

# ADVERSE EFFECTS OF MESSENGER RNA VACCINES

*An Evidence Review from the Penn Medicine Center for Evidence-based Practice*  
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## EVIDENCE SUMMARY

- There are no specific guidelines for use of messenger RNA (mRNA) vaccines or contraindications to mRNA vaccines.
- No large trials of any mRNA vaccine have been completed yet.
- The only evidence on safety of mRNA vaccines comes from small phase I and phase II trials of SARS-CoV-2 vaccines, with follow-up typically less than two months.
- Systemic adverse events such as fatigue, muscle aches, headache, and chills are common.
- Severe systemic adverse events were reported by 5 to 10 percent of trial subjects.
- Localized adverse events such as pain at the injection side are common.
- Both systemic and local adverse events usually are resolved within one or two days.
- The rate and severity of adverse events appears to be higher for the second dose of vaccine than for the first.
- Higher vaccine doses appear to increase the rate and severity of adverse events.
- Larger trials of SARS-CoV-2 vaccines are in progress, with results expected in mid-2021.
- There is not sufficient evidence to support any conclusions on the comparative safety of different mRNA vaccines.
- Direct evidence on the comparative safety of mRNA vaccines and other vaccines is lacking.

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## Introduction

The pandemic caused by the novel coronavirus SARS-CoV-2 (commonly called COVID-19) has had a devastating effect worldwide. Pharmaceutical manufacturers and government agencies are working urgently to develop a vaccine against this virus. The first of these vaccines are expected to gain Emergency Use Authorization from the US Food and Drug Administration this month.

Several different products are in development for potential use in the United States (Table 1), and they use different technologies to stimulate the desired immune response in vaccine recipients. The vaccines that are expected to receive authorization for use soonest are based on a novel lipid-encapsulated messenger RNA (mRNA) technology. The purpose of this Evidence Advisory is to identify and summarize high-level evidence on the safety of mRNA vaccines. Evaluation of the vaccines' effectiveness is outside the scope of this report. mRNA vaccines used for therapeutic purposes such as those used in cancer or HIV treatment are also outside the scope of this report. This report may include evidence on mRNA vaccines used against other diseases, including influenza, cytomegalovirus (CMV), rabies, and Zika, though it will be indirect evidence for the purpose of predicting the safety of SARS-CoV-2 vaccines. Presently, no such vaccines are licensed for use in the United States (1).

**Table 1. COVID-19 vaccines and candidates for use in the United States**

Manufacturer (product ID)	Technology	FDA EUA status	EU CMA status	UK status
Pfizer-BioNTech (BNT162)	mRNA	§-11 Dec 2020	†-1 Dec 2020	§-2 Dec 2020
Moderna (mRNA-1273)	mRNA	†-17 Dec 2020	†-1 Dec 2020	Not reported
AstraZeneca-Oxford (AZD1222)	Adenovirus (non-replicating viral vector)	Not yet pending	Initial review	†-27 Nov 2020
Janssen	Adenovirus (non-replicating viral vector)	Not yet pending	Initial review	Not reported
Novavax (NVX-CoV-2373)	Protein subunit	Not yet pending	Not yet pending	Not reported
GSK-Sanofi	Protein subunit	Not yet pending	Not yet pending	Not reported

Information last updated 18 December 2020

EUA—Emergency Use Authorization, CMA— conditional marketing authorization

†—FDA meeting scheduled (US) or application under evaluation (EU, UK)

§—EUA (US, UK) or CMA (EU) granted

## Previous CEP Reports

CEP has published a [Rapid Guidance Summary](#) on COVID-19 vaccines for women who are pregnant or lactating. The scope was limited to existing guidelines from public health agencies and professional societies, systematic reviews, and medical center policies. The report found that the American College of Obstetricians and Gynecologists and the Society for Maternal-Fetal Medicine sought to balance the possible risks of vaccination with the risks of remaining unvaccinated, and recommended shared decision-making by women and their physicians. Guidelines from United Kingdom sources recommended against COVID-19 vaccination for women who are pregnant or breastfeeding. Guidance from Penn Medicine and other US medical centers generally followed the ACOG and SMFM positions.

## Current UPHS policy

The University of Pennsylvania Health System does not have any written policy documents relevant to this topic. All UPHS hospitals, outpatient, and home care entities are vaccinating employees against SARS-CoV-2 using mRNA vaccines. The vaccinations are not mandatory.

## Methods

### CENTER FOR EVIDENCE-BASED PRACTICE PROTOCOL FOR SYSTEMATIC REVIEW

#### SPECIFIC AIM:

Identify and summarize high-level evidence relating to the safety of messenger RNA (mRNA) vaccines, particularly vaccines against the SARS-CoV-2 coronavirus.

#### METHODS:

**Study designs:** Evidence-based clinical practice guidelines issued by professional societies and national health systems, systematic reviews. Large primary studies will be reviewed if systematic reviews are lacking.

#### Inclusion and exclusion criteria:

**Participants:** Adults. Persons in high-risk groups will be analyzed separately if evidence permits.

**Interventions:** Immunization using a lipid-encapsulated mRNA vaccine. Vaccines against the SARS-CoV-2 coronavirus are of particular interest.

**Comparisons:** Not applicable.

**Outcomes:** Vaccine-related adverse events.

**Timing:** As reported by investigators.

**Setting:** All settings.

**Other:** Published in English

#### Data collection

**Databases:** NICE Evidence Search, ECRI Guidelines Trust, CADTH, INAHTA, Cochrane Library, web sites of relevant professional organizations, Medline, EMBASE

**Data synthesis (calculation of relative risks and confidence intervals, meta-analyses, exploration of heterogeneity):** Qualitative.

**NOTE:** CEP standard review methods, including scales for quality assessment of guidelines, systematic reviews, and primary studies can be found in the Methods section of the CEP web site. ([www.uphs.upenn.edu/cep/methods](http://www.uphs.upenn.edu/cep/methods))

## Literature Search

Searches were conducted on December 8 and 9, 2020 and were not limited by date.

**Table 2. Guideline search**

Database or organization	Keywords or syntax	Hits	Marked for retrieval	Included
ECRI Guidelines Trust	messenger or mRNA	2	0	0
	vaccine	51	0	0

**Table 3. Evidence clearinghouse search**

Search keywords	Evidence type	Hits	Marked for retrieval	Included
<b>NICE Evidence Search (NHS)</b>				
(mRNA or messenger) and vaccine	Guidance	19	1	1
	Policy and strategy	4	0	0
	Prescribing and technical	2	0	0
	Systematic reviews	15	1	1
	Economic evaluations	0	3	0
	Evidence summaries	38	0	0
	Health technology assessments	1	0	0
<b>Canadian Agency for Drugs and Technologies in Health (CADTH)</b>				
(mRNA OR messenger) AND vaccine		1	0	0
Vaccine (COVID evidence portal)		4	1	0
<b>ECRI Institute</b>				
mRNA OR messenger		68	1	0
vaccine AND adverse		91	†-1	0
<b>Health Information and Quality Authority (Ireland)</b>				
vaccine		2	0	0
<b>INAHTA International HTA Database</b>				
mRNA OR messenger		14	0	0
vaccine AND adverse		15	0	0
<b>McMaster PLUS (primary studies)</b>				
vaccine		34	†-4	0

European Medicines Agency			
Browsed	–	0	0
Centers for Disease Control and Prevention (vaccine subsite)			
mRNA	85	0	0

†-relevant hit(s) duplicated results of previous search

**Table 4. Systematic review search**

Database	Keywords or syntax	Hits	Marked for retrieval	Included
Cochrane Database of Systematic Reviews	mRNA OR messenger	3	0	0
	vaccine AND adverse	88	0	0
VA Evidence Synthesis Program (COVID-19)	vaccine	10	0	0
COVID-END (McMaster University)	browsed	–	0	0
EvidenceAid	Vaccine	10	1	0
Medline	included in main searches	–	–	–
EMBASE	included in main searches	–	–	–

**Table 5. Medline search**

Search	Syntax	Hits	Retrieved	Included
1	((messenger or mRNA) adj4 vaccin*).mp.	565	–	–
2	(RNA adj4 vaccin*).mp.	995	–	–
3	((SARS-CoV-2 or covid* or coronavir*) adj3 (vaccin* or immuniz*)).mp.	1,930	–	–
4	exp Vaccines/ae, to [Adverse Effects, Toxicity]	26,192	–	–
5	(adverse or complication or (side adj2 effect*)).mp.	2,487,957	–	–
6	(1 or 2 or 3) and (4 or 5)	268	–	–
	Delete 8 duplicate references within set	260	26	7

mp: keyword (title, abstract, subject heading)

**Table 6. EMBASE search**

Search	Syntax	Hits	Retrieved	Included
1	(mrna OR messenger) NEAR/4 vaccin*	755	–	–
2	('sars cov 2' OR covid* OR coronavir*) NEAR/3 (vaccin* OR immuniz*)	1,907	–	–
3	rna NEAR/3 vaccine	803	–	–
4	adverse OR complication OR (side NEAR/2 effect*)	4,666,186	–	–
5	(#1 OR #2 OR #3) AND #4	338	–	–
	exclude 187 duplicate references	151	5	0

**Table 7. Cochrane Central Register search**

Search	Syntax	Hits	Retrieved	Included
1	(mRNA OR messenger) AND vaccine (word variations automatically searched)	151	–	–
	exclude 15 duplicate references	136	4	0

**Table 8. ClinicalTrials.gov search**

Search	Syntax	Hits	Retrieved	Included
1	mRNA AND vaccine (search terms automatically expanded)	105	23	7
2	COVID AND vaccine (search terms automatically expanded)	297	297	7

**Table 9. EU ClinicalTrials register search**

Search	Syntax	Hits	Retrieved	Included
1	mRNA AND vaccine (search terms automatically expanded)	17	0	0
2	COVID AND vaccine (search terms automatically expanded)	4	1	1

**Table 10. medRxiv preprint search**

Search	Syntax	Hits	Retrieved	Included
1	mRNA AND vaccin*	163	–	–
	exclude 1 duplicate reference	162	5	3



## Results

### Guidelines

We found no guidelines regarding patient groups for whom mRNA vaccines should be avoided or other guidelines specific to mRNA vaccines. This is likely due to the lack of FDA or European approval for any mRNA vaccines before this month. General guidance on COVID-19 vaccination has been issued by Public Health England (Table 11). It is of low quality (Table 12) and based on limited evidence. Because no clinical trials involving children have been reported yet, and children have less risk of serious illness or death from COVID-19, vaccination of children is not recommended. For a summary of guidance on COVID-19 vaccines for women who are pregnant or breastfeeding, please see the [CEP Rapid Guidance Summary](#) on that topic.

**Table 11. Guideline recommendations**

Organization	Recommendation	Notes
<a href="#">Public Health England</a> 2020 (2)	<p>SARS-CoV-2 vaccine trials have only just begun in <u>children</u> and therefore, there are, very limited data on safety and immunogenicity in this group. Children and young people have a very low risk of COVID-19, severe disease or death due to SARS-CoV-2 compared to adults and so COVID-19 vaccines are not routinely recommended for children and young people under 16 years of age.</p> <p>Individuals who have <u>immunosuppression and HIV infection</u> (regardless of CD4 count) should be given COVID vaccine in accordance with the recommendations and contraindications stated in the Protocol and Green Book <a href="#">COVID-19 chapter</a>. These individuals may not make a full antibody response and should therefore continue to follow advice to avoid exposure unless they are advised otherwise by their doctor.</p> <p>Local reactions at the injection site were found to be fairly common after vaccination with BNT162b2. Over 80% of trial participants reported pain at the injection site. This occurred within 7 days after the injection and resolved after a few days</p>	<p>General guidance on COVID-19 vaccination.</p> <p>No specific guidance regarding mRNA vaccines.</p>

**Table 12. Guideline appraisal**

Guideline issuer	PHE	Guideline issuer	PHE
1: Transparency	C	5. Supporting evidence	C
2. Conflict of interest	NR	6. Recommendations	C
3. Development group	NR	7. External review	NR
4. Systematic review	C	8. Currency and updates	B

CEP Trustworthy Guideline Appraisal Scale available at [www.ups.upenn.edu/cep/methods](http://www.ups.upenn.edu/cep/methods)

## Systematic reviews

Two systematic reviews of SARS-CoV-2 vaccines were found by our searches (Table 13, Table 14). The first (3) was published in May 2020 with searches completed April 17, 2020. At that time, only one trial of an mRNA vaccine was found, and results of it had not been reported. The second systematic review (4) has not been peer-reviewed and published, but a preprint of the authors’ manuscript was posted to the medRxiv server on November 4, with searches completed on October 20. Five trials were meta-analyzed in this review, but only one of them (5) involved an mRNA vaccine. That trial was very small, and while it found a higher rate of adverse events in the vaccine group than in the placebo group, that difference was not statistically significant. All of the reported adverse events were minor, most were localized, and all resolved within days.

A “living” systematic review of COVID-19 vaccine studies is planned; its protocol was published in November 2020 (6). Serious adverse events will be a primary outcomes measure of the review, and minor adverse events will be a secondary outcome. There is no project website reported yet.

**Table 13. Systematic review findings**

Reviewer	Findings	Comment
Yuan 2020 (4)	Adverse event data from five clinical trials was meta-analyzed. Most of the reported adverse events were localized and all adverse events resolved within a few days. The one trial of an mRNA vaccine (5) included only 36 subjects and differences between vaccine and placebo group were not statistically significant. Unlike the other trials, the mRNA vaccine trial did not report adverse reactions by specific type. Overall risk of bias was not assessed, but the mRNA vaccine trial was at risk of attrition bias.	Review of SARS-CoV-2 vaccines. Unpublished preprint. <u>Meta-analysis combined results from trials of different types of vaccine technologies.</u>
Checucci 2020 (3)	A phase I trial of mRNA-1273 was in progress: results were not yet published. Six trials of other SARS-CoV-2-specific vaccines were also in progress, along with three trials of BCG vaccine for prevention of SARS-CoV-2 infection.	Review of SARS-CoV-2 vaccines.

**Table 14. Systematic review appraisal**

Review	Yuan	Checucci
1. Search terms described	Y	Y
2. Two or more databases	Y	Y
3. Inclusion/exclusion criteria	Y	N
4. Number of included/excluded	Y	Y
5. Two independent screeners	N	Y
6. Two independent reviewers	Y	Y

Review	Yuan	Checucci
7. Study quality assessed	Y	N
8. Heterogeneity assessed	Y	N
9. Publication bias assessed	Y	N
10. Studies described in evidence table	Y	N
11. Funding described, no conflict	Y	Y

CEP modified AMSTAR scale available at [www.ups.upenn.edu/cep/methods](http://www.ups.upenn.edu/cep/methods)

## Primary studies

Because of the urgent nature of the topic and the absence of high-level evidence, we proceeded to review and analyze results from primary studies of mRNA vaccines (Table 15). All of the mRNA vaccine safety data published to date is from early-phase clinical trials. Some of the data comes from non-peer-reviewed and unpublished manuscripts, as noted in the table. This data should be used with caution.

The studies are all small: they lack sufficient power to detect and assess the probability of uncommon adverse events, so the absence of such events in these trials should not be taken as evidence these events may not happen when mRNA vaccines are used more widely. Phase III trials that may yield more information on these events are in progress (Table 16) but their results should not be expected until mid-2021. Because the trials published to date were small, and done in part to optimize dosing, we will analyze their results only qualitatively.

No serious events as defined in FDA guidance (life-threatening, disabling, or requiring hospitalization) were reported in any of the trials. However, both systemic adverse events such as fatigue, headache, muscle aches, and chills; and localized adverse events such as pain at the injection site were very common in all of the trials. Most of the adverse events were mild, and resolved within one or two days. Serious events, defined as events that temporarily interfered with subjects' everyday activities, were reported by approximately 5 to 10 percent of study subjects. These too resolved within one or two days.

While there is not sufficient data to statistically test these observations, a few trends are seen in the data. First, the rate of adverse events and the rate of serious adverse events were higher after a subject's second injection compared to the first one. Second, subjects receiving higher doses of the vaccine reported more adverse events and more severe adverse events. There is a possible trend towards a reduced rate of adverse events in older subjects than in younger ones.

There is not sufficient data to permit any conclusions about the comparative safety of specific vaccines. While one study reported on mRNA influenza vaccines and another reported on a respiratory syncytial virus vaccine, there is not sufficient evidence to draw more generalized comparisons of the safety of mRNA vaccines compared to other types of vaccines.

**Table 15. Adverse events in published clinical trials of mRNA vaccines**

Study Product	Target Type	N Follow-up	Adverse events: (first dose, second dose)	Comment
NCT04283461 2020 (7) mRNA-1273	SARS-CoV-2 Phase I	40 8 weeks	Serious events: 0/40, 0/40 Severe systemic symptoms: 0/40, 2/40 (1 fatigue, 1 fever) Severe local symptoms: 0/40, 0/40 Any systemic symptoms: Low dose: 10/20, 9/20 Medium dose: 6/20, 15/19 Any localized symptoms: Low dose: 11/20, 13/20 Medium dose: 16/20, 18/19	Dose-ranging study in subjects aged 56 and older. Increased number and severity of symptoms with second dose compared to first dose. Low dose: 25 µg, medium dose: 100 µg Severe events defined as those preventing daily activity.
NCT04283461 2020 (8) mRNA-1273	SARS-CoV-2 Phase I	45 8 weeks	Serious events: 0/45, 0/42 Severe systemic symptoms: 0/45, 3/42 (3 chills, 2 fatigue, 1 fever, 1 headache, 1 myalgia) Severe local symptoms: 2/45, 2/42 (4 erythema, 1 swelling) Any systemic symptoms: Low dose: 5/15, 7/13 Medium dose: 10/15, 15/15; High dose: 8/15, 10/14 Any localized symptoms: Low dose: 10/15, 10/13 Medium dose: 15/15, 15/15; High dose: 15/15, 14/14	Dose-ranging study in subjects aged 18-55. Increased number and severity of symptoms with second dose compared to first dose. Low dose: 25 µg, medium dose: 100 µg, high dose: 250 µg.
NCT04380701, NCT04368728 2020 (5, 9-11) BNT162b1, BNT162b2	SARS-CoV-2 Phase I	195 1 week	Serious events: 0/192, 0/180 Severe systemic symptoms: vaccine: 3/156, 8/144; placebo: 0/36, 0/36 Severe local symptoms: V 1/183, P 0/180 (vaccine group: 1 pain at injection site) Specific adverse events (any severity): Fatigue: vaccine: 64/156, 79/144; placebo: 11/36, 10/36 Headache: vaccine: 57/156, 79/144; placebo: 5/36, 3/36 Chills: vaccine: 31/156, 49/144; placebo: 2/36, 1/36 Fever: vaccine: 13/156, 26/144; placebo: 0/36, 0/36 Injection site pain: vaccine: 29/36, 22/24 placebo: 5/15 (combined 1 <sup>st</sup> /2 <sup>nd</sup> )	Trial included arms for both the BNT162b1 and BNT162b2 vaccine candidates. AE rate appears to be higher for BNT162b1. Subgroups of patients aged 18-55 and 65-85 were included and reported. Vaccine groups 10 µg, 20 µg, 30 µg, 100 µg, plus placebo group Arm for high-dose vaccine (100 µg) halted after first dose because this dose was not well tolerated. Numbers of patients reporting any adverse event not reported; events were reported by type; with fatigue, headache, chills, and fever most common.

Study Product	Target Type	N Follow-up	Adverse events: (first dose, second dose)	Comment
NCT04368728 2020 (12) BNT162b1	SARS-CoV-2 Phase I	60 1 week	Serious events: 0/60 Specific adverse events (any severity) Fatigue: 35/60, 27/48 Headache: 33/60, 30/48 Muscle pain: 24/60, 23/48 Chills 25/60, 22/48 Injection site pain: 41/60, 32/60	Vaccine groups 1 µg, 10 µg, 30 µg, 50 µg, 60 µg. No placebo group. No second dose given to 60 µg vaccine group because of adverse reactions to second dose in 50 µg group. Numbers of patients reporting any adverse event not reported; events were reported by type; with fatigue, headache, muscle pain, and chills most common. Increased adverse events and increased severe events in higher-dose groups.
NCT 04449276 2020 (13) CVnCoV	SARS-CoV-2 Phase I	245 1 week	Serious events: V 0/215, P: 0/32 Severe systemic symptoms: vaccine: 22/215, 30/201; placebo: 0/32, 0/30 Severe local symptoms vaccine: 3/215, 0/201; placebo: 0/32, 0/30	Unpublished, non-peer reviewed manuscript. Vaccine groups 2 µg, 4 µg, 6 µg, 8 µg, 12 µg. Discrepancy between table and figure, data from figure were used.
Merck/Moderna 2020 (14) mRNA-V177	RSV Phase I	197 1 week (see note)	Serious events: vaccine 0/134, placebo 0/45 Medically attended adverse events: vaccine 58/134, placebo 24/45 Any systemic symptoms: vaccine: 100/134, placebo 16/45 Most common symptoms fatigue, headache, malaise Any local symptoms: vaccine: 131/134, placebo 7/45 Most common symptoms: pain, tenderness.	Single-dose vaccine. Follow-up 1 week for systemic and local symptoms, 1 year for serious events and medically-attended adverse events. Separate study arms for subjects aged 18-49 and subjects aged 60-79. Vaccine doses: younger: 25 µg, 100 µg, 200 µg; older: 25 µg, 100 µg, 200 µg, 300 µg. Frequency of adverse events similar in younger and older subjects, but severity appears to be greater in older subjects.
NCT03076385, NCT03345043 2019 (15)	Influenza (H10N8 and H7N8) Phase I	301 1 week	Serious events: 0/197, 0/170 Muscle pain: vaccine: 79/197, 57/170; placebo: 7/71, 1/63 Fatigue: vaccine: 51/197, 40/170; placebo: 9/71, 4/63 Headache: vaccine: 50/197, 47/170; placebo: 11/71, 7/63 Injection site pain: vaccine: 151/197, 118/170 placebo 7/71, 5/63	Adverse event rate higher for H10N8 vaccine than for H7N8 vaccine. Data from arms with intradermal injection not included in this table.

All studies were randomized controlled trials

Follow-up measured from date of first vaccine dose

## Trials in progress

Table 13 lists mRNA vaccine clinical trials registered in ClinicalTrials.gov that are expected to enroll 500 or more subjects. These will yield additional safety data once they are completed. The one relevant trial found in the European Clinical Trials Registry was also included in the US registry. No clinical trials of mRNA vaccines against pathogens other than SARS-CoV-2 have reached the 500 subject threshold.

**Table 16. Large clinical trials of mRNA vaccines**

Trial ID	Phase	Product	N	Status	Start	Completion
NCT04652102	II/III	CVnCoV	36,500	Not yet recruiting	Dec. 2020 (estimated)	March 2021
NCT04649151	II/III	mRNA-1273	3,000	Not yet recruiting	Dec. 2020 (estimated)	June 2022
NCT04649021	II	BNT162b2	960	Not yet recruiting	Dec. 2020 (estimated)	Dec. 2021
NCT04515147	II	CVnCoV	660	Recruiting	Sept. 2020	Nov. 2021
NCT04470427	III	mRNA-1273	30,000	†–Active, not recruiting	July 2020	Oct. 2022
NCT04405076	II	mRNA-1273	600	†–Active, not recruiting	May 2020	March 2021
NCT04368728	I/II/III	BNT162b1, BNT162b2	44,000	Recruiting	April 2020	Aug. 2021

Start–actual date of first patient enrollment.

Completion–projected primary completion date

†–not updated since before November 15, 2020

## Conclusions

The current evidence base on messenger RNA (mRNA) vaccines is made up entirely of small early-stage trials, nearly all of which examined only short-term outcomes. They lack sufficient power for testing the statistical significance of most results, and for assessing the risk of serious but uncommon adverse events.

The size of these trials and their dual purpose in evaluating dosing and safety precludes quantitative synthesis or GRADE analysis of their results, but there are a few trends that appear to be consistent across the different studies. Systemic adverse effects such as fatigue, headache, muscle aches, and chills are common following administration of mRNA vaccines, but they usually resolve within a day or two. Localized adverse effects, most notably pain at the injection site, are also common, and also resolve within a day or two. The rate of severe adverse effects (severe enough to interfere with a person’s daily activities) appears to be in the range of 5 to 10 percent. The rate and severity of adverse events increases with vaccine dose. The rate and severity of adverse events also appears to be greater following a second dose of vaccine than following the first.

Larger clinical trials of mRNA vaccines against the SARS-CoV-2 coronavirus are in progress, and their results are expected in mid-2021. Once evidence from those trials is published, more certain conclusions about the safety of these vaccines may be reached. Additional trials will be necessary to determine the relative safety of mRNA vaccines and vaccines using more established technologies.

Clinical guidance specific to the use of mRNA vaccines is lacking at this time, because of the lack of clinical evidence.

## Conflict of interest disclosures

None of the authors have any relevant financial relationships with commercial interests associated with the subject of this review. The CEP conflict of interest disclosure policy is found at [www.uphs.upenn.edu/cep/methods](http://www.uphs.upenn.edu/cep/methods). CEP reports are funded by the University of Pennsylvania Health System.

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