

Assessment of Comirnaty Injections of Pregnant Women in the Manufacturer's Risk Management Plan and by the European Medicines Agency: Mandatory Injections for Caregivers in France

Jérôme Sainton, MD

Engineer, General practitioner, Bioethicist, Cabinet médical « Le Ruisseau », Reims 51100, France;
email: dr.jerome.sainton@lilo.org

ABSTRACT

The objective of this note is to analyse the safety assessment of Comirnaty vaccination of pregnant women in the manufacturer's risk management plan (RMP) and in the European Medicines Agency (EMA) fact sheet, and to measure the impact on the recommendations that led to the mandatory vaccination of pregnant women caregivers and health-related professionals in France.

The evaluation of this safety was carried out in two phases. In the first phase, which ran from late 2020 to early 2022, the safety profile of the vaccine was not known in pregnant women. In the second phase, which ran from early 2022, the RMP and the EMA report data that were considered reassuring for short-term safety, but were limited. Long-term safety remains still unknown. The RMP is cautious and suggests that intentional injection of pregnant women will remain limited.

The detailed analysis of risk management by the manufacturer, the EMA and the French authorities reveals, to varying degrees, a lack of rigor. The EMA has disregarded certain elements of prudence maintained by the manufacturer, while the manufacturer has allowed the only real clinical trial that might determine any benefit-risk balance to lapse. What is more the only study was restricted to the third trimester of pregnancy. The French authorities recommended mandatory injection of pregnant women caregivers and health-related professionals at a time when the manufacturer and the EMA could provide no guarantees.

Keywords: *Comirnaty, guidelines COVID mRNA vaccine, mandatory vaccination during pregnancy, risk-benefit analysis,*

Introduction

The Control Group Survey of Unvaccinated Americans has recently raised concerns about the safety of vaccination in general, particularly in pregnant women. While based exclusively on data grounded in reports

from the affected individuals, a parent, or a legal guardian, it reported a risk increase of 697% for at least one chronic disorder/disease later in life after the individual's mother was exposed during pregnancy to one or more vaccines (Garner, 2022). While the Garner study is subject to “self-selection bias” (Tripepi, et al., 2010), it reminds us that pregnant women and their unborn children constitute a specific and vulnerable population in medical contexts. Romero et al. (2023) point out:

Because normal growth and development is a process that is just beginning with conception and continuing through childhood, adolescence, and adulthood, the detrimental effects of toxins and genetic corrupting factors can manifest over a lifetime (p. 902).

Vaccination against COVID-19, for itself, is unprecedented, both in its relationship to this type of virus (Totura & Bavari, 2019) and in its introduction of technological innovations not previously tested for large scale uses on humans (Seneff & Nigh, 2021; Nance & Meier, 2021). For those reasons and because of the limited or entirely missing studies of benefit-risk balance, it is impossible to say with any certainty at present how safe Comirnaty may or may not be. This remains to be determined, at the very least by carrying out analyses of all-cause mortality according to vaccination status, age group, and risk factors. Nevertheless, the results of some studies carried out among the youngest populations (Bardosh et al., 2022; Chiu et al., 2023; Mansanguan et al., 2022; Sun et al., 2022), or those analysing its impact on reproductive functions (Gat et al., 2022; Laganà et al., 2022) may not augur well.

In France, if they were caregivers or working in the health professions, pregnant women have been subject to mandatory injections against SARS-CoV-2 since summer 2021. Most of them received the Pfizer Comirnaty (BNT162b2) vaccine — which has recently been examined for its biochemistry by Segalla (2023).

The objective of this note is to analyse the elements related to the evaluation of the safety of vaccination of pregnant women with Comirnaty in terms of the following sources and their evolution over time:

- in the manufacturer Pfizer's Risk Management Plan (RMP) (§ 1) ;
- in the European Medicines Agency (EMA) ad hoc fact sheet (§ 2) ;
- and in the recommendations which, in France, led to the mandatory vaccination of pregnant women caregivers and health-related professionals (§ 3).

1. Pfizer's Risk Management Plan

The RMP is available on the EMA website (Pfizer, n.d.). In each of its versions, the RMP considers the issue of safety of vaccination of pregnant women at three levels: dedicated clinical trial; real-life safety studies; missing information and impact on the benefit-risk balance (see **Table 1**; Pfizer, 2020, 2021a, 2021b, 2021c, 2021d, 2022a, 2022b, 2022c).

CLINICAL TRIAL AND REAL-LIFE STUDIES

The clinical trial dedicated specifically to injections in pregnant women begins in the second half of 2021. This is “a phase 2/3 study to evaluate the safety, tolerability, and immunogenicity of [the BNT162b2 product] in healthy pregnant women” (Pfizer, 2021b, 2021c, 2021d, 2022a, 2022b, 2022c) and “to describe the safety of maternal immunization in infants born to breastfeeding maternal participants vaccinated [...] during pregnancy” (Pfizer, 2021c, 2021d, 2022a, 2022b, 2022c). In its general presentation, this trial is said

“to explore unexpected negative consequences [of maternal vaccination] to the embryo or foetus” (Pfizer, 2021d, 2022a, 2022b, 2022c).[†] The trial was to include “approximately 4000 pregnant women at 24 to 34 weeks gestation [...] being randomised in a 1:1 ratio to vaccine or placebo” (Pfizer, 2021b, 2021c).

The February 2022 version tells us that “enrolment of participants [...] was stopped on 25 October 2021 due to recruitment challenges as a result of global recommendations for COVID-19 vaccination in pregnant women”. In the end, only “a total of 348 (209 in phase 2 and 139 in phase 3) pregnant women at 24 to 34 weeks gestation were randomised in a 1:1 ratio to vaccine or placebo” (Pfizer, 2022a). The study report is due April 30, 2023.

In addition to this clinical trial, the RMP indicates that it will be possible to rely on real-life observational studies. These studies, which numbered three (Pfizer, 2020), then four (Pfizer, 2021c), and finally five (Pfizer, 2022a), are still in progress (Pfizer, 2022c, n.d.).

MISSING INFORMATION — RISK-BENEFIT IMPACT

Until early 2022, the RMP states that “*the safety profile of the vaccine is not known* in pregnant or breastfeeding women” but that “there may be pregnant women who choose to be vaccinated despite *the lack of safety data*” [my italics here and throughout what follows] (Pfizer, 2020, 2021a, 2021b, 2021c, 2021d). A few months earlier (i.e., prior to the November 2021 release), the RMP still stated that “it is not known if maternal vaccination with COVID-19 mRNA vaccine would have unexpected negative consequences to the embryo or foetus” (Pfizer, 2020, 2021a, 2021b, 2021c).

From the February 2022 version onwards, the RMP states that, while “the safety profile of the vaccine is not yet fully known in pregnant or breastfeeding women”, “however, post-marketing experience in pregnant women is available” (Pfizer, 2022a, 2022b, 2022c). It maintains its established recommendation from September 2021 that administration of Comirnaty during pregnancy “should only be considered when the potential benefits outweigh any potential risks for the mother and foetus” (Pfizer, 2021c, 2021d, 2022a, 2022b, 2022c).

In all versions from December 2020 to the present, the RMP considers pregnant women to be “a *vulnerable* population”, that “monitoring vaccine safety in pregnant women is *critical*”, and that “it is important to obtain long term follow-up on women who were pregnant at or around the time of vaccination so that any potential negative consequences to the pregnancy can be assessed”. In any case, it expects “likely *very limited intentional* vaccination of pregnant women” (Pfizer, 2020, 2021a, 2021b, 2021c, 2021d, 2022a, 2022b, 2022c).

COMMENTS

The elements relating to the clinical trial raise some questions. First, is the stated objective of “describ[ing] the safety of maternal immunisation in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy” entirely congruent with the overall objective of

[†] Here it may be useful to keep in mind Garner’s findings regarding long-range consequences of maternal vaccinations during pregnancy. In that survey, the traditional vaccine products used before 2020 were, according to the results of Romero et al. (2023) examining records of adverse events attributed to the COVID-19 products, many orders of magnitude less likely to cause harm to the pregnant women or to their babies in gestation.

“explor[ing] unexpected negative consequences [of maternal vaccination] to the embryo or foetus”? More importantly, how can one “explore unexpected negative consequences to the embryo or foetus” and, more broadly, how can this be done with respect to the 1st and 2nd trimesters, if the only pregnant women in this trial are already “at 24 to 34 weeks gestation” i.e., in their 3rd trimester?

Secondly, how can one hope for sufficient power in such a trial with 4,000 participants, when the pivotal study, eleven times better supplied, proved incapable of showing the efficacy of the Comirnaty injectable against the risk of severe adverse events? Notwithstanding, Fraiman et al. (2022) found that it was possible to calculate an *unfavourable* benefit-risk ratio when the COVID hospitalisations avoided by vaccination were weighed against the serious side effects caused by the injections. And how can one explain the failure of the manufacturers to anticipate the difficulties that finally forced them to reduce the sample-size of the trial by eleven times (thus ending up with a sample-size about 125 times smaller than that of the pivotal study) despite its “critical” importance?

Regarding the missing information and its impact on estimation of the benefit-risk balance, the RMP mentions the availability of “post-marketing experience in pregnant women” from early 2022. The RMP refers here to an analysis of US pharmacovigilance data by the *Centers for Disease Control and Prevention* (CDC), which is reassuring, particularly with regard to the risk of early “spontaneous” miscarriage (Shimabukuro et al., 2021b). But this study, which has many limitations, was found to be in need of correction three months after publication: in particular, it said *nothing* about the impact of Comirnaty on the risk of early spontaneous miscarriage (Brock & Thornley, 2021; NEMJ ed., 2021; Shimabukuro et al., 2021a, 2021b).

2. EMA Comirnaty fact sheet

The EMA Comirnaty fact sheet has a paragraph entitled “§ Can pregnant or breast-feeding women be vaccinated with Comirnaty [EMA, n.d.]?” That document has been subject to multiple changes (see **Table 2**; EMA, 2020, 2021b, 2022b, 2022c, 2022d).

CAN PREGNANT WOMEN BE VACCINATED WITH COMIRNATY?

Until February 2022, the EMA stated that “data on the use of Comirnaty during pregnancy are *very limited*” (EMA, 2020) and then “*limited*” (EMA, 2021b) and that “the decision on whether to use the vaccine in pregnant women should be made *in close consultation with a healthcare professional* after considering the benefits and risks” (EMA, 2020, 2021b).

In early 2022, the EMA issued a memorandum based on data that, although still limited, were considered reassuring about COVID vaccination of pregnant women (EMA, 2022a).

From March 2022, the relevant paragraph of the EMA Comirnaty fact sheet will state that “Comirnaty *can be used* during pregnancy” (EMA, 2022b, 2022c, 2022d).

COMMENTS

The data on which the EMA based its statement at the beginning of 2022 were mainly derived from observational studies.

Of these, the only prospective study (Kachikis et al., 2021) used a small sample-size, very few control subjects, and relied on self-reporting of symptoms, abnormalities, etc. introducing the potential for various biases.

All the others were either descriptive or retrospective and, with two exceptions (see below), extremely limited: due, on the one hand, to their methodology and, on the other hand, to the small number of subjects and the way in which information was collected (automated databases without clinical verification, voluntary recruitment, collection of data by self-completed questionnaire, etc.). The post-marketing study referenced in Pfizer's RMP mentioned above is one of these EMA references. Of these studies, it can be said that they did not detect a safety signal, but also that they were not designed to do so.

Two studies conducted using the *Vaccine Safety Datalink database* (built from those of the CDC and several American health systems) stand out because they were able to engage a substantial number of people from a large population. These data are reassuring, but they are nevertheless subject to limitations inherent to the methodology, as the authors point out (Kharbanda et al., 2021; Lipkind, 2022). Both studies also rely on the same data source. The reliability of the data source should be checked, particularly with regard to the categorization of vaccination status. An independent analysis of a similar database in the United Kingdom, for example, found a major categorization bias (Neil et al., 2022).

In any case, the level of safety of vaccination in pregnant women should be related to the level of protection conferred by it according to the principle of respecting the benefit-risk balance to the impacted individual. None of the EMA references seem to take that principle into consideration. However, one of the EMA references (UK Health Security Agency, 2021) refers to an interesting study which, though not designed to meet this need, does allow an indirect approach (Stock et al., 2022). It allows us to deduce that, for most pregnant women (without risk factors) and in the current context, the determination of an undoubtedly favorable benefit-risk balance would imply almost total and absolute safety and, to demonstrate this, a methodology would be required that none of the studies referenced by the EMA could possibly provide (see **Appendix**).

Finally, and not incidentally, all these estimates are about short-term safety. The long-term safety of Comirnaty vaccination during pregnancy is completely unknown (also see Romero et al., 2023) in this journal where they stress the long range impact on development of certain early toxic exposures). It should be noted that the Comirnaty product was exempted from any pre-clinical genotoxicity study.

3. Impact on mandatory vaccination of female caregivers and other health-related professionals in France

At the beginning of April 2021 in France, the Vaccine Strategy Guidance Board (*Conseil d'orientation de la stratégie vaccinale*) extended vaccination against COVID to all pregnant women, regardless of their individual risk factors (COSV, 2021a). At the end of July 2021, it stated that there was no reason not to carry out this vaccination in the first trimester of pregnancy (COSV, 2021b). The April 2021 opinion supposedly established the safety of vaccination in pregnant women on the basis of two articles (Male, 2021; Rasmussen & Jamieson, 2021) that affirmed its safety due to reporting the absence of a safety signal: (1) in

the manufacturer's pre-clinical animal study (21 births of injected rats[‡]), in rare cases of pregnant women inadvertently enrolled in the manufacturer's pivotal study, and in passive pharmacovigilance mainly from the US, with about 20,000 pregnant women vaccinated at that time. The later, July 2021 opinion was merely stated by the government agency without citing any reference studies to back it up.

The French National authority for health (*Haute autorité de santé*), for its part, declared at the beginning of March 2021 “that the administration of COVID-19 vaccines in pregnant women [was] not contraindicated” and that “it should be considered if the potential benefits outweigh the risks for the mother and the foetus” (HAS, 2021a). To the best of my knowledge, however, the agency has not subsequently revisited the issue. In particular, from summer 2021 onwards, no restriction or even mention is made of pregnant women in opinions on mandatory vaccination of health care workers (HAS, 2021b, 2021c, 2022).

Yet, in the spring and summer of 2021, the RMP was still saying categorically that “the safety profile of the vaccine is *not* known in pregnant or breastfeeding women” (Pfizer, 2021b), while the EMA had written earlier that “data on the use of Comirnaty during pregnancy are *very limited*” (EMA, 2020). Both agencies, as surprising as it might seem, were considering vaccination of pregnant women “despite the lack of safety data” (Pfizer, 2021b). But such a requirement would only be formalised, by the RMP, from September 2021, and on condition that the administration of Comirnaty during pregnancy “should *only be considered* when the potential benefits outweigh any potential risks for the mother and foetus” (Pfizer, 2021c), and in the case of the latter, “in close consultation with a healthcare professional after considering the benefits and risks” (EMA, 2020, 2021b).

As we have seen, it is only from the beginning of 2022 onwards that the EMA moved (and not without serious limitations) from the exception to the rule enabling a generalized permission: they wrote explicitly for the first time that “Comirnaty can be used during pregnancy” (EMA, 2022b). The manufacturer, for its part, however, would continue to recommend in 2022 that its product “should only be considered [during pregnancy] when the potential benefits outweigh any potential risks for the mother and foetus” and would continue to predict “likely very limited intentional vaccination of pregnant women” (2021c, 2021d, 2022a, 2022b, 2022c).

Conclusion

In accordance with the most elementary medical art, the RMP considers that pregnant women constitute “a vulnerable population” and that “monitoring vaccine safety in [them] is critical” (Pfizer, n.d.). At a minimum, therefore, the individual benefit-risk balance of Comirnaty vaccination in pregnant women should be determined.

In the RMP and in the EMA fact sheet, the safety assessment of Comirnaty vaccination of pregnant women has gone through two phases, revolving around the pivotal months of February-March 2022. In the first period, which runs from late 2020 to early 2022, safety cannot be guaranteed; the RMP is very clear that “the safety profile of the vaccine is *not* known in pregnant or breastfeeding women” (Pfizer, 2020, 2021a,

[‡] Fertility and reproductive toxicity was tested in rats. Injected rats showed 2.4 times more spontaneous pre-implantation abortions than non-injected rats, a signal that was not considered to be of concern as the loss rate was within the range of historical control data. The same was true for some congenital anomalies found in the offspring. All 21 pups born to injected rats were euthanised at 21 days of age (EMA, 2021a, p. 50).

2021b, 2021c, 2021d). In the second period, from early 2022, the RMP and the EMA report data that, although limited, are considered reassuring about short-term safety. These data are limited: neither the RMP nor the EMA are able to provide a quantified estimate of the benefit-risk balance. Yet this is required in order to comply with the manufacturer's current recommendation that the use of Comirnaty during pregnancy "should only be considered when the potential benefits outweigh any potential risks for the mother and foetus" (Pfizer, n.d.). This is especially true since long-term safety is still unknown. Logically, therefore, the RMP still expects "likely very limited intentional vaccination of pregnant women" (Pfizer, n.d.).

The detailed analysis of risk management by the manufacturer and the European safety agency reveals a lack of rigor. The EMA has disregarded certain elements of prudence that were maintained by the manufacturer, while the latter has allowed the only real clinical trial capable of determining an individual benefit-risk balance to fail. At the same time, had such a trial been conducted as planned, it was in any case not designed to provide a satisfactory assessment of safety during pregnancy because the first and second trimesters were excluded and the sample-size was reduced to a level that would have made reasonable inferences to the population uninformative. Concerning the recommendation of the French authorities to vaccinate all pregnant women, particularly in the case of mandatory COVID-19 injections for all caregivers and health-related professionals (including those who happened to be pregnant women), the decision was made at a time when the manufacturer and the EMA could not and did not provide any guarantees.

Conflicts of Interest

The author declares no conflicts of interest.

Legal Disclaimer

The information on the website and in the **IJVTPR** is not intended as a diagnosis, recommended treatment, prevention, or cure for any human condition or medical procedure that may be referred to in any way. Users and readers who may be parents, guardians, caregivers, clinicians, or relatives of persons impacted by any of the morbid conditions, procedures, or protocols that may be referred to, must use their own judgment concerning specific applications. The contributing authors, editors, and persons associated in any capacity with the website and/or with the journal disclaim any liability or responsibility to any person or entity for any harm, financial loss, physical injury, or other penalty that may stem from any use or application in any context of information, conclusions, research findings, opinions, errors, or any statements found on the website or in the **IJVTPR**. The material presented is freely offered to all users who may take an interest in examining it, but how they may choose to apply any part of it, is the sole responsibility of the viewer/user. If material is quoted or reprinted, users are asked to give credit to the source/author, and to conform to the non-commercial, no derivatives, requirements of the [Creative Commons License 4.0 NC ND](https://creativecommons.org/licenses/by-nc-nd/4.0/) or to any other license that takes precedence over it.

Appendix:

Indirect Approach to the Short-Term Individual Benefit-Risk Balance of Vaccination in Pregnant Women

In the specific case of pregnant women, the manufacturer insists that the administration of Comirnaty during pregnancy “should only be considered when the potential benefits outweigh any potential risks for the mother and foetus” (Pfizer, [n.d.](#)). In other words: under the strict conditions of a positive and certain individual benefit-risk balance.

One of the EMA references is based on a study that may allow us to indirectly approach this balance, at least in the short term. This is a prospective cohort study by Stock et al. on the benefit of vaccination of pregnant women across Scotland in the ten months following the roll-out of vaccination. In this study, the authors sought to assess the impact of COVID and vaccination on nearly 150,000 pregnancies (80,000 births at the time the analysis was completed). Of these 150,000 pregnancies, COVID was associated with the hospitalisation of 800 pregnant women, 100 of whom were in critical care (one of whom died), while 19 perinatal deaths occurred within one month of a COVID infection. Of all these serious events, vaccinated pregnant women appeared to be highly protected, with a relative vaccine efficacy of between 91% and 98% or even 100% (Stock et al., [2022](#)).

The calculation of this relative effectiveness is certainly open to criticism. Not only are we talking about events *associated with* and not *caused by* COVID, but the calculation of the vaccine effectiveness is also subject to major biases, among others:

- evaluation bias: as unvaccinated subjects are considered to be at greater risk of adverse outcomes than vaccinated subjects, they tend to be more likely to be hospitalised than their counterparts (part of the vaccine’s effectiveness stems from its presupposition, a trend I have seen in my practice as a field doctor);
- classification bias: in this study, vaccinated subjects who received their first dose in the three weeks prior to infection are categorised as unvaccinated, so that some number of events relating to the vaccinated will be falsely attributed to the unvaccinated — a bias potentiated by the coincidence of the start of the vaccination campaign for pregnant women during the Delta epidemic (Stock et al., [2022](#), fig.3), and further exacerbated by the probable phenomenon of sensitization to the disease in the two weeks following the first injection (Cunningham, [2021](#); Doshi, [2020](#), [2021a](#), [2021b](#); Lopez Bernal et al., [2021](#); Moustsen-Helms et al., [2021](#); Public Health Ontario, [2021](#), p. 4);
- confounding bias: events are compared without adjustment for socio-economic factors, a bias that is particularly critical for perinatal mortality.

The last two might be sufficient to explain the differences observed, given their order of magnitude. To neutralise these various biases, and to have a direct idea, in the end, of the short-term benefit-risk balance

of vaccination for pregnant women at that time, it would have been necessary to compare the incidence of the objective events in this study (mortality of pregnant women, perinatal mortality), all causes combined, according to a rigorous multivariate analysis, and according to correctly categorised vaccination status.

However, let us accept the calculation of the relative effectiveness on serious events in this study. Even disregarding, therefore, the above caveats, it is important to transpose this effectiveness into absolute effectiveness. Then, by approximation (the idea here being to identify orders of magnitude), vaccination would have offered a real risk reduction of about 0.5% against the risk of hospitalisation, 0.05% against the risk of entering critical care, 0.01% against the risk of perinatal death, and 0.001% against the risk of maternal death. Leaving aside the various biases, this would at best measure a real but extremely modest benefit from vaccination. The benefit would be all the more modest as the results of this national cohort do not distinguish between subjects more particularly at risk and others who are less at risk where the benefit might only be quantifiable in the former. Moreover, the study was conducted at a time when vaccine efficacy was best, circulating variants (alpha and delta) were the most dangerous, and naturally acquired immunity in the population was supposedly still modest. The Omicron context, however, reversed both of these points, further reducing any possible benefit.

We can therefore, indirectly, have an idea of the level of safety required for vaccination in pregnant women, as well as the level of quality of the experimental design purporting to evaluate it, so that the benefit-risk balance (in the short term) remains favorable. In the face of a low (barely quantifiable) disease-risk and treatment-benefit, one must ensure almost absolute safety, which requires an evaluation design of a scale and rigor far beyond those of currently available studies. Indeed, let us posit for a treatment the benefit of an absolute risk reduction of the order of 0.01%. To have 95% chance of detecting 1 risk of serious harm of the same order (0.01%) related to this treatment would require a randomized trial of 30,000 subjects in the group receiving the said treatment (Onakpoya, 2018). And such a protocol, already ambitious, would not be conclusive, as the identification of a single case is insufficient to establish a cause and effect relationship.

Tables

TABLE 1: RISK MANAGEMENT PLAN OF COMIRNATY (PFIZER) — EVOLUTION OF THE PARAGRAPHS RELATING TO VACCINATION DURING PREGNANCY

§ Clinical trials in pregnant women

Pfizer (version)	AEM (put online)	New or modified elements from one version to the next
Version n° 1.0 (Pfizer, 2020) 21/12/2020	March 2021	<ul style="list-style-type: none"> ● Exclusion from the pivotal clinical study “Women who are pregnant or breastfeeding: Reason for exclusion: To avoid use in a vulnerable population. / Is it considered to be included as missing information? Yes. / Rationale: It is not known if maternal vaccination with COVID-19 mRNA vaccine would have unexpected negative consequences to the embryo or foetus.” (p.58) ● On-going and planned additional pharmacovigilance activities “C4591015 Planned / [country] Not available / Planned clinical study to assess safety and immunogenicity in pregnant women who receive COVID-19 mRNA vaccine / Use in pregnancy and while breast feeding. Protocol draft submission: 28-Feb-2021

		Final CSR submission: 30-Apr-2023” (p.89)
Version n° 1.1 (Pfizer, 2021a) 17/03/2021	May 2021	<i>no change</i>
Version n° 2.0 (Pfizer, 2021b) 29/04/2021	June 2021	<ul style="list-style-type: none"> ● Clinical trial exposure (<i>new element</i>) <p>“C4591015: A phase 2/3 study to evaluate the safety, tolerability, and immunogenicity of SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older. Approximately 4000 pregnant women at 24 to 34 weeks gestation are being randomised in a 1:1 ratio to vaccine or placebo.” (p.28)</p>
Version n° 2.3 (Pfizer, 2021c) 24/09/2021	November 2021	<ul style="list-style-type: none"> ● On-going and planned additional pharmacovigilance activities (<i>modification</i>) <p>“C4591015 Ongoing / [country] Global / To assess safety and immunogenicity in pregnant women. In addition, exploratory objectives include: (a) To describe the immune response in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. (b) To describe the safety of maternal immunisation in infants born to breastfeeding maternal participants vaccinated with prophylactic COVID-19 mRNA vaccine during pregnancy. Use in pregnancy and while breast feeding. Final CSR submission: 30-Apr-2023” (p.119)</p>
Version n° 4.0 (Pfizer, 2021d) 25/11/2021	December 2021	<ul style="list-style-type: none"> ● Exclusion from the pivotal clinical study (<i>modification</i>) <p>“Women who are pregnant or breastfeeding / Reason for exclusion: To avoid use in a vulnerable population. Is it considered to be included as missing information? Yes. Rationale: Maternal vaccination with COVID 19 mRNA vaccine is being studied in C4591015 to explore unexpected negative consequences to the embryo or foetus.” (p.84)</p> <ul style="list-style-type: none"> ● Clinical trial exposure (<i>modification</i>) <p>“C4591015: A phase 2/3 placebo-controlled, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older.” (p.39)</p>
Version n° 5.0 (Pfizer, 2022a) 02/2022	April 2022	<ul style="list-style-type: none"> ● Clinical trial exposure (<i>modification</i>) <p>“C4591015: A phase 2/3 placebo-controlled, randomized, observer-blind study to evaluate the safety, tolerability, and immunogenicity of SARS-CoV-2 RNA vaccine candidate (BNT162b2) against COVID-19 in healthy pregnant women 18 years of age and older. A total of 348 (209 in phase 2 and 139 in phase 3) pregnant women at 24 to 34 weeks gestation were randomised in a 1:1 ratio to vaccine or placebo. [...] Enrolment of participants into study C4591015 was stopped on 25 October 2021 due to recruitment challenges as a result of global recommendations for COVID-19 vaccination in pregnant women and the increased availability of COVID-19 vaccines. Participants already enrolled will continue follow up evaluations until study end as planned.” (p.39)</p>
Version n° 7.1 (Pfizer, , 2022b) 09/2022	September 2022	<i>no change</i>

Version n° 9.0 (Pfizer, 2022c, n.d.) 11/2022	November 2022	<i>no change</i>
--	---------------	------------------

§ *Non-Interventional post-approval safety studies in pregnancy*

Pfizer (version)	AEM (put online)	New or modified elements from one version to the next
Version n° 1.0 (Pfizer, 2020) 21/12/2020	March 2021	“It is anticipated that initial use in pregnancy will be subject to local health authority recommendations regarding which individuals should be vaccinated and likely very limited intentional vaccination of pregnant women; therefore, initially this information will derive from 3 of the real-world safety studies (C4591010, C4591011, and ACCESS/VAC4EU). The MAA [marketing authorisation applicant] agrees that monitoring vaccine safety in pregnant women is critical” (p.80)
Version n° 1.1 (Pfizer, 2021a) 17/03/2021	May 2021	<i>no change</i>
Version n° 2.0 (Pfizer, 2021b) 29/04/2021	June 2021	<i>no change</i>
Version n° 2.3 (Pfizer, 2021c) 24/09/2021	November 2021	mention of a 4 th real-life study in progress
Version n° 4.0 (Pfizer, 2021d) 25/11/2021	December 2021	<i>modification</i> : “MAA [marketing authorisation applicant]” > “MAH [marketing authorisation holder]”
Version n° 5.0 (Pfizer, 2022a) 02/2022	April 2022	mention of a 5 th real-life study in progress
Version n° 7.1 (Pfizer, , 2022b) 09/2022	September 2022	<i>no change</i>
Version n° 9.0 (Pfizer, 2022c, n.d.) 11/2022	November 2022	<i>no change</i>

§ *Missing information — risk-benefit impact*

Pfizer (version)	AEM (put online)	New or modified elements from one version to the next
-----------------------------	-----------------------------	--

<p>Version n° 1.0 (Pfizer, 2020) 21/12/2020</p>	<p>March 2021</p>	<p>● Risks considered important for inclusion in the list of safety concerns in the RMP</p> <p>“Missing Information: Use in Pregnancy and while breast feeding / Risk-benefit impact: The safety profile of the vaccine is not known in pregnant or breastfeeding women due to their exclusion from the pivotal clinical study. Accordingly, maternal COVID-19 impact to either embryo or foetus is also not known. It is important to obtain long term follow-up on women who were pregnant at or around the time of vaccination so that any potential negative consequences to the pregnancy can be assessed and weighed against the effects of maternal COVID-19 on the pregnancy.” (pp.66-67)</p> <p>● Presentation of the missing information</p> <p>“Use in pregnancy and while breast feeding: The safety profile of the vaccine is not known in pregnant or breastfeeding women due to their exclusion from the pivotal clinical study. There may be pregnant women who choose to be vaccinated despite the lack of safety data. It will be important to follow these women for pregnancy and birth outcomes. The timing of vaccination in a pregnant woman and the subsequent immune response may have varying favourable or unfavourable impacts on the embryo/foetus. The clinical consequences of SARS-CoV-2 infection to the woman and foetus during pregnancy is not yet fully understood and the pregnant woman’s baseline health status may affect both the clinical course of her pregnancy and the severity of COVID-19. These factors and the extent to which the pregnant woman may be at risk of exposure to SARS-CoV-2 will influence the benefit risk considerations for use of the vaccine.” (p.70)</p>
<p>Version n° 1.1 (Pfizer, 2021a) 17/03/2021</p>	<p>May 2021</p>	<p><i>no change</i></p>
<p>Version n° 2.0 (Pfizer, 2021b) 29/04/2021</p>	<p>June 2021</p>	<p><i>no change</i></p>
<p>Version n° 2.3 (Pfizer, 2021c) 24/09/2021</p>	<p>November 2021</p>	<p>● Exposure of special populations included or not in clinical trial development programmes (<i>new element</i>)</p> <p>“Pregnant women: There is limited experience with use of COVID-19 mRNA vaccine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryo/foetal development, parturition or post-natal development. Administration of COVID-19 mRNA vaccine in pregnancy should only be considered when the potential benefits outweigh any potential risks for the mother and foetus.” (p.69)</p>
<p>Version n° 4.0 (Pfizer, 2021d) 25/11/2021</p>	<p>December 2021</p>	<p>● Risks considered important for inclusion in the list of safety concerns in the RMP (<i>modification</i>)</p> <p>“Missing Information: Use in Pregnancy and while breast feeding / Risk-benefit impact: The safety profile of the vaccine is not known in pregnant or breastfeeding women due to their initial exclusion from the pivotal clinical study, however one clinical study of the safety and immunogenicity of the COVID-19 vaccine in pregnant women is ongoing (C4591015); and 2 non-interventional studies (C4591009 and C4591011) to assess whether sub-cohorts of interest, such as pregnant women, experience increased risk of safety events of interest following receipt of the COVID-</p>

		19 vaccine are approved. It is important to obtain long term follow-up on women who were pregnant at or around the time of vaccination so that any potential negative consequences to the pregnancy can be assessed and weighed against the effects of maternal COVID-19 on the pregnancy.” (p.98)
Version n° 5.0 (Pfizer, 2022a) 02/2022	April 2022	<p>● Risks considered important for inclusion in the list of safety concerns in the RMP (<i>modification</i>)</p> <p>“Missing Information: Use in Pregnancy and while breast feeding / Risk-benefit impact: The safety profile of the vaccine is not fully known in pregnant or breastfeeding women due to their initial exclusion from the pivotal clinical study however, post-marketing experience in pregnant women is available (Shimabukuro et al., 2021b). Additionally one clinical study of the safety and immunogenicity of the COVID-19 vaccine in pregnant women is ongoing (C4591015); 2 non-interventional studies (C4591009 and C4591011) to assess whether sub-cohorts of interest, such as pregnant women, experience increased risk of safety events of interest following receipt of the COVID-19 vaccine are planned and another 2 non-interventional studies, C4591021 and C4591022, are ongoing. It is important to obtain long term follow-up on women who were pregnant at or around the time of vaccination so that any potential negative consequences to the pregnancy can be assessed and weighed against the effects of maternal COVID-19 on the pregnancy.” (p.104)</p> <p>● Presentation of the missing information (<i>modification</i>)</p> <p>“Use in pregnancy and while breast feeding: The safety profile of the vaccine is not yet fully known in pregnant or breastfeeding women due to their initial exclusion from the pivotal clinical study. There may be pregnant women who choose to be vaccinated. It is important to follow these women for pregnancy and birth outcomes. The timing of vaccination in a pregnant woman and the subsequent immune response may have varying favourable or unfavourable impacts on the embryo/foetus. The clinical consequences of SARS-CoV-2 infection to the woman and foetus during pregnancy are not yet fully understood but some data have suggested that pregnant women have an increased risk of severe disease and complications when affected by COVID-19. This information should be considered in the benefit-risk consideration for vaccination in pregnancy.” (p.117)</p>
Version n° 7.1 (Pfizer, , 2022b) 09/2022	September 2022	<p>● Risks considered important for inclusion in the list of safety concerns in the RMP (<i>modification</i>)</p> <p>“Missing Information: Use in Pregnancy and while breast feeding / Risk-benefit impact: The safety profile of the vaccine is not fully known in pregnant or breastfeeding women due to their initial exclusion from the pivotal clinical study however, post-marketing experience in pregnant women is available (Shimabukuro et al., 2021b). Additionally 2 clinical studies of the safety and immunogenicity of the COVID-19 vaccine in pregnant women are ongoing (C4591009 and C4591015); 1 non-interventional study (C4591011) to assess whether sub-cohorts of interest, such as pregnant women, experience increased risk of safety events of interest following receipt of the COVID-19 vaccine is planned and another 2 non-interventional studies, C4591021 and C4591022, are ongoing. It is important to obtain long term follow-up on women who were pregnant at or around the time of vaccination so that any potential negative consequences to the pregnancy can be assessed and weighed against the effects of maternal COVID-19 on the pregnancy. No data are available yet regarding the use of Comirnaty Original/Omicron BA.1 (15/15 mcg) and of Comirnaty Original/Omicron BA.4-5 (15/15 mcg) during pregnancy and breast</p>

		feeding.” (p.83)
Version n° 9.0 (Pfizer, 2022c, n.d.) 11/2022	November 2022	<i>no change</i>

TABLE 2: COMIRNATY FACT SHEET (EMA) — EVOLUTION OF THE PARAGRAPH RELATING TO VACCINATION DURING PREGNANCY

Late December 2020 (EMA, 2020)	“Animal studies do not show any harmful effects in pregnancy, however data on the use of Comirnaty during pregnancy are very limited. Although there are no studies on breast-feeding, no risk for breast-feeding is expected. The decision on whether to use the vaccine in pregnant women should be made in close consultation with a healthcare professional after considering the benefits and risks.”
Late November 2021 (EMA, 2021b)	“Animal studies do not show any harmful effects in pregnancy, however data on the use of Comirnaty during pregnancy are limited. Although there are no studies on breast-feeding, no risk for breast-feeding is expected. The decision on whether to use the vaccine in pregnant women should be made in close consultation with a healthcare professional after considering the benefits and risks.”
Early March 2022 (EMA, 2022b)	“Comirnaty can be used during pregnancy. A large amount of data from pregnant women vaccinated with Comirnaty during the second or third trimester of their pregnancy has been analysed and showed no increase in pregnancy complications. Although data in the first trimester of pregnancy are more limited, no increased risk of miscarriage was seen. Comirnaty can also be used during breast-feeding. Data from women who were breast-feeding after vaccination have not shown a risk of adverse effects in breast-fed babies.”
Early September 2022 (EMA, 2022c)	“Comirnaty can be used during pregnancy. A large amount of data from pregnant women vaccinated with Comirnaty during the second or third trimester of their pregnancy has been analysed and showed no increase in pregnancy complications. Although data in the first trimester of pregnancy are more limited, no increased risk of miscarriage was seen. Comirnaty can also be used during breast-feeding. Data from women who were breast-feeding after vaccination have not shown a risk of adverse effects in breast-fed babies. No data are currently available regarding the use of Comirnaty Original/Omicron BA.1 in pregnant or breastfeeding women. However, based on similarity with the original vaccine, including a comparable safety profile, Comirnaty Original/Omicron BA.1 can be used during pregnancy and breastfeeding.”
Late September 2022 (EMA, 2022d, n.d.)	“Comirnaty can be used during pregnancy. A large amount of data from pregnant women vaccinated with Comirnaty during the second or third trimester of their pregnancy has been analysed and showed no increase in pregnancy complications. Although data in the first trimester of pregnancy are more limited, no increased risk of miscarriage was seen. Comirnaty can also be used during breast-feeding. Data from women who were breast-feeding after vaccination have not shown a risk of adverse effects in breast-fed babies. No data are currently available regarding the use of the adapted vaccines in pregnant or breast-feeding women. However, based on similarity with the vaccine targeting the original strain, including a comparable safety profile, Comirnaty Original/Omicron BA.1 can be used during pregnancy and breast-feeding. In addition, based on the data available for Comirnaty and Comirnaty Original/Omicron BA.1, Comirnaty Original/Omicron BA.4-5 can also be used during pregnancy and breast-feeding.”

References

- Bardosh, K., Krug, A., Jamrozik, E., Lemmens, T., Keshavjee, S., Prasad, V., Makary, M. A., Baral, S., & Høeg, T. B. (2022). COVID-19 vaccine boosters for young adults: A risk benefit assessment and ethical analysis of mandate policies at universities. *Journal of Medical Ethics*. <https://doi.org/10.1136/jme-2022-108449>
- Brock, A. R., & Thornley, S. (2021). Spontaneous Abortions and Policies on COVID-19 mRNA Vaccine Use During Pregnancy. *Science, Public Health Policy, and the Law*, 4, 130–143. https://cf5e727d-d02d-4d71-89ff-9fe2d3ad957f.filesusr.com/ugd/adf864_2bd97450072f4364a65e5cf1d7384dd4.pdf
- Chiu, S.-N., Chen, Y.-S., Hsu, C.-C., Hua, Y.-C., Tseng, W.-C., Lu, C.-W., Lin, M.-T., Chen, C.-A., Wu, M.-H., Chen, Y.-T., Chien, T.-C. H., Tseng, C.-L., & Wang, J.-K. (2023). Changes of ECG parameters after BNT162b2 vaccine in the senior high school students. *European Journal of Pediatrics*, 1–8. <https://doi.org/10.1007/s00431-022-04786-0>
- COSV. (2021a). *Avis du 6 avril 2021: Élargissement des priorités d'accès à la vaccination anti-COVID-19*. https://www.mesvaccins.net/textes/avis_du_cosv_6_avril_2021pdf.pdf
- COSV. (2021b). *Avis du 21 juillet 2021: Concernant la vaccination des femmes enceintes au cours du 1er trimestre*. https://www.mesvaccins.net/textes/20210721_cosv_vaccination_femmes_enceintes.pdf
- Cunningham, A. S. (2021). *Why don't COVID-19 vaccine trials report statistics for the first 14 days?* <https://www.bmj.com/content/372/bmj.n728/rr-0>
- Doshi, P. (2020, November 26). *Pfizer and Moderna's "95% effective" vaccines—Let's be cautious and first see the full data*. The BMJ. <https://blogs.bmj.com/bmj/2020/11/26/peter-doshi-pfizer-and-modernas-95-effective-vaccines-lets-be-cautious-and-first-see-the-full-data/>
- Doshi, P. (2021a, January 4). *Pfizer and Moderna's "95% effective" vaccines—We need more details and the raw data*. The BMJ. <https://blogs.bmj.com/bmj/2021/01/04/peter-doshi-pfizer-and-modernas-95-effective-vaccines-we-need-more-details-and-the-raw-data/>
- Doshi, P. (2021b, February 5). *Clarification: Pfizer and Moderna's "95% effective" vaccines—we need more details and the raw data*. The BMJ. <https://blogs.bmj.com/bmj/2021/02/05/clarification-pfizer-and-modernas-95-effective-vaccines-we-need-more-details-and-the-raw-data/>
- EMA. (n.d.). *Comirnaty*. European Medicines Agency. Retrieved January 20, 2023, from <https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty>
- EMA. (2020, December 24). *Comirnaty | European Medicines Agency*. <https://web.archive.org/web/20201224012625/https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty>
- EMA. (2021a). *Assessment report: Comirnaty (EMA/707383/2020)*. European Medicines Agency. https://www.ema.europa.eu/en/documents/assessment-report/comirnaty-epar-public-assessment-report_en.pdf
- EMA. (2021b, November 27). *Comirnaty | European Medicines Agency*. <https://web.archive.org/web/20211127003600/https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty>
- EMA. (2022a, January 18). *COVID-19: Latest safety data provide reassurance about use of mRNA vaccines during pregnancy* [Text]. European Medicines Agency. <https://www.ema.europa.eu/en/news/covid-19-latest-safety-data-provide-reassurance-about-use-mrna-vaccines-during-pregnancy>
- EMA. (2022b, March 4). *Comirnaty | European Medicines Agency*. <https://web.archive.org/web/20220304093350/https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty>

- EMA. (2022c, September 2). *Comirnaty* | European Medicines Agency. <https://web.archive.org/web/20220902182626/https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty>
- EMA. (2022d, September 20). *Comirnaty* | European Medicines Agency. <https://web.archive.org/web/20220920090940/https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty>
- Fraiman, J., Erviti, J., Jones, M., Greenland, S., Whelan, P., Kaplan, R. M., & Doshi, P. (2022). Serious adverse events of special interest following mRNA COVID-19 vaccination in randomized trials in adults. *Vaccine*, 40(40), 5798–5805. <https://doi.org/10.1016/j.vaccine.2022.08.036>
- Garner, J. (2022). Health versus Disorder, Disease, and Death: Unvaccinated Persons Are Incommensurably Healthier than Vaccinated. *International Journal of Vaccine Theory, Practice, and Research*, 2(2), 670–686. <https://doi.org/10.56098/ijvtpr.v2i2.40>
- Gat, I., Kedem, A., Dviri, M., Umanski, A., Levi, M., Hourvitz, A., & Baum, M. (2022). COVID-19 vaccination BNT162b2 temporarily impairs semen concentration and total motile count among semen donors. *Andrology*, n/a(n/a). <https://doi.org/10.1111/andr.13209>
- HAS. (2021a). *Stratégie de vaccination contre le SARS-CoV-2—Actualisation des facteurs de risque de formes graves de la COVID-19 et des recommandations sur la stratégie de priorisation des populations à vacciner*. https://www.has-sante.fr/jcms/p_3240117/fr
- HAS. (2021b). *Avis n° 2021.0047/AC/SEESP du 8 juillet 2021 du collège de la Haute Autorité de santé relatif à l'adaptation de la stratégie vaccinale devant l'émergence de variants du SARS-CoV-2*. https://www.has-sante.fr/jcms/p_3277121/fr
- HAS. (2021c). *Avis n° 2021.0052/AC/SEESP du 15 juillet 2021 du collège de la Haute Autorité de santé relatif au projet de loi relatif à l'adaptation de nos outils de gestion de la crise sanitaire*. https://has-sante.fr/jcms/p_3278245/fr
- HAS. (2022). *Avis n°2022.0044/AC/SESPEV du 21 juillet 2022 du collège de la Haute Autorité de santé relatif à l'obligation de vaccination contre la COVID-19 des professionnels des secteurs sanitaire et médico-social*. https://has-sante.fr/jcms/p_3356224/fr
- Kachikis, A., Englund, J. A., Singleton, M., Covelli, I., Drake, A. L., & Eckert, L. O. (2021). Short-term Reactions Among Pregnant and Lactating Individuals in the First Wave of the COVID-19 Vaccine Rollout. *JAMA Network Open*, 4(8), e2121310. <https://doi.org/10.1001/jamanetworkopen.2021.21310>
- Kharbanda, E. O., Haapala, J., DeSilva, M., Vazquez-Benitez, G., Vesco, K. K., Naleway, A. L., & Lipkind, H. S. (2021). Spontaneous Abortion Following COVID-19 Vaccination During Pregnancy. *JAMA*, 326(16), 1629–1631. <https://doi.org/10.1001/jama.2021.15494>
- Laganà, A. S., Veronesi, G., Ghezzi, F., Ferrario, M. M., Cromi, A., Bizzarri, M., Garzon, S., & Cosentino, M. (2022). Evaluation of menstrual irregularities after COVID-19 vaccination: Results of the MECOVAC survey. *Open Medicine*, 17(1), 475–484. <https://doi.org/10.1515/med-2022-0452>
- Lipkind, H. S. (2022). Receipt of COVID-19 Vaccine During Pregnancy and Preterm or Small-for-Gestational-Age at Birth—Eight Integrated Health Care Organizations, United States, December 15, 2020–July 22, 2021. *MMWR. Morbidity and Mortality Weekly Report*, 71. <https://doi.org/10.15585/mmwr.mm7101e1>
- Lopez Bernal, J., Andrews, N., Gower, C., Robertson, C., Stowe, J., Tessier, E., Simmons, R., Cottrell, S., Roberts, R., O'Doherty, M., Brown, K., Cameron, C., Stockton, D., McMenamin, J., & Ramsay, M. (2021). Effectiveness of the Pfizer-BioNTech and Oxford-AstraZeneca vaccines on COVID-19 related symptoms, hospital admissions, and mortality in older adults in England: Test negative case-control study. *The BMJ*, 373, n1088. <https://doi.org/10.1136/bmj.n1088>
- Male, V. (2021). Are COVID-19 vaccines safe in pregnancy? *Nature Reviews Immunology*, 21(4), Article 4. <https://www.nature.com/articles/s41577-021-00525-y>

- Mansanguan, S., Charunwatthana, P., Piyaphanee, W., Dechkhajorn, W., Poolcharoen, A., & Mansanguan, C. (2022). Cardiovascular Manifestation of the BNT162b2 mRNA COVID-19 Vaccine in Adolescents. *Tropical Medicine and Infectious Disease*, 7(8), Article 8. <https://doi.org/10.3390/tropicalmed708019>
- Moustsen-Helms, I. R., Emborg, H.-D., Nielsen, J., Nielsen, K. F., Krause, T. G., Mølbak, K., Møller, K. L., Berthelsen, A.-S. N., & Valentiner-Branth, P. (2021). *Vaccine effectiveness after 1st and 2nd dose of the BNT162b2 mRNA COVID-19 Vaccine in long-term care facility residents and healthcare workers – a Danish cohort study*. <https://doi.org/10.1101/2021.03.08.21252200>
- Nance, K. D., & Meier, J. L. (2021). Modifications in an Emergency: The Role of N1-Methylpseudouridine in COVID-19 Vaccines. *ACS Central Science*, 7(5), 748–756. <https://doi.org/10.1021/acscentsci.1c00197>
- Neil, M., Fenton, N., Smalley, J., Craig, C., Guetzkow, J., McLachlan, S., Engler, J., Russell, D., & Rose, J. (2022). *Official mortality data for England suggest systematic miscategorisation of vaccine status and uncertain effectiveness of COVID-19 vaccination*. <https://doi.org/10.13140/RG.2.2.28055.09124>
- NEMJ ed. (2021). Correction: Preliminary Findings of mRNA COVID-19 Vaccine Safety in Pregnant Persons. *New England Journal of Medicine*, 385(16), 1536–1536. <https://doi.org/10.1056/NEJMc210016>
- Onakpoya, I. J. (2018). Rare adverse events in clinical trials: Understanding the rule of three. *BMJ Evidence-Based Medicine*, 23(1), 6–6. <https://doi.org/10.1136/ebmed-2017-110885>
- Pfizer. (n.d.). *Comirnaty (COVID-19 mRNA vaccine)—Risk Management Plan*. Retrieved January 21, 2023, from https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf
- Pfizer. (2020). *Comirnaty (COVID-19 mRNA vaccine)—Risk Management Plan—Version number: 1.0*. https://web.archive.org/web/20210203153702/https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf
- Pfizer. (2021a). *Comirnaty (COVID-19 mRNA vaccine)—Risk Management Plan—Version number: 1.1*. https://web.archive.org/web/20210505230527/https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf
- Pfizer. (2021b). *Comirnaty (COVID-19 mRNA vaccine)—Risk Management Plan—Version number: 2.0*. https://web.archive.org/web/20210602082901/https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf
- Pfizer. (2021c). *Comirnaty (COVID-19 mRNA vaccine)—Risk Management Plan—Version number: 2.3*. https://web.archive.org/web/20211114215356/https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf
- Pfizer. (2021d). *Comirnaty (COVID-19 mRNA vaccine)—Risk Management Plan—Version number: 4.0*. https://web.archive.org/web/20211218222945/https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf
- Pfizer. (2022a). *Comirnaty (COVID-19 mRNA vaccine)—Risk Management Plan—Version number: 5.0*. https://web.archive.org/web/20220415130551/https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf
- Pfizer. (2022b). *Comirnaty (COVID-19 mRNA vaccine)—Risk Management Plan—Version number: 7.1*. https://web.archive.org/web/20220930091217/https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf
- Pfizer. (2022c). *Comirnaty (COVID-19 mRNA vaccine)—Risk Management Plan—Version number: 9.0*. https://web.archive.org/web/20221124135059/https://www.ema.europa.eu/en/documents/rmp-summary/comirnaty-epar-risk-management-plan_en.pdf
- Public Health Ontario. (2021). *Confirmed Cases of COVID-19 Following Vaccination in Ontario: December 14, 2020 to October 31, 2021*. <http://web.archive.org/web/20211122182311/https://www.publichealthontario.ca/-/media/documents/ncov/epi/covid-19-epi-confirmed-cases-post-vaccination.pdf>

- Rasmussen, S. A., & Jamieson, D. J. (2021). Pregnancy, Postpartum Care, and COVID-19 Vaccination in 2021. *JAMA*, 325(11), 1099–1100. <https://doi.org/10.1001/jama.2021.1683>
- Romero, E., Fry, S., & Hooker, B. (2023). Safety of mRNA injectables administered during the first twenty-four months of the international COVID-19 injection program. *International Journal of Vaccine Theory, Practice, and Research*, 3(1), 891–910. <https://doi.org/10.56098/ijvtpr.v3i1.70>
- Segalla, G. (2023). Chemical-physical criticality and toxicological potential of lipid nanomaterials contained in a COVID-19 mRNA vaccine. *International Journal of Vaccine Theory, Practice, and Research*, 3(1), 787–817. <https://doi.org/10.56098/ijvtpr.v3i1.68>
- Seneff, S., & Nigh, G. (2021). Worse Than the Disease? Reviewing Some Possible Unintended Consequences of the mRNA Vaccines Against COVID-19. *International Journal of Vaccine Theory, Practice, and Research*, 2(1), 38–79. <https://doi.org/10.56098/ijvtpr.v2i1.23>
- Shimabukuro, T. T., Kim, S. Y., Myers, T. R., Moro, P. L., Oduyebo, T., Panagiotakopoulos, L., Marquez, P. L., Olson, C. K., Liu, R., Chang, K. T., Ellington, S. R., Burkel, V. K., Smoots, A. N., Green, C. J., Licata, C., Zhang, B. C., Alimchandani, M., Mba-Jonas, A., Martin, S. W., ... Meaney-Delman, D. M. (2021a). *Preliminary Findings of mRNA COVID-19 Vaccine Safety in Pregnant Persons (original publication)*. <https://web.archive.org/web/20210904040636/https://www.nejm.org/doi/pdf/10.1056/NEJMoa2104983?articleTools=true>
- Shimabukuro, T. T., Kim, S. Y., Myers, T. R., Moro, P. L., Oduyebo, T., Panagiotakopoulos, L., Marquez, P. L., Olson, C. K., Liu, R., Chang, K. T., Ellington, S. R., Burkel, V. K., Smoots, A. N., Green, C. J., Licata, C., Zhang, B. C., Alimchandani, M., Mba-Jonas, A., Martin, S. W., ... Meaney-Delman, D. M. (2021b). Preliminary Findings of mRNA COVID-19 Vaccine Safety in Pregnant Persons. *New England Journal of Medicine*, 384(24), 2273–2282. <https://doi.org/10.1056/NEJMoa2104983>
- Stock, S. J., Carruthers, J., Calvert, C., Denny, C., Donaghy, J., Goulding, A., Hopcroft, L. E. M., Hopkins, L., McLaughlin, T., Pan, J., Shi, T., Taylor, B., Agrawal, U., Auyeung, B., Katikireddi, S. V., McCowan, C., Murray, J., Simpson, C. R., Robertson, C., ... Wood, R. (2022). SARS-CoV-2 infection and COVID-19 vaccination rates in pregnant women in Scotland. *Nature Medicine*, 28(3), Article 3. <https://doi.org/10.1038/s41591-021-01666-2>
- Sun, C. L. F., Jaffe, E., & Levi, R. (2022). Increased emergency cardiovascular events among under-40 population in Israel during vaccine rollout and third COVID-19 wave. *Scientific Reports*, 12(1), 6978. <https://doi.org/10.1038/s41598-022-10928-z>
- Totura, A. L., & Bavari, S. (2019). Broad-spectrum coronavirus antiviral drug discovery. *Expert Opinion on Drug Discovery*, 14(4), 397–412. <https://doi.org/10.1080/17460441.2019.1581171>
- Tripepi, G., Jager, K. J., Dekker, F. W., & Zoccali, C. (2010). Selection Bias and Information Bias in Clinical Research. *Nephron Clinical Practice*, 115(2), c94–c99. <https://doi.org/10.1159/000312871>
- UK Health Security Agency. (2021). *COVID-19 vaccine surveillance report—Week 47*. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/1036047/Vaccine_surveillance_report_-_week_47.pdf