Viewpoint

Randomised clinical trials of COVID-19 vaccines: do adenovirus-vector vaccines have beneficial non-specific effects?

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Abstract

To examine the possible non-specific effects (NSEs) of the novel COVID-19 vaccines, we reviewed the randomised control trials (RCTs) of mRNA and adenovirus-vector COVID-19 vaccines reporting overall mortality, including COVID-19 deaths, accident deaths, cardiovascular deaths and other non-COVID-19 deaths. For overall mortality, with 74,193 participants and 61 deaths (mRNA:31; placebo:30), the relative risk (RR) for the two mRNA vaccines compared with placebo was 1.03 (95% CI=0.63-1.71). In the adenovirus-vector vaccines there were 122,164 participants and 46 deaths (vaccine:16; controls:30). The RR for adenovirus-vector vaccines versus placebo/control vaccine was 0.37 (0.19-0.70). The adenovirus-vector vaccines were associated with protection against COVID-19 deaths (RR=0.11 (0.02-0.87)) and non-accident, non-COVID-19 deaths (RR=0.38 (0.17-0.88)). The two types of vaccines differed significantly with respect to impact on overall mortality (p=0.030) as well as non-accident, non-COVID-19 deaths (p=0.046). The placebo controlled RCTs of COVID-19 vaccines were halted rapidly due to clear effects on COVID-19 infections. However, the data presented here argue for performing RCTs of mRNA and adeno-vectored vaccines head-to-head comparing long-term effects on overall mortality.

INTRODUCTION

Within the current understanding of vaccines, it is logical to assume that COVID-19 vaccines reduce overall mortality corresponding to the number of COVID-19 deaths prevented.

However, there is now ample evidence that vaccines can have broad heterologous effects on the immune system[1,2]. These effects can lead to additional protection or increasing susceptibility to unrelated infections or even other non-infectious immune mediated diseases[3]. Therefore, as it has now been established in numerous studies, vaccines may have completely unexpected effects on overall mortality, different from what could be anticipated based on the protection against the vaccine-targeted disease.

The current system for testing vaccines does not incorporate this possibility. When the new COVID-19 vaccines were tested in randomised clinical trials (RCTs) against placebo/control vaccine, the trials were not designed to assess the effect on overall mortality. The possibility for observing such effects was further hampered by the short follow-up in these trials, as the individuals from the control groups received the vaccine after 3-6 months, following the "emergency use authorisation". Hence, though it was anticipated that the new COVID-19 vaccines would reduce overall mortality, especially in the context of a pandemic, this has not been formally studied.

Given the public health importance, we used the final study reports currently available from the clinical testing to examine the impact of mRNA and adenovirus-vector COVID-19 vaccines on overall mortality, including COVID-19-related mortality, accidents, cardiovascular deaths and other non-COVID-19 mortality.

METHODS

In January 2022, we searched PubMed for RCTs of mRNA and adenovirus-vector COVID-19 vaccines as well as the web-site: https://covid19.trackvaccines.org/vaccines/approved/ for approved COVID-19 vaccines. For all registered RCTs for mRNA and adenovirus-vector vaccines with more than 1,000 participants, we used the registration number to search for related publications. For each trial we also used the trial registration numbers to identify the most recent report.

RCTs of adolescents and children were not included as there were no deaths in these studies. Most RCTs used a placebo, but, as indicated in Supplementary Table 1, a few RCTs used a control vaccine.

The RCTs reported deaths as part of the safety assessment. We have grouped non-health-related deaths due to suicide, homicide, overdose, trauma and traffic accidents as "accidents". Apart from COVID-19 deaths and accidents, a large part of non-COVID-19 deaths were due to cardiovascular diseases. We therefore analysed overall mortality in the following categories: COVID-19 deaths, accidents, cardiovascular deaths, and other non-COVID-19 deaths. The two last groups were also combined in the category "non-accident, non-COVID-19 deaths" which covered deaths of natural causes other than COVID-19.

Several RCTs did not report the deaths by randomisation group or in sufficient detail to distinguish between these categories. In these cases, we wrote to the main authors to ask for the missing information. The additional information obtained in this way is described in Acknowledgements.

In the main analyses we examined the mortality risk rather than the mortality rate, as follow-up time was not reported in a consistent manner. Follow-up was reported as median or mean days of follow-up from 1st vaccination, from 2nd vaccination, or from 7 to 14 days after 2nd vaccination (Supplementary Table 1). Sometimes the focus was the individuals who were seronegative at enrolment, while sometimes the safety data-set covered everybody who had been enrolled in the trial. To assess the approximate follow-up time in the different trials and the crude mortality rates by 10,000 person-years (pyrs), we estimated the days of follow-up in the control groups from the 1st vaccination in the safety data set; in trials which did not report time from first vaccination but from the 2nd vaccination we assumed that participants followed the prescribed number of days between the 1st and 2nd dose of vaccine (Supplementary Table 2).

The mortality data from several studies were combined using the Mantel-Haenszel estimator providing risk ratios (RRs).

RESULTS

We identified three RCTS of mRNA vaccine[4-6] and six RCTs of adenovirus-vector COVID-19 vaccines[7-13] with mortality data available (Supplementary Table 1).

mRNA vaccines

The two major RCTs of mRNA vaccines, produced by Pfizer and Moderna, included 74,193 adults (>16 or >18 years of age) among whom there were 61 deaths (31 vaccine-recipients, 30 placebo-recipients).[4,5] These vaccines were not associated with lower overall mortality, the overall RR being 1.03 (0.63-1.71) (Table 1). The third RCT of mRNA vaccine, from CureVac[6], reported 8

deaths in the vaccine group and 6 in the placebo group, suggesting a similar trend as in the other two mRNA trials. However, the deaths in the CureVac RCT were not reported by cause of death, and since the vaccine has now been withdrawn due to low vaccine efficacy, it has not been included in Table 1.

The Pfizer[4] and Moderna[5] vaccines were associated with a lower risk of COVID-19 death (Table 1). As expected, they were not associated with the risk of accidental deaths. Fifty percent of the non-COVID-19 deaths (27/54) were cardiovascular; there was no beneficial effect of the vaccines on such deaths (RR=1.45 (0.67-3.13)). The RR for non-accident, non-COVID-19 death was 1.17 (0.67-2.05) (Table 1).

Adenovirus-vector vaccines

The five RCTs of adenovirus-vector COVID-19 vaccines presented in Table 2 included 122,164 adults among whom there were 46 deaths (16 vaccine-recipients, 30 controls). The interim report of the Ad5-nCoV RCT[13] did not report the causes of deaths by randomisation groups.

The adenovirus-vector vaccines were associated with a reduction in overall mortality, the RR being 0.37 (0.19-0.70) (Table 2). This was due to lower COVID-19 mortality (RR=0.11 (0.02-0.87)) and lower cardiovascular mortality (0 vs. 5 deaths, Table 2).

The trend for lower overall mortality was consistent in the larger trials of AstraZeneca[7-10] (RR=0.50 (0.22-1.15)) and Johnson&Johnson[11] (RR=0.19 (0.05-0.64)), but not in the Gam-COVID-Vac RCT[12], which had few deaths. The AstraZeneca RCTs in UK and Brazil[10] used a control vaccine rather than a placebo, but there were too few events to examine whether that had an impact.

Twenty-six percent (12/46) of deaths in the adenovirus-vector vaccines RCTs were due to accidents. The non-accident, non-COVID-19 RR was 0.38 (0.17-0.88) in the adenovirus-vector RCTs (Table 2).

Comparison of mRNA and adenovirus-vector vaccines

Both types of vaccines protected against COVID-19 death but had differential effects on overall mortality (p=0.030) (Figure 1). Compared with the mRNA RCTs, the RR for overall mortality was lower in the adenovirus RCTs, with a ratio-ratio of 0.36 (0.16-0.82) ((0.37 (0.19-0.70)/1.03 (0.63-1.71)) (Tables 1 and 2). The two groups of vaccines also differed with respect to “non-accident, non-COVID-19 mortality” (test of homogeneity, p=0.046). The impact differed most strongly for cardiovascular deaths (p=0.03) (Tables 1 and 2). Compared with the mRNA vaccines (Table 1),

both Johnson&Johnson (p=0.01) and AstraZeneca (p=0.15) tended to have lower overall mortality.

Sensitivity analyses

If the underlying mortality rates for different causes of death differed in the RCTs, this could affect the comparison between mRNA and adenovirus-vector vaccines. In the unvaccinated control groups (Supplementary Table 2), accidents and COVID-19 deaths were slightly more common in the adenovirus-vector trials than in the mRNA trials. However, there was no difference in the rates of "non-accident, non-COVID-19 deaths" in the mRNA (16/10,000 pyrs) and adenovirus-vector vaccine trials (15/10,000 pyrs).

DISCUSSION

Based on the RCTs with the longest possible follow-up, mRNA vaccines had no effect on overall mortality despite protecting against fatal COVID-19. On the other hand, the adenovirus-vector vaccines were associated with lower overall mortality and lower non-accident, non-COVID-19 mortality. The pattern of effects was internally consistent in the RCTs of mRNA and adenovirus-vector vaccines, respectively.

An intrinsic limitation for the estimation of overall mortality during the COVID-19 pandemic is the nature of the cohorts studied. Most of the volunteers participating in the trials were adult individuals in general good health, resulting in low COVID-19 and overall mortality. In a real-life situation in which the COVID-19 vaccines are administered to highly vulnerable populations with high COVID-19-dependent mortality, significant gains in overall mortality are expected, also for mRNA vaccines. However, the intriguing differences in the effects on non-accident, non-COVID-19 mortality are likely to persist, and should be further investigated in future studies.

The contrast suggests that adenovirus-vector vaccines compared with placebo have beneficial non-specific effects, reducing the risk of non-COVID-19 diseases. The most important cause of non-COVID-19 death was cardiovascular disease, against which the data for the current RCTs suggest that the adenovirus-vector vaccines provide significant protection.

Strength and limitations

The number of deaths in these RCTs was limited and chance can therefore have played a role in these findings. However, the internally consistent effect and the large difference in effect sizes between the two vaccine types speaks against "chance" as the main explanation.

Differences between the study populations in the trials of the two vaccine types could have biased the comparison. A slightly larger proportion of the participants from the adenovirus-RCTs may have been from middle- and low-income countries (Supplementary Table 1), so different disease patterns and level of care could have influenced the number of deaths.

Regarding causes of death, the mRNA RCTs had longer follow-up and more individuals were infected with COVID-19 than in the adenovirus-vector vaccine RCTs (Supplementary Table 1), but there were more COVID-19 deaths in the adenovirus-vector RCTs (Supplementary Table 2). Participants in the mRNA RCTs may have had access to better health care during COVID-19 infection and this may have reduced the estimated impact of mRNA vaccines on overall mortality. Furthermore, it cannot be excluded that different research groups had different criteria for diagnosing COVID-19 death and non-COVID-19 death, so that the RRs for COVID-19 deaths and non-COVID-19 deaths would change if uniform criteria had been used. However, this would not affect overall mortality estimates, which still differ substantially for the adenovirus-vector vaccines in relation to the mRNA vaccines.

There was a higher proportion of accidents in the adenovirus-vector vaccine RCTs and when accidents were excluded, the contrast between mRNA and adenovirus-vector vaccines became stronger. Cardiovascular deaths were more common in the mRNA RCTs; participants in these trials may have had more co-morbidity or more events because they had longer follow-up (Supplementary Table 1). However, the effect of COVID-19 vaccines on cardiovascular events differed, being beneficial for the adenovirus-vector vaccines but not for the mRNA vaccines. The lack of impact of mRNA vaccines on cardiovascular morbidity is supported by a recent epidemiological survey in France[14]. Altogether, it is unlikely that the different mortality trends for the mRNA versus the adenovirus-vector RCTs can fully explain the contrast between the two types of vaccines.

Since there are well established sex-differences in the immune system, it is important to report and analyse data by sex[15]. This was unfortunately not possible for the present study, since the RCTs only reported deaths by randomisation allocation, not by sex. However, in the key RCTs[4,5,7,11] the sex-distribution was similar, and thus differences in sex-enrolment in the RCTs are unlikely to explain the differential effect of the two types of vaccines.

Beneficial effects on overall mortality were recently reported in an observational study from Buenos Aires in Argentina which mainly used non-mRNA vaccines[16]. In contrast to the RCTs of

mRNA vaccines, an observational study from CDC[17] reported lower rates of non–COVID-19 mortality among mRNA-vaccinated individuals. However, these observational studies have numerous sources of bias, including healthy vaccinée bias, and merely underscore that RCTs are needed to address the association between vaccination and overall health.

Interpretation

The substantial mortality reduction associated with adenovirus-vector vaccines is surprising and may be difficult to understand if the expectation is that vaccines only protect against death from the target-disease. The result may be interpreted as implausible and dismissed[18]. It is therefore important to take into consideration that such non-specific effects, and their immunological basis, have been established for several other vaccines. For example, RCTs have shown that BCG vaccine against tuberculosis (TB) reduces neonatal mortality by more than a third[19,20], and this effect was not due to prevention against TB, but by protection against deaths from sepsis and respiratory infections. Immunological studies have shown that such effects are indeed biologically plausible; BCG positively affects the innate immune system leading to enhanced resistance towards a broad range of pathogens[21]. Furthermore, BCG vaccine has been associated with decreased systemic inflammation[22]. While such immunological studies are yet to be conducted for adenovirus-vector vaccines, it is still within current knowledge that adenovirus-vector vaccines could have beneficial non-specific effects, as indicated by the RCT data.

Immunological mechanisms

The different adenovirus-vector vaccines are based on different adenovirus vectors[23], e.g. ChAdOx1 was derived from chimpanzee adenovirus, Johnson&Johnson uses adenovirus 26, and Gam-COVID-Vac used first adenovirus 26 and then adenovirus 5. Pre-existing immunity against the vector may thus differ between the various vaccines. Furthermore, different vaccine technologies were applied, with regards to choices of production cell lines, viral signal peptides etc[23], so it is quite likely that the different adenovirus-vector vaccines could have different non-specific effects if the RCTs had been sufficiently large to measure differences. So far, only the Johnson&Johnson and the AstraZeneca vaccines have been examined in studies large enough to assess differences in mortality; these two vaccine types appeared to have similar beneficial non-specific effects on overall mortality. Non-specific effects of vaccines have been observed to differ between live-attenuated vaccines and non-live vaccines[2]. We speculate that even though the

adenovirus-vector is replication deficient, it may prime the immune system in a way similar to a "live" vaccine[2].

The Pfizer and Moderna mRNA vaccines are technologically very similar[23]. However, there are subtle differences between the two vaccines, both with respect to the RNA and the carriers, and a higher amount of RNA per dose is used in the Moderna vaccine. The present analysis had low power to detect differences in effect between the two mRNA vaccines. A recent study has reported that the Pfizer/BioNTech mRNA vaccines modulate transcriptional profiles in innate immune cells[24], but the impact on the antimicrobial functions of these cells is not yet known. In an animal study the lipid nanoparticles carrying the vaccine were associated with enhanced inflammation[25].

Similar to mRNA vaccines, adenovirus-vector vaccines are intended to result in the production of S proteins from a specific mRNA in cells of the vaccinée. The pathway to this effect is however substantially more complex than with mRNA vaccines, because it takes a detour of the adenoviral DNA through the nucleus (where it remains extrachromosomal) and requires a number of additional cellular processes, including RNA transcription and processing[23]. It is unclear whether such differences between the two vaccine types could play a role for their apparently different effects on overall mortality. Future comprehensive studies on the heterologous immune effects of both mRNA and adenovirus-vector COVID-19 vaccines are warranted.

Implications

Major differences in the overall mortality impact between two of the major types of COVID-19 vaccines used in the world are of obvious public health importance.

While mass-vaccination programs with COVID-19 vaccines are rolled out, data on their effects on non-COVID-19 mortality should be collected. As COVID-19 mortality comes under better control due to herd immunity and increasing vaccination coverage, the impact on non-COVID-19 mortality becomes particularly important from a public health perspective. Unfortunately, the opportunity for conducting large-scale RCTs vaccine-vs-placebo trials passed once the vaccines were introduced generally in the population. To throw light on the potential differences in non-specific effects between vaccine types, one way forward would be for public health authorities to conduct RCTs comparing the mRNA vaccines and adenovirus-vector vaccines for their effect on overall COVID-19 mortality as well as non-COVID-19 mortality.

Even if effects within the group of adenovirus-vector vaccines would turn out to be more heterogeneous with longer follow-up and when more studies have been published, it seems clear that the overall health effects of the Johnson&Johnson and AstraZeneca vaccines should be tested against the leading mRNA vaccines. In addition, future trials of new COVID-19 vaccines should be compelled to report mortality data by cause and sex. Post-licensure monitoring and evaluation should also focus on overall, non-accidental mortality.

CONCLUSIONS

Potential differences in the effects of adenovirus-vector and mRNA vaccines on overall mortality, if true, could have a major impact on global health. If validated in additional studies, the protective heterologous effects of adenovirus-based vaccines on non-COVID-19 mortality, in addition to their effectiveness against SARS-CoV-2 infection, may represent an important advantage in vulnerable populations in which cardiovascular mortality is important. The differences in heterologous effects between various vaccine types need to be explored and, if confirmed, taken into consideration when planning future public health policy.

Ironically, the rich countries in Europe and USA have emphasized the more expensive mRNA vaccines because these vaccines have slightly better short-term vaccine efficacy against COVID-19 than the relatively inexpensive adenovirus-vector vaccines, and due to the detection of a rare blood clotting disorder associated with the adenovirus-vector vaccines. While this decision is understandable in the short-term during a situation with high COVID-19-related mortality, in the endemic situation in which COVID-19-related deaths have decreased this decision may need to be reassessed. Otherwise, if the protective effects of adenovirus-vector vaccines on overall mortality in the RCTs reflect the reality, this could turn out to be a very costly decision, both economically and health wise.

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Conflict of interest: nothing to declare.

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Data sharing: All relevant data has already been published.

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Table 1. Overall and non-COVID-19 mortality in the RCTs of mRNA vaccines

Pfizer vs placebo[4]			
	Vaccine group (deaths/N)	Placebo group (deaths/N)	Relative risk (95% CI)
Overall mortality	15/21926	14/21921	1.07 (0.52-2.22)
COVID-19 mortality	1/21926	2/21921	0.50 (0.05-5.51)
Cardiovascular mortality**	9/21926	6/21921	1.50 (0.53-4.21)
Other non-COVID-19 mortality	5/21926	5/21921	1.00 (0.29-3.45)
Accident mortality#	0/21926	1/21921	0.0
Non-accident, non-COVID-19 mortality	14/21926	11/21921	1.27 (0.58-2.80)
Moderna vs placebo[5]			
Overall mortality	16/15184	16/15162	1.00 (0.50-2.00)
COVID-19 mortality	1/15184	3/15162	0.33 (0.03-3.20)
Cardiovascular mortality**	7/15184	5/15162	1.40 (0.44-4.40)
Other non-COVID-19 mortality	6/15184	7/15162	0.86 (0.29-2.55)
Accident mortality##	2/15184	1/15162	2.00 (0.18-22.02)
Non-accident, non-COVID-19 mortality	13/15184	12/15162	1.08 (0.49-2.37)
Combined for Pfizer and Moderna vs placebo*			
Overall mortality	31/37110	30/37083	1.03 (0.63-1.71)
COVID-19 mortality	2/37110	5/37083	0.40 (0.08-2.06)
Cardiovascular mortality	16/37110	11/37083	1.45 (0.67-3.13)
Other non-COVID-19 mortality	11/37110	12/37083	0.92 (0.40-2.08)
Accidents	2/37110	2/37083	1.00 (0.14-7.09)
Non-accident, non-COVID-19 mortality	27/37110	23/37083	1.17 (0.67-2.05)

Notes: In the Pfizer and Moderna trials there were discrepancies between the number of deaths presented in the flow chart and in the text/tables; we have used the numbers in the text/tables. The Pfizer study could have more than one cause ascribed to a death; there was a total of 17 diagnoses among the 15 deaths in the vaccinated group, and 17 diagnoses among 14 deaths in the placebo group, thus, some overlap cannot be excluded.

*Mantel-Haenszel estimate

**Judged as cardiovascular deaths: From the Pfizer trial: “Myocardial infarction”(N=2); “Hypertensive heart disease” (N=1); “Haemorrhagic stroke” (N=1); “Cardiorespiratory arrest” (N=2); “Cardiac failure congestive” (N=1); “Cardiac arrest” (N=5); “Arteriosclerosis” (N=2); “Aortic rupture” (N=1). From the Moderna trial: “Myocardial infarction” (N=5;) “Cardiopulmonary arrest” (N=3); “End stage congestive heart failure” (N=1); “Cardiac arrest” (N=1); “Provisional diagnosis, sudden fatal event, likely myocardial infarction”(N=1), “Death suspected due to coronary heart disease, probably due to complications of diabetes mellitus” (N=1).

There was one death due to an overdose.

There were three deaths due to suicide (2) and head trauma (1).

Table 2. Overall and non-COVID-19 mortality in the RCTs of adenovirus-vector vaccines

	Vaccine group (deaths/N)	Placebo group (deaths/N)	Relative risk (95% CI)
AstraZeneca vs placebo US/Chile/Peru[7]			
Overall mortality	7/21587	7/10792	0.50 (0.18-1.42)
COVID-19 mortality	0/21587	2/10792	0.0
Cardiovascular mortality**	0/21587	2/10792	0.0
Other non-COVID-19 mortality	3/21587	3/10792	0.50 (0.10-2.48)
Accidents¤	4/21587	0/10792	N/A
Non-accident, non-COVID-19 mortality	3/21587	5/10792	0.30 (0.07-1.25)
AstraZeneca vs placebo South-Africa [8,9]			
Overall mortality	1/1011	3/1010	0.33 (0.03-3.20)
COVID-19 mortality	0/1011	0/1010	N/A
Cardiovascular mortality	0/1011	0/1010	N/A
Other non-COVID-19 mortality	0/1011	0/1010	N/A
Accidents##	1/1011	3/1010	0.33 (0.04-3.20)
Non-accident, non-COVID-19 mortality	0/1011	0/1010	N/A
AstraZeneca vs control vaccine UK, Brazil[10]			
Overall mortality	2/11218	3/10901	0.65 (0.11-3.88)
COVID-19 mortality	0/11218	1/10901	0.0
Cardiovascular mortality	0/11218	0/10901	N/A
Other non-COVID-19 mortality	2/11218	1/10901	1.94 (0.18-21.43)
Accidents###	0/11218	1/10901	0.0
Non-accident, non-COVID-19 mortality	2/11218	1/10901	1.94 (0.18-21.43)
Johnson&Johnson vs placebo[11]			
Overall mortality	3/21895	16/21888	0.19 (0.05-0.64)
COVID-19 mortality	0/21895	5/21888	0.0
Cardiovascular mortality**	0/21895	2/21888	0.0
Other non-COVID-19 mortality	3/21895	7/21888	0.43 (0.11-1.66)
Accidents ####	0/21895	2/21888	0.0
Non-accident, non-COVID-19 mortality	3/21895	9/21888	0.33 (0.09-1.23)
Gam-COVID-Vac vs placebo [12]			
Overall mortality	3/16427	1/5435	0.99 (0.10-9.54)
COVID-19 mortality	2/16427	0/5435	N/A
Cardiovascular mortality**	0/16427	1/5435	0.0
Other non-COVID-19 mortality	0/16427	0/5435	N/A
Accidents #####	1/16427	0/5435	N/A

Non-accident, non-COVID-19 mortality	0/16427	1/5435	0.0
Combined*			
Overall mortality	16/72138	30/50026	0.37 (0.19-0.70)
COVID-19 mortality	2/72138	8/50026	0.11 (0.02-0.87)
Cardiovascular mortality	0/72138	5/50026	0.065 (0.01-0.41)***
Other non-COVID-19 mortality	8/72138	11/50026	0.58 (0.23-1.45)
Accidents	6/72138	6/50026	0.69 (0.19-2.58)
Non-accident, non-COVID-19 mortality	8/72138	16/50026	0.38 (0.17-0.88)

Notes: In the AstraZeneca paper, data from UK and Brazil trials, using meningitis vaccine in the control group, were published in a meta-analysis with data from a South Africa trial[8,9] which used placebo. The South African trial has also been reported separately. We maintained the division in placebo and control vaccine. The RCT of Ad5-nCoV[13] vaccine did not present causes of death by randomisation group.

*Mantel-Haenszel estimate

**Judged as cardiovascular deaths: From AstraZeneca: “cardiac arrest”; “hemorrhagic transformation stroke” + “ischemic stroke”. From Johnson&Johnson trial: “acute myocardial infarction”; “cardiac failure”. From Gam-COVID-Vac trial: “haemorrhagic stroke”.

***Due to 0 events among the vaccinated we used the Peto OR method for pooling trial results.

There were four deaths: overdose (2), accident, road traffic accident.

There were four deaths: gunshot, blunt force trauma to head, homicide, suicide.

There was one death: traumatic brain injury

There were two deaths: overdose, suicide

#####There was one death: fracture of thoracic vertebra.

Figure 1. Forest plot comparing estimated effects of mRNA COVID-19 vaccines versus placebo and of adenovirus-vector COVID-19 vaccines versus placebo/control vaccine with respect to impact on overall mortality, COVID-19 mortality, cardiovascular death and non-accident, non-COVID-19 mortality.

Supplementary table 1. Background information about included RCTs

	Pfizer [4]	Moderna [5]	CVnCoV [6]	AZ US/Chile/Peru [7]	AZ South Africa [8,9]	AZ UK/Brazil[10]	Johnson&Johnson [11]	Gam-COVID-Vac[12]	Ad5-nCoV[13]
N	44,165	30,415	39,680	32,451	2021	22119	39,321	21,977	36,717
Vaccine	mRNA	mRNA	mRNA	Chimpanzee Adenovirus Y25	Chimpanzee Adenovirus Y25	Chimpanzee Adenovirus Y25	Human Adenovirus 26	Human Adenovirus 26 and 5	Human Adenovirus 5
No of doses	2	2	2	2	2	2	1	2	1
Phase	2/3	3	2b/3	3	1/2	1/2/3	3	3	3
Randomisation ratio	1:1	1:1	1:1	2:1	1:1	1:1	1:1	3:1	1:1
Intervention	BNT162b2	mRNA-1273	CVnCoV	AZD1222	AZD1222	AZD1222	Ad26.COV2.S	Gam-COVID-Vac	Ad5-nCoV
Control group	Saline	Placebo*	Saline	Saline	Saline	Control vaccine (MenACWY)	Saline	Vaccine buffer	Vaccine buffer
Vaccine efficacy#	91% (89-93%)	93% (91-95%)	48% (31-61%)	74% (65-81%)	22% (-50-60%)	67% (57-74%)	67% (59-73%)	92% (86-95%)	58% (40-70%)
Age enrolled (years)	16+	18+	18+	18+	18-65	18+	18+	18+	18+
Male %	51	53	55	56	57	42	55	61	71
Age (mean or median (range))	51 (16-91)	51 (18-95)	43 (IQR 31-54)	50 (18-100)	30 (18-64)	83%<55years	52 (18-100)	45 (SD 12)	38 (18-94)
Geographical location	US, Argentina, Brazil, South Africa, Germany, Turkey	US	Belgium, Germany, Netherlands, Spain, Argentina, Colombia, Dominican	US, Chile, Peru	South Africa	UK, Brazil	US, Argentina, Brazil, Chile, Colombia, Mexico, Peru, South Africa	Russia	Argentina, Chile, Mexico, Pakistan, Russia

			Republic, Mexico, Panama, Peru						
Proportion recruited in the US	76%	100%	0%	89%	0%	0%	44%	0%	0%
Enrolment period and data cut-off	July 27, to Oct 29, 2020 Data cut-off March 13, 2021	July 27 to Oct 23, 2020 Data cut-off March 26, 2021	Dec 11, 2020 to April 12, 2021 Data cut-off June 18, 2021	Aug 28, 2020, to Jan 15, 2021	June 24 and Nov 9, 2020	April 23 and Dec 6, 2020 Data cut-off Dec 6, 2020	Sept 21, 2020, to Jan 22, 2021 Data cut-off Jan 22, 2021	Sept 7 to Nov 24, 2020 Data cut-off Nov 24, 2020	Sept 22, 2020 to Jan 15, 2021 Data cut-off Jan 15, 2021
Duration of follow-up	Mean follow-up from 7 days after 2nd dose: 108 days	Median follow-up from 1st dose: 5.3 months	Mean follow-up from 15 days after 2nd dose: 48 days	Median follow-up from 2nd dose: 61 days	Median follow-up from 1st dose: 156 days	Mean follow-up from 1st dose: 4.2 months	Median follow-up: 58 days	Median follow-up from 1st dose: 48 days	Median follow-up from 28 days post-vaccination: 45 days
Follow-up days in control group	2,937,414	2,441,082	N/A	960,488	157,560	1,384,427	1,269,504	260,880	N/A
COVID-19 infection in control group	4.1% (850/20713)	5.3% (744/14164)	1.2% (145/12211)	1.5% (130/8550)	3.2% (23/717)	2.9% (248/8581)	1.8% (348/19544)	1.3% (62/4902)	1.5% (211/14586)
Cardiovascular deaths: % of all deaths	52% (15/29)	38% (12/32)	No inf	14% (2/14)	0%	0%	11% (2/19)	25% (1/4)	No inf
COVID-19 death: % of all deaths	10% (3/29)	13% (4/32)	No inf	14% (2/14)	0%	20% (1/5)	26% (5/19)	50% (2/4)	No inf

Notes: # The calculations of vaccine efficacy differ with respect to the number of days after vaccination that observation is started; *no information on preparation

Supplementary Table 2. The rate of causes of death per 10,000 person-years (pyrs) in the control groups by type of vaccine

Cause of death	Rate deaths per 10,000 pyrs (number of deaths/pyrs) in the control group		Relative risk (95% CI) mRNA vs Adenovirus-vector vaccine in the control group
	mRNA RCTs: 14,725.5 pyrs	Adenovirus-vector RCTs: 11,041 pyrs	
COVID-19 deaths	3.4 (5/14726)	7.2 (8/11041)	0.47 (0.15-1.43)
Accidents	1.4 (2/14726)	5.4 (6/11041)	0.25 (0.05-1.24)
Non-accident, non-COVID-19 deaths	15.6 (23/14726)	14.5 (16/11041)	1.08 (0.57-2.04)
Overall mortality	20.4 (30/14726)	27.2 (30/11041)	0.75 (0.45-1.24)

Figure 1. Forest plot comparing estimated effects of mRNA COVID-19 vaccines versus placebo and of adenovirus-vector COVID-19 vaccines versus placebo/control vaccine with respect to impact on overall mortality, COVID-19 mortality, cardiovascular death and non-accident, non-COVID-19 mortality.