

REVIEW



Exploring the relationship between experience of vaccine adverse events and vaccine hesitancy: A scoping review

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ABSTRACT

Fear of side effects is the main motive for vaccine refusal. However, before the COVID-19 pandemic, little attention had been paid to the actual experience of adverse events and its relationship with vaccine hesitancy. This scoping review aimed to analyze the impact of VH on EAE and vice versa. We reviewed 55 articles. Most of the studies focused on COVID-19 vaccination and employed cross-sectional surveys with self-reported indicators. These studies identified significant correlations between EAE and VH. Social cognitive models shed some light on the influence of EAE on VH, while the converse is usually explained by the nocebo effect that predominately accounts for the converse. This emerging research field is hampered by significant inconsistencies in theoretical explanations, assessments of the relationship, and measurements of these two phenomena. A more comprehensive consideration of individual experience, both objective and subjective, would help develop more effective vaccine communication strategies and improve pharmacological surveillance.

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Introduction

Adverse events occur with vaccines, as with all pharmaceutical products. Although most of them are relatively benign, the potential danger of vaccines appears to be a central factor both in anti-vaccination advocacy claims and vaccine hesitancy.¹ The direct and indirect experience of adverse events, whether observed personally or reported by formal or informal sources like television or social media, can impact vaccine acceptance (Figure 1). Additionally, vaccine hesitancy has the potential to influence how people respond to vaccination or interpret ailments following vaccination. This raises the question of how individuals think and react to adverse events, and whether their views are congruent with those of health experts. This literature review aims to explore specifically the complex relationship between vaccine hesitancy and vaccine adverse events following vaccination.

Over the last 10 years, the growing research attention on vaccine hesitancy has led to a heightened awareness of the public's concerns about potential side effects. This research has identified and assessed a diversity of determinants of vaccine hesitancy such as complacency, trust in public and medical actors, experiences of marginalization, and poverty.¹⁻⁴ Concerns regarding vaccine safety are one of – if not the – main motive for vaccine refusal and for this reason have been analyzed extensively.⁵⁻⁷ However, the literature on vaccine hesitancy has mainly focused on perceptions of the safety of vaccines rather than actual experience of adverse events.⁸ But recent studies have suggested that vaccine hesitancy can be associated with a higher propensity to experience

adverse events.^{8,9} For instance, meta-analyses of clinical trial data of COVID-19 vaccines suggested an association between psychosocial factors, including vaccine-induced stress and vaccine hesitancy, and the incidence of adverse events.^{10,11} At the population level, vaccination perception appeared to influence the frequency of adverse event reporting.^{9,12} Reciprocally, several other recent studies have suggested that the experience of adverse events could have a long-term influence on vaccine attitudes and behaviors.¹

It is imperative that further research is conducted to ascertain how individuals interpret the actual experience of adverse events. In addition, it is crucial to establish whether individuals who are hesitant about vaccines are more likely to report experiencing adverse events or whether the experience of adverse events is more likely to be reported by people who are hesitant about vaccines. Work conducted during the pandemic has also questioned the direction of the relationship between vaccine hesitancy and the experience of adverse events. Indeed, some studies have the COVID-19 vaccination campaign has underlined the importance of studying this complex relationship between the experience of adverse events and vaccine hesitancy. The scale of this campaign, the reactivity of these vaccines, the number of doses and the reticence that these vaccines elicited in many parts of the world have both exacerbated the potential experience of adverse events attributed (correctly or incorrectly) to vaccination as well as their overlap with reticence. As a consequence, experts debated on the recommended degree of transparency and

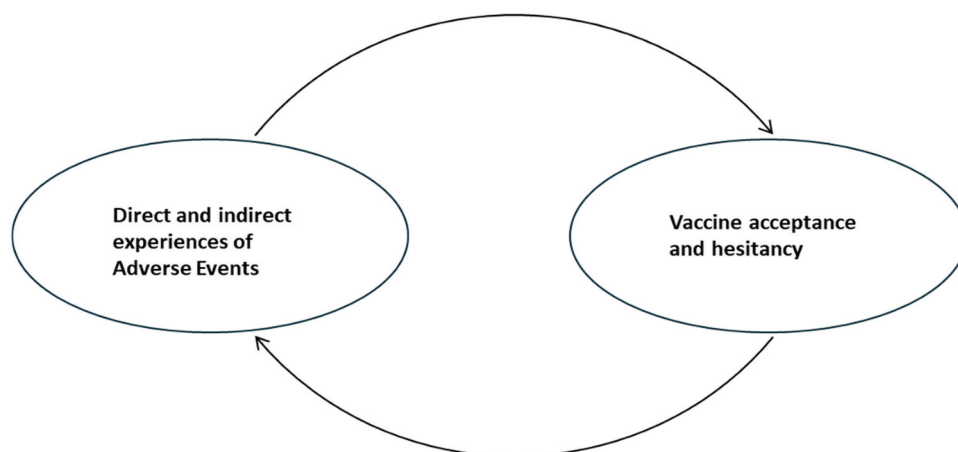


Figure 1. Causality between adverse events experiences and vaccine hesitancy.

pedagogy when communicating on adverse effects to avoid artificial reporting following antivaccine mobilizations.^{13–15}

In this scoping review, we screened the scientific literature to identify all empirical investigations existing on the relationship between vaccine hesitancy and experiences of adverse events. We assess the evidence that substantiates a causal relationship between the experience of adverse events and the methodologies used in existing studies and describe the main theoretical frameworks used to make sense of this relationship.

Materials and methods

This scoping review analyzed empirical research from articles published before October 2022. We focused on studies addressing personally experienced adverse events and attitudes toward vaccination among the general population. We used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews (PRISMA-ScR) statement¹⁶ as a guide to design this literature review (Supplementary file, Table S1).

Eligibility criteria

The eligibility criteria for this scoping review are presented in the Supplementary file (Supplementary file, Table S2).

Population

Studies involving general adult population samples were included in this review. To favor comparability, we excluded articles focusing on subgroups of the population (children, adolescents, pregnant women and healthcare professionals for instance).

Main research variables

This study focused on personal experiences of adverse events after vaccination, which we will call self-reported adverse events in the rest of the paper. It should be noted that this term does not presuppose the existence of causality. Consequently, this literature review considers all

reports, regardless of whether the adverse events can really be attributed to vaccines or not. Regarding the measures for vaccination attitudes, we considered all articles including measures referencing any measures on the attitudes toward vaccination.

Study characteristics

Published, primary studies were included in this scoping review. They include randomized control trials, non-randomized trials, observational studies (cohort studies, cross-sectional studies), quasi-experimental studies (quality improvement projects, uncontrolled pre- and posttest designs, experimental designs), chart reviews, case studies and modeling studies. We excluded from the analysis review articles, editorials, opinion pieces, abstracts, conference posters, and gray literature.

Searching strategy

We searched on PubMed every article containing words related to the experience of adverse events and to vaccine hesitancy in their title, abstract or MeSH terms. Those keywords were selected on the pubmed database (see Supplementary file). We first developed an exploratory search strategy. This search strategy was then validated by its capacity to identify the five articles used as targets.

Selection of sources

After this exploratory search, we added filters after a first check of our database (based on successive rounds of random sampling and readings). Our database was then filtered using semi-automatic strategy assistance, to identify and drop all the articles containing selected words (by character string) across PubMed metadata. We designed a data extraction grid to standardize our data extraction from eligible studies (Supplementary file, Table S3). In cases of missing or inconsistent information, we discussed the extracted data between authors to decide.

Results

Articles identified

The database query returned the first corpus of 7890 articles (Figure 2). First, we automatically filtered the corpus to remove duplicates and articles failing to clearly meet inclusion criteria. We reviewed 1283 abstracts, assessed 131 full-text articles for eligibility, and finally included 55 among them in our study.^{8,17–70} We summarized their characteristics such as aims, sample, study types, measures of self-reported adverse events, outcomes, other variables included and main results (Supplementary file, Table S3).

Study characteristics

Most of these articles have been published since the emergence of COVID-19, with only three exceptions (52/55). Thus, most studies pertained to COVID-19 vaccination (45/55). Nevertheless, vaccines in general and other vaccines such as HPV, influenza and monkeypox were also discussed.

These articles presented data collected from 27 different countries across the world (graph 1). Regarding the

methodology used, most studies used questionnaire-based surveys for data collection (47/55, mainly cross-sectional, only five were longitudinal). The rest used qualitative methods (5/55), and experiments (3/55). In terms of data collection, except for a few studies reporting data collected directly after vaccination (4/55), the rest were retrospective, collecting information between each of the two doses or after the first booster dose was implemented. Although most of the papers based their sample on a large enough size to achieve statistical significance, only 13/55 ensured the representation of the general population. Among the 55 studies, 12 excluded unvaccinated participants.

Regarding the direction of the relationship between the self-report of side effects and attitudes toward vaccines, 33/55 studies took the personal experience of side effects among the independent variables that predict attitudes toward vaccines. 15/55 studies analyzed attitudes toward vaccines as an independent variable, while 7/55 studies approached the topic from a different perspective (e.g. qualitative research). Overall, only 17 articles defined the analysis of the relationship between self-reported side effects and vaccine hesitancy as one of the main research objectives, for the others it was a secondary or marginal aim. Consequently, the

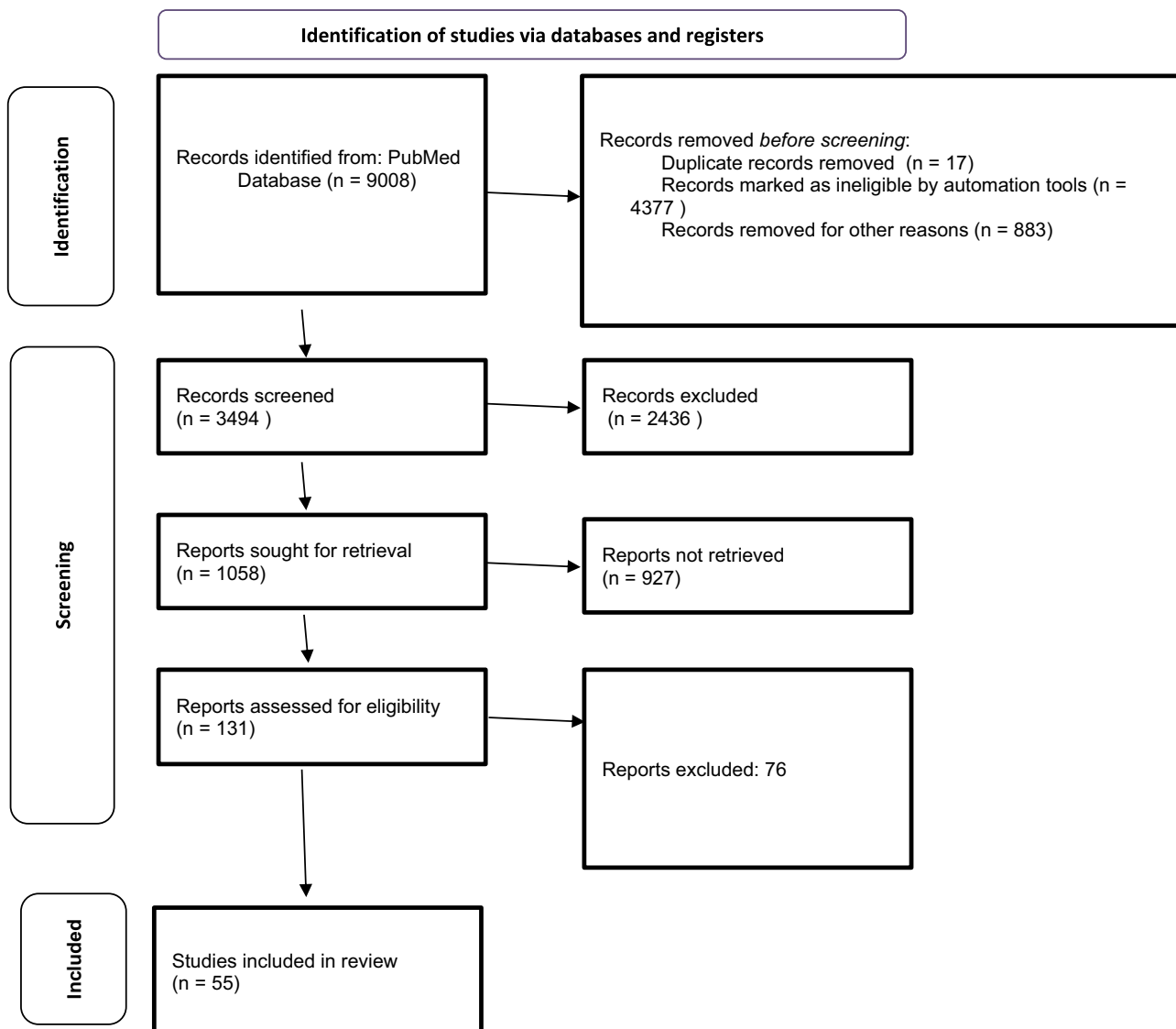


Figure 2. Prisma flowchart.

theoretical discussion of the relationship between vaccine hesitancy and side effects is limited and most of the time non-existent in the paper (see section below).

How attitudes toward vaccines and experience of adverse events are measured

Regarding vaccine hesitancy, most articles made the distinction between attitudes toward vaccines and intentions to vaccinate. For that matter, half of them included at least one measure of willingness to receive a vaccine, and 40 measured knowledge, attitudes, perceptions or beliefs related to vaccines. Thus, measures and definitions of hesitancy were operationalized with a wide range of variables. Self-designed items were used in about a third of the reviewed articles (20/55), most of them were explicitly based on literature, while eight provided no details. Around 15% (8/55) used standardized scales or adapted short versions (Table 1,^{71–74}) such as variations on the psychological antecedent scale – 5 C, 7 C,^{44,69} the Vaccination Attitudes Examination scale – VAX^{24,31,32,43} and the World Health Organization's Behavioural and Social Drivers of Vaccination survey.³⁰

Regarding the experience of side effects, only six articles employed preexisting standardized measures (Table 2,^{75–77}). Twelve provided literature-based justifications for their measures, while half of all articles provided no justification for their measures. The GASE instrument and Side Effect Attribution Scale, originally constructed to assess general properties of side effects (presence and intensity), were adapted for the context of vaccination in three papers, using lists from 12 to 36 symptoms or adapting the CDC's list of common side effects of the vaccine under scrutiny.^{24,31,32,35,62} Another scale adapted for the research question was the Life Events Checklist, consisting of 17 questions designed to screen for exposure to distressing life events.³⁰ Overall, listing symptoms resulted in a higher reporting of side effects. For example, Clemens et al.³¹ presented the percentage of the most

common side effects (that is, 81% Pain in the injection site, 73% Fatigue and 61% Headache, $n = 551$), while Geers et al.,³⁵ presented the proportion of reported side effects and how many of these were severe (95% had at least one side effect and 21.4% reported experiencing an intense side effect, $n = 551$). These results differ significantly from the studies that included reported side effects as a measure of reasons for refusal (e.g., 2%, $n = 601$, had a serious adverse reaction in Abullais et al.,¹⁷ while 18.5%, $n = 601$, indicated that they were unlikely to receive a booster vaccination because of adverse reactions to their original COVID-19 vaccination in Neely and Scacco.⁵³

A plurality of methods leading to scattered results

Differences in the methods made it difficult to draw precise comparisons between the studies' results. Among the studies conducting quantitative analyses of cross-sectional surveys (42/55), 32 used general linear models, 6 performed only descriptive analyses and 4 used other statistical methods based on structural equation models or in machine techniques. The studies also vary greatly regarding the diversity, and number of control variables included in the models (Table 3). This is important because studies have shown that cultural or social variables can have a significant effect and therefore be a confounder for experiencing adverse events or vaccine hesitancy. For instance, only six articles considered information sources about vaccines among potential confounding factors. Intensive social media use and information consumption were shown significant in two cases.^{31,41} Clemens et al.³¹ measured the effect of information from social media and personal acquaintances on perceived side effects, using before-and-after assessments. They found that these variables were able to predict post-vaccination expectations and effects.

Among the 32 that used general linear models, 18 considered vaccination attitudes and intentions as a dependent variable, 13 considered self-reported side effects as a dependent

Table 1. Standardized measurement tools for vaccination attitudes.

Measurement description	Cited by
World Health Organization's Behavioural and Social Drivers of Vaccination survey for COVID-19 adult vaccination (long version 22 items, recommended short version 5 items). Explores five dimensions about vaccination thinking and feeling, motivation, social processes and practical issues (WHO, [73]).	Christou-Ergos et al., [30]
5C psychological antecedents (original version 15 items, short version 5 items). Correlated to relevant psychological concepts, such as attitude, perceived personal health status and invulnerability, self-control, preference for deliberation, and communal orientation (collective responsibility), among others (Betsch et al., [71]).	Kwok et al., [44]
7C scale(original version 21 items, short version 7 items). Revised version of the 5C scale including two new factors : complacency (adherence to regulations) and conspiracy (endorsement of conspiratorial beliefs) (Geiger et al., [72])	Williams et al., [69]
Vaccine Attitudes Examination Scale (original version 12 Items). Allows to identify those with vaccination resistance and comprises four factors: mistrust of vaccine benefit, worries about unforeseen future effects, concerns about commercial profiteering, and a preference for natural immunity. (Martin et Petrie, [74])	Bender et al., [24]; Clemens et al., [31]; Crum et al., [32]; Kleitman et al., [43]

Table 2. Standardized measurement tools for adverse events self-reported experience.

Measurement description	Cited by
General Assessment of Side Effects (GASE) questionnaire (original version 36 items, 4 likert scale). Structured screening of general side effects with a patient based approach, measures severity of symptoms from not presence to severe (Rief et al., [75])	Bender et al., [24]; Clemens et al., [31]; Geers et al., [35]
Life Events Checklist 5 (LEC-5) (original version 17 items, 6 options : Happened to me, Witnessed it, Learned about it, Not sure, Doesn't apply). Exposure to potentially traumatic events (Gray et al., [76])	Christou-Ergos et al., [30]
Side Effect Attribution Scale (original version 50 items, two answer levels Yes/No and 5 likert scale). Provides assessment of symptom attribution beliefs (McKrill et al., [77])	Smith et al., [63]; Crum et al., [32]

Table 3. Percentage of independent variables included in models (total and significant) for the two outcomes of interest.

Variable included in general linear model (threshold = 3)	Self reported adverse events (n = 13)		Vaccination attitudes (n = 18)	
	freq(%)	sign*(%)	freq(%)	sign*(%)
Age	77	54	67	44
Gender	77	69	56	11
Attitudes Towards Vaccination In General	38	31	67	50
Education	46	23	50	22
Chronic Conditions	38	23	39	22
Covid Antecedents	31	8	39	11
Covid Risk Perception	23	8	39	28
Region	15	8	39	22
Income	15	0	39	22
Type Of Vaccine	46	46	17	17
Antecedents Of Side Effects	23	8	22	17
Vaccination Antecedents	8	8	39	28
Side Effects Concerns	31	23	22	17
Number Of Doses	31	23	22	17
Occupation	23	8	28	11
Marital Status	15	0	28	6
Health Habits	23	0	17	6
Injection Anxiety	8	8	17	11
Information Sources	15	15	11	11
Ethnicity	15	0	11	6
Trust In Government	8	8	11	6
Side Effects Severity	0	0	17	17
Political Affiliation	8	0	11	6
Co-Medication	8	8	11	6
Health Status	8	0	11	6
Indirect Experience Of Side Effects	15	8	6	0
Allergies	15	0	6	6

variable and 1 studied the directionality of the relationship between those variables.

Among the 18 studies investigating the experience of side effects as an explanation for vaccination attitudes and behaviors, the majority dealt with vaccination intentions ($n = 15/18$; 12 on booster doses against COVID-19, one on vaccination intentions against COVID, and one on monkeypox vaccination). Ten out of 18 articles found significant negative correlations between these variables in their statistical models.

Among the 13 articles which examined the effect of vaccine hesitancy on self-reported side effect experience, 8 aimed to identify predictors of self-reported side effects, 3 to track these side effects, 1 focused on general vaccination experiences, and another on attitudes toward vaccination. Vaccination attitudes and perceptions, including general attitudes and perceived barriers for vaccination, were statistically significant in four articles.^{37,41,50,57} One⁵⁷ dealt with vaccination in general while the rest with COVID-19 vaccination.^{21,31,41,49,52,54,59,61,62} In a unique study, authors found no statistically significant association between self-reported-side effects and attitudes toward vaccines.²⁸ Among these studies, two articles included specific measures for anxiety and perceived susceptibility, in both cases the results were significant.^{50,59} Hesitancy and concerns about side effects were the most common measures. Concerns about side effects and feeling at risk of side effects were statistically significant in the four articles including such items in their model.^{31,50,57,59}

Only one study proposed to assess the directionality of the relationship between the two variables.⁸ They found that a significant and quantifiable amount of the self-reporting of COVID-19 vaccine's adverse events was predicted by previous negative attitudes toward the vaccine (i.e., hesitancy).⁸

Others proposed interventions designed to alter subjects' expectations of side effects and to adapt communication strategies. These 3 articles tested hypotheses regarding the formulation of side effects. Two of them proposed interventions that addressed individuals' possible negative expectations using message framing (e.g. positive framing) and controlled the effects of these interventions by socio-demographic variables, expectations of side effects, in particular the possibility of having intense side effects. In Crum et al.'s (2023) study, participants in the "treatment" groups reported fewer symptoms after vaccination, less concern about side effects and greater willingness to receive future vaccinations;³² Bender et al. (2023) found that a change in the formulation of side effects had no effect on participants' satisfaction with them.²⁴ They observed significant effects of positive framing among the most reluctant individuals, but found no significant effects on vaccination intentions. The third study, compared to design for active, participant-centered vaccine surveillance in Canada, described adverse events reports and vaccination attitudes to evaluate the usefulness of an app-based survey.⁵⁶

Adding to those quantitative studies, four more used qualitative methodologies with different aims. Three of them focused on experiences of side effects (one was related to HPV and the second to the COVID vaccine). The remaining study addressed reasons for participating in clinical trials. These studies highlighted different themes. They described how respondents' assessment of vaccine safety was affected by factors such as whether people trusted medical advice, the influence of other sources (family and social media), and the vaccine's manufacturer and mechanism of action of the vaccine.

Conceptualization of the relationship between the experience of adverse events and attitudes to vaccines

Since the relationship between self-reported side effects and vaccine hesitancy was generally not the main purpose of the research, the results were not often commented on. Hence, only 9 articles discussed these associations. In addition, most of the articles (46/55) did not explicitly reference a conceptual framework to interpret the results. Nevertheless, discussions still drew on insights from existing public health frameworks.

Discussions on the impact of the experience of side effects on attitudes to vaccines relied on common understandings of behaviors centering on risk assessment. However, only six articles explicitly cited a social cognitive model of health behavior.^{35,38,47,63,67} This included the health belief model (HBM), the theory of planned behavior (TPB), and the Necessity Concern Framework. These theoretical frameworks enabled them to hypothesize both a relationship between self-reported side effects and experience and between vaccine hesitancy and intention to get vaccinated. Some authors also provided theoretical frameworks centering on the influence of the informational context on individual behavior.^{31,50}

Discussions about the impact of side effects on vaccine hesitancy overlooked the difference between the actual experience of side effects and anticipation of experience (i.e. concerns of side effects). A few studies have suggested that perceived severity of side effects and concerns about side effects, rather than direct experience of side effects, may affect future acceptance.⁶² They proposed alternatively that people may have perceived side effects as evidence that the vaccine is “working,” increasing motivation to have a second dose.⁶² Otherwise, when vaccine hesitancy or vaccine intentions were not associated with previous vaccine experiences, one study argued that this could be because side effects were mild²⁹ and other authors argued that psychological variables were better predictors of positive vaccination attitudes. For instance, Geers et al. (2022) “found that trust in vaccine development, worry about the COVID-19 pandemic, and low concerns about vaccine side effects predicted intentions to obtain a booster, supporting the models of health behavior (TPB, HBM, PMT).”³⁵

Explanations of the impact of vaccine hesitancy on the experience of adverse events centered on psychosocial processes in the experience of side effects, such as via the nocebo effect. The nocebo effect is defined in terms of the mechanisms involved in the appearance of adverse effects after vaccination that cannot be explained by the pharmacological or biological actions of vaccines. Bender et al. (2023), Clemens et al. (2023), Khouri et al. (2023) and Schäffer et al. (2023) described the nocebo effect as resulting from psychological and neurobiological mechanisms.^{24,31,41,59} There is a consensus among authors that nocebo effects may have been induced by expectations of experiencing adverse events. Schaffer et al. draw on Webster et al.’s classical review of the literature on the nocebo effects⁷⁸ to underline three mechanisms involved in the causation of nocebo effects: learning, negative expectations and misattribution (p. 10).⁵⁹ In Webster et al. (2016), misattribution consists in “misattribute(ing) pre-existing symptoms to the effects of a new exposure,” negative expectations affect the experience of adverse because they “can make the individual more likely to attend to new or current sensations, and

attribute them to the exposure (...). The response expectancy theory suggests that it is also possible for negative expectations to act more directly, with an expectation of, for example anxiety, being itself provokes anxiety thereby directly causing the negative effect that was expected (...);” and learning “can elicit nocebo effects through association or social observation. For example, if an inert stimulus has been previously paired with a symptom-inducing stimulus (...) which may occur through conscious or nonconscious mechanisms (...), or through observing someone else experience symptoms to the same exposure” (p. 4).⁷⁸

Most forms of explanations provided by the authors of the studies reviewed here fall within these three broad categories, i.e. learning, negative expectations, and misattribution.

Regarding the role of learning in the experience of nocebo effects following vaccination, Schaffer et al. suggested that this learning mechanism can explain why those who experienced more adverse events after the first dose of the COVID-19 vaccine also presented more and more severe adverse events after the second dose.⁵⁹ Other experiential and observational learning mechanisms were also underlined in the studies of Clemens et al. (2023) and Hoffman et al. (2022).^{8,31}

The mechanism, focusing on negative expectations, implies that symptoms reported by respondents were the result of psychosomatic mechanisms. Khouri et al. (2023) underlined on that matter that pain neuromodulators (e.g. cholecystikinin and the cerebral region implicated in anxiety) have been associated with the nocebo effect.⁴¹ In some studies,^{8,41,59} the experience of side effects was explained as a subjective interpretation of pain. For instance, Schäffer et al. (2023) argued that reporting higher levels of anxiety, depression, and somatosensory amplification were predisposing factors. They argued that it was a consequence of mechanisms including “cognitive, emotional, and behavioral factors such as selective attention toward interoceptive cues, amplified perception of benign bodily sensations, and maintenance of these processes through catastrophizing cognitive interpretations and unhelpful illness behaviors” (p. 11).⁵⁹ Khouri et al. (2022) agreed that the greater perceived impact of self-reported side effects in reluctant individuals could be an expression of doubts or anxiety about vaccination.⁴¹

Mattarozzi et al. (2023) differentiated between affective (i.e. fear of side effects) and cognitive (i.e. expectation of side effects) components, the cognitive dimension affected the number and severity of side effects.⁵⁰ In the studies of Khouri et al. (2023) and Schäffer et al. (2023), attitudes regarding vaccination were interpreted as measures of expectations. These authors argued that the association between variables could be affected by cognitive bias, such as self-fulfilling prophecy, and doubts about vaccination.^{28,32}

Regarding misattribution, Schaffer et al. (2023) observed that the risk for adverse effects increased with the severity of baseline symptoms (15 days prior vaccination), indicating misattribution of preexisting symptoms.⁵⁹ Other studies evoked misattribution of preexisting symptoms either as a part of nocebo mechanisms^{24,31,79} or as alternative explanation vaccine adverse events were incorrectly attributed as being the source of experienced symptoms,^{8,35,41,50} echoing debates in the wider nocebo literature.⁷⁸

A few authors did not refer to the nocebo effect. Christou-Ergos et al., 2023, highlighted that their findings may also reflect cognitive biases. In such cases, vaccination decisions and vaccine attitudes are rooted in intuitions rather than objective evidence and heightened anxiety, can alter the way individuals perceive and recall experiences and may have biased perceptions of self-reported side effects.³⁰

Discussion

The literature on the relationship between vaccine hesitancy and the experience of adverse events has grown spectacularly during the COVID-19 epidemic. The interest for this research topic is fueled by the rise of vaccine hesitancy in the past decade and the organization of the biggest adult vaccination campaign in history. Reviewing this literature, we found that the assessment of adverse events by the general public often diverges largely from that of health authorities. Overall, these studies show that having experienced adverse events has a negative impact on attitudes to vaccination and that having negative attitudes toward vaccines results in more frequent and more acute experiences of adverse events.

public health experts have expressed concerns regarding the impact of negative expectations and fears related to the epidemic and its management on the public's assessment of vaccines.^{10,11} The implications of these findings for public health are that vaccinologists should also examine how individuals experience vaccines in addition to considering perceptions of vaccines and discourses on vaccine safety. People are not only influenced by what they read and hear, they also experience vaccines intimately. Intimacy here refers to one's capacity to make sense of oneself, positively, but also negatively through fear and disgust.⁸⁰ Such an idea has previously been explored in public health studies around the fear that the needle can elicit because of the negative experience of being pricked.³⁰ Personal accounts of vaccine adverse events have been shown to evolve with individual experience (eg.,^{81,82}), presenting challenges for effective communication strategies that counter false narratives while addressing public concerns and supporting people to navigate their intimate experiences of symptoms.⁸³ Such an issue is likely to grow as adult vaccines are developed, thanks to recent advances in vaccine technology.⁸⁴

A second implication of those results concerns the reporting and assessment of adverse events. Meta-analyses of COVID-19 vaccine side effects during clinical trials have underlined the potential impact of negative expectations which can skew the assessment of vaccines.^{10,11} Our review of the literature buttresses this concern as vaccine hesitant individuals tended to report more adverse events and to attribute adverse events to vaccination. Nevertheless, this causality still needs further exploration as some studies do not find this relation, comparisons between studies remain difficult due to differences in methodologies, and few studies mobilize experimental methods (for an exception, see³¹).

Our results highlight some contemporary challenges for pharmacovigilance. It would be a mistake to explain all discrepancies between expert and public assessments of adverse events with rather incomplete references online

disinformation and to psychosomatic mechanisms such as the Nocebo effect. While these factors may play a significant role, it is imperative to recognize that adverse reactions can also stem from biological factors, including vaccine components, genetic predisposition, and pharmaceutical effects that necessitate surveillance and acknowledgment to ensure safety and enhance public confidence in vaccines.^{85–87} Additionally, under-reporting of adverse events, especially non-severe ones, is a crucial issue for the assessment of the risk–benefit balance of all pharmaceuticals, including vaccines.^{78,88,89} Its importance is made visible by the active pharmacosurveillance systems set up by health authorities in many countries, which consist in facilitating the reporting of adverse events by the public.^{90,91}

Such data may lead to the identification of previously unknown adverse effects. Additionally, they also pose questions regarding the risk–balance ratio for healthy adults of vaccines such as against the flu, where the number of missed workdays and unpleasant symptoms can significantly impact the overall disease burden. If vaccines do cause more adverse events among the hesitant because of neurological mechanisms that underlie psychosomatic symptoms and the nocebo effect,⁸⁸ it raises an important question for public health: should doctors and public health officials take attitudes to vaccines into consideration when recommending a given vaccine? Addressing this question requires balancing transparency with the need to foster trust and adherence to vaccination programs.

The present review presents a preliminary investigation into the intricate interrelationships between vaccine hesitancy and the occurrence of adverse events. Our findings revealed a diversity of methodologies, definitions and sometimes contradictory findings, highlighting the need for more conceptual clarity and standardized approaches in future research. The references to the nocebo effect is a case in point. In some studies, the term is employed to signify the misattribution of an event to a vaccine, whereas in others, it denotes the phenomenon of negative expectations exerting tangible biological effects on the body's response to the vaccine. But more importantly, the term is never really defined in most studies, which is a significant limitation. Achieving theoretical precision is crucial to advance in this field and go beyond pervasive misconceptions (for exceptions^{31,50,59}). These mechanisms are inherently distinct, and it is plausible that interventions effective against one aspect may not be effective against the other. In a recent scoping review, Sweeney et al. (2022) identified a preponderance of non-systematic reviews and a dearth of high-quality primary research on nocebo effects, with a particular focus on pain and psychological conditions.⁹²

Despite its vast scope, the biomedical literature appears unsatisfactory in elucidating the relationship between vaccine hesitancy and adverse effects. One aspect of this is that the literature analyzed in this review makes a very limited recourse to insights from the social and human sciences. The fact that much of the social and human sciences is published via books and book chapters could also have added to disciplinary affinities with biomedical approaches.⁹³ This is for instance the case of pioneering work conducted by Jennifer Reich's on vaccine hesitancy.⁹⁴

Reich's work illuminates the ways in which the ramifications of adverse reactions and the operational mechanisms of vaccine injury compensation systems influence the private family decisions of individuals. Such decisions may result in a decline in trust in government and a reduction in shared investments in health and social welfare in a society that is increasingly self-centered. To address this gap, interdisciplinary engagement is essential. A comprehensive overview of diverse perspectives, elucidating the underlying factors that shape lay approaches to immunity and prevention, as well as the current institutional arrangements and potential avenues for improvement at every level, from vaccine development to public policies, including surveillance, mandates, and compensatory regulations.^{95–99} Social and human sciences approaches are essential to develop an in-depth understanding of the mechanisms by which people identify certain symptoms as vaccine side effects (or not), yielding more complete information about adverse events people are experiencing or about demographic information that could be relevant to be included in surveys (e.g.^{100–102}). Furthermore, they would help to uncover possible biases that might stem from the aforementioned epistemic constraints, including those similar to those found in the placebo and emotional research using the current preferred cognitive theory.¹⁰³ Furthermore, the inclusion of researchers from diverse backgrounds may help to mitigate certain forms of bias and yield more precise data.^{104–106}

Conclusion

The current interest from the scientific literature on adverse events prompts a broader examination of the management of pharmacovigilance, particularly in the context of vaccinations.

The growing literature on adverse events following vaccination and vaccine hesitancy highlights the need for a far more nuanced and comprehensive approach to pharmacovigilance and public health. It is imperative to better acknowledge and incorporate the experiences of the general public in relation to adverse effects. This includes systems for active pharmacovigilance to capture underreported events, particularly non-severe ones and leveraging these insights to refine the assessment of risk-balance for vaccines.

Furthermore, public health strategies must go beyond countering misinformation to actively support individuals as they process and interpret their own health experiences. This involves recognizing the intimate nature of vaccine experiences and tailoring communication strategies that address both scientific and personal concerns. Interdisciplinary engagement, particularly the integration of social sciences with biomedical research, is essential to uncover the mechanisms by which people identify symptoms as vaccine-related and to mitigate biases that may arise from epistemic constraints.

Ultimately, a comprehensive public health approach should not only to counter false narratives but also accompany individuals in processing health experiences, thereby fostering trust and collaboration. This article does not discuss the

potential impact of societal reactions to vaccine inequality on vaccine hesitancy, which could be a limitation and could be addressed in the future research.^{107–109} By combining diverse perspectives, refining public health messaging and enhancing pharmacovigilance systems, it becomes possible to promote a more nuanced understanding of adverse events and improve the effectiveness of vaccination programs. These efforts are necessary to build a resilient and equitable public health framework that can address both current and future challenges in immunization and beyond.

CRediT authorship contribution statement

Fátima Gauna: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Visualization, Writing – original draft, Writing – review and editing.

Jeremy K. Ward: Conceptualization, Data curation, Formal analysis, Methodology, Validation, Writing – original draft, Writing – review and editing.

Jean-Luc Cracowski: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review and editing.

Charles Khouri: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Validation, Writing – review and editing.

Jocelyn Raude: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – review and editing.

All authors attest that they meet the ICMJE criteria for authorship.

Data availability statement

The data in this scoping review were extracted from previously published articles. The spreadsheet organizing the data extracted can be requested from the corresponding author and will be provided upon reasonable request.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Ethics approval and consent to participate

The research did not include human participants, and ethics approval requirement did not apply

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