



Global COVID-19 vaccine hesitancy among elderly: A systematic review

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ABSTRACT

Background & Objectives: Elderly infected with COVID-19 has high mortality risk, and the protection from COVID-19 vaccine is limited by vaccine hesitancy. The information of vaccine hesitancy in elderly is incomplete and fragmented. In this study, we attempt to examine the level of vaccine hesitancy in elderly and the related factors in global perspectives.

Methods: A systematic review was conducted to include observational studies of COVID-19 vaccine hesitancy in elderly from January 2020 to September 2021. Search strategies covering COVID-19 vaccine, vaccine hesitancy and elderly in four databases of PUBMED, MEDLINE, EMBASE and COCHRANE LIBRARY were adopted. Studies reporting COVID-19 vaccine hesitancy prevalence in elderly were included. A meta-analysis of the vaccine hesitancy prevalence was performed. The primary outcome is the vaccine hesitancy prevalence in elderly population globally. The secondary outcomes are the factors of COVID-19 vaccine hesitancy among elderly.

Results: Initial 479 articles were included for screening, with 54 studies included for meta-analysis of COVID-19 vaccine hesitancy in elderly and 6 studies included for qualitative analysis of factors for vaccine hesitancy. The overall prevalence of vaccine hesitancy was 27.7 % (95 % C.I: 23.8–31.6 %). The prevalence was significantly higher in Asia than in Europe (35.3 % VS 17.9 %, $p < 0.05$). The vaccine hesitancy was significantly higher before the launch of the vaccine than after (30.3 % VS 18.7 %, $p < 0.05$). Important factors of vaccine hesitancy in elderly identified were low income, low education, perception of COVID-19 being more contagious, more vaccine side effects and lower vaccine efficacy.

Conclusions: COVID-19 vaccine hesitancy is an important problem in elderly, with geographical variation. Tailored policy and strategies targeting the hesitancy factors were required to promote COVID-19 vaccine to elderly.

1. Introduction and literature review

COVID-19 pandemic caused 528 million infections and 6.29 million deaths [1] since its emergence in December 2019. Meta-analysis on epidemiological data showed that the infection fatality ratio (IFR) increased exponentially with increasing age, with a significant change at 65 years old [2]. IFR was less than 0.75 % for patients younger than 65 years old, but it increased to more than 2.5 % for those above 65 years old. COVID-19 vaccine was effective in decreasing severe infection and mortality [3,4]. However, the vaccine hesitancy was high among elderly in Hong Kong [5].

Vaccine hesitancy is defined as delay in acceptance or refusal of vaccination despite availability of vaccination services [6]. General factors of vaccine hesitancy are categorized into individual or group influences, contextual influences and vaccination specific issues.

Scoping review and rapid systematic review [7,8] have found factors for high COVID-19 vaccine hesitancy in general population in most of the countries being younger age, females, minor ethnicity and lower income or education level.

While many previous studies have assessed the COVID-19 vaccine hesitancy determinants, most of them were studying the general population with limited data focusing on elderly population. Furthermore, most previous studies were carried out before the launch of COVID-19 vaccine. The association of timing of vaccine availability with the outbreak status and vaccine hesitancy prevalence is still unknown. After finalization of the protocol of this systematic review, first systematic review in elderly COVID-19 vaccine hesitancy was published in October 2021. With inclusion of limited studies, it reported the prevalence of unwillingness and uncertainty to vaccinate being 27.03 % and 19.33 % respectively [9].

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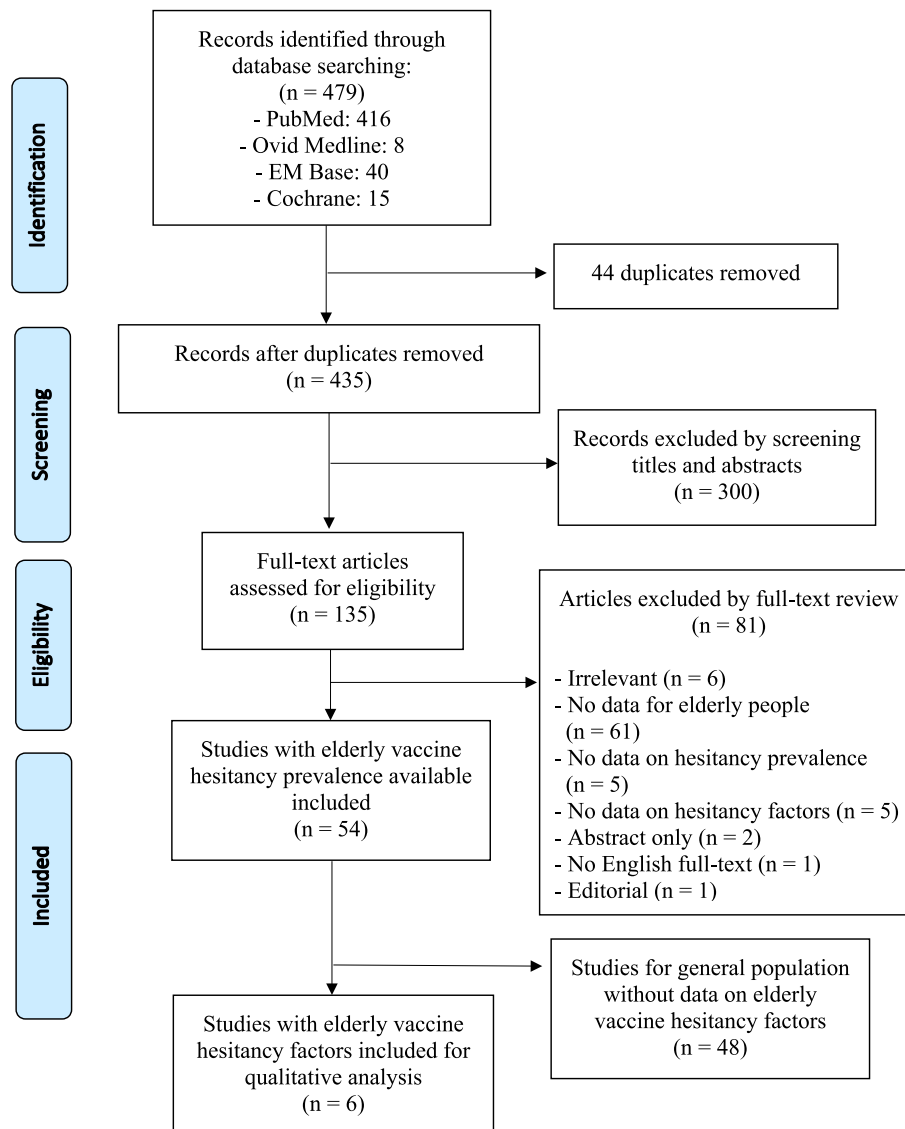


Fig. 1. PRISMA flow-chart.

2. Aims and objectives

Our review question is “Is COVID-19 vaccine hesitancy a common phenomenon in elderly?” The primary objective of this review is to assess the pooled hesitancy prevalence among elderly in the global perspectives. Secondary objective is to determine the factors of COVID-19 vaccine hesitancy in elderly.

With the high vaccine hesitancy rate and low vaccine uptake rate among elderly in Hong Kong, understanding the determinants of vaccine hesitancy in this subgroup of population is important for healthcare workers and public health policy makers to identify measures to promote vaccine uptake, and hence protect this vulnerable group from COVID-19 infection.

3. Methods

3.1. Protocol and registration

The protocol of this systematic review followed the PRISMA-P statement [10] and was registered at PROSPERO registry (CRD42022313483) in February 2022.

3.2. Study design and eligibility criteria

This is a systematic review designed for qualitative data synthesis on COVID-19 vaccine hesitancy in elderly based on available literature. It followed the PRISMA guidelines [11]. Inclusion criteria for this systematic review were observational studies from January 2020 to September 2021, which reported COVID-19 vaccine hesitancy with focus in elderly population or in the general population with elderly being a sub-group. These included cross-sectional, cohort and case-controlled studies. Only published and peer-reviewed articles retrievable in English language were included. Commentaries, editorials, letters, conference proceedings, position statements of organizations and expert opinions were excluded. Secondary studies including reviews and meta-analyses were also excluded. Primary studies without an abstract will be excluded as the screening for titles and abstracts is impossible.

3.3. Data sources and searches

Published observational studies from January 2020 to September 2021 were searched in the PUBMED, MEDLINE, EMBASE and COCHRANE LIBRARY. The search strategy was composed of three main themes, including COVID-19 vaccine, vaccine hesitancy and elderly.

Table 1
Characteristics of the included studies and the vaccine hesitancy.

| Author | Year | Country/ City | End of data collection | Vaccine launched | Data collection method | Elderly sample size | Minimum age | Hesitancy (%) |
|----------------------|------|------------------|---------------------------|---------------------|---------------------------|------------------------|-------------|------------------|
| Qin [15] | 2021 | China | 13/3/2020 | No | online survey | 30 | 55 | 31.25 |
| Luk [16] | 2021 | HK | 23/4/2020 | No | telephone | 495 | 60 | 38.3 |
| Li [17] | 2021 | China | 14/6/2020 | No | face-to-face | 236 | 58 | 16.1 |
| Wong [18] | 2021 | HK | 27/8/2020 | No | telephone | 823 | 55 | 31.9 |
| Alqudeimat [19] | 2021 | Kuwait | 1/9/2020 | No | online survey | 344 | 55 | 57.85 |
| Kishore [20] | 2021 | India | 10/11/2020 | No | online survey | 33 | 60 | 27.27 |
| Mohamed [21] | 2021 | Malaysia | 15/12/2020 | No | online survey | 175 | 60 | 58.29 |
| Syed Alwi [22] | 2021 | Malaysia | 29/12/2020 | No | online survey | 82 | 60 | 36.6 |
| Abedin [23] | 2021 | Bangladesh | 71/1/2021 | No | face-to-face | 267 | 60 | 38.6 |
| Machida [24] | 2021 | Japan | 18/1/2021 | No | online sent to e-mail | 779 | 65 | 25.5 |
| Ali [25] | 2021 | Bangladesh | 31/1/2021 | No | face-to-face | 31 | 61 | 38.7 |
| Ahmed [26] | 2021 | Pakistan | Apr-21 | Yes | online survey | 47 | 60 | 17 |
| Boon-Itt [27] | 2021 | Thailand | Apr-21 | No | online survey | 49 | 65 | 59.2 |
| Zhao [28] | 2021 | China | 26/4/2021 | Yes | online survey | 601 | 60 | 35.4 |
| Khankeh [29] | 2021 | Iran | May-21 | Yes | face-to-face | 220 | 60 | 11.4 |
| Thanapluetiwong [30] | 2021 | Thailand | 25/7/2021 | Yes | telephone | 282 | 60 | 44.3 |

[^] Study included for qualitative analysis.

This strategy was adapted from previous systematic reviews evaluating vaccine hesitancy for other vaccines [12]. The following search terms for the three main themes were used: (COVID OR coronavirus OR SARS-COV-2) AND (vaccine hesitancy OR vaccine refusal OR vaccine acceptance) AND (elderly OR aged population OR advanced age). The same search strategy was used for the four databases.

3.4. Study selection

Study selection was performed in three stages from identifying studies, screening titles and abstracts to full-text review by two independent reviewers. Inconsistent results were resolved by consensus. The search results were pooled in the EndNote X9 to identify and remove duplicate search results. Titles and abstracts were screened first and finally full text of the articles was screened using the inclusion and exclusion criteria.

3.5. Data collection and items

Data was extracted from selected studies, which included first author, the country, year of publication, COVID-19 vaccine hesitancy prevalence in elderly, data collection method and end date. Data on potential factors of vaccine hesitancy including gender, race, socioeconomic class, education level, outbreak status during the

availability of vaccine, vaccine safety and adverse events were extracted. Data items were input into Microsoft Excel with pre-defined format. Data extraction was done by two independent reviewers. Inconsistent data was reviewed for accuracy.

3.6. Data analysis and result synthesis

A PRISMA flowchart diagram was used to show the numbers and reasons of the exclusion of studies at each stage of the review. The characteristics of the included studies was summarized with descriptive statistics, including year of study, continent and country of study, number of study participants and methodology of data collection. Meta-analysis of the elderly COVID-19 vaccine hesitancy prevalence was performed using OpenMeta[Analyst]. Random effect model [13] was used for computational model for analysis as studies were included globally. I^2 metric test was used to assess heterogeneity across the studies. $I^2 > 50\%$ will be considered as significant heterogeneity. Publication bias was assessed by visual inspection of funnel plots [14].

All studies having secondary outcome results were used to present a narrative summary of COVID-19 vaccine hesitancy factors. According to the Strategic Advisory Group of Experts (SAGE) on immunization [6], the factors were grouped into three main categories of contextual influences, individual or group influences and vaccination specific issues for assessment.

Table 1b
Europe.

| Author | Year | Country/City | End of data collection | Vaccine launched | Data collection method | Elderly sample size | Minimum age | Hesitancy (%) |
|-----------------|------|----------------------|---------------------------|---------------------|------------------------------------------------------|------------------------|----------------|------------------|
| Kourlaba [31] | 2021 | Greece | 3/5/2020 | No | computer assisted tel or web | 374 | 55 | 32.6 |
| Ward [32] | 2020 | France | 4/5/2020 | No | online survey | 1234 | 64 | 10.7 |
| Fadda [33] | 2021 | Switzerland south | 15/5/2020 | No | telephone | 19 | 64 | 36.8 |
| La Vecchia [34] | 2020 | Italy | 28/9/2020 | No | interview (computer assisted) | 444 | 55 | 41.8 |
| Sethi [35] | 2021 | UK | 9/10/2020 | No | online survey | 1466 | 60 | 11.12 |
| Kessels [36] | 2021 | Belgium | 16/10/2020 | No | survey | 748 | 55 | 16.65 |
| Robertson [37] | 2021 | UK | 1/12/2020 | No | telephone or online | 4352 | 55 | 9.4 |
| Malesza [38] | 2021 | Germany | 17/1/2021 | Yes | face-to-face | 1037 | 76 | 21.8 |
| Valerio [39] | 2021 | Italy | 16/2/2021 | Yes | online survey | 1538 | 61 | 3.6 |
| Raciborski [40] | 2021 | Poland | 18/4/2021 | Yes | telephone + online + personal (computer assisted) | 357 | 60 | 23.35 |
| Galle [41] | 2021 | Italy | Aug-21 | Yes | online sent to phone | 1041 | 65 | 6.95 |

[^] Study included for qualitative analysis.

Table 1c
North America.

| Author | Year | Country/ City | End of data collection | Vaccine launched | Data collection method | Elderly sample size | Minimum age | Hesitancy (%) |
|----------------------|------|--------------------------------|-----------------------------------|------------------|--------------------------|------------------------------------------|-------------|-------------------------|
| Shih [42] | 2021 | USA | 2020/3/22 | No | online survey | 242 | 56 | 37 |
| Kelly [43] | 2021 | USA | Apr-2020 | No | survey online to address | 511 | 65 | 15.1 |
| Szilagyi [44] | 2021 | USA | 1st: 14/4/2020 2nd: 16/3/2021 | Yes | online survey | No data | 65 | 1st: 33.8 2nd: 17.55 |
| Fisher [45] | 2020 | USA | 20/4/2020 | No | online survey | 298 | 60 | 23.5 |
| Reiter [46] | 2020 | USA | May-2020 | No | online survey | 504 | 65 | 24 |
| Ruiz [47] | 2021 | USA | 16/6/2020 | No | online survey | 255 | 55 | 30.75 |
| Wagner [48] | 2021 | USA | 20/7/2020 | No | telephone + online | 189 | 65 | 40.45 |
| Nguyen [49] | 2021 | USA | 1st: 1/10/2020 2nd: 20/12/2020 | Yes | online survey | No data | 65 | 1st: 29.8 2nd: 18.7 |
| Holaday [50] | 2021 | USA | Nov-2020 | No | online survey | 6715 | 65 | 38.5 |
| Unroe [51] | 2021 | USA – Indiana | 2020/11/17 | No | survey online to phone | 938 | 60 | 35.9 |
| Nikolovski [52] | 2021 | USA | 20/11/2020 | No | mobile apps | 7402 | 65 | 8.7 |
| Salmon [53] | 2021 | USA | 7/12/2020 | No | online survey | 865 | 60 | 39 |
| Siegler [54] | 2021 | USA | 1st: 8/12/2020 2nd: 21/4/2021 | Yes | online survey | 400 | 55 | 1st: 26 2nd: 7 |
| Ogilvie [55] | 2021 | Canada | 10/12/2020 | No | online survey | 1370 | 60 | 15.8 |
| Daly [56] | 2021 | USA | 1st: 5/1/2021 2nd: 29/3/2021 | Yes | online survey | No data | 60 | 1st: 36.2 2nd: 21 |
| Szilagyi [57] | 2021 | USA | 19/1/2021 | No | online survey | 1536 | 65 | 28.2 |
| Garcia [58] | 2021 | USA | 11/2/2021 | No | online survey | 715 | 65 | 15.5 |
| El-Mohandes [59] | 2021 | USA – NYC, LA, Dallas, Chicago | Apr-21 | Yes | Not mentioned | Nat:596 NY: 284 LA: 263 Da: 217 Chi: 275 | 60 | 7.95 |
| Fernandez-Penny [60] | 2021 | USA – Philadelphia | 11/5/2021 | Yes | face-to-face | 307 | 56 | 10.25 |

[^] Study included for qualitative analysis.

Table 1d
South America, Oceania, Africa and multiple continents.

| Author | Year | Country/ City | End of data collection | Vaccine launched | Data collection method | Elderly sample size | Minimum age | Hesitancy (%) |
|----------------------------|------|------------------------------------------|------------------------|------------------|------------------------|---------------------|-------------|---------------|
| South America | | | | | | | | |
| Oliveira [61] | 2021 | Brazil | 30/10/2020 | No | online survey | No data | 60 | 22.8 |
| Macinko [62] | 2021 | Brazil | Nov-2020 | No | telephone | 6681 | 50 | 29.1 |
| Oceania | | | | | | | | |
| Seale [63] | 2021 | Australia | 24/3/2020 | No | online survey | 198 | 70 | 9.1 |
| Thaker [64] | 2021 | New Zealand | 13/7/2020 | No | online survey | 354 | 56 | 21.5 |
| Africa | | | | | | | | |
| Echoru [65] | 2021 | Uganda | 9/2020 | No | online survey | 50 | 60 | 42 |
| Multiple Continents | | | | | | | | |
| Trent [66] | 2021 | United States, United Kingdom, Australia | Sep-2020 | No | online survey | 727 | 65 | 11 |
| Kaadani [67] | 2021 | 22 Arab countries | 14/1/2021 | No | online survey | 39 | 65 | 41 |
| Qunaibi [68] | 2021 | 23 Arab + 122 other | 29/1/2021 | No | online survey | 664 | 60 | 77.6 |

[^] Study included for qualitative analysis.

4. Results

4.1. Search results

The PRISMA flow-chart was shown in Fig. 1. Initially 479 articles were identified, in which 44 were duplicate results. After screening out 300 articles by the titles and abstracts, 135 full-text articles were reviewed. 54 studies [15–68] with elderly vaccine hesitancy prevalence reported were included, giving total sample size of 49,699 elderly. For factors of vaccine hesitancy, most studies were for general population

without subgroup analysis for elderly. Target study population was elderly only in 6 of the studies [30,33,38,41,52,62]. They were included for qualitative analysis for elderly vaccine hesitancy factors.

4.2. Study characteristics

The main descriptive findings of the 54 included studies, including author, city or country of study, publication year, data collection method and end date, elderly sample size and minimum age, were charted in Table 1 and grouped by continents. Most of the studies were

a) Overall

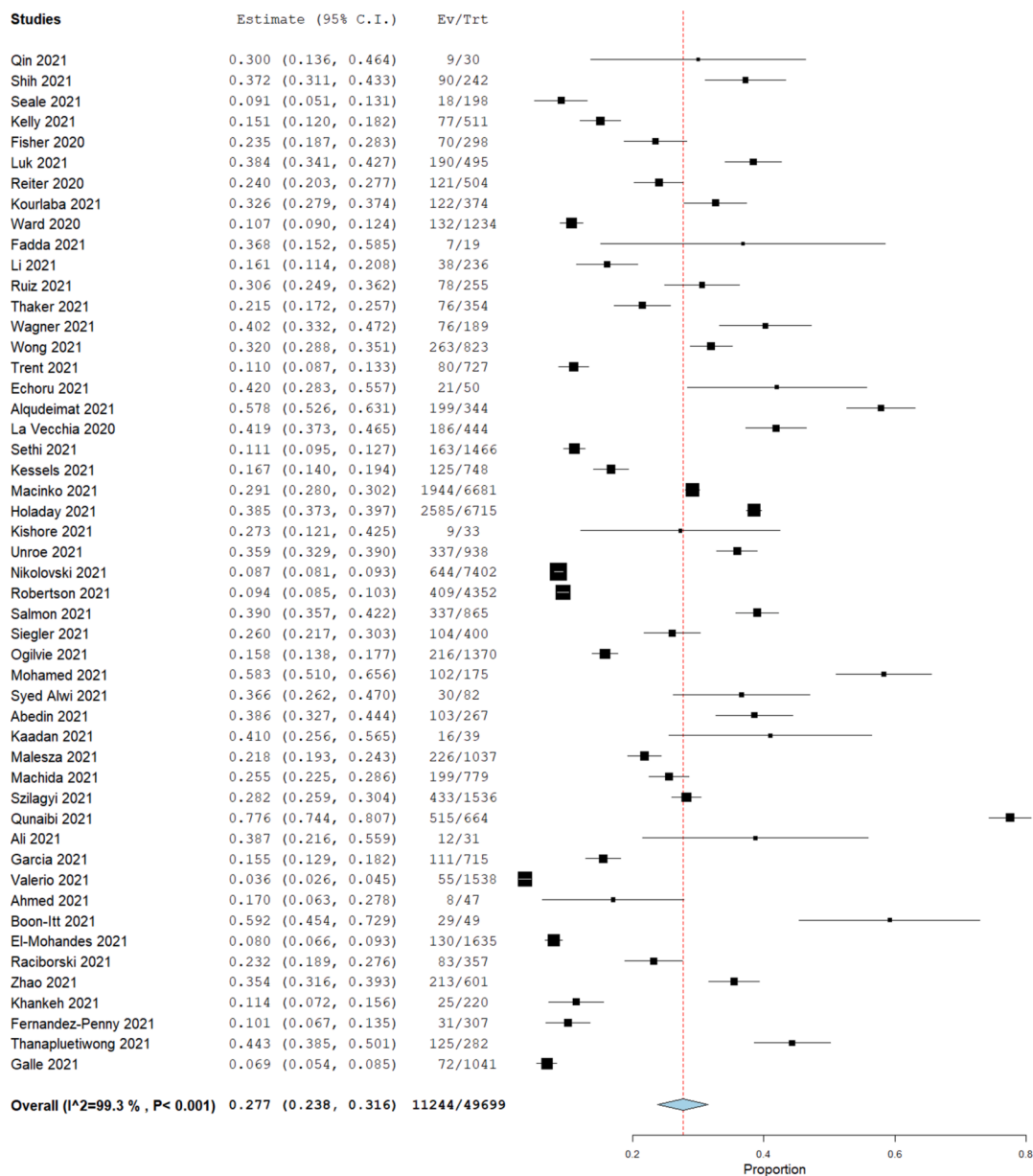


Fig. 2. Forest plots of the prevalence of COVID-19 vaccine hesitancy.

from North America (n = 19), followed by Asia (n = 16), Europe (n = 11), South America (n = 2), Oceania (n = 2) and Africa (n = 1). The remaining 3 studies were multi-national studies covering more than 1 continent. 34 studies collected data in 2020 and 20 studies finished data collection in 2021, in which only 14 studies collected data after the vaccine was launched. 4 studies were longitudinal studies [44,49,54,56].

4.3. COVID-19 vaccine hesitancy prevalence in elderly

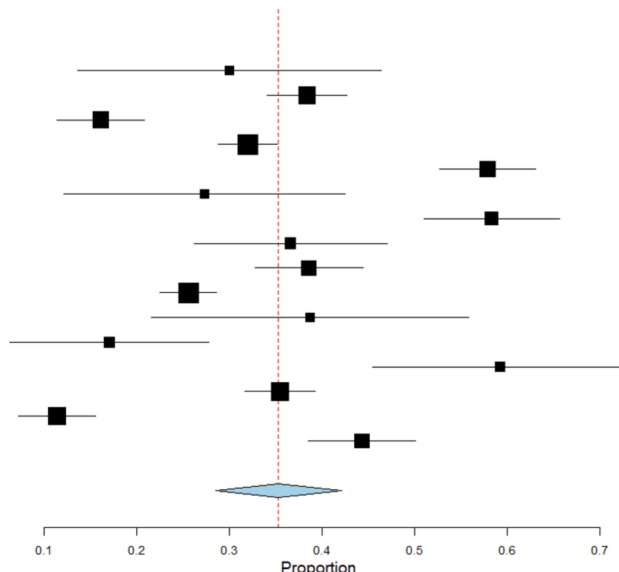
The prevalence of the COVID-19 vaccine hesitancy in elderly from individual studies was listed in Table 1. Four studies reported the elderly vaccine hesitancy prevalence but not the number of elderly population studied, and therefore not included in the meta-analyses. The overall vaccine hesitancy prevalence across the included studies was 27.7 %

(95 % C.I: 23.8–31.6 %), with high heterogeneity ($I^2 = 99.3\%$) (Fig. 2a). The prevalence was significantly higher in Asia than in Europe (35.3 % VS 17.9 %, $p < 0.05$) (Fig. 2b & c). The prevalence in North America was 24.7 % (95 % C.I: 17.8–31.6 %) (Fig. 2d), which was similar to the overall prevalence.

Four studies [44,49,54,56] were longitudinal studies comparing the vaccine hesitancy before and after the launch of the vaccine of the same studied population. All studies were conducted in USA. The hesitancy prevalence ranged from 26 % to 38.3 % before the availability of the vaccine. All of the studies reported a lower hesitancy prevalence after the launch of the vaccine (7–21 %). Meta-analyses of the vaccine hesitancy of all included studies were performed with stratification to the availability of vaccine. The hesitancy prevalence was 30.3 % (95 % C.I: 25.7–35.0 %) before the launch of the vaccine from 39 included studies (Fig. 2e). The prevalence after the vaccine launched from 11 included

b) Asia

| Studies | Estimate (95% C.I.) | Ev/Trt |
|------------------------------------------------------|-----------------------------|------------------|
| Qin 2021 | 0.300 (0.136, 0.464) | 9/30 |
| Luk 2021 | 0.384 (0.341, 0.427) | 190/495 |
| Li 2021 | 0.161 (0.114, 0.208) | 38/236 |
| Wong 2021 | 0.320 (0.288, 0.351) | 263/823 |
| Alqudeimat 2021 | 0.578 (0.526, 0.631) | 199/344 |
| Kishore 2021 | 0.273 (0.121, 0.425) | 9/33 |
| Mohamed 2021 | 0.583 (0.510, 0.656) | 102/175 |
| Syed Alwi 2021 | 0.366 (0.262, 0.470) | 30/82 |
| Abedin 2021 | 0.386 (0.327, 0.444) | 103/267 |
| Machida 2021 | 0.255 (0.225, 0.286) | 199/779 |
| Ali 2021 | 0.387 (0.216, 0.559) | 12/31 |
| Ahmed 2021 | 0.170 (0.063, 0.278) | 8/47 |
| Boon-Itt 2021 | 0.592 (0.454, 0.729) | 29/49 |
| Zhao 2021 | 0.354 (0.316, 0.393) | 213/601 |
| Khankeh 2021 | 0.114 (0.072, 0.156) | 25/220 |
| Thanapluetiwong 2021 | 0.443 (0.385, 0.501) | 125/282 |
| Overall (I²=95.79 % , P< 0.001) | 0.353 (0.285, 0.421) | 1554/4494 |



c) Europe

| Studies | Estimate (95% C.I.) | Ev/Trt |
|------------------------------------------------------|-----------------------------|-------------------|
| Kourlaba 2021 | 0.326 (0.279, 0.374) | 122/374 |
| Ward 2020 | 0.107 (0.090, 0.124) | 132/1234 |
| Fadda 2021 | 0.368 (0.152, 0.585) | 7/19 |
| La Vecchia 2020 | 0.419 (0.373, 0.465) | 186/444 |
| Sethi 2021 | 0.111 (0.095, 0.127) | 163/1466 |
| Kessels 2021 | 0.167 (0.140, 0.194) | 125/748 |
| Robertson 2021 | 0.094 (0.085, 0.103) | 409/4352 |
| Malesza 2021 | 0.218 (0.193, 0.243) | 226/1037 |
| Valerio 2021 | 0.036 (0.026, 0.045) | 55/1538 |
| Raciborski 2021 | 0.232 (0.189, 0.276) | 83/357 |
| Galle 2021 | 0.069 (0.054, 0.085) | 72/1041 |
| Overall (I²=98.38 % , P< 0.001) | 0.179 (0.135, 0.223) | 1580/12610 |

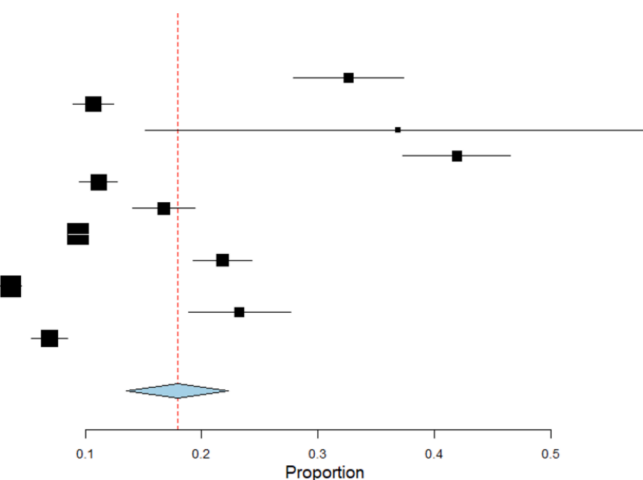


Fig. 2. (continued).

studies was 18.7 % (95 % C.I: 13.0–24.3 %), which was statistically significant lower (Fig. 2f).

4.4. Factors of COVID-19 vaccine hesitancy prevalence in elderly

The 6 studies targeting elderly population were carried out in Switzerland, Brazil, USA, Germany, Thailand and Italy. The Swiss study [33] was a qualitative study with 19 participants for the attitude towards the COVID-19 vaccine. The data on factors of vaccine hesitancy was from an open-ended question and the factors were simply concluded. The main individual, contextual and vaccine-specific factors of vaccine hesitancy were personal perception of health and past experiences, decreased number of COVID-19 cases and efficacy and safety of vaccine respectively.

The remaining 5 articles studied the relative risks or odds ratios of different factors of vaccine hesitancy. Due to the great heterogeneity of the questionnaire design of individual studies, quantitative analysis for combined effects of the vaccine hesitancy factors was not appropriate. Instead, a narrative summary categorized into individual influence, contextual influence and vaccine-specific factors was shown in Table 2.

For individual influence, if only statistically significant results from

included studies were considered, lower income [52] and lower education [41,52] were factors of vaccine hesitancy. However, contradictory results were found for gender [41,52] and elder age group within the elderly population [41,62] as factors of vaccine hesitancy.

For contextual influence, more COVID-19 fatality was associated with lower vaccine hesitancy, which was studied only by the Brazilian study [62]. Perception of COVID-19 being more contagious was also associated with lower vaccine hesitancy as shown in the study by USA [52] and Germany [38]. Lack of trusted source of COVID-19 information was one of the factors of vaccine hesitancy as shown in the Thai [30] and Italian [41] study, but the German study [38] found contradictory result.

For vaccine specific issues, vaccine side effects were analyzed by the studies from USA [52], Germany [38] and Italy [41]. All showed perception of more vaccine side effects being a significant factor of vaccine hesitancy. Perception of lower vaccine efficacy was another significant factor of vaccine hesitancy as shown in the studies from USA [52] and Germany [38].

d) North America

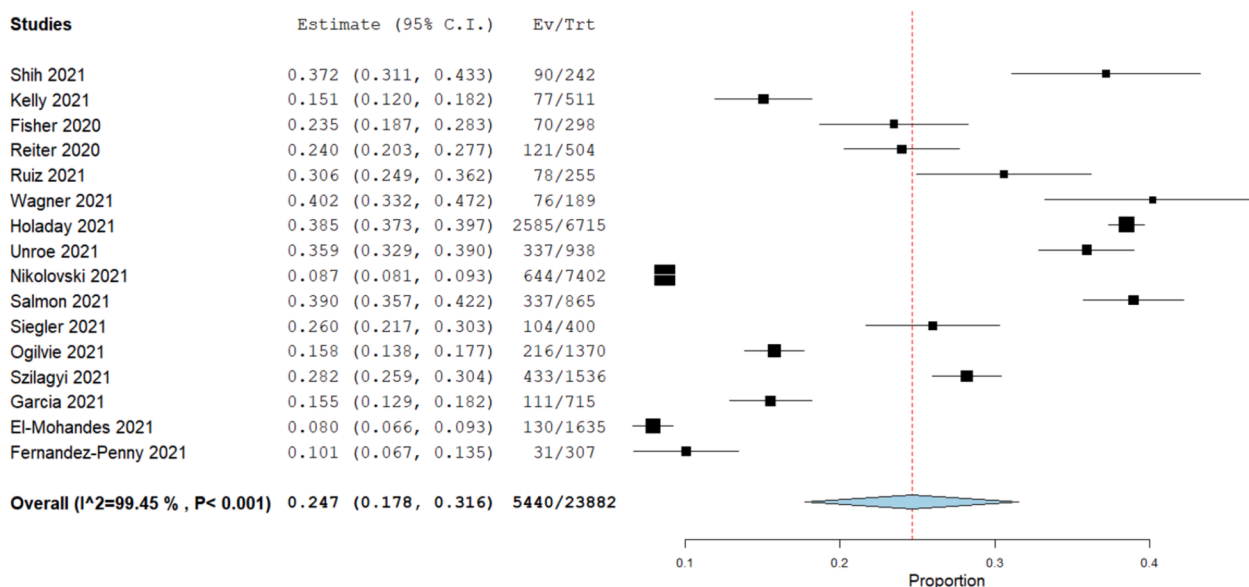


Fig. 2. (continued).

5. Discussion

Upon finalization of the protocol of this systematic review, there was no published systematic review or registered protocol on the topic of COVID-19 vaccine hesitancy in elderly. One systematic review and meta-analysis on this topic [9] was published in October 2021, which searched for studies until 18th June 2021. Fifteen studies with 9753 elderly were included. To the best of our knowledge, our systematic review was the only one with comprehensive inclusion of studies covering worldwide data as in April 2024. Total 54 studies were included from literature search between January 2020 and September 2021. Sample size of more than 49,600 elderly people recruited globally showed the overall prevalence of COVID-19 vaccine hesitancy being around 27.7%. Our result was similar to the previous meta-analysis [9]. However, the prevalence of vaccine hesitancy by the previous meta-analysis was separated into 2 parts of unwillingness to vaccinate and uncertainty to vaccinate. The prevalence of uncertainty to vaccinate was higher in American countries (25.57%) than in European countries (11.62%), but the study failed to demonstrate the geographical difference of prevalence of unwillingness to vaccinate. Our result provided additional information on the prevalence of COVID-19 vaccine hesitancy in elderly in Asia (35.3%), which was significantly higher than in western countries. Our systematic review also reported vaccine hesitancy from Oceania and Africa, which were not included in the previous meta-analysis.

Our result showed that COVID-19 vaccine hesitancy is significant in elderly, especially in Asian countries or cities. The COVID-19 vaccine uptake rate in elderly is lower than younger age groups in Hong Kong and many countries. In countries with vaccine readily available, vaccine hesitancy is the main reason for low vaccine uptake rate. We should understand the significance of vaccine hesitancy and the factors to improve vaccine hesitancy and hence the uptake rate to protect elderly, community and healthcare system.

There was wide geographical variation in vaccine hesitancy across different continents. Only 1 study in Africa was included. It showed the vaccine hesitancy was 42%, but it was not representative due to single study. The second highest vaccine hesitancy was in Asia. There were many contributing factors. Generally, the socioeconomic status is lower in Asian countries than western countries, especially those in South Asia.

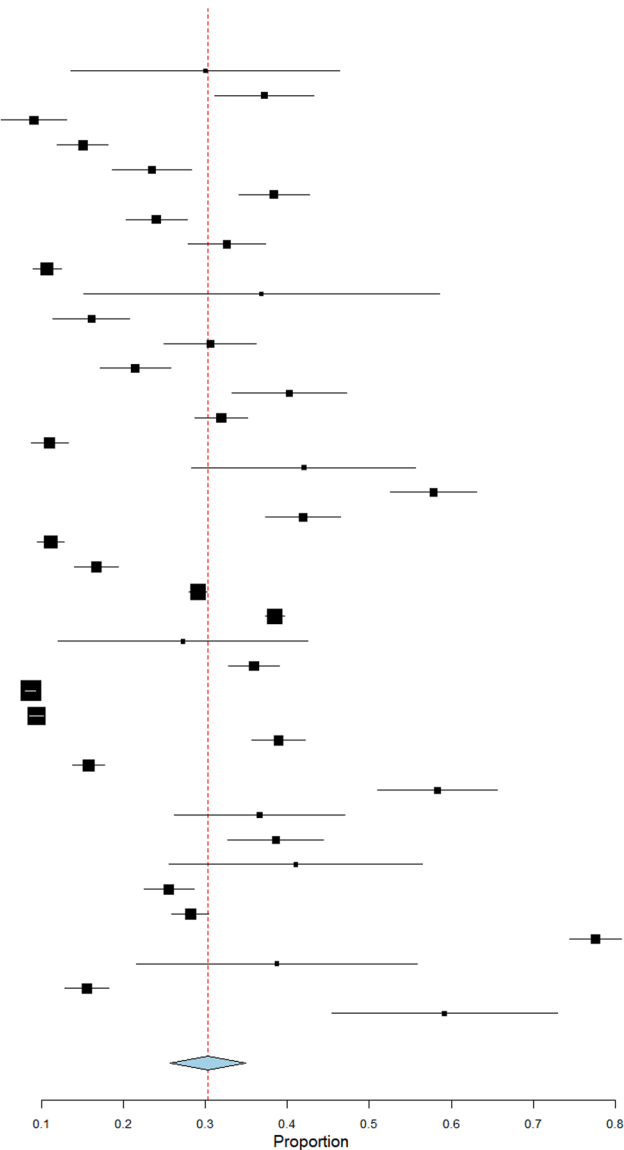
Lower digital health literacy in elderly in some Asian countries was another factor [69]. These contributed to misinformation and less confidence in COVID-19 vaccine. Cultural and religious beliefs in some Asian regions would impact the vaccine hesitancy. One reason was the possible conflict of vaccine ingredients with religious practices. Government trust is another important contributing factor. Many South Asian countries were governed by more dictatorial governments. In Southeast Asia, past government performance, low transparency and limited communication channels jeopardized public trust towards government and hence vaccine acceptance [70].

Our result also showed the vaccine hesitancy decreased following the availability of the vaccine. It may be explained by the contextual influence and vaccine specific issues as factors of vaccine hesitancy. Serial nationwide cross-sectional studies and longitudinal studies found that not only vaccine hesitancy, but also related factors were in dynamic evolution. With COVID-19 virus evolution, different waves of COVID-19 outbreak, increasing availability of COVID-19 vaccines, widespread reports of vaccine adverse effects and changing government policy on vaccine, the contextual factors and individual perception changed a lot. Vaccine was launched after few waves of COVID-19 outbreaks in most of the countries. People may have stronger perception of the highly contagious COVID-19. The longer time the vaccine was launched, safety and efficacy of the vaccine was reported more. These may contribute to the overall decreased hesitancy towards the novel vaccine.

Concerning factors of vaccine hesitancy, individual influence is not amenable but should be understood to identify the at-risk group for vaccine refusal. Lower income and lower education were persistently shown as important factors in our result, many previous studies and the previous meta-analysis [9]. One of the proposed theory to explain the reasons of people having vaccine hesitancy is the knowledge, attitude and practice (KAP) model. The lower income and education groups were believed to have less knowledge and hence less access to correct information of COVID-19 and vaccine [71]. This contributed the hesitancy towards vaccine. Factors of contextual influence and vaccine-specific issues can be amenable. By understanding that contagiousness of COVID-19, vaccine efficacy and safety are important factors, education on these issues should be delivered to elderly by their trusted bodies, such as healthcare professionals and health authority of the government [62].

e) Before launch of vaccine

| Studies | Estimate (95% C.I.) | Ev/Trt |
|------------------------------------------------------|-----------------------------|--------------------|
| Qin 2021 | 0.300 (0.136, 0.464) | 9/30 |
| Shih 2021 | 0.372 (0.311, 0.433) | 90/242 |
| Seale 2021 | 0.091 (0.051, 0.131) | 18/198 |
| Kelly 2021 | 0.151 (0.120, 0.182) | 77/511 |
| Fisher 2020 | 0.235 (0.187, 0.283) | 70/298 |
| Luk 2021 | 0.384 (0.341, 0.427) | 190/495 |
| Reiter 2020 | 0.240 (0.203, 0.277) | 121/504 |
| Kourilaba 2021 | 0.326 (0.279, 0.374) | 122/374 |
| Ward 2020 | 0.107 (0.090, 0.124) | 132/1234 |
| Fadda 2021 | 0.368 (0.152, 0.585) | 7/19 |
| Li 2021 | 0.161 (0.114, 0.208) | 38/236 |
| Ruiz 2021 | 0.306 (0.249, 0.362) | 78/255 |
| Thaker 2021 | 0.215 (0.172, 0.257) | 76/354 |
| Wagner 2021 | 0.402 (0.332, 0.472) | 76/189 |
| Wong 2021 | 0.320 (0.288, 0.351) | 263/823 |
| Trent 2021 | 0.110 (0.087, 0.133) | 80/727 |
| Echoru 2021 | 0.420 (0.283, 0.557) | 21/50 |
| Alqudeimat 2021 | 0.578 (0.526, 0.631) | 199/344 |
| La Vecchia 2020 | 0.419 (0.373, 0.465) | 186/444 |
| Sethi 2021 | 0.111 (0.095, 0.127) | 163/1466 |
| Kessels 2021 | 0.167 (0.140, 0.194) | 125/748 |
| Macinko 2021 | 0.291 (0.280, 0.302) | 1944/6681 |
| Holaday 2021 | 0.385 (0.373, 0.397) | 2585/6715 |
| Kishore 2021 | 0.273 (0.121, 0.425) | 9/33 |
| Unroe 2021 | 0.359 (0.329, 0.390) | 337/938 |
| Nikolovski 2021 | 0.087 (0.081, 0.093) | 644/7402 |
| Robertson 2021 | 0.094 (0.085, 0.103) | 409/4352 |
| Salmon 2021 | 0.390 (0.357, 0.422) | 337/865 |
| Ogilvie 2021 | 0.158 (0.138, 0.177) | 216/1370 |
| Mohamed 2021 | 0.583 (0.510, 0.656) | 102/175 |
| Syed Alwi 2021 | 0.366 (0.262, 0.470) | 30/82 |
| Abedin 2021 | 0.386 (0.327, 0.444) | 103/267 |
| Kaadan 2021 | 0.410 (0.256, 0.565) | 16/39 |
| Machida 2021 | 0.255 (0.225, 0.286) | 199/779 |
| Szilagyi 2021 | 0.282 (0.259, 0.304) | 433/1536 |
| Qunaibi 2021 | 0.776 (0.744, 0.807) | 515/664 |
| Ali 2021 | 0.387 (0.216, 0.559) | 12/31 |
| Garcia 2021 | 0.155 (0.129, 0.182) | 111/715 |
| Boon-Itt 2021 | 0.592 (0.454, 0.729) | 29/49 |
| Overall (I²=99.32 % , P< 0.001) | 0.303 (0.257, 0.350) | 10172/42234 |



f) After launch of vaccine

| Studies | Estimate (95% C.I.) | Ev/Trt |
|------------------------------------------------------|-----------------------------|------------------|
| Siegler 2021 | 0.260 (0.217, 0.303) | 104/400 |
| Malesza 2021 | 0.218 (0.193, 0.243) | 226/1037 |
| Valerio 2021 | 0.036 (0.026, 0.045) | 55/1538 |
| Ahmed 2021 | 0.170 (0.063, 0.278) | 8/47 |
| El-Mohandes 2021 | 0.080 (0.066, 0.093) | 130/1635 |
| Raciborski 2021 | 0.232 (0.189, 0.276) | 83/357 |
| Zhao 2021 | 0.354 (0.316, 0.393) | 213/601 |
| Khankeh 2021 | 0.114 (0.072, 0.156) | 25/220 |
| Fernandez-Penny 2021 | 0.101 (0.067, 0.135) | 31/307 |
| Thanapluetiwong 2021 | 0.443 (0.385, 0.501) | 125/282 |
| Galle 2021 | 0.069 (0.054, 0.085) | 72/1041 |
| Overall (I²=98.51 % , P< 0.001) | 0.187 (0.130, 0.243) | 1072/7465 |

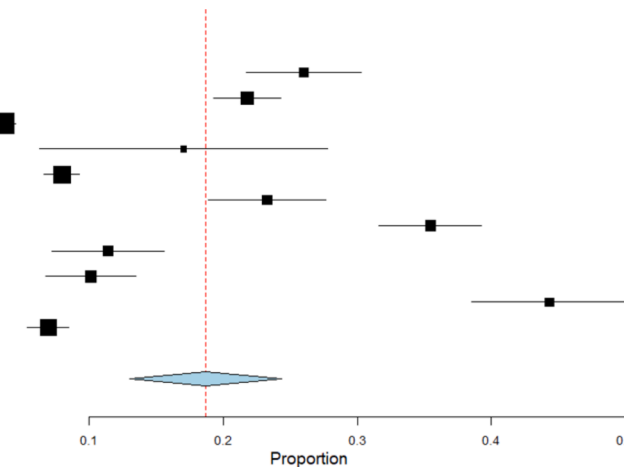


Fig. 2. (continued).

Table 2
Factors of COVID-19 vaccine hesitancy.

| Factors | RR/OR for vaccine hesitancy | | | | |
|------------------------------------------------|-----------------------------|------------------------|-------------------------|----------------------------------|---------------------|
| | Brazil Macinko [62] | USA Nikolovski [52] | Germany Malesza [38] | Thailand Thanapluetiwong [30] | Italy Galle [41] |
| Individual influence | | | | | |
| Elder age group | 2.46* | 0.78 | 0.89 | 1.78 | 0.15* |
| Gender (Female) | 1.3 | 2.04* | 0.10 | 1.32 | 0.59* |
| Higher education | 1.25 | 0.45* | 0.17 | 0.39 | 0.54* |
| Higher income | No data | 0.38* | 0.12 | Not significant | No data |
| Chronic disease | 1.13 | No data | 1.87 | No data | No data |
| Contextual influence | | | | | |
| More COVID-19 cases | 0.99 | No data | No data | 0.15 | No data |
| More COVID-19 fatality | 0.89* | No data | No data | No data | No data |
| Perceive COVID-19 more contagious | No data | 0.22* | 0.86* | No data | No data |
| Lack of trusted source of COVID-19 information | 1.71 | No data | 0.98* | 2.55* | 2.42* |
| Vaccine specific issues | | | | | |
| Perceived more vaccine side effects | No data | 5.26* | 1.15* | No data | 5.78* |
| Perceived higher protection from vaccine | No data | 0.03* | 0.625* | No data | No data |

RR: relative risks.

OR: Odds ratios.

* Statistically significant, $p < 0.05$.

Understanding the problems of vaccine hesitancy in elderly and contributing factors, we propose that government should organize educational campaigns to elderly, especially those less educated and in the lower socio-economic class. Outreach teams to elderly nursing homes should be established for the educational campaigns. The focus of the education material should be on the high contagion of COVID-19, low side effect profile of and high protection from the vaccine.

Our study is the most comprehensive systematic review including global studies after launching of the vaccine. PRISMA guideline [11] was adhered. However, there are few limitations of our systematic review. First, most of the studies included were collecting data by online survey and self-administered questionnaires. There would be sample selection bias towards more knowledgeable and healthier elderly. There would be limitation to generalize the results to the whole elderly population. Those more fragile elderly with multiple co-morbidities and limited mobility were less likely to participate in the individual studies. Indeed, they are the most vulnerable population from COVID-19 infection, who need to be protected most by vaccination. This group of elderly was the one with less access to online information about the vaccine and COVID-19. This was associated with vaccine scepticism. Therefore, our study probably underestimated the prevalence of COVID-19 vaccine hesitancy in elderly.

Second, the definitions of elderly population were heterogenous in the included studies. Different studies use different minimum age, which was detailed in Table 1. Overall 24 % of included studies used age cut-off of 55 to 59, 44 % used age cut-off of 60 to 64 and 26 % used age cut-off of 65. Meta-analyses of the vaccine hesitancy were conducted with stratification to these three groups of age cut-off. The hesitancy rates were 28.5 %, 30.3 % and 25.3 % respectively, which were similar to the overall hesitancy prevalence of 27.7 %.

Third, there was publication bias in our meta-analysis. Reviewing the countries in individual studies, many Asian countries and some European countries were not included. Under-reporting from these countries is possible.

Fourth, there was great heterogeneity of the data. We have performed different subgroup analyses including continents of the studying country, timing with launch of vaccine and the minimum age cut-off of elderly. Great heterogeneity persisted in the subgroup analyses suggesting diverse sources of heterogeneity. The questionnaire designs from different studies varied greatly. The measurement tools of vaccine hesitancy from individual studies also differ, including 5-point or 7-point

Likert scale and simply yes or no scale. These affected the accuracy of our combined results.

6. Conclusions

This systematic review reported the prevalence of COVID-19 vaccine hesitancy in elderly in different countries and continents. Geographical variation exists, but the problem of vaccine hesitancy is overall significant, especially in Asia. Vaccine hesitancy in elderly depends on many factors. Tailored policy and specific strategies targeting on these factors should be implemented by public health policy makers to promote vaccine uptake in elderly.

7. Contributor

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CRediT authorship contribution statement

M.C. Law: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **P.K.F. Chiu:** Formal analysis, Data curation.

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All authors attest they meet the ICMJE criteria for authorship.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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