What the public think about participation in medical research during an influenza pandemic – an international cross-sectional survey

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ABSTRACT

Objectives: The public and patients are primary contributors and beneficiaries of pandemic-relevant clinical research. However, their views on research participation during a pandemic have not been systematically studied. We aimed to understand public views regarding participation in clinical research during a hypothetical influenza pandemic.

Study design: International cross-sectional survey

Methods: We surveyed the views of nationally representative samples of people in Belgium, Poland, Spain, Ireland, United Kingdom, Canada, Australia and New Zealand, using a scenario-based instrument during the 2017 regional influenza season. Descriptive and regression analyses were conducted.

Results: Of the 6804 respondents, 5572 (81·8%) thought pandemic-relevant research was important and 5089 (74·8 %) thought "special rules" should apply to make this research feasible. Respondents indicated willingness to take part in lower-risk (4715, 69·3%) and higher-risk (3585 52·7%) primary care, and lower-risk (4780, 70·3%) and higher-risk (4113, 60·4 %) Intensive Care Unit (ICU) study scenarios. For primary care studies, most (3972, 58·4%) participants preferred standard enrolment procedures such as prospective written informed consent, but 2327 (34·2%) thought simplified procedures would be acceptable. For ICU studies, 2800, (41·2%) preferred deferred consent and 2623 (38·6%) preferred prospective third-party consent. Greater knowledge about pandemics, trust in a health professional, trust in government, therapeutic misconception and experience of ICU as a patient or carer predicted increased willingness to participate in pandemic-relevant research.

Conclusions: Our study indicates current public support for pandemic-relevant clinical research.

Tailored information, and initiatives to advance research literacy and maintain trust are required to support pandemic-relevant research participation and engagement.

Highlights

- There is strong public support for pandemic-relevant clinical research initiatives.
- Willingness to participate in research and to be enrolled under more permissive approaches depends on the type of research and key participant factors.
- Knowledge about pandemics, trust in professionals and in government, therapeutic misconception and experience of critical illness influence willingness to participate in pandemic-relevant research.

INTRODUCTION

The centenary of the 1918 Influenza pandemic presents a stark reminder of global vulnerability to infectious disease health threats[1]. One third of the global population became infected, resulting in 50-100 million deaths. Advances in science, technology, medicine, health systems, and coordination mechanisms have strengthened global preparedness to respond to future pandemics[2]. However, as evidenced during the 2009 H1N1 pandemic, insufficient capability to rapidly generate evidence through clinical research implemented during the pandemic itself results in significant gaps in our preparedness for pandemics. Emerging data from clinical research is vital to inform public health responses, for example, through robust disease severity assessments that account for clinical presentation across the illness severity spectrum[3] and to inform clinical management guidelines[4,5]. During the H1N1 pandemic, clinical management guidelines were necessarily based on expert opinion as scientific evidence was not available. Expert guidance recommended use of oseltamivir, for example, which was widely prescribed to patients with acute respiratory infections at significant cost to healthcare systems. However, the opportunity to evaluate the clinical and cost effectiveness of oseltamivir in prospective trials was missed, as intervention studies could not be delivered in time to enrol patients during the pandemic itself[3] and little evidence was generated about the prudence of stockpiling these antivial agents.

Oseltamivir is now widely regarded as standard of care for the treatment of patients at higher risk of complications from influenza, despite no available prospective trial evidence to support its use in severely ill patients[6], and this now presents an ethical dilemma for its evaluation in a randomised placebo-controlled trial. The newly launched WHO global influenza strategy includes research and innovation for diagnostics, vaccines and treatments as one of four priorities for pandemic preparedness[7].

There are multiple and persistent political, contractual, administrative, logistic and regulatory challenges that must be navigated for clinical studies to be open for recruitment in time to enrol patients during peak pandemic waves. One approach to unblocking these barriers involves pre-funding active clinical research networks, such as those in the Platform foR European Preparedness Against (Re-)emerging Epidemics (PREPARE). PREPARE conducts multi-site, pan-European clinical studies in community, hospital and critical care settings that address important study questions during inter-pandemic periods of seasonal influenza. These research active networks would re-orientate their inter-pandemic research activities in the event of a public health emergency, thereby reducing the time needed to recruit and prepare research sites. PREPARE clinical trials employ novel adaptive platform designs with response adaptive randomisation that shortens the time to identifying a superior performing treatment[8-10] These trials evaluate the comparative effectiveness of routinely available treatments and allow for rapid inclusion of an additional trial arm to evaluate novel therapeutics if these become available.

The success of these initiatives, however, is dependent on research and clinical staff being willing to enrol patients[11], and patients being willing to participate. Research enrolment processes that are time consuming, unnecessarily detailed and burdensome will deter patient enrolment, even among those patients who would be otherwise willing to participate[12] Existing enrolment models will likely be ill suited to the highly pressured conditions of pandemic-relevant research[13] and less burdensome, risk proportionate consent models may be acceptable. In addition, residual clinical samples e.g. nasal swabs and blood samples, collected and stored after clinical procedures would be an important resource for pandemic relevant ID research and development of new diagnostic tests. Currently these samples are

not routinely stored, and consent for using and sharing samples and associated clinical data for research and test development, vary between countries, presenting a challenge to multi site, pan-European research efforts[14,15].

As the primary contributors and potential beneficiaries of pandemic-relevant research, patients and the public are key, and often underrepresented, stakeholders in research preparedness. While these groups have been consulted for public health pandemic planning[16-19], there have been no systematic efforts to capture their views relevant to participation in clinical research conducted during an influenza pandemic. Further, understanding public views should inform preparations for appropriate, proportionate regulation and oversight of pandemic-relevant research. To advance preparedness to deliver a clinical research response in a pandemic scenario, we aimed to address this gap.

METHODS

We conducted an international cross-sectional survey involving a nationally representative sample of respondents in each of Belgium, Spain, Poland, Ireland, the United Kingdom, Canada, Australia and New Zealand. These countries were selected as involved with or affiliated to the PREPARE consortium. European member states were selected to include a country from each of northern, southern, eastern and western Europe, as defined by the United Nations macro geographical regions[20]. These countries were also included in qualitative work that informed the survey development. Respondents aged 18-65years in each country, except Poland (age range 18-59 years), were invited via a pre-recruited online panel hosted by the Ipsos Group. Ipsos Group is a market research company that regularly conducts online research for academic institutions. This group administered data collection. Ipsos Group generated quotas on age, gender, employment status and region in all countries, setting targets based on the most up-to-date census data to ensure that the sample profile was in-line with the nationally representative proportions in that country. Ipsos Group addressed any small imbalances in the sample by weighting the final data set. All analyses used weighted data.

Data collection

Data were collected via an online survey in March 2017 in Northern hemisphere countries and in July –Aug 2017 in Southern hemisphere countries, to coincide with regional influenza seasons. Potential respondents were invited to take part in the survey in batches, in order to control the sample profile. Data collection was planned to continue until the target sample size (850 per country, 6800 total) was reached. The selection of the sample size was pragmatically driven and involved balancing the size of the sample that we would need to identify differences between countries with the cost of administering the survey via Ipsos Group across multiple countries.

Data collection instrument

We developed a scenario-based instrument in which respondents were asked to imagine there is an influenza pandemic and they were being invited to participate in clinical research in primary and critical care settings (Box 1; supplementary material). In both scenarios, respondents were asked for their views on taking part in a low and higher risk clinical trial, and to indicate their preferences related to notification and consent for participating in the low-risk study. Low risk scenarios involved comparison of two medications that were routinely used in everyday clinical practice. Higher risk scenarios involved patients receiving either a new medication that had passed safety testing or a placebo. Finally, respondents were asked for their views on the acceptability of any surplus clinical samples (blood or swabs for example), that had been collected as part of clinical care, being subsequently used for pandemic research, without explicit patient consent being solicited for their use. We used illustrations to enhance brief explanations of key concepts.

To develop the survey tool, we consulted the public in four European countries[12] to identify content domains for the survey (July-November 2015). We reviewed relevant literature[5,13,21-23] and sought expert opinion to prioritise content domains. We also identified demographic and attitudinal variables[12] that might explain willingness to participate in pandemic-relevant research. These variables included age, being a parent, having had experience of critical illness (as a patient, family member or close friend of a patient) and therapeutic misconception[24] (i.e. research participants holding a belief that research usually or always results in individual benefits as opposed to understanding that the purpose of research

158 is to produce generalizable findings relevant to a population). To refine the wording and response format
159 of the survey questions, we conducted cognitive interviewing using the think aloud technique[25].
160 Changes to the survey were made iteratively, at three time points. The data collection instrument was
161 circulated for comment to colleagues in Belgium, Spain, Poland, Australia and New Zealand to ensure
162 applicability to their healthcare context. The final version of the instrument was translated into Flemish,
163 French, Spanish and Polish and back translated to ensure accuracy. Before the survey was distributed,
164 a small segment of the overall target group of respondents completed the survey and data were reviewed
165 to identify any difficulties. No changes were required following this soft launch.

166 *Analysis*

167 We combined survey responses into three categories (strongly disagree/disagree, neutral and
168 agree/strongly agree) and ran ordinal regression models to examine demographic and attitudinal factors
169 predictive of respondent willingness to participate in primary care and ICU studies and willingness for
170 routinely collected clinical samples to be used for pandemic-relevant research. To identify suitable
171 candidate variables for regression models, we first conducted univariate associations using a chi squared
172 test. Candidates that were significant at $p<0{\cdot}01$ in univariate analyses were then included. Factors that
173 account for how participants would like to be consented were examined in an exploratory post-hoc
174 analysis using a logistic regression. To explore whether any factors predicted willingness to engage
175 with an alternate approach to consent, we created a binary variable that classified respondents as only
176 willing to consider the standard "Opt in" consent models (box 1) versus willing to consider any of the
177 other options. This variable was used as the outcome in logistic regression models that included only
178 those participants that expressed willingness to take part in each scenario study. In order to assess the
179 impact of missing data at baseline and possible bias arising from data not being missing completely at
180 random (MCAR) the regression models were reanalysed using multiple imputation with chained
181 equations, which is valid under a less restrictive missing at random (MAR) assumption. The results did
182 not differ substantially from the complete case analysis, which suggests there is not substantial bias due
183 to missing data. Data were analysed using STATA version 15.0.
184

Ethics, consent, sponsorship, ethical treatment of human subjects

Participants gave voluntary consent for their involvement in the survey. All data were held in accordance with the Data Protection Act.

RESULTS

A total of 6804 members of the public completed the survey: 850 in each of Ireland, Spain, Belgium, and New Zealand, and 851 in each of Poland, the United Kingdom, Australia and Canada (table 1). Response rates were not calculated due to the quota sampling technique used.

Public attitudes to clinical research

Respondents considered it important that medical research is conducted during an influenza pandemic (5572, 81·9%) and that special rules should apply to make it easier to do pandemic-relevant research (5089, 74·8%). Results were similar across countries, with the exception of respondents from Poland who indicated lower agreement with the importance of medical research in a pandemic (538 of 831, 64·7%).

Primary Care: willingness to participate in low and higher risk scenarios

A majority of respondents were willing to take part in both the lower risk (4715, 69·3%) and higher risk (3585, 52·7%) primary care study (Figures 1a and 1b). A small proportion of respondents were unwilling to take part in the low risk scenario (792, 11·6%), and 1466 (21·6%) respondents were unwilling to take part in the higher risk scenario. The differences in proportion endorsing each response varied significantly by country ($\chi^2 p<0{\cdot}001$) for both the low and high-risk scenarios (figures 1a and 1b and table 2). Being female (compared with male) was associated with decreased willingness to take part in the high-risk primary care scenario (table 2). For both low and higher risk primary care scenarios, the less knowledge respondents had about pandemics, the lower their reported willingness to take part. Having had ICU experience, trust in a doctor, trust in the government and therapeutic misconception were variables associated with greater willingness to participate in both scenarios (table 2).

Primary care: notification and consent preferences for enrolment to low risk CER scenario

Of those respondents willing to take part in the low risk primary care scenario (4715, 69·3%), the majority preferred standard opt-in consent procedures as a first choice (2742, 58·2%), although nearly a third (1371, 29·1%) selected opt-out consent as a first choice (table 3). Automatic inclusion was the least preferred option (461, 9·79%). Of those respondents who indicated willingness to take part in the primary care study, respondents from Spain (compared with the UK) were less likely to accept enrolment under alternate consent models (table 4). A low level of pandemic knowledge was associated with non-acceptance of enrolment under alternative consent models, while having had ICU experience and having greater trust in government were variables associated with acceptance of enrolment under alternate consent models (table 4).

ICU: willingness to participate in low and higher risk scenarios

The majority of respondents expressed willingness to take part in both the lower risk (4780, 70·3%) and higher risk (4113, 60·4%) ICU studies (ICU studies (Figures 2a and 2b). A χ^2 test comparing proportion endorsing each response against country was statistically significant ($p<0·001$) for both the low and high-risk scenarios. Older age groups were associated with being more willing to participate in the higher risk ICU scenario (table 5). A low level of pandemic knowledge was associated with being less willing to participate in both ICU research scenarios. Having had ICU experience, having greater trust in a doctor, greater trust in the government and higher levels of therapeutic misconception were all associated with being more willing to take part in both ICU scenarios (table 5).

ICU: notification and consent preferences for enrolment to low risk CER scenario

Of those respondents willing to take part in the low risk ICU scenario (4780, 70·3%), deferred consent given either by a doctor (1345, 28·1%) or a family member (958, 20·0%) were the first choice preferences (table 6). Prospective "opt-in" informed consent procedures was the first choice preference for 35·3% respondents (n=1686). Only 592 (12·4%) respondents indicated that they preferred automatic inclusion (i.e. without consent being provided). Of the respondents who were willing to take part in the ICU study, those that had some experience of ICU, were living with someone rather than alone, and

had greater trust in government, were more likely to engage with alternative consent models for the low risk ICU scenario (table 7).

Attitudes to use of surplus routinely collected clinical samples for research

5256 (77·2%) of respondents indicated that they would be willing for any surplus of their routinely collected clinical samples to be used for pandemic relevant studies during an outbreak itself, and only slightly fewer 4871 (71·6%) were happy for them to be used after an outbreak without additional consent being sought. 4940 72·6% were willing for their genetic materials to be used for research, and 3869 (56·9%) were willing for their samples to be used for non pandemic-relevant studies. A trend for age was observed, with older respondents across each age category being more likely to accept their excess routinely collected clinical samples being used for pandemic-relevant research (table 8). Greater trust in a doctor, greater trust in government and higher levels of therapeutic misconception were associated with willingness for clinical samples to be used for research.

DISCUSSION

Members of the public across eight OECD countries support medical research being delivered in response to a pandemic of influenza and a majority of respondents would be willing to take part in medical research in both primary and critical care settings. While the majority of respondents wanted to provide prospective informed consent for enrolment to primary care studies, a substantial minority would consider alternatives. Deferred consent was acceptable to the majority of respondents for enrolment to ICU studies. Pandemic knowledge, trust in health professionals, in government, and experience of critical illness influence indicative willingness to participate. Therapeutic misconception and wanting access to novel therapeutics through trial participation were also predictive of willingness to participate. A majority of respondents were also supportive of their surplus clinical samples being used for research without specific consent.

A strength of this study is the extensive piloting and refinement used in the development of the survey instrument . We also used images to enhance explanations of core concepts. However, we were unable

to fully assess participant interpretation of these ideas and it is possible that some concepts were not uniformly understood. A limitation of the instrument is that it employed hypothetical scenarios and respondent views might change with actual experience. However, respondents' expressed willingness to participate in research has been shown to provide a moderate estimate of actual participation[26]. We do not consider our findings to be a substitute for involvement of the public or for good participatory practice[27] when planning pandemic-relevant studies. Our survey used quota sampling, a non-probabilistic sampling method, and the appropriateness of drawing population wide inferences using this approach has been questioned by some. This was an online survey that required respondents to access the Internet to complete it. Given the high proportion of internet penetration in the countries surveyed in 2017[28], we do not anticipate the digital divide to have impacted on representativeness of the sample. Our findings may be influenced by self-selection bias in that respondents had signed up to an online panel. We are also unable to evaluate the impact of potential nonresponse bias. The survey addressed complex ideas that may not have been uniformly understood. Despite our efforts to address this by using cognitive interviewing in designing the survey, varying interpretation of survey questions represents potential for non-sampling error. Respondents were from countries in the OECD as these were relevant to PREPARE clinical studies and are vulnerable to influenza pandemics. Lower and Middle Income Countries bear the greatest burden of infectious disease outbreaks and findings from our survey do not inform research preparedness in these regions.

Recent debates regarding comparative effectiveness research have highlighted the inflexibility of standard recruitment processes and argued for more adaptable enrolment protocols in circumstances where informed consent may not be possible, or ethically necessary[29-31]. Others have also identified a substantive minority of respondents supportive of alternate consent procedures for low risk pragmatic trials[32-34]. However, our study is the first to consider this question in the context of a pandemic. Current ethical guidelines[35,36] and new regulations[37] offer some guidance for emergency research and endorse adapted models of enrolment (e.g. deferred consent) where patents lack capacity to consent themselves. Where patients have capacity (for example, enrolment to a primary care trial), even in the event of a public health emergency, current guidelines[35,36] endorse prospective informed consent process

regardless of risk through trial participation. Findings from our survey support this approach. In contrast, experience from public involvement in the design of a pre-positioned clinical trial protocol in the UK found that alternatives (verbal consent or opt-out consent) were acceptable[21]. This study was unable to adopt these alternate consent procedures however as they were considered not acceptable under current legislation governing clinical trials of investigative medicinal products (CTIMPs) in Europe.

This tension between pragmatic and acceptable informed consent processes and guiding legislation represents a notable bottleneck in the viability of clinical research being conducted in a public health emergency. In Europe, the forthcoming Clinical Trials Regulation (No 536/2014)[37] that will govern the conduct of CTIMPs in European Union member states recognises the need for expediting clinical trial applications for approval in a public health emergency, however, no mention is made of acceptable adaptations to consent procedures that are proportionate to study risk or to the context of crisis in the event of a pandemic. This legislation includes a new category of "low intervention" clinical study, recognising that not all clinical trials present the same degree of risk to research participants and simplified informed consent procedures are deemed acceptable for enrolment to "low intervention" cluster trials conducted in a single member state (article 30). However this does not extend to pan-European or individually randomised trials.

Similar tensions exist in debates about residual clinical samples being used for pandemic-relevant research purposes. Like others who have considered this question[38,39] albeit in a non pandemic context, we identified public willingness to donate excess clinical samples for research. These findings require further consideration in relation to consent requirements for the use of residual clinical samples and associated data[14]. For pandemic-relevant research, sample and data sharing across countries will be important and full de-identification of patient data may not be possible, particularly at the early stages of an outbreak. The General Data Protection Regulation (GDPR), legislation that aims to harmonise and strengthen the rules for protecting individual's privacy rights within the EU may inadvertently create barriers to this process. Clarity regarding interpretation of new EU legislation and the

implications for pandemic relevant studies is needed if the significant investment in establishing a clinical research infrastructure to respond to these public health threats can be fully realised.

Our study found strong support for pandemic-relevant research and a need for wider debate about more permissive approaches to enrol patients into low risk comparative effectiveness research in this context. Experience of critical illness, trust in doctors and in government, and knowledge about pandemics were key explanatory factors. These insights should inform communication and recruitment planning for delivering a pandemic research response, for example, in the PREPARE consortium. Active efforts to engage and involve the public are required in order to build knowledge about pandemics and about the value of research and what research participation in research involves. Key messages, such as uncertainty regarding the superiority of the experimental agent and the purpose of research to produce generalizable results rather than to confer individual benefit, and the distinction between research participation and receipt of clinical care, should be well communicated. For patients, attention to how participation in research is framed, for example, in the wording of participant information sheets can mitigate risk of therapeutic misconception[40]. For the wider public, initiatives that open the way to dialogue and deliberation and that that build research literacy are needed, for example through citizen science and tailored engagement initiatives across communities. Invariably, an infectious disease pandemic will bring with it an epidemic of fear, at which point it will be too late to address these gaps. The research community must be ready to counter the rumours and conspiracy theories that will inevitably circulate with a response that champions the contribution of scientific evidence in protecting health and saving lives.

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Ethics statement: Nothing to declare. The survey was administered outside of a healthcare setting by Ipsos Mori, an international ISO 20252 accredited market research company. Respondents voluntarily signed up in advance to the question panel and completion of the questionnaire indicated consent to participate. Respondents were able to refuse to participate in the questionnaire at any stage in the process. All data were processed in accordance with the UK Data Protection Act 1998.

Contributors: NG led the study design, data collection instrument development, cognitive interviewing, contributed to analysis and interpretation and drafted the manuscript. CCB conceived the idea, and contributed to study design, analysis and interpretation. JM wrote the statistical analysis plan and supervised the analysis. NAF contributed to study design, analysis and interpretation. VH conducted statistical analyses and contributed to interpretation. MG contributed to study design, instrument development, cognitive interviewing and materials. AW contributed to administering the study. KH contributed to study design and interpretation. SARW contributed to analysis and interpretation. AN contributed to study design, analysis and interpretation. All authors contributed to writing the manuscript.

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Figure 1a: Willingness to take part in low risk primary care scenario

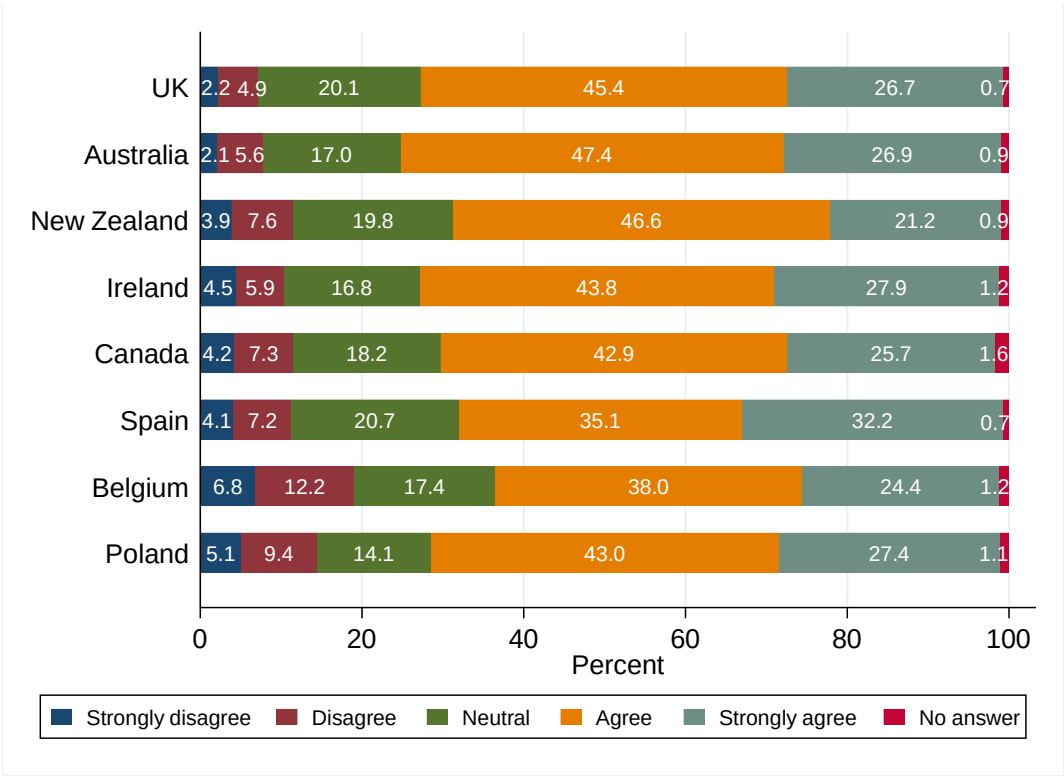


Figure 1b: Willingness to take part in higher risk primary care scenario

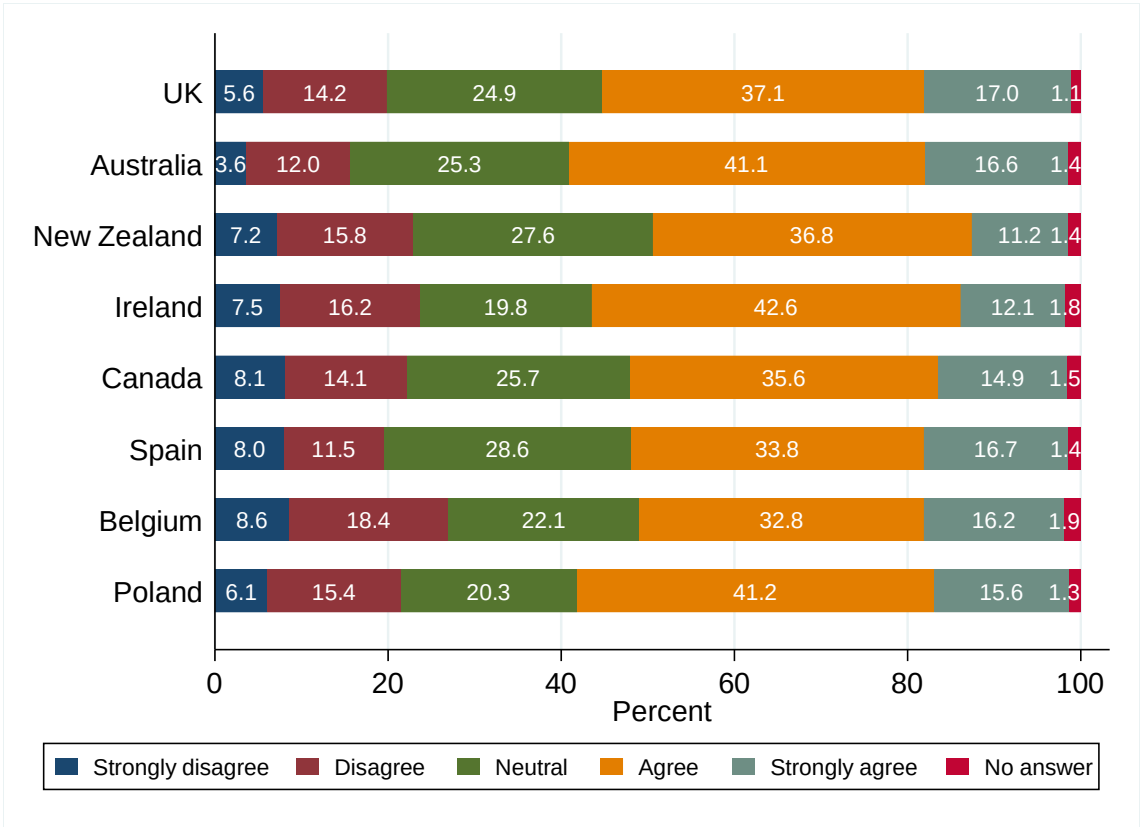


Figure 2a Willingness to take part in low risk ICU scenario

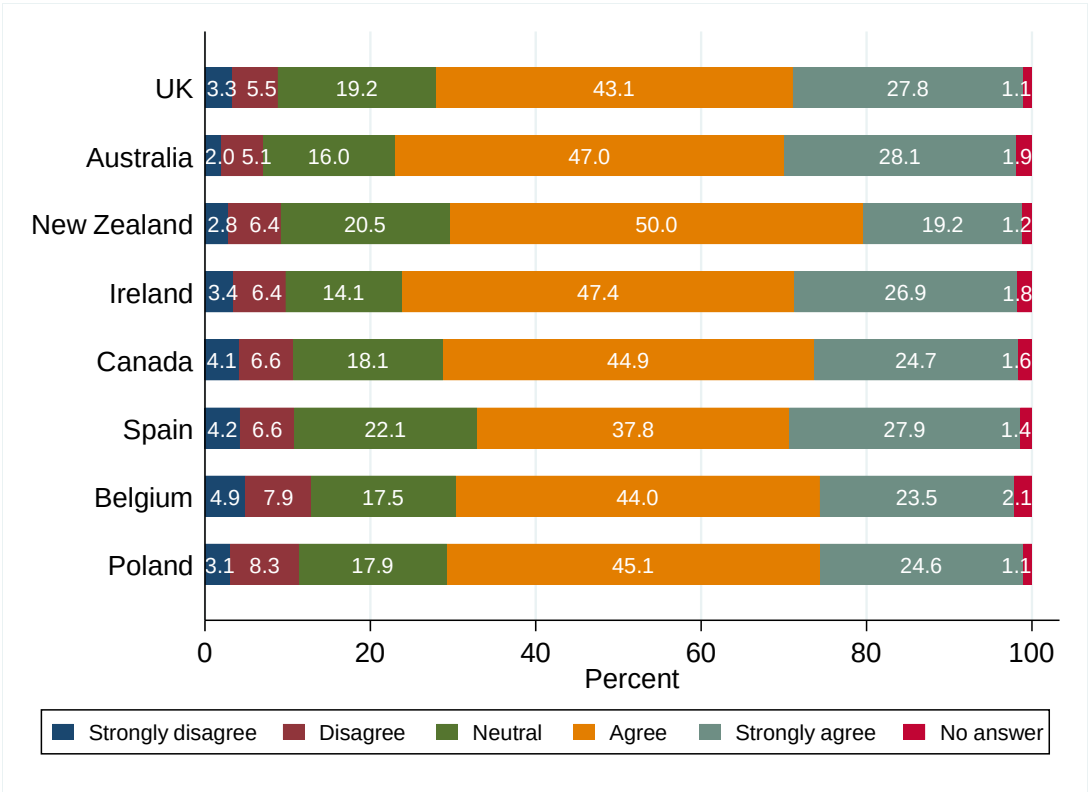
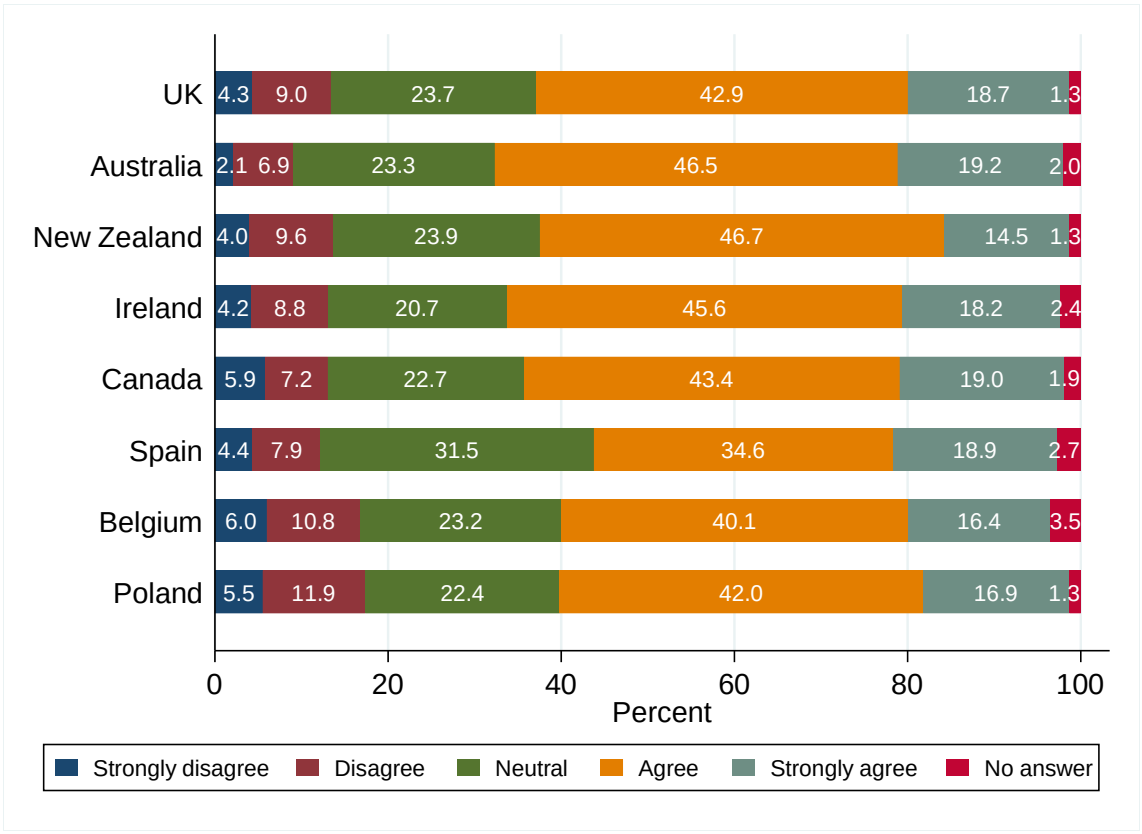


Figure 2b Willingness to take part in higher risk ICU scenario



Box 1: Consent options provided for primary care and Intensive Care Unit Comparative Effectiveness Research scenarios

For both low-risk scenarios, respondents were informed that 'information about the study would be circulated via newsletters, posters, and media outlets'.

Primary care CER scenario: comparison of two routinely used medications

- **Automatic enrolment:** You would be automatically included in the study. When being prescribed the medication, the doctor wouldn't mention the research.
- **Opt-out:** Sign me up automatically, but remind me of the study when I get the medicine and give me a chance to opt out. When being prescribed the medication, the doctor would give you more information and you would have a chance to opt out of the study if you-wished.
- **Opt-in:** Ask me to sign up when I am due to get the medicine. When being prescribed the medication, the doctor would explain the study and a researcher would ask you to sign up (prospective informed consent)

ICU CER scenario: comparison of two routinely available treatments

- **Deferred consent (family):** Include me immediately, family decides later if that's ok. You would be automatically included in the study. As soon as they could be contacted, a close family member would then decide whether or not you should stay included in the study.
- **Deferred consent (doctor):** Include me immediately, doctor decides later if that's ok. You would be immediately included in the study. A hospital doctor who is not a researcher in the study but who knew about it would decide whether or not you should stay included in the study.
- **Automatic enrolment:** Include me immediately, don't ask my or anyone's consent. You would be automatically included in the study without asking your consent or anyone consenting on your behalf.
- **Opt-in:** Don't include me until a family member says it's ok. You would not be included in the study until a close family member could be contacted to make that decision on your behalf (prospective informed consent provided by a third party if the patient lacks capacity)

Table 1: Demographic characteristics of the sample

Characteristic	*UK (N=851)*	*Australia (N=851)*	*New Zealand (N=850)*	*Ireland (N=850)*	*Canada (N=851)*	*Spain (N=850)*	*Belgium (N=850)*	*Poland (N=851)*	*Overall (N=6804)*
Age									
18-24	132 (15·51%)	105 (12·34%)	110 (12·94%)	117 (13·76%)	110 (12·93%)	92 (10·82%)	117 (13·76%)	133 (15·63%)	916 (13·46%)
25-34	181 (21·27%)	190 (22·33%)	165 (19·41%)	197 (23·18%)	173 (20·33%)	183 (21·53%)	172 (20·24%)	230 (27·03%)	1,491 (21·91%)
35-44	185 (21·74%)	197 (23·15%)	191 (22·47%)	208 (24·47%)	173 (20·33%)	221 (26·00%)	183 (21·53%)	196 (23·03%)	1,554 (22·84%)
45-54	179 (21·03%)	188 (22·09%)	201 (23·65%)	176 (20·71%)	213 (25·03%)	194 (22·82%)	196 (23·06%)	185 (21·74%)	1,532 (22·52%)
55-65 (55-59 Poland only)	174 (20·45%)	171 (20·09%)	183 (21·53%)	152 (17·88%)	182 (21·39%)	160 (18·82%)	182 (21·41%)	107 (12·57%)	1,311 (19·27%)
Gender									
Male	429 (50·41%)	422 (49·59%)	383 (45·06%)	407 (47·88%)	408 (47·94%)	425 (50·00%)	425 (50·00%)	428 (50·29%)	3,327 (48·90%)
Employment status:									
Employed full-time	444 (52·17%)	374 (43·95%)	374 (44·00%)	438 (51·53%)	496 (58·28%)	377 (44·35%)	420 (49·41%)	483 (56·76%)	3406 (50·06%)
Employed part-time	144 (16·92%)	166 (19·51%)	152 (17·88%)	80 (9·41%)	108 (12·69%)	83 (9·76%)	93 (10·94%)	70 (8·23%)	896 (13·17%)
Self-employed	58 (6·82%)	47 (5·52%)	84 (9·88%)	48 (5·65%)	70 (8·23%)	52 (6·12%)	35 (4·12%)	54 (6·35%)	448 (6·58%)
Unemployed, job seeking	34 (4·00%)	60 (7·05%)	58 (6·82%)	66 (7·76%)	39 (4·58%)	149 (17·53%)	53 (6·24%)	64 (7·52%)	523 (7·69%)
Unemployed not job seeking	82 (9·64%)	98 (11·52%)	95 (11·18%)	84 (9·88%)	61 (7·17%)	55 (6·47%)	95 (11·18%)	58 (6·82%)	628 (9·23%)
Retired	50 (5·88%)	58 (6·82%)	34 (4·00%)	46 (5·41%)	58 (6·82%)	39 (4·59%)	70 (8·24%)	40 (4·7%)	395 (5·81%)
Student / full- time education	30 (3·53%)	38 (4·47%)	44 (5·18%)	73 (8·59%)	13 (1·53%)	79 (9·29%)	71 (8·35%)	51 (5·99%)	399 (5·86%)
Other	9 (1·06%)	10 (1·18%)	9 (1·06%)	15 (1·76%)	6 (0·71%)	16 (1·88%)	13 (1·53%)	31 (3·64%)	109 (1·6%)
Education									
No completed education	3 (0·35%)	2 (0·24%)	6 (0·71%)	3 (0·35%)	2 (0·24%)	6 (0·71%)	15 (1·76%)	4 (0·47%)	41 (0·6%)
Primary education	4 (0·47%)	3 (0·35%)	3 (0·35%)	6 (0·71%)	0 (0%)	26 (3·06%)	12 (1·41%)	7 (0·82%)	61 (0·9%)
Lower secondary	168 (19·74%)	93 (10·93%)	92 (10··82%)	37 (4·35%)	19 (2·23%)	111 (13·06%)	93 (10·94%)	9 (1·06%)	622 (9·14%)
Upper secondary	254 (29·85%)	124 (14·57%)	126 (14·82%)	124 (14·59%)	143 (16·80%)	162 (19·06%)	270 (31·76%)	353 (41·48%)	1,556 (22·87%)
Post-secondary vocational	23 (2·7%)	263 (30·9%)	217 (25·53%)	162 (19·06%)	304 (35·72%)	127 (14·94%)	29 (3·41%)	91 (10·69%)	1,216 (17·87%)
Tertiary education	394 (46·30%)	360 (42·31%)	375 (44·11%)	510 (60%)	377 (44·30%)	410 (48·23%)	427 (50·24%)	378 (44·42%)	3231 (47·49%)
Prefer not to say	5 (0·59%)	6 (0·71%)	31 (3·65%)	8 (0·94%)	6 (0·71%)	8 (0·94%)	4 (0·47%)	9 (1·06%)	77 (1·13%)

Table 2: Factors predictive of willingness to participate in low and higher risk pandemic-relevant studies in primary care

Variable		Primary care low risk			Primary care high risk		
		OR	se	p	OR	se	p
Country				<0·0001			<0·0001
	UK	1·00	·	·	1·00	·	·
	Australia	0·90	0·12	0·441	1·15	0·13	0·217
	New Zealand	0·82	0·11	0·128	0·85	0·09	0·138
	Ireland	1·07	0·14	0·626	1·11	0·12	0·363
	Canada	0·69	0·09	0·005	0·85	0·09	0·138
	Spain	0·55***	0·07	<0·0001	0·77	0·08	0·016
	Belgium	0·44***	0·06	<0·0001	0·71**	0·08	0·002
	Poland	0·75	0·10	0·036	1·04	0·12	0·757
Age				0·3594			0·246
	18-24	1·00	·	·	1·00	·	·
	25-34	1·08	0·13	0·504	0·97	0·10	0·773
	35-44	1·20	0·15	0·133	1·17	0·12	0·131
	45-54	1·24	0·16	0·084	1·04	0·11	0·706
	55-65 (55-59 Poland only)	1·28	0·18	0·077	1·04	0·12	0·763
Gender							
	Male	1·00	·	·	1·00	·	·
	Female	1·05	0·07	0·468	0·79***	0·04	<0·0001
Working status							
	Working	1·00	·	·	1·00	·	·
	Not working	0·92	0·08	0·374	0·87	0·06	0·059
SES				0·264			0·989
	A	1·00	·	·	1·00	·	·
	B	1·17	0·14	0·200	1·04	0·10	0·725
	C1	1·01	0·12	0·939	1·00	0·10	0·996
	C2	0·98	0·13	0·873	0·99	0·11	0·913
	D	1·21	0·21	0·259	1·04	0·15	0·766
	E	0·93	0·13	0·611	1·04	0·13	0·747
Faith				0·061			0·334
	Muslim	0·55*	0·15	0·026	1·03	0·26	0·901
	Christian	1·00	·	·	1·00	·	·
	Jewish	0·56	0·23	0·159	0·58	0·21	0·124
	Hindu	1·19	0·45	0·653	1·19	0·36	0·566
	Buddhist	1·07	0·35	0·831	0·65	0·16	0·084
	Other	1·11	0·08	0·139	0·99	0·06	0·836
Education				0·158			0·749
	No completed education	1·00	·	·	1·00	·	·
	Primary education (ISCED 1)	0·63	0·31	0·343	0·69	0·31	0·406

Variable		Primary care low risk			Primary care high risk		
		OR	**se**	**p**	**OR**	**se**	**p**
	Lower secondary education (ISCED 2)	0·75	0·29	0·458	0·94	0·33	0·850
	Upper secondary education (ISCED 3)	0·81	0·31	0·574	0·92	0·32	0·810
	Post-secondary including pre-vocational or vocational education but not tertiary	0·91	0·35	0·814	0·88	0·31	0·704
	Tertiary education first level (ISCED 5)	0·99	0·38	0·974	0·84	0·29	0·616
	Tertiary education advanced level (ISCED 6)	1·08	0·50	0·868	1·03	0·42	0·940
Number of children in household				0·733			0·921
	None	1·00	·	·	1·00	·	·
	Only younger children	1·06	0·14	0·672	0·94	0·10	0·593
	Only older children	0·94	0·08	0·462	0·99	0·07	0·844
	Older and younger children	1·08	0·17	0·620	0·93	0·12	0·583
Marital status				0·268			0·036
	Single (never married)	1·00	·	·	1·00	·	·
	Living with partner	1·00	0·10	0·972	1·05	0·09	0·578
	Married /Civil partnership	0·93	0·09	0·456	1·01	0·08	0·899
	Separated	1·07	0·31	0·826	1·61	0·41	0·061
	Divorced	0·89	0·15	0·491	1·16	0·17	0·288
	Widowed	1·32	0·48	0·436	2·40**	0·75	0·005
	Prefer not to say	0·25	0·14	0·017	0·56	0·32	0·311
Knowledge about pandemics				<0·0001			< 0·0001
	Yes	1·00	·	·	1·00	·	·
	Just a little	0·92	0·08	0·294	0·80**	0·06	0·001
	No	0·59***	0·05	<0·0001	0·61***	0·05	<0·0001
ICU experience							
	No	1·00	·	·	1·00	·	·
	Yes	1·17	0·08	0·017	1·25***	0·07	<0·0001
Perceived health							
	Poor	1·00	·	·	1·00	·	·
	Good	1·07	0·09	0·439	1·11	0·08	0·131
Trust in GP				<0·0001			<0·0001
	Disagree	1·00	·	·	1·00	·	·
	Neutral	2·02***	0·24	<0·0001	1·67***	0·19	<0·0001
	Agree	3·18***	0·36	<0·0001	2·15***	0·23	<0·0001
Trust in government				<0·0001			<0·0001
	Low	1·00	·	·	1·00	·	·
	Neutral	1·74***	0·21	<0·0001	2·00***	0·24	<0·0001
	High	2·58***	0·35	<0·0001	3·10***	0·39	<0·0001
Therapeutic misconception				<0·0001			< 0·0001

Variable		Primary care low risk			Primary care high risk		
		OR	**se**	**p**	**OR**	**se**	**p**
	Low	1·00	·	·	1·00	·	·
	Neutral	2·54***	0·32	<0·0001	1·45**	0·18	0·003
	High	8·82***	1·18	<0·0001	2·72***	0·35	<0·0001
Access to new medication							0·0124
	Disagree				1·00	·	·
	Neutral				1·19	0·08	0·014
	Agree/				1·22**	0·09	0·005

Note: OR=Odds ratio; se = Standard error; *p<0·05, **p<0·01, ***p<0·001

Estimates obtained from multiple ordinal regression models

Table 3: Consent preferences for inclusion in low risk study in primary care during an influenza pandemic

	First choice		Second choice		Third choice	
	All	Willing*	All	Willing	All	Willing
Automatic inclusion: "Include me automatically"	587 (8·63)	461 (9·78)	598 (8·79)	466 (9·88)	4404 (64·73)	3196 (67·78)
Opt-out: "Include me automatically, but remind me of the study when I get the medicine and give me a chance to opt out"·	1740 (25·57)	1371 (29·08)	4000 (58·79)	2841 (60·25)	317 (4·66)	232 (4·92)
Opt-in: "Only sign me up when I am due to get the medicine"·	3972 (58·38)	2742 (58·15)	1502 (22·07)	1169 (24·79)	724 (10·64)	602 (12·77)
No option preferred	505 (7·42)	141 (2·99)	704 (10·35)	239 (5·07)	1359 (19·97)	685 (14·53)

*Proportion of respondents who indicated "agree" or "strongly agree" when asked whether they would be willing to take part in he primary care low risk scenario (4715 of 6804, 69·3%)

Table 4: Factors predictive of willingness to engage with alternate consent models in low risk primary care including only participants who were "willing to take part"

Variable		OR	se	p
Country				0·006
	UK	1·00	·	·
	Australia	0·58	0·17	0·059
	New Zealand	0·78	0·25	0·441
	Ireland	1·53	0·55	0·231
	Canada	1·20	0·43	0·615
	Spain	0·54*	0·16	0·035
	Belgium	0·85	0·26	0·590
	Poland	1·59	0·58	0·205
Gender				
	Male	1·00	·	·
	Female	0·91	0·15	0·568
SES				0·006
	A	1·00	·	·
	B	1·00	0·33	0·995
	C1	0·88	0·29	0·702
	C2	0·71	0·25	0·331
	D	0·41*	0·15	0·013
	E	1·28	0·47	0·511
Education				0·290
	No completed education	1·00	·	·
	Primary education (ISCED 1)	0·72	0·69	0·735
	Lower secondary education (ISCED 2)	1·82	1·46	0·456
	Upper secondary education (ISCED 3)	2·00	1·56	0·377
	Post-secondary (incl. pre-vocational or vocational)	3·19	2·56	0·148
	Tertiary education – first level (ISCED 5)	2·03	1·58	0·363
	Tertiary education – advanced level (ISCED 6)	2·98	3·16	0·304
	Prefer not to say	1·30	1·70	0·839
ICU experience				
	No	1·00	·	·
	Yes	1·85***	0·32	<0·001
Illness experience				
	No	1·00	·	·
	Yes	0·73	0·20	0·254
Number of children in household				0·993
	0	1·00	·	·
	1	1·06	0·23	0·980
	2	0·98	0·24	0·942
	3 +	0·98	0·0·34	0·948
Faith				0·219
	Muslim	0·34*	0·17	0·033

Variable		OR	se	p
	Christian	1·00	·	·
	Jewish	0·57	0·60	0·593
	Hindu	1·80	1·86	0·571
	Other	1·08	0·18	0·659
Knowledge of pandemics				0·011
	A great deal/ fair amount	1·00	·	·
	Just a little	0·89	0·19	0·595
	Hear of but know nothing about/ never heard of	0·55**	0·13	0·009
Trust in government				<0·001
	Low	1·00	·	·
	Neutral	3·52***	1·02	<0·001
	High	3·17***	0·97	<0·001
Therapeutic misconception				0·782
	Low	1·00	·	·
	Neutral	1·37	0·62	0·493
	High	1·29	0·58	0·571

Note: OR=Odds ratio; se = Standard error; *p<0·05, **p<0·01, ***p<0·001

Estimates obtained from multiple logistic regression model

Table 5: Factors predictive of willingness to participate in low and higher risk pandemic-relevant studies in ICU

Variable		ICU low risk			ICU high risk		
		OR	se	p	OR	se	p
Country				<0·0001			<0·0001
	UK	1·00	·	·	1·00	·	·
	Australia	1·22	0·16	0·125	1·12	0·13	0·364
	New Zealand	0·98	0·13	0·863	1·02	0·12	0·877
	Ireland	1·30*	0·17	0·047	1·19	0·14	0·152
	Canada	0·85	0·11	0·209	0·99	0·12	0·923
	Spain	0·68**	0·09	0·003	0·58***	0·07	<0·0001
	Belgium	0·77*	0·10	0·043	0·74*	0·09	0·012
	Poland	0·89	0·12	0·392	0·76*	0·10	0·028
Age				0·117			0·013
	18-24	1·00	·	·	1·00	·	·
	25-34	1·24	0·14	0·069	1·07	0·12	0·547
	35-44	1·18	0·14	0·159	1·33*	0·15	0·011
	45-54	1·30*	0·16	0·036	1·36**	0·16	0·008
	55-65 (55-59 Poland only)	1·06	0·15	0·660	1·37*	0·17	0·013
Gender							
	Male	1·00	·	·	1·00	·	·
	Female	0·93	0·06	0·254	0·95	0·06	0·407
Working status							
	Working	1·00	·	·	1·00	·	·
	Not working	0·98	0·09	0·801	1·01	0·08	0·906
SES				0·0181			0·0786
	A	1·00	·	·	1·00	·	·
	B	1·31*	0·16	0·021	1·30*	0·14	0·015
	C1	1·17	0·14	0·195	1·15	0·13	0·198
	C2	1·05	0·14	0·693	1·15	0·14	0·235
	D	1·07	0·17	0·690	1·17	0·18	0·305
	E	0·87	0·12	0·343	0·97	0·13	0·810
Faith				0·223			0·013
	Muslim	0·76	0·22	0·340	0·59*	0·15	0·042
	Christian	1·00	·	·	1·00	·	·
	Jewish	0·48	0·18	0·056	0·54	0·22	0·128
	Hindu	0·66	0·21	0·197	0·76	0·25	0·405
	Buddhist	0·72	0·22	0·279	0·60	0·17	0·063
	Other	0·98	0·07	0·731	1·10	0·07	0·134
Education				0·131			0·090
	No completed education	1·00	·	·	1·00	·	·
	Primary education (ISCED 1)	0·71	0·34	0·482	0·47	0·22	0·099

Variable		ICU low risk			ICU high risk		
		OR	se	p	OR	se	p
	Lower secondary education (ISCED 2)	0·97	0·37	0·939	0·90	0·33	0·773
	Upper secondary education (ISCED 3)	0·79	0·30	0·525	0·78	0·28	0·492
	Post-secondary including pre-vocational or vocational education but not tertiary	0·89	0·34	0·769	0·78	0·28	0·500
	Tertiary education first level (ISCED 5)	1·01	0·38	0·970	0·92	0·33	0·812
	Tertiary education advanced level (ISCED 6)	1·04	0·47	0·939	1·10	0·48	0·817
Number of children in household				0·401			0·3586
	None	1·00	·	·	1·00	·	·
	Only younger children	0·83	0·10	0·128	0·84	0·10	0·145
	Only older children	0·92	0·08	0·347	0·98	0·08	0·822
	Older and younger children	0·87	0·13	0·358	0·84	0·12	0·206
Marital status				0·396			0·1500
	Single (never married)	1·00	·	·	1·00	·	·
	Living with partner	0·89	0·09	0·274	0·91	0·09	0·336
	Married /Civil partnership	1·06	0·10	0·545	0·94	0·08	0·500
	Separated	1·52	0·48	0·189	1·20	0·33	0·512
	Divorced	1·16	0·19	0·380	1·13	0·18	0·453
	Widowed	1·46	0·51	0·275	1·81	0·61	0·078
	Prefer not to say	0·88	0·56	0·844	0·37	0·21	0·077
Knowledge about pandemics				<0·0001			<0·0001
	Yes	1·00	·	·	1·00	·	·
	Just a little	0·86	0·07	0·0560	0·74***	0·06	0·0001
	No	0·60***	0·06	<0·0001	0·55***	0·05	<0·0001
ICU experience							
	No	1·00	·	.	1·00	·	·
	Yes	1·16	0·08	0·024	1·20**	0·07	0·003
Perceived health							
	Poor	1·00	·	·	1·00	·	·
	Good	0·97	0·08	0·699	1·26**	0·10	0·002
Trust in GP				<0·0001			<0·0001
	Disagree	1·00	·	·	1·00	·	·
	Neutral	1·34**	0·16	0·016	1·63***	0·20	<0·0001
	Agree	1·76***	0·20	<0·0001	2·27***	0·25	<0·0001
Trust in government				<0·0001			<0·0001
	Low	1·00	·	·	1·00	·	·
	Neutral	2·21***	0·27	<0·0001	2·66***	0·32	<0·0001
	High	3·72***	0·50	<0·0001	4·06***	0·53	<0·0001
Therapeutic misconception				<0·0001			<0·0001
	Low	1·00	·	·	1·00	·	·

Variable	ICU low risk			ICU high risk		
	OR	se	p	OR	se	p
Neutral	1·74***	0·22	<0·0001	0·95	0·12	0·680
High	4·35***	0·59	<0·0001	1·58***	0·21	0·001
Access to new medication						<0·0001
Disagree				1·00	·	·
Neutral				1·48***	0·11	<0·0001
Agree/				4·85***	0·41	<0·0001

Note: OR=Odds ratio; se = Standard error; *p<0·05, **p<0·01, ***p<0·001

Estimates obtained from multiple ordinal logistic regression models

Table 6: Consent preferences for inclusion in low risk study in ICU during an influenza pandemic

	First choice		Second choice		Third choice		Fourth choice	
	All	Willing*	All	Willing	All	Willing	All	Willing
Deferred consent (family) Include me immediately, family decides later if that's ok	1163 (17·09)	958 (20·04)	2236 32·86)	1690 (35·36)	1620 (23·81)	1223 (25·59)	741 (10·89)	499 (10·44)
Deferred consent (doctor): Include me immediately, doctor decides later if that's ok	1637 (24·06)	1343 (28·09)	2077 (30·53)	1582 (33·10)	1809 (27·78)	1266 (26·49)	294 (4·32)	221 (4·62)
Automatic enrolment: Include me immediately, don't ask my or anyone's consent	718 (10·55)	592 (12·38)	945 (13·89)	724 (15·15)	1269 (18·65)	995 (20·82)	2649 (38·93)	1945 (40·69)
Opt-in: Don't include me until a family member says it's ok	2623 (38·55)	1686 (35·27)	621 (9·13)	458 (9·58)	1056 (15·52)	884 (18·49)	1576 (23·16)	1344 (28·12)
No preference recorded	663 (9·74)	201 (4·21)	925 (13·59)	326 (6·82)	1050 (15·43)	412 (8·62)	1544 (22·69)	771 (16·13)

*Proportion of respondents who indicated "agree" or "strongly agree" when asked whether they would be willing to take part in the primary care low risk scenario

Table 7 Binary logistic regression of participant consent preferences for low risk ICU study during an influenza pandemic including only participants who were willing to participate

Variable		OR	se	p
Country				0·004
	UK	1·00	·	·
	Australia	1·25	0·33	0·399
	New Zealand	1·47	0·42	0·185
	Ireland	2·67**	0·86	0·002
	Canada	1·16	0·32	0·583
	Spain	0·83	0·21	0·478
	Belgium	0·74	0·18	0·205
	Poland	1·27	0·34	0·368
Age				0·580
	18-24	1·00	·	·
	25-34	0·86	0·21	0·525
	35-44	0·80	0·21	0·391
	45-54	1·06	0·28	0·832
	55-65 (55-59 Poland only)	0·77	0·21	0·347
Gender				
	Male	1·00	·	·
	Female	0·69**	0·10	0·008
SES				0·024
	A	1·00	·	·
	B	1·08	0·29	0·763
	C1	0·85	0·22	0·538
	C2	0·71	0·20	0·223
	D	0·81	0·28	0·536
	E	1·74	0·57	0·085
Education				0·013
	No completed education	1·00	·	·
	Primary education (ISCED 1)	0·60	0·51	0·550
	Lower secondary education (ISCED 2)	2·19	1·49	0·250
	Upper secondary education (ISCED 3)	2·28	1·50	0·210
	Post-secondary including pre-vocational or vocational education but not tertiary	2·50	0·1·68	0·173
	Tertiary education – first level (ISCED 5)	1·88	1·22	0·173
	Tertiary education – advanced level (ISCED 6)	0·85	0·64	0·834
	Prefer not to say	0·45	0·41	0·385
ICU Experience				
	No	1·00	·	·
	Yes	2·00**	0·29	<0·001
Illness Experience				
	No	1·00	·	·
	Yes	0·85	0·21	0·524
Perceived health				
	Poor	1·00	·	·
	Good	1·13	0·20	0·492
Number of people in household				0·693

Variable		OR	se	p
	1	1·00	·	·
	2	0·66	0·17	0·109
	3	0·74	0·21	0·296
	4	0·72	0·22	0·280
	5	0·65	0·25	0·270
	6	1·21	0·80	0·769
	7	1·39	1·49	0·760
			·	·
Number of children				0·972
	0	1·00	·	·
	1	0·92	0·19	0·676
	2	0·97	0·27	0·918
	3 +	1·05	0·45	0·906
Marital status				
	On their own	1·00	·	·
	Living with someone	1·68**	0·29	0·003
Knowledge of pandemics				0·248
	A great deal/ fair amount	1·00	·	·
	Just a little	0·97	0·17	0·875
	Hear of but know nothing about/ never heard of	0·76	0·15	0·154
Trust in government				0·003
	Low	1·00	·	·
	Neutral	2·33**	0·62	0·001
	High	2·54*	0·71	0·001
Therapeutic misconception				0·479
	Low	1·00	·	·
	Neutral	1·36	0·45	0·356
	High	1·47	0·48	0·238

Note: OR=Odds ratio; se = Standard error; *p<0·05, **p<0·01, ***p<0·001

Estimates obtained from multiple logistic regression model

Table 8: Factors predictive of willingness to donate excess from clinical samples for pandemic-relevant research

		Overall		
		OR	se	p
Country				<0·001
	UK	1·00	·	·
	Australia	0·66	0·10	0·004
	New Zealand	0·69*	0·10	0·012
	Ireland	0·83	0·12	0·201
	Canada	0·69*	0·10	0·014
	Spain	0·46***	0·07	<0·001
	Belgium	0·71*	0·11	0·024
	Poland	0·48***	0·07	<0·001
Age				<0·001
	18-24	1·00	·	·
	25-34	1·34*	0·16	0·011
	35-44	1·55***	0·18	<0·001
	45-54	1·98***	0·24	<0·001
	55-65 (55-59 Poland only)	2·29***	0·31	<0·001
Gender				
	Male	1·00	·	·
	Female	1·04	0·07	0·585
Employment status				
	Working	1·00	·	·
	Not working	1·07	0·10	0·488
SES				0·0024
	A	1·00	·	·
	B	1·23	0·16	0·127
	C1	1·05	0·14	0·705
	C2	0·81	0·11	0·142
	D	0·81	0·14	0·208
	E	0·83	0·13	0·217
Faith				0·0204
	Muslim	0·59	0·17	0·063
	Christian	1·00	·	·
	Jewish	1·19	0·61	0·731
	Hindu	0·57	0·18	0·082
	Buddhist	0·92	0·30	0·801
	Other	1·18*	0·09	0·033
Knowledge about pandemics				<0·001
	A great deal/ fair amount	1·00	·	·
	Just a little	0·96	0·09	0·625
	Hear of but know nothing about/ never heard of	0·70***	0·07	<0·001
ICU Experience				
	No	1·00	·	·
	Yes	1·34	0·10	<0·001
Perceived overall health				
	Poor	1·00	·	·
	Good	1·15	0·10	0·106

Trust in GP				<0·001
	Strongly disagree/disagree	1·00	·	·
	Neutral	1·10	0·14	0·472
	Agree/strongly agree	1·95***	0·24	<0·001
Trust in government				<0·001
	Low	1·00	·	·
	Neutral	2·40***	0·31	<0·001
	High	4·84***	0·71	<0·001
Therapeutic misconception				<0·001
	Low	1·00	·	·
	Neutral	1·00	0·15	0·989
	High	1·60**	0·25	0·002

Note: OR=Odds ratio; se = Standard error; *p<0·05, **p<0·01, ***p<0·001

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