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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: This is an international cross-sectional survey.
Methods: We surveyed the views of nationally representative samples of people in Belgium, Poland, Spain, Ireland, the 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 be applied to make this research feasible. The 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 the government, therapeutic misconception and having had ICU experience as a

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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.

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 are 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 opinions 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 effectiveness 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 antiviral agents. Oseltamivir is now widely regarded as the 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 World Health Organization global influenza strategy includes research and innovation for diagnostics, vaccines and treatments as one of the 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 unblock these barriers involves prefunding active clinical research networks, such as those in the Platform foR European Preparedness Against (Re-)emerging Epidemics (PREPARE). PREPARE conducts multisite, pan-European clinical studies in the community, the hospital and critical care settings that address important study questions during interpandemic periods of seasonal influenza. These research-active networks would reorientate their interpandemic research activities in the event of a public health emergency, thereby reducing the time needed to recruit and prepare research sites. PREPARE clinical trials use novel adaptive platform designs with response-adaptive randomisation that shortens the time in 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, for example, 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 multisite, pan-European research efforts.[14,15]

As the primary contributors and potential beneficiaries of pandemic-relevant research, patients and the public are the key and often underrepresented, stakeholders in research preparedness. Although 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. Furthermore, 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 from Belgium, Spain, Poland, Ireland, the UK, 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 macrogeographical regions.[20] These countries were also included in qualitative work that informed the survey development. Respondents aged 18–65 years from each country, except Poland (age range, 18–59 years), were invited via a prerecruited online panel hosted by the Ipsos Group. The Ipsos Group is a market research company that regularly conducts online research for academic institutions. This group administered data collection. The 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. The 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–August 2017 in Southern hemisphere countries, to coincide with regional influenza seasons. Potential respondents were invited to take part in the survey in batches, to control the sample profile. Data collection was planned to continue until the target sample size (850 per country, 6800 in 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 the Ipsos Group across multiple countries.

Data collection instrument

We developed a scenario-based instrument in which the respondents were asked to imagine that 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, the respondents were asked for their views in taking part in a low- and high-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. High-risk scenarios involved patients receiving either a new medication that had passed safety testing or a placebo. Finally, the 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 the relevant literature[5,13,21–23] and sought expert opinions 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 is to produce generalisable findings relevant to a population). To refine the wording and response format of the survey questions, we conducted cognitive interviewing using the think-aloud technique.[25] Changes to the survey were made iteratively, at three time points. The data collection instrument was circulated for comment to colleagues in Belgium, Spain, Poland, Australia and New Zealand to ensure applicability to their healthcare context. The final version of the instrument was translated into Flemish, French, Spanish and Polish and back translated to ensure accuracy. Before the survey was distributed, a small segment of the overall target group of respondents completed the survey, and data were reviewed to identify any difficulties. No changes were required after this soft launch.

Analysis

We combined survey responses into three categories (strongly disagree/disagree, neutral and agree/strongly agree) and ran ordinal regression models to examine demographic and attitudinal factors predictive of respondents' willingness to participate in primary care and intensive care unit (ICU) studies and willingness for routinely collected clinical samples to be used for pandemic-relevant research. To identify suitable candidate variables for regression models, we first conducted univariate associations using a chi-squared test. Candidates that were significant at $P < 0{\cdot}01$ in univariate analyses were then included. Factors that account for how participants would like to be consented were examined in an exploratory post hoc analysis using a logistic regression. To explore whether any factors predicted willingness to engage with an alternate approach to consent, we created a binary variable that classified respondents as only willing to consider the standard 'opt-in' consent models (box 1) versus willing to consider any of the other options. This variable was used as the outcome in logistic regression models that included only those participants who expressed willingness to take part in each scenario study. To assess the impact of missing data at the baseline and possible bias arising from data not being missing completely at random, the regression models were reanalysed using multiple imputation with chained equations, which is valid under a less restrictive missing at random assumption. The results did not differ substantially from the complete case analysis, which suggests there is no substantial bias due to missing data. Data were analysed using STATA version 15.0.

Ethics, consent, sponsorship and ethical treatment of human subjects

The 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 from Ireland, Spain, Belgium and New Zealand, and 851 from Poland, the UK, Australia and Canada (Table 1). Response rates were not calculated owing to the quota sampling technique used.

Public attitudes to clinical research

The respondents considered it important that medical research is conducted during an influenza pandemic (5572, 81.9%) and that special rules should be applied to make it easier to conduct pandemic-relevant research (5089, 74.8%). The results were similar across countries, with the exception of the 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 high-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 (Fig. 1a and b). 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-squared $P < 0{\cdot}001$) for both the low- and high-risk scenarios (Fig. 1a and b and Table 2). Being a female (compared with a male) was associated with decreased willingness to take part in the high-risk primary care scenario (Table 2). For both low-

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 (years)									
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%)	1491 (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%)	1554 (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%)	1532 (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%)	1311 (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%)	3327 (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									
Not 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 education	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 education	254 (29.85%)	124 (14.57%)	126 (14.82%)	124 (14.59%)	143 (16.80%)	162 (19.06%)	270 (31.76%)	353 (41.48%)	1556 (22.87%)
Postsecondary vocational education	23 (2.7%)	263 (30.9%)	217 (25.53%)	162 (19.06%)	304 (35.72%)	127 (14.94%)	29 (3.41%)	91 (10.69%)	1216 (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 (106%)	77 (1.13%)

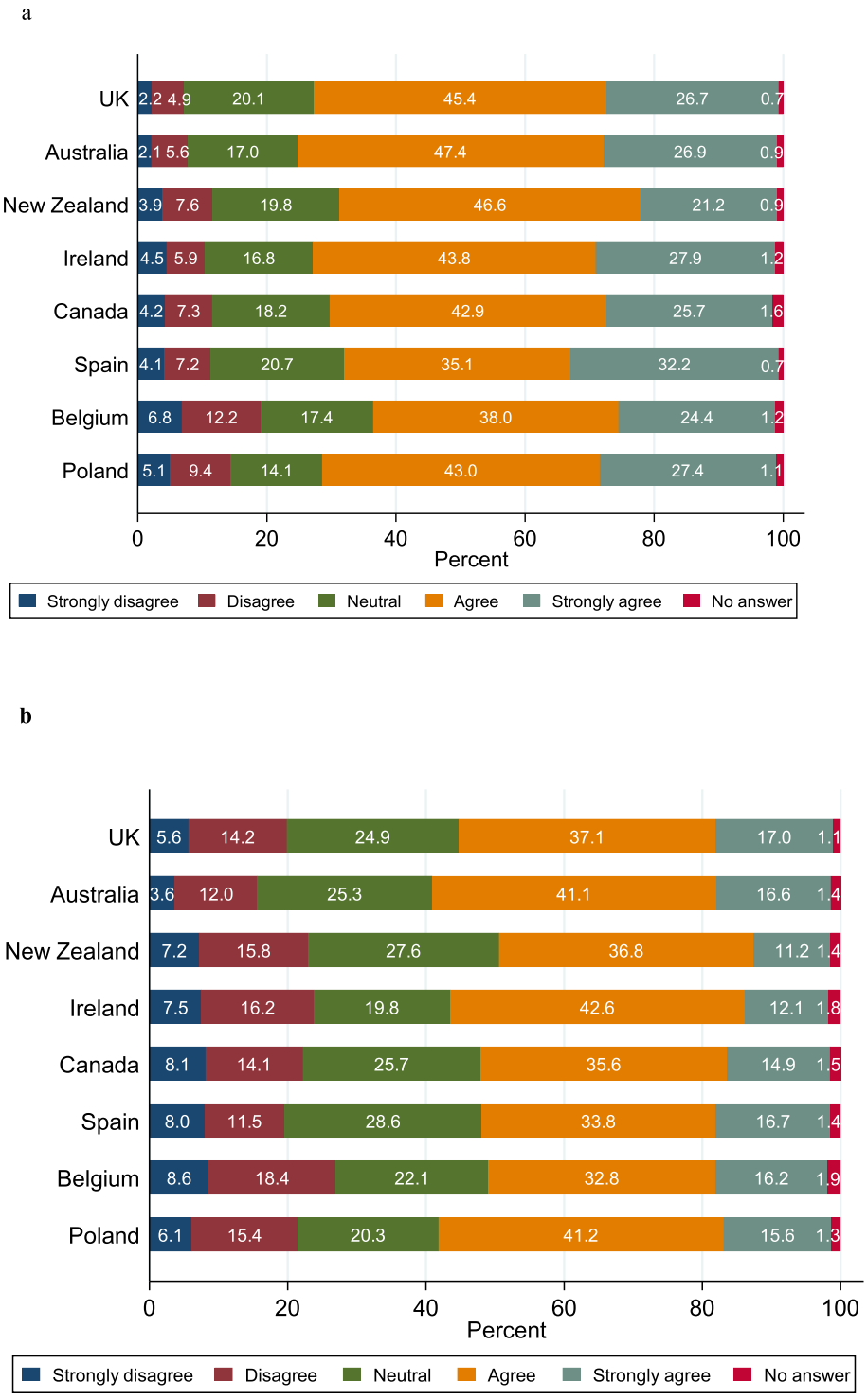

Fig. 1 – (a) Willingness to take part in the low-risk primary care scenario. (b) Willingness to take part in the higher risk primary care scenario.

and high-risk primary care scenarios, the less knowledge the 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 in the low-risk comparative effectiveness research (CER) scenario

Of those respondents willing to take part in the low-risk primary care scenario (4715, 69.3%), the majority preferred the standard

Table 2 – Factors predictive of willingness to participate in low- and high-risk pandemic-relevant primary care studies.

Variable	Low-risk primary care studies			High-risk primary care studies		
	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 (years)			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
Not completed education	1.00			1.00		
Primary education (ISCED 1)	0.63	0.31	0.343	0.69	0.31	0.406
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
Postsecondary including prevocational 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 the 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 a 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

(continued on next page)

Table 2 – (continued)

Variable	Low-risk primary care studies			High-risk primary care studies		
	OR	se	P	OR	se	P
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 the 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
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/strongly agree				1.22**	0.09	0.005

Estimates obtained from multiple ordinal regression models.
ICU = intensive care unit; OR = odds ratio; se = standard error; SES = socioeconomic status; ISCED = International Standard Classification of Education; GP = general practitioner.
*P < 0.05.
**P < 0.01.
***P < 0.001.

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, the 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, whereas having had ICU experience and having greater trust in the government were variables associated with acceptance of enrolment under alternate consent models (Table 4).

ICU: willingness to participate in low- and high-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; Fig. 2a and b). A chi-squared test comparing proportion endorsing each response against country gave statistically significant results ($P < 0{\cdot}001$) 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, having 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 in the 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

Table 3 – Consent preferences for inclusion in the low-risk primary care study during an influenza pandemic.

Response options	First choice		Second choice		Third choice	
	All	Willing[a]	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)

[a] 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 (4715 of 6804, 69.3%).

Table 4 – Factors predictive of willingness to engage with alternate consent models in the low-risk primary care study 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
Not 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
Postsecondary (including prevocational 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 the household			0.993
0	1.00		
1	1.06	0.23	0.980
2	0.98	0.24	0.942
3+	0.98	0.034	0.948
Faith			0.219
Muslim	0.34*	0.17	0.033
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
Heard of but know nothing about/never heard of	0.55**	0.13	0.009
Trust in the 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

ICU = intensive care unit; OR = odds ratio; se = standard error; SES = socioeconomic status; ISCED = International Standard Classification of Education.
Estimates obtained from the multiple logistic regression model.
*P < 0.05.
**P < 0.01.
***P < 0.001.

(1345, 28.1%) or a family member (958, 20.0%) was the first choice preferences (Table 6). Prospective 'opt-in' informed consent procedures were 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 who had some ICU experience, were living with someone rather than alone and had greater trust in the 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

A total of 5256 (77.2%) 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. A total of 4940 (72.6%) respondents 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 the 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 Organisation for Economic Cooperation and Development (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. Although the majority of respondents wanted to provide prospective informed consent for enrolment in primary care studies, a substantial minority would consider

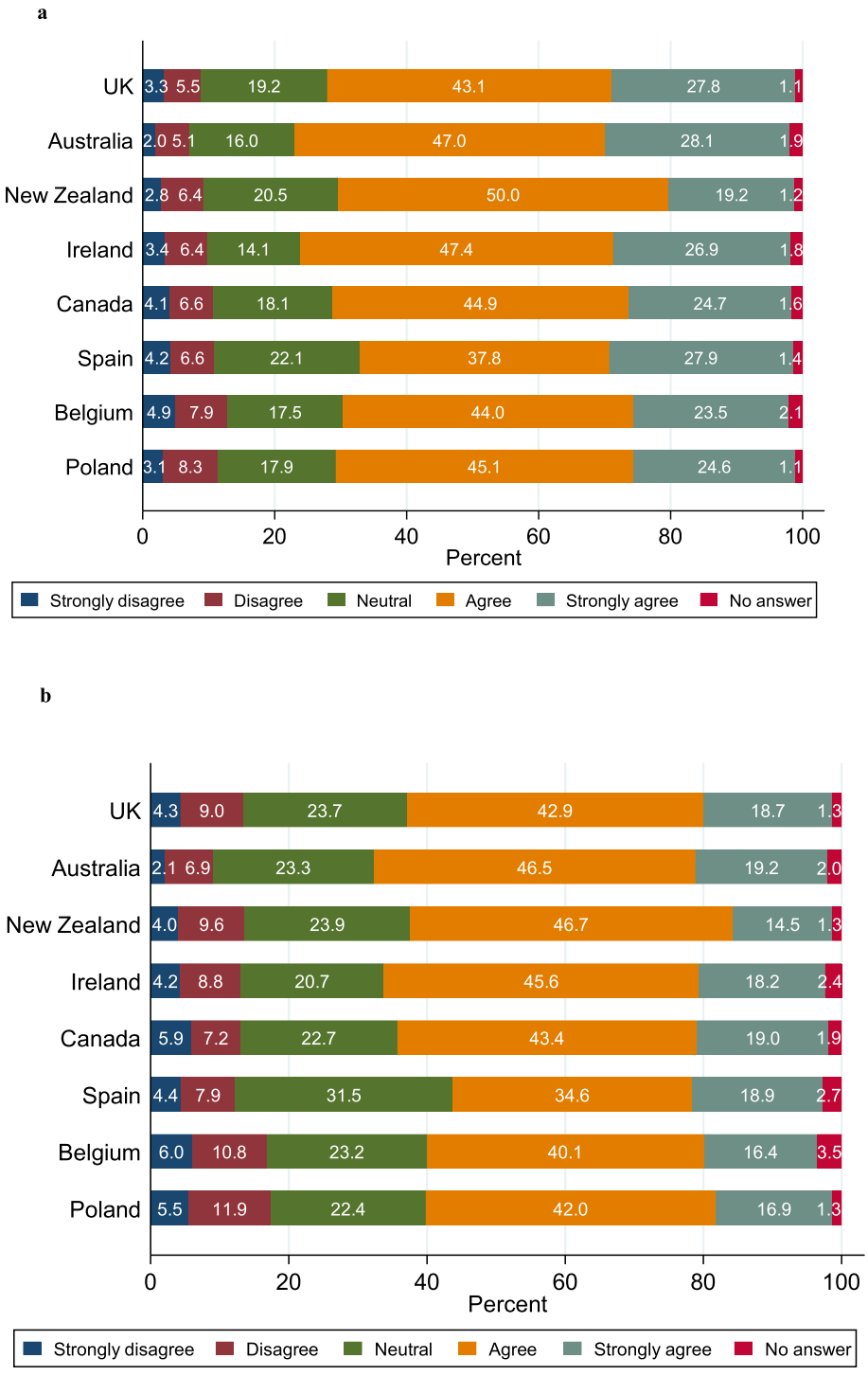

Fig. 2 – (a) Willingness to take part in the low-risk ICU scenario. (b) Willingness to take part in the higher risk ICU scenario. ICU = intensive care unit.

alternatives. Deferred consent was acceptable to the majority of respondents for enrolment in ICU studies. Pandemic knowledge, trust in health professionals and in the 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

Table 5 – Factors predictive of willingness to participate in low- and high-risk pandemic-relevant studies in the ICU.

Variable	Low-risk ICU study			High-risk ICU study		
	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 (years)			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
Not completed education	1.00			1.00		
Primary education (ISCED 1)	0.71	0.34	0.482	0.47	0.22	0.099
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
Postsecondary including prevocational 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 the 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 a 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

(continued on next page)

Table 5 – (*continued*)

Variable	Low-risk ICU study			High-risk ICU study		
	OR	se	P	OR	se	P
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 the 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		
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/strongly agree				4.85***	0.41	<0.0001

ICU = intensive care unit; OR = odds ratio; se = standard error; SES = socioeconomic status; ISCED = International Standard Classification of Education; GP = general practitioner.
Estimates obtained from multiple ordinal logistic regression models.
*P < 0.05.
**P < 0.01.
***P < 0.001.

Table 6 – Consent preferences for inclusion in the low-risk ICU study during an influenza pandemic.

Response options	First choice		Second choice		Third choice		Fourth choice	
	All	Willing[a]	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)

ICU = intensive care unit.
[a] 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.

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 used hypothetical scenarios, and respondents' 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 non-

Table 7 – Binary logistic regression of participant consent preferences for the 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 (years)			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
Not 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
Postsecondary including prevocational or vocational education but not tertiary	2.50	0.17	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 the household			0.693
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
Heard of but know nothing about/never heard of	0.76	0.15	0.154
Trust in the 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

ICU = intensive care unit; OR = odds ratio; se = standard error; SES = socioeconomic status; ISCED = International Standard Classification of Education.
Estimates obtained from the multiple logistic regression model.
*P < 0.05.
**P < 0.01.
***P < 0.001.

response 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. The respondents were from countries in the OECD as these were relevant to PREPARE clinical studies and are vulnerable to influenza pandemics. Low- and middle-income countries bear the greatest burden of infectious disease outbreaks, and the 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 patients lack capacity to consent themselves. Where patients have capacity (for example, enrolment in 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. The 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

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

Variable	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 (years)			<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
Heard 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 the 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

ICU = intensive care unit; OR = odds ratio; se = standard error; SES = socioeconomic status; ISCED = International Standard Classification of Education; GP = general practitioner.
*P < 0.05.
**P < 0.01.
***P < 0.001.

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 (EU) 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 that simplified informed consent procedures are deemed acceptable for enrolment in '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. As 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 deidentification of patient data may not be possible, particularly at the early stages of an outbreak. The General Data Protection Regulation, 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 in low-risk comparative effectiveness research in this context. Experience of critical illness, trust in doctors and in the 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 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 generalisable 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 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.

Author statements

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Ethical approval

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 study at any stage in the process. All data were processed in accordance with the UK Data Protection Act 1998.

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Competing interests

None declared.

Author contributions

N.G. led the study design, data collection instrument development and cognitive interviewing, contributed to analysis and interpretation and drafted the manuscript. C.C.B. conceived the idea and contributed to study design, analysis and interpretation. J.M. wrote the statistical analysis plan and supervised the analysis. N.A.F. contributed to study design, analysis and interpretation. V.H. conducted statistical analyses and contributed to interpretation. M.G. contributed to study design, instrument development, cognitive interviewing and materials. A.W. contributed to administering the study. K.H. contributed to study design and interpretation. S.A.R.W. contributed to analysis and interpretation. A.N. contributed to study design, analysis and interpretation. All authors contributed to writing the manuscript.

REFERENCES

1. Dicke T. Waiting for the flu: cognitive inertia and the Spanish influenza pandemic of 1918–19. *J Hist Med Allied Sci* 2015;**70**(2):195–217.
2. Leigh J, Moon S, Garcia E, Fitzgerald G. *Is global capacity to manage outbreaks improving? – an analysis*. Geneva: Graduate Institute of International and Development Studies; 2018.
3. Simonsen L, Higgs E, Taylor RJ, et al. Using clinical research networks to assess severity of an emerging influenza pandemic. *Clin Infect Dis* 2018;**67**(3):341–9.
4. Commission on a Global Health Risk Framework for the Future G. *The neglected dimension of global security: a framework to counter infectious disease crises*. 2016.
5. Lurie N, Manolio T, Patterson AP, Collins F, Frieden T. Research as a part of public health emergency response. *N Engl J Med* 2013;**368**(13):1251–5.
6. Hurt AC, Kelly H. Debate regarding oseltamivir use for seasonal and pandemic influenza. *Emerg Infect Dis J* 2016;**22**(6).
7. WHO, editor. *WHO. Global Influenza strategy 2019-2030*; 2019. Geneva.
8. Butler CC, Coenen S, Saville BR, et al. A trial like ALIC(4)E: why design a platform, response-adaptive, open, randomised controlled trial of antivirals for influenza-like illness? *ERJ Open Res* 2018;**4**(2):00046–2018.
9. Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. *J Am Med Assoc* 2015;**313**(16):1619–20.
10. Webb SA, Nichol AD. Bending the pandemic curve: improving decision-making with clinical research. *Crit Care Med* 2018;**46**(3):442–6.
11. Burns KE, Rizvi L, Tan W, Marshall JC, Pope K. Participation of ICUs in critical care pandemic research: a province wide, cross-sectional survey. *Crit Care Med* 2013;**41**(4):1009–16.
12. Gobat NH, Gal M, Butler CC, et al. Talking to the people that really matter about their participation in pandemic clinical research: a qualitative study in four European countries. *Health Expect : An Int J Public Particip Health care Health Policy* 2018;**21**(1):387–95.
13. Gobat NH, Gal M, Francis NA, et al. Key stakeholder perceptions about consent to participate in acute illness research: a rapid, systematic review to inform epi/pandemic research preparedness. *Trials* 2015;**16**:591.
14. Rebers S, Vermeulen E, Brandenburg AP, et al. A randomised controlled trial of consent procedures for the use of residual tissues for medical research: preferences of and implications

for patients, research and clinical practice. *PLoS One* 2016;**11**(3):e0152509.
15. Caliendo AM, Gilbert DN, Ginocchio CC, et al. Better tests, better care: improved diagnostics for infectious diseases. *Clin Infect Dis : An Off Publ Infect Dis Soc America* 2013;**57**(Suppl 3):S139–70.
16. Daugherty Biddison EL, Gwon H, Schoch-Spana M, et al. The community speaks: understanding ethical values in allocation of scarce lifesaving resources during disasters. *Annals American Thoracic Soc* 2014;**11**(5):777–83.
17. Levin D, Cadigan RO, Biddinger PD, Condon S, Koh HK. Joint Massachusetts Department of Public Health-Harvard Altered Standards of Care Working G. Altered standards of care during an influenza pandemic: identifying ethical, legal, and practical principles to guide decision making. *Disaster Med Public Health Prep* 2009;**3**(Suppl 2):S132–40.
18. Schoch-Spana M, Franco C, Nuzzo JB, Usenza C. Working Group on Community Engagement in Health Emergency P. Community engagement: leadership tool for catastrophic health events. *Biosecurity & Bioterrorism* 2007;**5**(1):8–25.
19. Silva DS, Gibson JL, Robertson A, et al. Priority setting of ICU resources in an influenza pandemic: a qualitative study of the Canadian public's perspectives. *BMC Public Health* 2012;**12**:241.
20. United Nations Statistics Division. *Composition of macro geographical (continental) regions, geographical sub-regions, and selected economic and other groupings*. 2016. accessed First accessed: 3.05.2015; Updated: 29.11.2016, http://unstats.un.org/unsd/methods/m49/m49regin.htm - europe.
21. Lim WS, Brittain C, Duley L, et al. Blinded randomised controlled trial of low-dose Adjuvant Steroids in Adults admitted to hospital with Pandemic influenza (ASAP): a trial 'in hibernation', ready for rapid activation. *Health Technol Assess* 2015;**19**(16):1–78 [vii-viii].
22. Venkatesan S, Myles PR, McCann G, et al. Development of processes allowing near real-time refinement and validation of triage tools during the early stage of an outbreak in readiness for surge: the FLU-CATs Study. *Health Technol Assess* 2015;**19**(89):1–132.
23. GHRF Commission. *The neglected dimension of global security: a framework to counter infectious disease crises*. 2016.
24. Appelbaum PS, Anatchkova M, Albert K, Dunn LB, Lidz CW. Therapeutic misconception in research subjects: development and validation of a measure. *Clin Trials* 2012;**9**(6):748–61.
25. Jobe JB, Mingay DJ. Cognitive research improves questionnaires. *Am J Public Health* 1989;**79**(8):1053–5.
26. Halpern SD, Metzger DS, Berlin JA, Ubel PA. Who will enroll? Predicting participation in a phase II AIDS vaccine trial. *J Acquir Immune Defic Syndr* 2001;**27**(3):281–8.
27. Hankins C. *Good participatory practice guidelines for trials of emerging (and re-emerging) pathogens that are likely to cause severe outbreaks in the near future and for which few or no medical countermeasures exist (GPP-EP)*. WHO: WHO; 2016.
28. *Internet World Stats*. 2019. https://www.internetworldstats.com/stats4.htm. [Accessed 13 May 2017].
29. Faden RR, Beauchamp TLPD, Kass NESD. Informed consent, comparative effectiveness, and learning health care. *N Engl J Med* 2014;**370**(8):766–8.
30. McKinney Jr RE, Beskow LM, Ford DE, et al. *Use of altered informed consent in pragmatic clinical research*. London, England: Clinical trials; 2015.
31. Truog RD, Robinson W, Randolph A, Morris A. Is informed consent always necessary for randomized, controlled trials? *N Engl J Med* 1999;**340**:804–7.
32. Nayak RK, Wendler D, Miller FG, Kim SY. Pragmatic randomized trials without standard informed consent? *A National Survey. Annals Internal Med* 2015;**163**(5):356–64.
33. Dal-Ré R, Carcas AJ, Carné X, Wendler D. Public preferences on written informed consent for low-risk pragmatic clinical trials in Spain. *Br J Clin Pharmacol* 2017;**83**(9):1921–31.
34. Dal-Ré R, Carcas AJ, Carné X, Wendler D. Patients' beliefs regarding informed consent for low-risk pragmatic trials. *BMC Med Res Methodol* 2017;**17**(145).
35. Council for International Organisations of Medical Sciences. *International ethical guidelines for health-related research involving humans*. Geneva: CIOMS publications; 2016.
36. World Health Organisation. *Guidance for managing ethical issues in infectious disease outbreaks. Geneva*. 2016.
37. European Parliament and Council. Regulation (EU) No 536/2014 of the European parliament and of the council. In: Union E, editor. *Off J Eur Union*. European Union; 2014.
38. Lewis C, Clotworthy M, Hilton S, et al. Public views on the donation and use of human biological samples in biomedical research: a mixed methods study. *BMJ Open* 2013;**3**(8):e003056.
39. Lewis C, Clotworthy M, Hilton S, et al. Consent for the use of human biological samples for biomedical research: a mixed methods study exploring the UK public's preferences. *BMJ Open* 2013;**3**(8):e003022.
40. Christopher PP, Appelbaum PS, Truong D, Albert K, Maranda L, Lidz CW. Reducing therapeutic misconception: a randomised intervention trial in hypothetical clincial trials. *PLoS One* 2017;**12**(9):e0184224.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.puhe.2019.07.005.