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Multivariable Logistic Regression Analysis of Factors associated with COVID-19 Vaccine Hesitancy

By

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Masters of Public Health

Global Epidemiology

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B.A., University of California, Berkeley, 2016

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An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
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Abstract

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Introduction

In 2019, a new coronavirus was identified and subsequently led to a global pandemic, directing many public health efforts towards development of effective vaccines. With the rapid development and rollout of the COVID-19 vaccine amid the ongoing pandemic, willingness to receive an FDA-approved vaccine is not guaranteed; vaccine hesitancy will play a key role in determining vaccine population impact globally.

Methods

We analyzed surveys (n=4,269) completed by participants in the United States, China, India, Indonesia, and Malaysia, gathered by the University of Michigan School of Public Health. Due to limited literature on the association between prior acceptance of vaccinations and future vaccine hesitance, the multivariable logistic regression analysis of this work looked at the association between having received a prior flu vaccine within the past twelve months and COVID-19 vaccine hesitancy, stratified by low-and middle-income countries (LMIC) and high-income countries (United States). It also assesses the association between COVID-19 vaccine hesitancy and other family and social characteristics.

Results

In both LMICs and the United States, receiving a prior flu vaccine had a negative association with being hesitant towards the COVID-19 vaccine, however, the association is notably stronger in the United States, with an odds ratio (OR) of 0.2 (95%CI=0.1, 0.2), compared to 0.8 (95%CI=0.7, 1) in LMICs. Living in a rural area and lower monthly income both had a positive association with being hesitant towards the COVID-19 vaccine, with stronger associations seen in the United States.

Discussion

This analysis showed that an individual's flu vaccine history may impact the likelihood of hesitancy towards new vaccines, including to prevent COVID-19. Previous studies on vaccine hesitancy are abundant; however, limited studies specifically explore the association between vaccine hesitancy and prior vaccination. Because vaccine hesitancy is specific to culture, geography, and disease, and it is understudied in LMICs, it is very challenging to generalize COVID-19 LMIC vaccine hesitancy. As more data become available, opportunities to study attitudes and behaviors towards the COVID-19 vaccine will emerge, and they may build upon the findings of this analysis done in the early stages of the COVID-19 pandemic.

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Introduction

The introduction of human vaccination is one of the most successful public health interventions in history. The cumulative impact of vaccines on human health and well-being is evidenced by prolonged life expectancy, elimination of disruptive community epidemics, alleviation of parental fears about crippling childhood diseases, and economic savings from averted morbidity and disability. [1] To successfully control vaccine-preventable diseases in communities and prevent morbidity and mortality at the population level, high vaccination rates should be achieved and maintained. [2]

Despite recognition of vaccine as one of the most successful public health measures, vaccine hesitancy is growing. The World Health Organization [3] listed vaccine hesitancy as one of the top 10 health threats in 2019. The Strategic Advisory Group of Experts (SAGE) Working Group on vaccine hesitancy defines this phenomenon as "the delay in acceptance or refusal of vaccination despite availability of vaccination services." [4] The complex and context-specific nature of vaccine hesitancy requires better understanding of its distribution and determinants by time, place, population, and target disease. [4] The ongoing COVID-19 pandemic and rapid development and rollout of COVID-19 vaccines have sparked international debate over their efficacy and safety, inevitably leading to discussions about COIVD-19 vaccine hesitancy.

Determinants of vaccine hesitancy include both individual factors, such as emotions, values, risk perceptions, knowledge, or belief, as well as social, cultural, political, and historical factors. [5, 6] Vaccine hesitancy for COVID-19 vaccines will likely develop over time, taking shape in the context of different subgroups. [4, 7] HPV vaccination programs in Denmark demonstrated that

even strong, well-organized vaccination campaigns can be quickly disrupted when vaccine safety concerns emerge. [8]

Experience with Ebola vaccine in Africa showed how social and political resistance arise during introduction of a new vaccine even amid a public health emergency. [9] Although lessons are inevitably learned from vaccine interventions and campaigns of the past, vaccine hesitancy persists globally; many challenges lie ahead as COVID-19 vaccination campaigns prepare to launch.

The development and rollout of COVID-19 vaccines happened as rapidly as we have ever seen, increasing the odds for vaccine failure, which can detrimentally impact COVID-19 vaccine acceptance. [10] Given the recency of the COVID-19 pandemic, research on global attitudes towards the COVID-19 vaccines is limited, but it is critical we prioritize understanding population and subgroup perceptions of the COVID-19 vaccines to increase their success. [11]

The importance and need to study vaccine hesitancy for COVID-19 vaccines in various populations and subgroups can be partially met by analyzing results from global cross-sectional surveys conducted by the University of Michigan. This survey collects important information on risk factors for COVID-19 vaccine hesitancy and includes population-based data from the United States, China, Taiwan, Indonesia, India, and Malaysia. Specifically, the survey data allow for investigation of the association between receiving a prior flu vaccination within the past 12 months and COVID-19 vaccine hesitancy. This relationship has not been widely studied, but it may be important, because recent vaccination history may predict hesitancy towards new vaccines in general and specifically as it pertains to COVID-19 vaccines. Family and country

characteristics were also included in this analyses, as vaccine hesitancy may be influenced by a number of social, political, and economic factors.

Methods

The current analysis used data from a series of cross-sectional surveys conducted by the University of Michigan research team in the United States, China, Taiwan, Indonesia, India, and Malaysia. The purpose of these surveys was to assess the prevalence of COVID-19 vaccine hesitancy before and during vaccine rollout. The surveys were first administered in March 2020 in the United States and China, followed by the additional data collection in Taiwan, Indonesia, India, and Malaysia starting in August 2020. Public datasets from these surveys are include data collected in March, June, August, and November 2020. Data used for the analyses in this paper came from the November 2020 dataset for the United States, Taiwan, Indonesia, India, and Malaysia, and the August 2020 dataset for China.

The aim of this analysis was to answer the question: What was the association between having received a flu vaccine within the last 12 months and current COVID-19 vaccine hesitancy? The exposure of interest (prior flu vaccine) and outcome (COVID-19 vaccine hesitancy) were both expressed as binary variables. A descriptive analysis compared the distribution of participant characteristics between vaccine hesitant and non-hesitant groups (Table 1). COVID-19 vaccine hesitancy was measured based on the sum of 10 vaccine hesitancy questions in the survey from the World Health Organization (WHO) SAGE on immunizations working group. Each question corresponded to different scores on a vaccine hesitancy scale, ranging from 1 to 5, with the total score ranging from 10 to 50. The binary outcome variable for vaccine hesitancy was defined as the total score of > 25, using ten questions used to determine the vaccine hesitancy score (Table 2).

The analyses controlled for sociodemographic and family characteristics, including living in rural vs. urban area; monthly income level; whether the participant had a parent > 50 years of age; or a child < the age of 18. Monthly income levels were specific to the cost-of-living and economy in each country (Table 3). All results were adjusted for residence in a high-income (HIC) or low-middle income country (LMIC). Data from Taiwan were excluded from this analysis because surveys administered did not include a prior flu vaccine question. The United States was the only survey site in HIC.

Logistic regression models were used to calculate crude and adjusted odds ratios (OR) and the corresponding 95% confidence intervals (CI) reflecting the associations of the main independent variable of interest (history of past flu vaccine) and covariates with COVID-19 vaccine hesitancy.

The initial adjusted model included all two-way interactions between the history of flu vaccination and each covariate: $Logit\ [P(Y=1)] = \beta_0 + \beta_1 FLU + \gamma_1 PARENT50 + \gamma_2 CHILD18 + \gamma_3 INCOME + \gamma_4 RURAL + \gamma_5 LMIC + \delta_1 FLU*LMIC + \delta_1 FLU*RURAL + \delta_1 FLU*CHILD18$

In the presence of statistically significant and meaningful effect modification, stratified models were used. All analyses were carried out in SAS 9.4™ (SAS Institute, Cary, North Carolina).

Results

The descriptive analyses compared the distributions of participant characteristics across vaccine hesitancy groups (Table 1). Among 4,269 survey respondents, 38% met the definition of vaccine hesitancy and 42% reported receiving a flu vaccination within the past 12 months. The vaccine-hesitant group included fewer persons with prior flu vaccination (33%) compared to the non-vaccine hesitant group (47%). Persons with low income (34%) and rural residents (34%) were greater in the vaccine hesitant group than corresponding percentages groups that did not meet the definition of vaccine hesitancy (20% and 23%, respectively).

The distribution among those who had at least one parent >50 years of age and at least one child < 18 years were similar between the two groups. Respondents from LMIC were only slightly lower (74% vs. 79%) among vaccine-hesitant participants than among participants who were not vaccine hesitant.

The initial multivariable logistic regression model included three statistically significant interaction terms reflecting effect modification with the main association of interest (i.e., between prior flu vaccine within the last 12 months and vaccine hesitancy) by three covariates: having a child < 18; living in a rural area; and residence in an LMIC (Table 4). A comparison of stratum-specific estimates for these three covariates demonstrated that residency in LMIC was the strongest effect modifier (Table 5). The remaining results were presented separately for persons residing in LMIC and those residing in the United States.

The results of the multivariable logistic regression among participants from LMICs showed the odds of vaccine hesitancy was about 20% lower among survey respondents who received a flu

vaccine in the previous 12 months compared to those who did not receive flu vaccine (95% CI=0.7,1) (Table 6). They also showed an inverse relation between vaccine hesitancy income levels. Compared to high-income (reference), estimates for upper-middle, lower-middle- and low-income groups were OR=1.1 (95%CI=0.9,1.3), OR=1.4 (95%CI=1.1, 1.7) and OR=1.9 (95%CI=1.6,2.4), respectively.

There was evidence that vaccine hesitancy was greater among person living in a rural areas (OR=1.3;95% CI=1.1,1.6); whereas corresponding results for having a parent >50 years of age and for having a child <18 years were in the opposite direction, but not statistically significant (Table 6).

When data were limited to survey respondents from the United States, the inverse association between prior flu vaccination and vaccine hesitancy (OR=0.2; 95% CI=0.1, 0.2) and the positive association between living in a rural area and vaccine hesitancy (OR=1.7; 95% CI=0.3,2.4) were stronger than the corresponding associations observed among LMIC residents (Table 7). The inverse association between income and vaccine hesitancy among U.S. participants was similar to that in LMIC; however, the increase appeared less monotonic.

Another notable finding was the strong association with having a child < 18 years in the United States (OR=1.9;95%CI=1.3, 2.6) which contrasted with the null result observed in LMIC (Tables 6 and 7).

Discussion

Receiving prior flu vaccination was associated with lower COVID-19 vaccine hesitancy while controlling for geographic sociodemographic factors. The analyses demonstrated that some associations differed substantially in LMIC versus those in the United States. While in LMIC, receiving a prior flu vaccine within the past 12 months was related to lower COVID-19 vaccine hesitancy, this inverse association was stronger in the United States. Another notable difference between results was the greater vaccine hesitancy observed among persons with young children in the United States compared to LMIC. On the other hand, the association with income levels and living in rural vs. urban areas were generally similar, albeit not identical.

Previous studies on vaccine hesitancy are abundant; however, very few specifically explored the association between vaccine hesitancy and decision making of prior vaccinations. Additionally, most previous studies either focused entirely on LMICs or HICs, as drivers of vaccine hesitancy may vary greatly even within geographic borders. [12] One previous U.S. study on COVID-19 vaccine hesitancy showed rural residents and individuals with lower income were more likely to report vaccine hesitancy towards the COVID-19 vaccine. [13] Both results are consistent with our findings.

Literature have shown poor vaccine uptake associated with lower socioeconomic status. [14-18] This is usually attributed to disparities in access, affordability, and awareness. [19, 20] Contrary to our findings, some literature have shown affluent individuals in HIC to be more vaccine hesitant and may have lower vaccine uptake [21].

We note vaccine hesitancy may not be generalizable across all diseases. Unique to the COVID-19 vaccines is the speed in which they were developed and the element of novelty and newness that influences vaccine hesitant attitudes and behaviors that do not necessarily apply to other diseases in the aforementioned studies. Finally, because vaccine hesitancy is specific to culture, geography, and disease, and it is understudied in LMICs, it is very challenging to generalize COVID-19 LMIC vaccine hesitancy. More research is needed.

The United States was the only high-income country in this analysis. This data restriction limits the ability to generalize results seen in the U.S. cohort to other HIC. On the other hand, previous research demonstrated that drivers of vaccine hesitancy (e.g., confidence, complacency, convenience or constraints, risk calculation, and collective responsibility) appeared to operate across HIC. [22, 23] These observations serve as a reminder that vaccine hesitancy is complex and a dynamic social process that "reflects multiple webs of influence, meaning, and logic." [24] People's views and practices on vaccination are conditional on evolving personal and social circumstances, which have the potential to change over time. [24]

This analysis was specific to vaccine hesitancy towards the COVID-19 vaccine. Given the recent COVID-19 vaccine rollout and ongoing pandemic, evidence on attitudes toward the COVID-19 vaccine is relatively sparse. Of particular value may be the ability to compare COVID-19 vaccine hesitancy between LMIC and HIC. Factors influencing vaccine acceptance often vary between high- and low-resource settings. [25]

Noteworthy limitations of this analysis include the cross-sectional design of the survey, relatively limited geographic representation of LMIC and especially non-LMIC, and limited information on data collection methods of the survey, including response rates and possible

selection bias. Additionally, data in the survey did not consistently include questions on factors such as education or religion, which have been shown to play an important role in vaccine hesitancy.

Conclusions

This analysis showed that an individual's flu vaccine history may impact the likelihood of hesitancy towards new vaccines, including ones to prevent COVID-19. Findings suggested that in both LMIC and HIC, those with history of not receiving flu vaccines were more likely to be hesitant towards new vaccines. This may be especially true for HIC such as the United States. Clinicians and public health practitioners may consider developing new methods of targeting vaccine hesitancy by focusing on past health behavior.

Understanding the barriers to receiving flu vaccines in different settings could inform more effective intervention strategies to increase uptake of new vaccines, such as COVID-19 vaccines. An area of further study should be to examine socioeconomic levels in the context of country-level income levels. As our analyses, show, lower monthly income levels are associated with higher vaccine hesitancy in both LMIC and HIC, and more could be explored in how these different income levels manifest differently in more specific contexts at the country level. Furthermore, a longitudinal study measuring vaccine hesitancy over time may be more beneficial than a cross-sectional survey to broaden and deepen understanding of hesitancy toward new vaccines.

In the context of COVID-19, it may be best to use a longitudinal study design to see how COVID-19 vaccine hesitancy changes from before the COVID-19 pandemic to after COVID-19 elimination or stabilization to an endemic state. As more data become available, many opportunities to study attitudes and behaviors towards the COVID-19 vaccine will emerge, and they may build upon the findings of this analysis in the early stages of the COVID-19 pandemic.

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Tables

Table 1. *Study Population Characteristics Categorized by Vaccine Hesitancy Status, 2020*

Participant Characteristics		Total N (%)	Vaccine Hesitant N (%)*	Not Vaccine Hesitant N (%)*
Prior flu vaccine				
	Yes	1,775 (41.6)	538 (32.9)	1231 (47)
	No	2,494 (58.4)	1099 (67.1)	1390 (53)
Has Parent >50				
	Yes	3320 (77.8)	1251 (76.4)	2065 (78.8)
	No	949 (22.2)	386 (23.6)	556 (21.2)
Has Child <18				
	Yes	2421 (56.7)	884 (54)	1534 (58.5)
	No	1848 (43.3)	753 (46)	1087 (41.5)
Income Level				
	Low	1065 (25)	549 (33.5)	513 (19.6)
	Lower-Middle	1035 (24.2)	415 (25.4)	615 (23.5)
	Upper-Middle	1242 (29.1)	398 (24.3)	843 (32.2)
	High	927 (21.7)	275 (16.8)	650 (24.8)
Rural				
	Yes	1166 (27.31)	558 (34.1)	605 (23.1)
	No	3103 (72.69)	1079 (65.9)	2016 (76.9)
LMIC				
	Yes	3283 (76.9)	1214 (74.2)	2069 (78.9)
	No	986 (23.1)	423 (25.8)	552 (21.1)
Total		4269 (100)	1637 (38.3)	2621 (61.4)

* All percentages are in columns, except the bottom row.
Abbreviation: LMIC=Low-middle income countries

Table 2. *Vaccine hesitancy questions from World Health Organization (WHO) Strategic Advisory Group of Experts (SAGE) on immunization working group*

L1	Vaccines are important for my health.
L2	Vaccines are effective.
L3	Being vaccinated is important for the health of others in my community.
L4	All recommended routine vaccines recommended are beneficial.
L5	New vaccines carry more risks than older vaccines.
L6	The information I receive about vaccines from official sources is reliable and trustworthy.
L7	Getting vaccines is a good way to protect me from disease.
L8	Generally, I follow vaccine recommendations from my doctor or healthcare provider.
L9	I am concerned about serious adverse effects of vaccines.
L10	I do NOT need vaccines for diseases that are no longer common.

Table 3. *Monthly Income level Categories for each Country in Study Population*

	United States	**China**	**India**	**Indonesia**	**Malaysia**
Low	up to $1,999	up to 4,999元	up to 7,500 INR	up to $1,999	up to RM2,999
Lower-Middle	$2,000-4,999	5,000-9,999元	7,501-15,000 INR	$2,000-4,999	RM3,000-5,999
Upper-Middle	$5,000-9,999	10,000-19,999元	15,000-400,000 INR	$5,000-9,999	RM6,000-8,999
Upper	at least $10,000	at least 20,000元	at least 40,000 INR	at least $10,000	at least RM9,000

Table 4. *Multivariable analysis of the association between prior flu vaccine receipt and COVID-19 vaccine hesitancy with interactions*

Participant characteristics	Crude OR (95% CI)	Adjusted OR (95% CI)
Prior flu vaccine		
No	1 (ref)	1 (ref)
Yes	0.6 (0.5, 0.6)	0.1 (0.1, 0.2)
Has Parent >50		
No	1 (ref)	1 (ref)
Yes	0.9 (0.8, 1)	0.9 (0.7, 1)
Has Child <18		
No	1 (ref)	1 (ref)
Yes	0.8 (0.7, 0.9)	0.9 (0.8, 1.1)
Income Level		
High	1 (ref)	1 (ref)
Upper-Middle	1.1 (0.9, 1.3)	1 (0.9, 1.3)
Lower-Middle	1.6 (1.3, 1.9)	1.3 (1.1, 1.6)
Low	2.5 (2.1, 3)	2 (1.68, 2.49)
Rural		
No	1 (ref)	1 (ref)
Yes	1.7 (1.5, 2)	1.3 (1.1, 1.5)
LMIC		
No	1 (ref)	1 (ref)
Yes	0.8 (0.7, 0.9)	0.3 (0.3, 0.4)
Significant Interactions		**OR (p-value)**
LMIC× Prior flu vaccine		4.1 (p<0.0001)
Rural× Prior flu vaccine		1.4 (p=0.01)
Child <18× Prior flu vaccine		1.5 (p=0.007)

Abbreviations: OR=odds ratio; CI-confidence interval; LMIC=Low-middle income countries

Table 5. *Association between prior flu vaccine receipt and COVID-19 vaccine hesitancy, stratified by statistically significant interaction variables*

Participant characteristics		Stratified association OR (95% CI)
Has Child <18		
	No	0.1 (0.1, 0.2)
	Yes	0.2 (0.1, 0.3)
Rural		
	No	0.1 (0.1, 0.2)
	Yes	0.2 (0.1, 0.3)
LMIC		
	No (United States)	0.1 (0.1, 0.2)
	Yes	0.5 (0.4, 0.7)

Abbreviations: OR=odds ratio; CI-confidence interval; LMIC=Low-middle income countries

Table 6. *Multivariable analysis of association between prior flu vaccine receipt and COVID-19 vaccine hesitancy among LMIC participants*

Participant characteristics		OR (95% CI)
Prior flu vaccine		
	No	1 (ref)
	Yes	0.8 (0.7, 1)
Has Parent >50		
	No	1 (ref)
	Yes	0.8 (0.7, 1)
Has Child <18		
	No	1 (ref)
	Yes	0.9 (0.7, 1)
Income Level		
	High	1 (ref)
	Upper-Middle	1.1 (0.9, 1.3)
	Lower-Middle	1.4 (1.1, 1.7)
	Low	1.9 (1.6, 2.4)
Rural		
	No	1 (ref)
	Yes	1.3 (1.1, 1.6)

Abbreviations: OR=odds ratio; CI-confidence interval; LMIC=Low-middle income countries

Table 7. *Multivariable analysis of the association between prior flu vaccine receipt and COVID-19 vaccine hesitancy among US participants*

Participant characteristics		OR (95% CI)
Prior flu vaccine		
	No	1 (ref)
	Yes	0.2 (0.1, 0.2)
Has Parent >50		
	No	1 (ref)
	Yes	0.9 (0.7, 1.2)
Has Child <18		
	No	1 (ref)
	Yes	1.9 (1.3, 2.6)
Income Level		
	High	1 (ref)
	Upper-Middle	0.9 (0.6, 1.5)
	Lower-Middle	1.1 (0.7, 1.7)
	Low	2.4 (1.5, 3.8)
Rural		
	No	1 (ref)
	Yes	1.7 (1.3, 2.4)

Abbreviations: OR=odds ratio; CI-confidence interval