine arm and sixteen (0.07%) in the placebo died throughout the trial (RR 0.19; 95% CI 0.05–0.64; Supplemental Figure S2b). The overall certainty of the evidence was low (Table 3).

### Any Serious Adverse Events

Serious adverse events were defined as any adverse event that was life-threatening, transmitted by medical machinery, resulted in prolonged disability, required hospital
admission, death or was determined to be medically important based on investigator judgement. Eighty-three (0.4%) participants in the vaccine arm and ninety-six (0.4%) in the placebo arm reported serious adverse events during the trial (RR 0.86; 95% CI 0.64–1.16; Supplemental Figure S3a). The overall certainty of the evidence was low (Table 3).

Related Unsolicited Serious Adverse Events

Seven (0.03%) participants in the vaccine arm and two (0.01%) in the placebo experienced unsolicited serious adverse events related to the vaccination (RR 3.50; 95% CI 0.73–16.84; Supplemental Figure S3b). The overall certainty of the evidence was low.

4. Discussion

The findings from RCTs assessing the efficacy of vaccines for the prevention of COVID-19 shows that all five vaccines were effective in preventing symptomatic COVID-19 infection. Relative risk reduction across all five vaccine trials ranged from 45% to 96%. Absolute risk reduction in symptomatic COVID-19 ranged from 6 to 17 per 1000 and was not associated with a significant increase in serious adverse events compared to placebo. The overall certainty of evidence was low to moderate across the included trials. This overall efficacy was similar for any time after the first dose and after the pre-determined effective periods for each vaccine (Supplemental Figure S1a,b). While J&J, Sputnik, and Moderna were associated with statistically significant reductions in risk of developing severe COVID-19 after the effective period, Pfizer and AstraZeneca were not, which is most likely due to the fact that the outcome is secondary, and thus not powered to detect this small difference (Supplemental Figure S1c). There were zero COVID-19 deaths in the vaccine arms of all trials except for Sputnik (Supplemental Figure S2). All five vaccines were associated with non-significant reductions in COVID-19-related deaths and all-cause mortality with two exceptions; Sputnik vaccine was associated with a non-significant increase in COVID-19-related deaths in the vaccine group due to a failure of pre-trial COVID-19 screening, and Pfizer had zero COVID-19-related deaths (Supplemental Figure S1). J&J was the only vaccine associated with a statistically significant reduction in all-cause mortality (Supplemental Figure S1b).

The benefit and safety profile favored all vaccines. However, the certainty of evidence varied from very low, low, moderate or high across vaccine trials (Tables 1–3, Supplemental Tables S1 and S2). The certainty of evidence was downrated due to mostly imprecision and risk of bias for multiple outcomes across all vaccines. Main reasons for risk of bias included primary and secondary outcomes that were reported following the per-protocol approach (Sputnik, Moderna, Pfizer) and data that were not available for all participants vaccinated (J&J) or randomized (AstraZeneca, J&J). Primary reasons for imprecision were wide confidence intervals or those indicating the possibility of no effect, possibly due to a low number of events in the placebo arms. Furthermore, another important consideration is the heterogeneity in outcome definitions across vaccines. For example, the Sputnik trial defined severe COVID-19 as a positive PCR test in addition to severe systemic or respiratory symptoms. Meanwhile, the Moderna, Pfizer, and Johnson & Johnson trials all had definitions of severe COVID-19 that encompassed the Sputnik trial and included participants that had a positive PCR with severe neurologic, cardiac, hepatic or renal symptoms. Another example of trial heterogeneity is in the number of doses and length of time delineating the ‘effective period’ of each vaccine. Johnson & Johnson was the only single dose vaccine with a 28-day effective period. For two dose vaccines, the effective vaccine period varied across trials: Day 1 of second vaccination (Sputnik), day 7 (Pfizer), and day 14 (Moderna and AstraZeneca). To facilitate public health decision making, we suggest that future clinical trials engage in a more transparent reporting process by providing all outcomes after the first dose, after the second dose (if applicable), and after the designated effective period. For the interim, we encourage our readers to consider efficacy in the manner reported in this paper.

On a note of caution, the results do not provide answers on the comparative efficacy of vaccines as that would require conducting head-to-head clinical trials. Since each
clinical trial was conducted within unique populations and time frames, unaccountable covariates may have exerted influence in unforeseen ways both in the magnitude and direction of effect. For this reason, drawing conclusions about the relative efficacy of each vaccine represents a transitive fallacy, which has been logically demonstrated as an important consideration for interpreting multiple clinical trials that investigate a given class of interventions [16]. We emphatically caution against comparing the relative efficacy of different vaccine trials with the current available evidence, which would require a different methodology and study design.

The understanding of COVID-19 and the vaccination effort is a rapidly evolving field with many clinical trials being performed and a multitude of scientific literature rapidly being published. This analysis is limited by the number of studies included into the GRADE evidence assessment. Further limitations to our analysis stem from the heterogeneity of study design and outcome definitions across each trial assessed. Specifically, the inclusion criteria for the multiple variables assessed among trials differed slightly between trials. Careful and detailed evaluation of the study protocols were required to effectively group comparable variables for our analysis. Another example of trial heterogeneity is in the number of doses and length of time delineating the ‘effective period’ of each vaccine. Johnson & Johnson was the only single dose vaccine with a 28-day effective period. For two dose vaccines, the effective vaccine period varied across trials: Day 1 of second vaccination (Sputnik), day 7 (Pfizer), and day 14 (Moderna and AstraZeneca). To facilitate public health decision making, we suggest that future clinical trials engage in a more transparent reporting process by providing all outcomes after the first dose, after the second dose (if applicable), and after the designated effective period for each trial.

Our analysis confirmed that all five vaccines were safe with no significant association between vaccination and adverse events across all trials. These results should facilitate shared decision making and possibly help in addressing vaccine hesitancy [17]. Additionally, adverse events that occurred are rare. The incidence of Guillain Barré syndrome (GBS) as an example is 5.8 per million doses of Pfizer, AstraZeneca or Moderna compared to 479 per million COVID-19 positive cases [19]. Similarly, thrombotic events of 3.83 cases per million doses [20] of J&J versus 0.08% of COVID-19 positive patients equate to 80,000 per million [21]. Myocarditis was observed in 2.3 per 100,000 persons among people with one dose of mRNA vaccines versus estimates as high as 15% in COVID-19 positive patients [22], and additional widespread accounts of myocardial injury in hospitalized COVID-19 patients [23]. Since vaccination decreases the risk of COVID-19 infection, it also provides an absolute decrease in the risk of the above-mentioned pathologies that have been identified as associated with the vaccines.

In summary, the five vaccines evaluated in our paper are safe and effective for preventing COVID-19. Our analyses suggest room for improvement in the conduct and reporting the results of large-scale clinical trials to better facilitate shared decision making. When multiple clinical trials assessing the efficacy of a given intervention are anticipated, a uniform simplified standard of data reporting may be warranted. One possibility could include reporting outcomes utilizing both the intention-to-treat and per-protocol methods after each dose and after the designated effective period for each vaccine. In conjunction with clear public communication, this suggested that transparent reporting may reduce vaccine hesitancy and improve trust in health institutions [24]. Notwithstanding room for improvement, the evidence from these trials is sufficiently strong to suggest that, from a public health standpoint, there should be no bias in terms of which vaccines to utilize. Rather, vaccination initiatives should be chosen based on availability, accessibility, public acceptance, and cost.

**Supplementary Materials:** The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/vaccines10122065/s1, Figure S1: Forest plot illustrating the efficacy of various vaccines for preventing (A) Any symptomatic cases, (B) Symptomatic cases after effective period and (C) Severe cases after effective period of COVID-19 in adults. Figure S2: Forest
plot illustrating the efficacy of various vaccines for preventing (A) COVID-19 related mortality, (B) All-cause mortality in adults. Figure S3: Forest plot illustrating the efficacy of various vaccines for preventing (A) any serious adverse event, (B) related unsolicited serious adverse events. Table S1: GRADE evidence profile denoting the benefits and risks associated with Sputnik vaccine for the prevention of COVID-19 in adults. Table S2: GRADE evidence profile denoting the benefits and risks associated with Astrazeneca vaccine for the prevention of COVID-19 in adults.

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Appendix A. Vaccine, Trial, and Participant Characteristics

Sputnik:
Vaccine Characteristics
The Gamaleya GamCovidVac (Sputnik V) is a heterologous recombinant adenovirus (rAd)-based vaccine. The vaccine trial utilized rAd26 and rAd5 vectors for the two doses, respectively. The placebo was a vaccine buffer composition without the rAD vectors.

Trial setting
The blinded randomized controlled trial (RCT) was conducted at 25 hospitals and polyclinics throughout Moscow, Russia.

Participants
All adults were without a history of serious infectious disease (e.g., HIV and hepatitis), vaccine-induced reaction, COVID-19 infection (negative SARS-CoV-2 IgM and IgG antibody) or respiratory illness within the 14 days prior to enrollment. Participants with a history of hypersensitivity reactions as well as a variety of chronic diseases were excluded from the trial. Additionally, 21,977 participants randomized into five age strata (18–30, 31–40, 41–50, 51–60, >60) were assigned to two study groups via a stratified interactive web response system (IWRS) with a 3:1 ratio to the vaccine arm. Moreover, 21,977 participants were randomized, of which 16,501 randomized to the vaccine arm and 5476 randomized to the placebo arm. Furthermore, 1537 subjects (9.5%) in the vaccine arm and 574 (10.5%) in the placebo arm were excluded since they had not received the second dose at the time of analysis or had protocol violations.

Vaccine Schedule and Follow-Up
Participants received two vaccinations intramuscularly in the deltoid with a 21-day interval between the doses. The follow-up was 180 days after the first shot involving five on-site visits.

AstraZeneca:
Vaccine Characteristics
The AstraZeneca-Oxford ChAdOx1 nCov-19 vaccine is a replicant-deficient chimpanzee adenoviral vector (ChAdOx1) containing the spike protein gene. Placebo varied across trials and included saline and meningococcal group A, C, W, and Y conjugate vaccines.

Trial setting
Four RCTs were conducted in the UK, Brazil, and South Africa. The article only reported outcomes from two trials, COV002, which occurred at nineteen sites across England, Wales, and Scotland, and COV003, which occurred at six sites across Brazil.

Participants
Inclusion criteria included healthy, non-pregnant adults who would refrain from blood donation during the trial. Across the four trials, 12,082 and 11,766 participants were randomized into the vaccine and placebo arms, respectively. Randomization was completed via block randomization and was stratified by the study site and group. COV002 and COV003 were both single-blind trials. Additionally, 6275 (52%) participants in the vaccine arm and 5937 (50%) participants in the placebo arm were excluded from the primary analysis for multiple reasons. All participants in the COV001 and COV007 trials were excluded since the studies had fewer than five cases of COVID-19. Additional reasons for exclusion include HIV positivity, baseline COVID-19 seropositivity, and the analysis was completed before the effective period of the vaccination.

Vaccine Schedule and Follow-Up

Participants received two vaccinations intramuscularly with a variable interval between doses. Additionally, 3400 participants received their second dose before 6 weeks following the first dose, and 3292 participants received their second dose more than 12 weeks after the first dose. Timing inconsistency was, in part, due to a change in protocol while trials were completed that allowed for a specific cohort of participants to receive a second dose. The COV002 trial consisted of two cohorts: One cohort that received two standard doses of vaccine (SD/SD cohort) and one cohort that received a low dose of vaccine for their first shot and a standard dose of vaccine for their second shot (LD/SD cohort). The LD/SD cohort only had 18–55-year-old participants, while the SD/SD cohort had any eligible adults. The COV003 trial administered standard doses for both vaccines. Median follow-up was 3.4 months.

Moderna:
Vaccine Characteristics
The mRNA-1273 vaccine is a lipid nanoparticle-encapsulated mRNA-based vaccine that encodes for the spike protein. The placebo was saline.

Trial setting
The RCT occurred at 99 sites across the USA.

Participants
Inclusion criteria included adults with no history of COVID-19 infection and who were not at a high risk of contracting COVID-19 or high risk for having a severe COVID-19 infection. Additionally, 15,210 participants were randomized into both the vaccine and placebo arms. Randomization for this observer-blind trial was completed via a centralized interactive response technology system and stratified by age and COVID-19 risk complication criteria. Moreover, 1076 (7%) participants in the vaccine arm and 1137 (7%) participants in the placebo arm were excluded from the primary analysis due to protocol deviations, baseline seropositivity or the analysis was completed before receiving the second dose.

Vaccine schedule and follow-up
Participants received two injections intramuscularly 28 days apart. Follow-up duration for reporting adverse events was up to 759 days.

Pfizer:
Vaccine characteristics
The BNT162b2 vaccine is a lipid nanoparticle-formulated nucleoside-modified RNA vaccine that encodes for the spike protein. The placebo was saline.

Trial setting
The RCT occurred at 152 sites across the USA, Argentina, Brazil, South Africa, Germany, and Turkey.

Participants
Inclusion criteria included anyone 16 years of age and older with no history of COVID-19 infection or immunocompromised state who were healthy or had stable chronic medical conditions. Additionally, 43,548 participants were randomized via an interactive web-based system. Moreover, 100 participants did not receive an injection, yielding vaccine and placebo arms of 21,720 and 21,728 participants, respectively. Furthermore, 3522 (16%) participants in the vaccine arm and 3403 (16%) participants in the placebo arm were excluded from the primary analysis due to dropping out, baseline seropositivity, inadequate follow-up or other protocol deviations.

Vaccine Schedule and Follow-Up

Participants received two injections intramuscularly in the deltoid 21 days apart. Follow-up duration for reporting adverse events was up to 6 months.

Johnson & Johnson:
Vaccine Characteristics
The Ad26.COV2.S vaccine is a recombinant, replication-incompetent human adenovirus type 26 vector encoding the spike protein. The placebo was saline.

Trial Setting
The RCT occurred at sites across Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa, and the USA.

Participants
Inclusion criteria included any independent adults between ages 18–60 or adults ≥ 60 in good or stable health, including a BMI <30 kg/m2. The double-blind trial was randomized in a 1:1 ratio via a web-response system and stratified according to trial site, age group, and coexisting conditions associated with an increased risk in severe COVID-19 infection. Additionally, 44,325 participants were randomized, with 22,174 participants assigned to the vaccine arm and 22,151 participants assigned to the placebo arm. Moreover, 2868 (13%) of those in the vaccine arm and 2973 (13%) of those in the placebo arm were excluded from the primary analysis due to protocol deviations or baseline seropositivity.

Vaccine Schedule and Follow-Up
Participants received one intramuscular injection. Follow-up duration for reporting adverse events was up to 6 months. Participants received PCR tests on entry day and on days 29 and 71, and the median participant follow-up was 58 days.

References


