



# COVID-19 vaccines and patients with multiple sclerosis: willingness, unwillingness and hesitancy: a systematic review and meta-analysis

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## Abstract

**Objective** The purpose of this study was to determine the pooled prevalence of vaccination willingness, unwillingness, and hesitancy among patients with multiple sclerosis.

**Methods** Databases including PubMed, Scopus, EMBASE, Web of Science, and Google Scholar were searched. by two expert researchers, as well as references in the included studies, which were published before October 2021.

**Results** Three hundred eighty articles were found in four data bases. One hundred eighty-two studies remained following deleting duplicates. Finally, ten studies remained for the meta-analysis. Totally, 5983 patients with MS were assessed. The pooled prevalence of willingness to vaccination among patients with MS was 76% (95% CI: 67–85%) ( $I^2=98.4\%$ ,  $p<0.001$ ). Unwillingness pooled prevalence to vaccination among patients with MS was 2% (95% CI: 2–3%) ( $I^2=97.9\%$ ,  $p<0.001$ ). Hesitancy pooled prevalence to vaccination among patients with MS was 0% ( $I^2=98\%$ ,  $p<0.001$ ).

**Conclusion** According to the findings of this systematic review and meta-analysis, more than two-thirds of patients with MS were willing to obtain COVID-19 vaccines.

**Keywords** COVID-19 · Vaccine · Multiple sclerosis

## Introduction

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for COVID-19 infection and was first introduced in China and is now in the pandemic stage [1]. Patients with underlying disease, especially autoimmune disease, were considered at higher risk of the severe form of the disease [2]. A comprehensive review and

meta-analysis assessed the pooled prevalence of COVID-19 infection and hospitalization in patients with MS to be 4% and 10%, respectively [3].

Vaccination against SARS-CoV-2 is the primary long-term strategy to stop this pandemic all over the world [4]. Concerns about vaccination were raised among patients with MS and their health care providers regarding disease exacerbation, side effects, and efficacy [5]. Willingness to get vaccines differs among nations, age groups, and genders [6]. Previous studies reported various rates of willingness regarding SARS-CoV-2 vaccination among patients with MS. So, we designed this systematic review and meta-analysis to estimate the pooled prevalence of vaccination willingness among MS patients.

## Methods

Databases including PubMed, Scopus, EMBASE, Web of Science, and Google Scholar were searched by two expert researchers, as well as references of the included studies published before October 2021.

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Our search strategy was:

((Sclerosis AND multiple) OR (sclerosis AND disseminated) OR “disseminated sclerosis” OR “multiple sclerosis” OR “acute fulminating” OR MS OR “Multiple sclerosis”) AND (“COVID 19 Vaccin\*” OR (Vaccin\* AND COVID-19) OR “COVID-19 Virus Vaccin\*” OR (Vaccin\* AND “COVID-19 Virus”) OR (“Virus Vaccin\*” AND COVID-19) OR “COVID-19 Virus Vaccin\*” OR “COVID 19 Virus Vaccin\*” OR (“Virus Vaccin\*” AND COVID-19) OR “COVID19 Virus Vaccin\*” OR (Vaccin\* AND “COVID19 Virus”) OR (“Virus Vaccin\*” AND COVID19) OR “COVID19 Vaccin\*” OR (Vaccin\* AND COVID19) OR “SARS-CoV-2 Vaccin\*” OR “SARS CoV 2 Vaccin\*” OR (Vaccin\* AND SARS-CoV-2) OR “SARS2 Vaccin\*” OR (Vaccin\* AND SARS2) OR “Coronavirus Disease 2019 Vaccin\*” OR “Coronavirus Disease 2019 Virus Vaccin\*” OR “Coronavirus Disease-19 Vaccin\*” OR (Vaccin\* AND “Coronavirus Disease-19”) OR “Coronavirus Disease 19 Vaccin\*” OR “COVID 19 Vaccin\*” OR (Vaccin\* AND “COVID 19”) OR “2019-nCoV Vaccin\*” OR “2019 nCoV Vaccin\*” OR (Vaccin\* AND 2019-nCoV) OR “2019 Novel Coronavirus Vaccin\*” OR “2019-nCoV Vaccin\*” OR “2019 nCoV Vaccin\*” OR (Vaccin\* AND 2019-nCoV) OR “COVID-19 Vaccin\*” OR “SARS Coronavirus 2 Vaccin\*”) AND (willingness OR accept\* OR demand OR (vaccine\* AND readiness) OR (vaccine\* AND readiness) OR Hesita\* OR (vaccine\* AND hesita\*) OR (vaccine\* AND accept\*) OR (vaccine\* AND uptake\*) OR (vaccine\* AND adopt\*) OR Attitude\* OR decision-making OR (decision AND making) OR (health AND behaviour) OR “conspiracy theories” OR “conspiracy belie\*” OR “obtain COVID-19 vaccin” OR (vaccine AND intention)).

### Inclusion criteria

Our inclusion criteria were based on cross-sectional studies that reported the patients with MS who answered questions regarding COVID-19 vaccination. All answers were based on questions designed in the surveys.

### Exclusion criteria

Our exclusion criteria were non-English studies, case reports, case–control, letters to the editor, and cross-sectional studies with no clear criteria.

We extracted data given the demographic data, article characteristics, the number of those

willing to have vaccination, and the number of those who were hesitant or unwilling.

### Risk of bias assessment

The Newcastle–Ottawa quality assessment scale (NOS) that was adapted for cross-sectional studies was investigated for the risk of bias [7].

### Statistical analysis

We did all statistical analyses using STATA (Version 14.0; Stata Corp LP, College Station, TX, USA). We used random effects to estimate pooled prevalence. To determine heterogeneity, inconsistency ( $I^2$ ) was calculated.

### Results

We found 380 studies in the databases; following eliminating duplicates, 182 studies remained. Finally, ten articles used for conducting meta-analysis (Fig. 1).

Ten articles were included. Totally, 5983 MS patients were assessed.

The characteristics of the included studies are shown in Table 1.

The pooled prevalence of willingness to vaccination among patients with MS was 76% (95% CI: 67–85%) ( $I^2 = 98.4%$ ,  $p < 0.001$ ) (Fig. 2).

The pooled prevalence of unwillingness to vaccination among patients with MS was 2% (95% CI: 2–3%) ( $I^2 = 97.9%$ ,  $p < 0.001$ ) (Fig. 3).

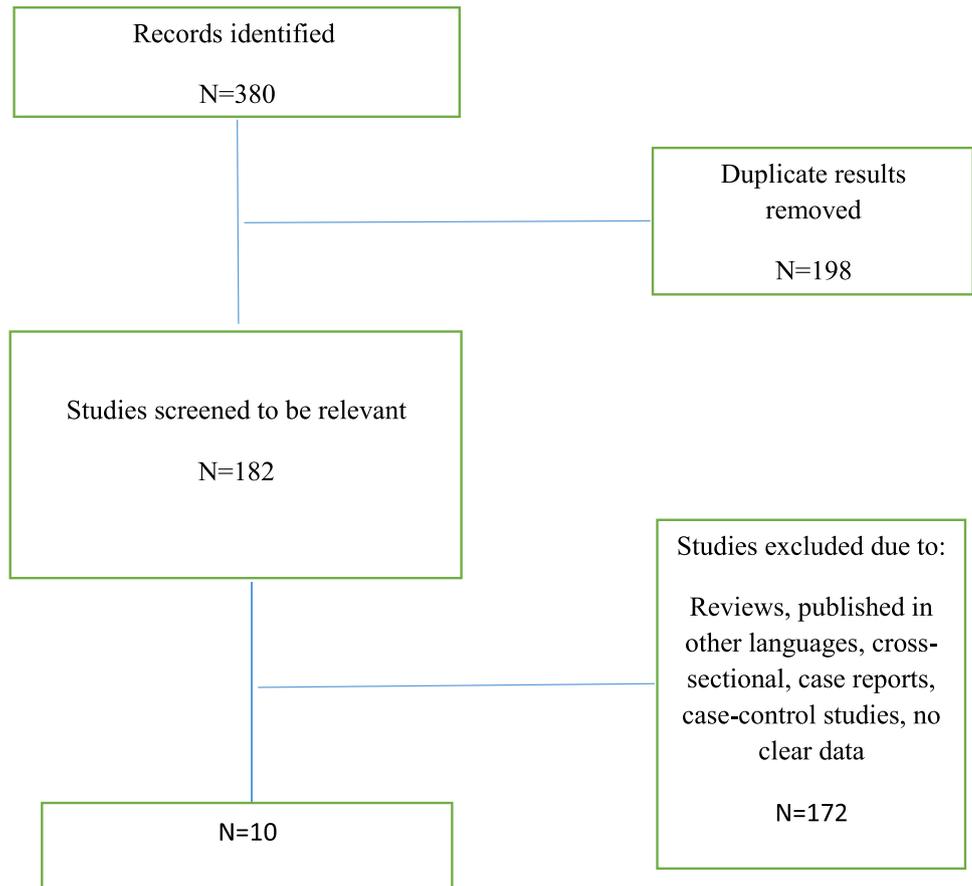
The pooled prevalence of hesitancy to vaccination among patients with MS was 0% ( $I^2 = 98%$ ,  $p < 0.001$ ) (Fig. 4).

The percentage of willingness, unwillingness, and hesitancy in patients with MS to get COVID-19 vaccines is shown based on countries (Fig. 5).

### Discussion

This study is the first systematic review and meta-analysis to assess the willingness, unwillingness, and hesitancy rates regarding COVID-19 vaccination among patients with MS.

The results show that the pooled willingness rate was 76%, ranging from 49 to 94%. The pooled prevalence of

**Fig. 1** Flow chart summarizing the selection of eligible studies

unwillingness was 2%, and the higher rate of unwillingness was reported by Ehde et al. [5]. They conducted a cross-sectional study enrolling 486 patients with MS in an online survey. Two-thirds of the participants were willing to get the COVID-19 vaccine, while 15% were unwilling. In their study, higher age and noticing a higher risk of contracting COVID-19 were two independent factors of predicting willingness.

In a survey by Huang et al. in the UK, 94% of patients with MS that were willing to get vaccines were higher than the general population (67%). Higher age, education level, and previous experience of influenza vaccine were associated with COVID-19 vaccination willingness. Female gender and no progressive type of the disease was associated with unwillingness in their survey [4].

Serrazina et al. reported willingness in 80% of 256 Portuguese patients with MS, while older patients and those with underlying diseases were more willing to obtain COVID-19 vaccines. Vaccination unwillingness was related to fewer concerns regarding COVID-19

infection and less impact of the disease on their lives [13]. In their study, the cases that wanted to postpone the vaccination were uncertain about the efficacy and safety of available vaccines.

It is shown that if patients had enough vaccination information, they were more willing to get the COVID-19 vaccination, and more hesitancy was related to more desire to get information. It was reported that if patients got their information from health care providers or National MS Societies, they trust more [5]. Previously, a physician's advice was the most promoting factor of vaccination among the general population [15]. Vaccination of the MS population may prevent severe infection, hospitalization, disease exacerbation, and medication cessation, especially disease modifying therapies (DMTs) which are crucial for MS relief [16, 17]. So, providing enough trusty information by health care providers play an essential role in vaccination willingness among MS patients and preventing complications following no vaccination.

**Table 1** Demographic information, and number of willingness, unwillingness, and hesitancy in patients with MS to get COVID-19 vaccines

Author/country	Surveys	Sample size	Respondents by sex	Age (mean/SD)	MS subtype	Expanded Disability Status Scale (EDSS)/patient determined disease steps (PDDS)	Measure of willingness	Reasons of willingness	Reasons of unwillingness	Reasons of hesitancy	NOS quality assessment
Xiang et al./Full text/USA/June 2021 [8]	Electronic	401	Male: 88 Female: 312 Missing: 1	51.1 (13.5)	Relapsing remitting: 290 Primary progressive: 30 Secondary progressive: 52 Unknown: 29	NR	Willingness: 281 Unwillingness: 29 Hesitant: 91	NR	NR	NR	7 out of 10
Ehde et al./Full text/USA/July 2021 [9]	Electronic	338	NR	NR	NR	NR	Willingness: 265 Unwillingness/Hesitant: 73	NR	-Efficacy: 18 -Short-term side effects: 19 -Long-term side effects: 23 -Process of vaccine approval: 20 -First one to receive vaccine: 16 -Health conditions/medical history: 20 -Religious beliefs: 5 -Others get vaccine first: 14 -Availability of vaccine: 5 -Dislike of needles: 4 -Want additional information: 18 -Not concern about COVID-19: 12 -More worried about vaccine than infection: 19	-Efficacy: 31 -Short-term side effects: 35 -Long-term side effects: 46 -Process of vaccine approval: 36 -First one to receive vaccine: 38 -Health conditions/medical history: 45 -Religious beliefs: 4 -Others get vaccine first: 34 -Availability of vaccine: 16 -Dislike of needles: 5 -Want additional information: 45 -Not concern about COVID-19: 22 -More worried about vaccine than infection: 32	7 out of 10

**Table 1** (continued)

Author/country	Surveys	Sample size	Respondents by sex	Age (mean/SD)	MS subtype	Expanded Disability Status Scale (EDSS)/patient determined disease steps (PDDS)	Measure of willingness	Reasons of willingness	Reasons of unwillingness	Reasons of hesitancy	NOS quality assessment
Uhr et al./Full text/[10]USA/June 2021	Electronic	701	Female: 553 Male: 148	-Willingness (n = 537): 56.5 (11.7) -Hesitant (n = 164): 51.94 (10.6)	Relapsing remitting: 459 Progressive: 242	PDDS: 3(1–5)	Willingness: 537 Unwillingness: 36 Hesitant: 128	-Important for health: 523/537 -Effectiveness: 524/537 -Important for the health of others: 531/537 -All vaccines offered by government are beneficial: 465/537 -More risks: 166/537 -Reliable and trustworthy resources: 431/537 -Protecting from getting disease: 522/537 -Doctor or health care provider recommends: 489/537 -Side effects: 174/537 -No need vaccine to not common diseases: 27/537	-Important for health: 101/164 -Effectiveness: 112/164 -Important for the health of others: 122/164 -All vaccines offered by government are beneficial: 62/164 -More risks: 76/164 -Reliable and trustworthy resources: 49/164 -Protecting from getting disease: 100/164 -Doctor or health care provider recommends: 105/164 -Side effects: 114/164 -No need vaccine to not common diseases: 14/164	6 out of 10	
Moniz Dionísio et al./Full text/Portugal/June 2021 [11]	Telephone and electronic	270	Female: 205 Male: 65	NR	Clinically isolated syndrome: 4 Relapsing remitting: 168 Primary progressive: 18 Secondary progressive: 10 Unknown: 70	NR	Willingness: 132 Unwillingness: 32 Hesitant: 106	NR	NR	NR	6 out of 10

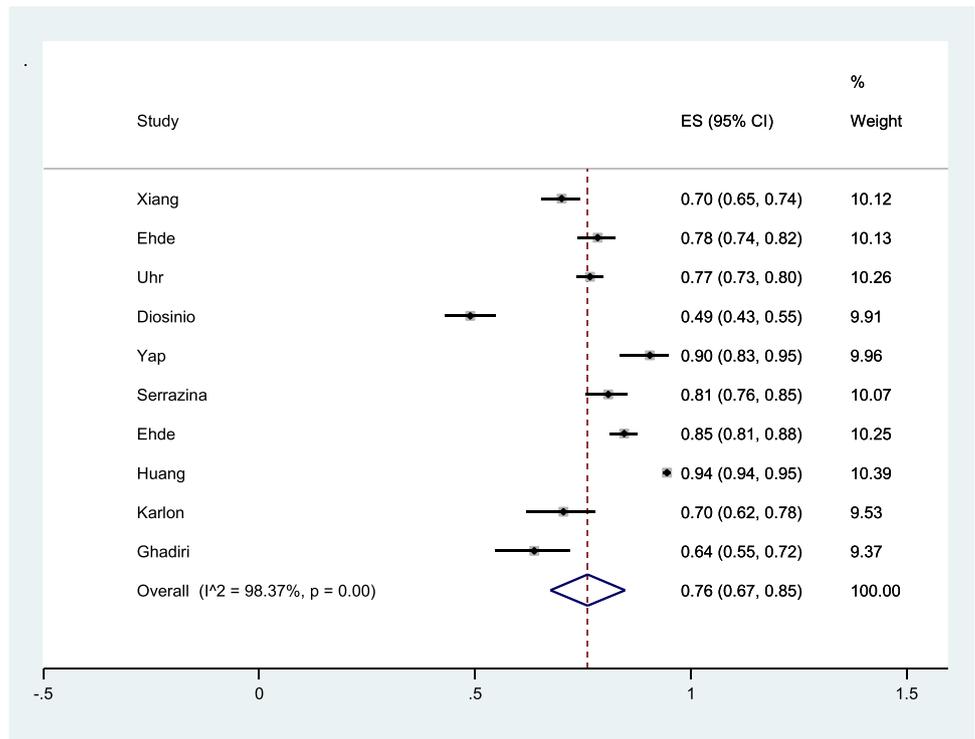
Table 1 (continued)

Author/country	Surveys	Sample size	Respondents by sex	Age (mean/SD)	MS subtype	Expanded Disability Status Scale (EDSS)/patient determined disease steps (PDDS)	Measure of willingness	Reasons of willingness	Reasons of unwillingness	Reasons of hesitancy	NOS quality assessment
Yap et al./Ireland/Full text/September 2021 [12]	Clinical interview	105	Female: 73 Male: 32	47.3 (12.8)	Relapsing remitting: 74 Progressive: 31	EDSS: 2.0 (1–6)	Willingness: 95 Hesitant: 10	-Vaccine was accessible: 84	NR	- Safety: 4 -Not enough realize about it: 2 -Not tested in MS: 1 -MS relapsing remitting: 1 -Will not work: 1 -Currently pregnant: 1	5 out of 10
Serrazina et al./Full text/Portugal/March 2021 [13]	Electronic	256	Female: 187 Male: 69	45 [18–77]	NR	NR	Willingness: 207 Unwillingness: 7 Hesitant: 42	NR	NR	NR	7 out of 10
Ehde et al./Full text/USA/January 2021 [5]	Electronic	486	Female: 395 Male: 84 Non-binary: 2 Transgender: 1 Other/Prefer Not to Say/No answer: 4	55.7 (12.6)	Clinically isolated syndrome: 5 Relapsing remitting: 316 Primary progressive: 48 Secondary Progressive: 80 Unknown: 5	NR	Willingness: 411 Unwillingness: 75	NR	NR	NR	6 out of 10
Huang et al./Full text/UK/July 2021 [4]	Electronic	3191	Female: 2346 Male: 845	NR	Progressive: 1126 Relapsing remitting: 2065	NR	Willingness: 3013 Unwillingness: 178	NR	NR	NR	6 out of 10

**Table 1** (continued)

Author/country	Surveys	Sample size	Respondents by sex	Age (mean/SD)	MS subtype	Expanded Disability Status Scale (EDSS)/patient determined disease steps (PDDS)	Measure of willingness	Reasons of willingness	Reasons of unwillingness	Reasons of hesitancy	NOS quality assessment
Ghadiri et al./Iran/May 2021 [14]	Electronic	113	Female: 88 Male: 26	36 (9.61)	Progressive: 23 Relapsing remitting: 91	EDSS: 2.99 (± 1.80)	Willingness: 72/113 Unwillingness: 9/113 Hesitant: 32/113	-Vaccine is more effectiveness: 85/114 -Cause relapse in MS: 10/113 -Disease progression in MS: 7/113 -Serious side effects: 20/114 -More side effects in MS patients: 16/112 -Preventing coronary heart disease in patients with MS is similar to health people: 58/114 -Vaccine should be a priority for MS patients: 78/114	-Vaccine is more effectiveness: 4/114 -Cause relapse in MS: 32/113 -Disease progression in MS: 39/113 -Serious side effects: 30/114 -More side effects in MS patients: 24/112 -Preventing coronary heart disease in patients with MS is similar to health people: 8/114 -Vaccine should be a priority for MS patients: 1/114 78/114	-Vaccine is more effectiveness: 25/114 -Cause relapse in MS: 71/113 -Disease progression in MS: 67/113 -Serious side effects: 64/114 -More side effects in MS patients: 72/112 -Preventing coronary heart disease in patients with MS is similar to health people: 48/114 -Vaccine should be a priority for MS patients: 35/114	7 out of 10
Karlon et al./Israel/Abstract/October 2021	Electronic	122	NR	NR	NR	NR	Willingness: 86 Unwillingness: 7 Hesitant: 29	-disease worsening/MS Relapse: 14 -Safety of vaccine: 6	NR	NR	4 out of 10

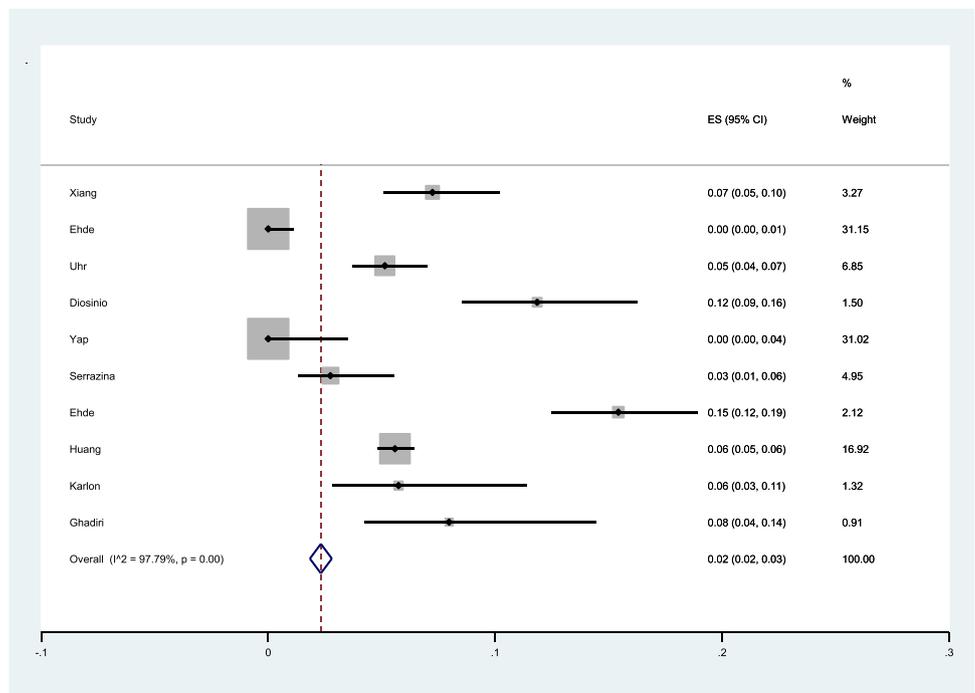
**Fig. 2** The pooled prevalence of willingness to vaccination among patients with MS



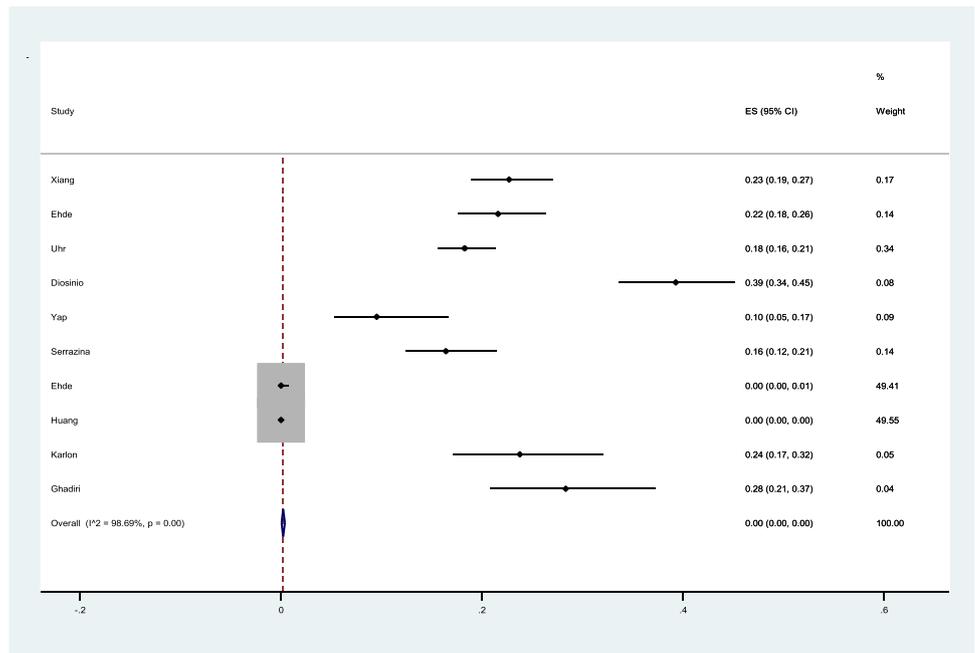
Changing attitude in hesitant and unwilling individuals to get COVID-19 vaccines has been important to have a successful vaccination. According to the

Wang et al. study, which is performed among 1047 and 1000 individuals, respectively, in the first wave in February and the third wave on August–September

**Fig. 3** The pooled prevalence of unwillingness to vaccination among patients with MS



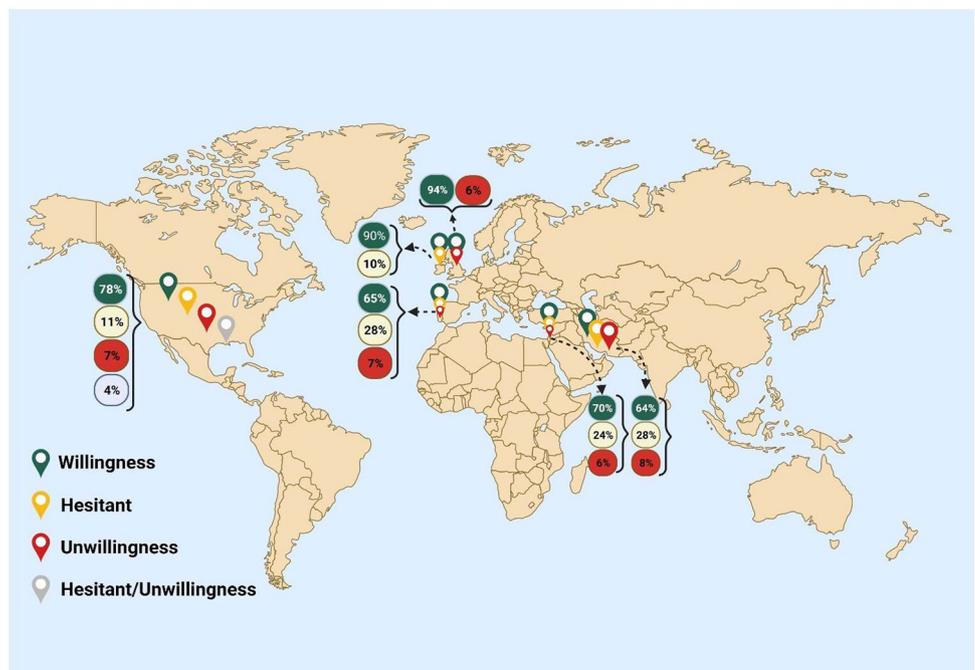
**Fig. 4** The pooled prevalence of hesitancy to vaccination among patients with MS



2020 in Hong Kong, participants who worked and received the influenza vaccine in the last year accepted more to get the vaccine in the first wave. Hesitancy was raised in the second wave. The reasons for hesitation were vaccine efficacy (63.2%), the vaccine is not unnecessary (24.5%), the short time

to manufacture vaccines (4.8%), and concern about safety or side effects of the vaccines (4.6%) [18]. In another cross-sectional study conducted in China in March and November–December among 791 individuals, there was a 3% decrease in willingness to get vaccines due to concern about approval. Changing in

**Fig. 5** All results of willingness, hesitancy, and unwillingness based on countries. Created with BioRender.com



intention was significant by attitude for the necessity, price, history, and physicians' advice [18].

Regarding Raciborski et al.'s investigation between January and April 2021, hesitancy of getting vaccination in Poland was due to worry about side effects. In this study, younger men groups (18–34 years) declared more unwillingness to get the vaccine [19]. These investigations have not been conducted among patients with multiple sclerosis.

This study had some strengths. First, it included all published studies up to now. Second, we evaluated willingness, unwillingness, and hesitancy in patients with MS.

## Conclusion

According to the findings of this systematic review and meta-analysis, more than two-thirds of patients with MS were willing to obtain COVID-19 vaccines.

## Declarations

**Ethical approval** Not applicable.

**Conflict of interest** The authors declare no competing interests.

**Research involving human participants and/or animals.** None.

**Informed consent** Not applicable.

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