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Supplementary appendix

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COVID-19 vaccine hesitancy in a representative working-age population in France: a survey experiment based on vaccine characteristics

eAppendix 1: Sample size, study sample and data collection

Sample size

The minimum sample size required for a discrete choice experiment (DCE) depends on the specific hypotheses to be tested.[1] As there was no prior on parameter values for a DCE on COVID-19 vaccine characteristics, we relied on the standard parametric approach for a choice probability to approximate the minimum sample size:[2]

$$n \geq \frac{(1-p)}{rpa^2} \times (\ \Phi^{-1}(1-\frac{\alpha}{2}))^2$$

Where p is the true population probability, r is the number of choice tasks per respondent, a is the accuracy level around the true population probability, Φ^{-1} is the inverse of the cumulative normal distribution function, and α is the significance level.

To be conservative, we calculated the minimum sample size on the assumption that COVID-19 vaccine acceptance is 50% (p=50%). Each respondent completed 8 choices (see below). Thus, to estimate p within 4% of the true p value with a confidence level of 95%, the minimum sample size required was 300. However, respondents with prior SARS-CoV-2 infection were excluded from the randomized experiment and each selected respondent was randomly allocated to two information blocks before the DCE according to a full factorial design (3 blocks on herd immunity x 2 blocks on GP advice on vaccination). Assuming 10% prior infections during the first wave of SARS-CoV-2 in the French working age population, the survey sample size was fixed to 2,000 participants to allow measuring COVID-19 vaccine acceptance in each block combination.

Study sample

The study sample was randomly selected from an online survey research panel of more than 700,000 French adults developed and maintained by BVA Group (Paris, France), an opinion survey research firm (www.bva-group.com). Prior information on the panellists was used by BVA to determine eligibility and draw a stratified random sample with oversampling of panellists with low response rates. To limit coverage bias, random sampling was stratified to match French official census statistics for gender, age (18–24; 25–34; 35–44; 45–54; 55–64), education (left school with no qualifications; some high school or apprenticeship of vocational qualification; high school graduate; university graduate), household size (1; 2; 3; 4 members or more), area of residence (rural area; urban area from 2,000 to 19,999 inhabitants; urban area from 20,000 to 99,999 inhabitants; urban area of 100,000 inhabitants or more; Paris area), and region of residence (Ile-de-France including Paris area; North-East; North-West; South-East; South-West). To limit selection bias, panellists with low response rates were oversampled relative to others, e.g. fifty panellists with a 1% chance to take the survey were randomly drawn for one panellist with a 50% chance. In addition, panellists were invited by email to participate to an “academic survey” about “protective behaviours against the Coronavirus (SARS-CoV-2) and the COVID-19 disease caused by Coronavirus”. This initial invitation did not mention the words “vaccine” or “vaccination”. A total of 70,861 households were randomly drawn to reach the sample size of 2,000 from June 22 to July 3, 2020 (two weeks).

Data collection and explanatory variables

The online questionnaire contained six sections. Each section is presented below along with the explanatory variables of COVID-19 vaccine acceptance used in the main model (see manuscript). All variables that may be associated with pandemic vaccination behaviour[3, 4] were included in the model after excluding redundant variables.

Section 1. Background information (8 questions + 3 conditional questions)

- All stratification variables used in the sampling procedure:
  - Gender (women; men)
  - Age group in years(18–24; 25–34; 35–44; 45–54; 55–64)
  - Education achievement (some high school; high school graduate; university graduate) after regrouping “left school with no qualifications” with “some high school or apprenticeship of vocational qualification” (no differences on COVID-19 vaccine acceptance)
  - Household size separated into the number of adults (1; 2; ≥3) and children (0; 1; 2; ≥3)
  - Area of residence (rural area; urban area <100,000 inhabitants; urban area ≥100,000 inhabitants) after regrouping urban areas “from 2,000 to 19,999 inhabitants” and “20,000 to 99,999 inhabitants” (no differences on COVID-19 vaccine acceptance) and Paris area with urban areas of 100,000 inhabitants or more
  - Region of residence (Ile-de-France including Paris area; North-East; North-West; South-East; South-West)
- Working status variables:
  - Worker in the private sector (including self-employed or free-lancer), worker in the public sector, or not working (including student, unemployed, retired, other)
  - Healthcare worker in contact with patients (yes; no) among self-reported workers in the private or public sector

Section 2. State of health and prevention behaviours (8 questions + 6 conditional questions)

- Vaccination behaviour in the past:
  - Past compliance with recommended vaccination, e.g., vaccination for tetanus or before traveling abroad (always; sometimes; never)
  - Two other questions on vaccination behaviour (vaccination against seasonal flu in the previous 3 winters; vaccination against swine flu pandemic in 2009) were not included in the model because of the high correlations between answers to the three questions on vaccination behaviour and higher relevance of the attitudinal question in the French working age population that is usually not vaccinated against seasonal flu[5] and even less against swine flu pandemic[6]
- Risk factors of a severe form of COVID-19:[7]
  - Pregnancy status (yes; no)[8] among 18-50 years old women
  - Smoking status (former/current smoker; never smoker)[9] after regrouping “former smoker” and “current smoker” (no differences on COVID-19 vaccine acceptance)
  - Body mass index (obesity (≥30 kg/m^2); overweight (25-30 kg/m^2); normal weight or underweight (≤25 kg/m^2))[10]
  - Hypertension (yes; no)[11, 12]

  - Chronic condition other than hypertension (yes; no) after regrouping self-reported diabetes mellitus, asthma, chronic lung disease other than asthma, chronic arterial disease, chronic heart disease, chronic kidney disease, or cancer
- Section 3. COVID-19 experience (2 questions + 4 conditional questions)
  - Prior SARS-CoV-2 infection (yes; no) after regrouping self-reported hospital admission for COVID-19 disease, COVID-19 symptoms (with a positive test for SARS-CoV-2 infection or medical confirmation), or no COVID-19 symptoms (with a positive test for SARS-CoV-2 infection). After exclusion of participants with prior SARS-CoV-2 infection, the remaining variables became:
    - Had COVID-19 symptoms (without medical confirmation) (yes; no)
    - Had a test for SARS-CoV-2 infection (with negative result) (yes; no)
  - Knows someone who got COVID-19 (yes with hospital admission; yes without hospital admission; no)
- Section 4. Uptake of protective measures other than vaccination against SARS-CoV-2 infection (6 questions). All questions were considered redundant with the outcome study, i.e., COVID-19 vaccine acceptance.
- Section 5. Individual risk perceptions (5 questions)
  - Perceived severity of COVID-19 if infected (very severe; somewhat severe; not particularly severe; not severe at all; don't know)
  - Four visual analogue scales on the perceived risk of getting infected at different time points (just before the lockdown; currently; in the fall) and the perceived risk of death if infected were not included in the model because of the high correlations between answers to the five questions on risk perceptions and higher reproducibility of the question with ordinal answers.
- Section 6. Randomized experiment on the acceptance of vaccine against SARS-CoV-2 (see below)
  - Randomized information block on the collective benefits of herd immunity with communication on a herd immunity target (>50% of adults aged 18-64 years old must be immunized (either by vaccination or infection); >50% of adults must be immunized (either by vaccination or infection); no information on herd immunity)[13-16]
  - Randomized information block on the advice of the general practitioner on COVID-19 vaccination (recommendation; no opinion)[3, 17-19]
  - Discrete choice experiment (DCE) on vaccine characteristics

To control order response bias from subjective assessment, the direction of all ordinal scales was randomly allocated (12 questions) after stratification on gender and education (high school or university graduate vs. not). On average, the online questionnaire took 11 minutes to complete.

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eAppendix 2: Survey experiment

Section one: background information on COVID-19 vaccination

"In the following questions, we will ask you about possible vaccines against Coronavirus infection. Several scenarios are being considered for when new vaccines against Coronavirus infection become available in 2021.

Please read all information carefully.

[33% randomly allocated to herd immunity block "no information", stratified by gender and high school/university graduate]

Vaccination is an individual choice that helps protect against the risk of being infected.

[33% randomly allocated to herd immunity block ">50% in all adults", stratified by gender and high school/university graduate]

Vaccination is an individual choice that helps protect against the risk of being infected.

- If many people are vaccinated in 2021, Coronavirus will no longer be able to circulate in the population
- If few people are vaccinated in 2021, it will be necessary to wait until many people have been infected so that the Coronavirus can no longer circulate in the population

Scientific studies make it possible to estimate that at least 1 in 2 adults must be immunised against the Coronavirus (either by vaccination or infection) to achieve herd immunity in France, i.e. end of the epidemic and return to a normal life without protective measures.

[33% randomly allocated to herd immunity block ">50% in all working age adults", stratified by gender and high school/university graduate]

Vaccination is an individual choice that helps protect against the risk of being infected.

- If many people are vaccinated in 2021, Coronavirus will no longer be able to circulate in the population
- If few people are vaccinated in 2021, it will be necessary to wait until many people have been infected so that the Coronavirus can no longer circulate in the population

Scientific studies make it possible to estimate that at least 1 in 2 adults between 18 and 64 years old must be immunised against the Coronavirus (either by vaccination or infection) to achieve herd immunity in France, i.e. end of the epidemic and return to a normal life without protective measures.

All the vaccination scenarios considered have the following points in common:

[50% randomly allocated to general practitioner block "recommends vaccination", stratified by gender and high school/university graduate]

- Your general practitioner recommends that you are vaccinated against Coronavirus infection

[50% randomly allocated to general practitioner block “no opinion on vaccination”, stratified by gender and high school/university graduate]

- Your general practitioner offers no opinion on vaccination against Coronavirus infection

[To all]

- Vaccination is carried out by a health care professional
- Vaccination is free
- Vaccination is done by injection
- Minor side-effects are possible, but they usually disappear a few days after vaccination

The vaccination scenarios being considered differ in five features:

[Random allocation of the order of attributes; same order kept in the discrete choice experiment]

- Effectiveness of new vaccines: new vaccines may be more or less effective in reducing the risk of being infected with Coronavirus and of developing a severe form of COVID-19 disease
- Safety of new vaccines: serious side-effects are possible but rare. This risk will be better known when more people have been vaccinated (from several thousand at the start to tens of millions at the end of the vaccination campaign)
- The manufacturer of vaccine
- The place to be vaccinated

Eight situations will now be described to you each with different vaccination scenarios. Please state what you would do in each of these eight situations, taking into account the information presented to you.

Please read this information carefully as it changes in every situation. Take your time to read all the information and make your choice accordingly. There is no "right" or "wrong" answer, it's your opinion in each situation that counts.”

Section two: discrete choice experiment on COVID-19 vaccine characteristics

Selection of COVID-19 vaccine characteristics and levels

COVID-19 vaccine characteristics and corresponding levels were selected using a sequential process.[1, 2] First, we conducted a review of discrete choice experiments on pandemic vaccination[3-5] and used information on COVID-19 vaccines available by June 2020[6] to select characteristics and levels that could apply to COVID-19 vaccines. This led to a list of eight characteristics that were tested in think-aloud interviews with an expert panel. Second, based on interviews, we removed four vaccine characteristics that were placed in the background information on COVID-19 vaccination (i.e., collective benefits of vaccination on SARS-CoV-2 transmission and advice of the general practitioner on vaccination were considered as experimental variables; no out-of-pocket costs were expected for COVID-19 vaccination in the French healthcare context; and the frequency of minor serious side-effects of vaccines had little weight in decision making). In addition, we decided to present vaccine safety depending on the risk of serious side-effects that may be assessable in vaccine phase 3 trials (1/10,000) or shortly after the launch of worldwide vaccination campaigns (1/100,000) rather than the speed of the vaccine assessment and approval (fast-trask vs. normal) as it may be redundant with the country of the vaccine manufacturer. Accordingly, four characteristics at different levels were used to describe pandemic vaccines in the discrete choice experiment (**eTable 2.1**): *vaccine efficacy*; *vaccine safety*; *country of vaccine manufacturer*; and *place to be vaccinated*.

eTable 2.1. COVID-19 vaccine characteristics and levels

Characteristics		Characteristic levels
Risk of being infected with SARS-CoV-2	4	↘ 100% ↘ 90% ↘ 80% ↘ 50%
Risk of rare but serious side-effects from the vaccine	2	1/100,000 vaccinated people 1/10,000 vaccinated people
Manufacturer of the vaccine	3	Headquarters in the European Union Headquarters in the United States of America Headquarters in China
Place to be vaccinated	3	Your general practice Your local pharmacy or by a non-medical healthcare worker you know Mass vaccination centre

Design of the discrete choice experiment

Based on vaccine characteristics and levels, there were 72 hypothetical vaccines and 2,556 possible choice tasks between two hypothetical vaccines. A D-efficient experimental design with vague priors for a multinomial logit (MNL) model was created with NGENE software (ChoiceMetrics, 2014) to reduce the number of choice tasks to eight (**eTable 2.2**). The aim of the experimental design is to create a subset of all possible choice tasks that minimises the determinant of the variance-covariance matrix for a given number of choice tasks. The design specified to identify the main effects only of the four characteristics which are included in a linear additive utility function in which one characteristic, vaccine efficacy, had four levels, one characteristic, risk of serious side-effects, had two levels and two characteristics, vaccine manufacturer and place to be vaccinated, had three levels. The model was specified to allow the characteristics' levels to be included in an MNL model as dummy variables. Vague priors were included in that specified the direction of expected preferences for each characteristic: higher vaccine efficacy, lower risk of serious side-effects, manufacturers outside of China and not being vaccinated at a mass vaccination centre were assumed to be preferred. A set of three candidate designs were created using a modified Federov algorithm combined with a swapping algorithm. The best design was then selected based on the best D-error of the design and lowest Pearson correlations between characteristics.

To control for ordering effects, the order of the eight choice tasks was randomised across participants, and the order of the four vaccine characteristics was randomised across participants while remaining fixed throughout the experiment for any participant.

eTable 2.2. Eight choice tasks selected in the experimental design

Choice task	Vaccine	Vaccine efficacy	Vaccine safety	Vaccine manufacturer	Place to be vaccinated	Vaccine uptake in all participants (n=1,942)	Vaccine uptake without outright vaccination refusal (n=1,382)
1	A	80%	1/100,000	China	Your general practice	343 (17.7)	343 (24.8)
	B	90%	1/10,000	European Union	Mass vaccination centre	821 (42.3)	821 (59.4)
2	A	100%	1/10,000	European Union	Your general practice	1009 (52.0)	1009 (73.0)
	B	50%	1/100,000	China	Mass vaccination centre	184 (9.5)	184 (13.3)
3	A	90%	1/10,000	China	Your general practice	332 (17.1)	332 (24.0)
	B	80%	1/100,000	European Union	Your local pharmacy	862 (44.4)	862 (62.4)
4	A	100%	1/100,000	United States of America	Mass vaccination centre	784 (40.4)	784 (56.7)
	B	50%	1/10,000	European Union	Your general practice	405 (20.9)	405 (29.3)
5	A	80%	1/10,000	China	Mass vaccination centre	152 (7.8)	152 (11.0)
	B	90%	1/100,000	United States of America	Your general practice	954 (49.1)	954 (69)
6	A	50%	1/10,000	United States of America	Your local pharmacy	265 (13.6)	265 (19.2)
	B	100%	1/100,000	China	Your general practice	794 (40.9)	794 (57.5)
7	A	50%	1/100,000	European Union	Mass vaccination centre	623 (32.1)	623 (45.1)
	B	100%	1/10,000	China	Your local pharmacy	477 (24.6)	477 (34.5)
8	A	90%	1/100,000	European Union	Your local pharmacy	1065 (54.8)	1065 (77.1)
	B	80%	1/10,000	United States of America	Mass vaccination centre	165 (8.5)	165 (11.9)

Note: Refusal of both vaccines A and B is deducted from 1-uptake of vaccines A or B in each choice task.

Estimation of the hurdle repeated discrete choice models

The single and double hurdle repeated discrete choice models[7] were estimated using maximum likelihood techniques with R statistical software (3.6.3) under linux Ubuntu 18.04. Estimations were made using three optimization algorithms to ensure that convergence was reached: Nelder-Mead method that only uses function values, the conjugate gradients method, and Quasi-Newton method based on the Broyden, Fletcher, Goldfarb and Shanno (BFGS) algorithm. The variance-covariance matrix was estimated using the empirical hessian matrix obtained in the final quasi-Newton estimation. Standard errors of parameter estimates were computed from the variance-covariance matrix. The R program is available from the authors.

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eTable 1. COVID-19 vaccination behaviour predicted in the French working age population in realistic scenarios of a mass vaccination campaign

Outright vaccination refusal			29.4% (28.6-30.2)	
Vaccine efficacy	**Vaccine safety**	**Vaccine manufacturer**	**Vaccine acceptance without outright vaccination refusal**	**Vaccine acceptance in the whole sample**
50%	1/10,000	China	36.8% (36.3-37.3)	27.4% (26.8-28.0)
50%	1/10,000	United States of America	46.7% (46.1-47.2)	34.5% (33.8-35.2)
50%	1/10,000	European Union	61.0% (60.5-61.6)	44.6% (43.9-45.4)
50%	1/100,000	China	48.0% (47.5-48.6)	35.5% (34.8-36.2)
50%	1/100,000	United States of America	58.1% (57.6-58.7)	42.6% (41.9-43.3)
50%	1/100,000	European Union	71.4% (70.9-71.8)	51.7% (50.9-52.5)
90%	1/10,000	China	57.9% (57.4-58.5)	42.4% (41.7-43.2)
90%	1/10,000	United States of America	67.4% (66.9-67.9)	49.0% (48.2-49.8)
90%	1/10,000	European Union	78.9% (78.5-79.2)	56.8% (56.0-57.6)
90%	1/100,000	China	68.6% (68.1-69.1)	49.9% (49.1-50.6)
90%	1/100,000	United States of America	76.7% (76.3-77.1)	55.4% (54.6-56.2)
90%	1/100,000	European Union	85.7% (85.4-86.0)	61.3% (60.5-62.1)

Note: Several features of a mass vaccination campaign were fixed and included the communication on the benefits of herd immunity and implications for adults aged 18-64 years old; vaccination in mass vaccination centres; and no opinion of general practitioners on vaccination.