

Pandemic influenza is a strong motivator for participation in vaccine clinical trials among HIV-positive Canadian adults

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BACKGROUND: HIV-positive patients represent an immunosuppressed population at risk for severe influenza. In the event of a pandemic, such as 2009 H1N1, rapid implementation of vaccine clinical trials in target populations will be critical. In the present paper, knowledge and attitudes of HIV-positive adults regarding seasonal/pandemic influenza vaccination were evaluated, and facilitators and barriers to participation in vaccine clinical trials were explored.

METHODS: A validated, 70-item, self-administered questionnaire was distributed to all HIV patients presenting for routine follow-up at eight Canadian Institutes of Health Research Canadian HIV Trials Network (CTN) sites from October 2008 to February 2009, as well as all participants in CTN trial 237. This study has representation from all Canadian provinces.

RESULTS: In total, 610 HIV-positive adults responded (298 CTN 237 participants; 312 non-CTN 237 participants). Most reported receiving influenza vaccine last season (83% of CTN 237 participants versus 83% non-CTN 237 participants; P not significant) and most would receive a pandemic influenza vaccine if offered (76% versus 73%; P not significant). A majority believed that it was important to include HIV patients in vaccine clinical trials (65% versus 53%; $P < 0.001$) and would agree to participate in trials of a pandemic vaccine if invited (86% versus 51%; $P \leq 0.0001$). Predictors of willingness to participate in a pandemic vaccine trial were 'desire to be protected from pandemic flu', OR 4.5 (95% CI 2 to 8) and 'desire to help others', OR 2.3 (95% CI 1.3 to 4.5). 'Fear of needles', OR 0.49 (95% CI 0.1 to 1.5) and 'need for extra blood tests', OR 0.49 (95% CI 0.2 to 1.4) were key barriers to participation.

CONCLUSION: Most HIV-positive Canadian adults surveyed receive influenza vaccination. Protection from pandemic influenza is considered important and is a motivator for receiving influenza vaccine and future trial participation. Modifiable barriers to these objectives identified in the present study should be the focus of efforts to increase influenza immunization in this population.

Key Words: HIV-positive adult attitudes; Pandemic influenza; Public health; Vaccine uptake

Persons with HIV represent an important population of immunosuppressed patients. In the event of influenza pandemic, such as the current 2009 swine-origin H1N1 strain, it will be important to ensure protection of this group through immunization and, thus, rapid implementation of trials to evaluate candidate pandemic influenza vaccines in this population will be critical. HIV infection may predispose individuals to increased

La pandémie de grippe incite fortement les adultes canadiens VIH-positifs à participer à des essais cliniques sur les vaccins

HISTORIQUE : Les patients VIH-positifs constituent une population immunodéprimée exposée à un risque de grippe grave. Dans les cas de pandémie, comme celle de la grippe AH1N1 2009, la mise en place rapide d'essais cliniques sur des vaccins chez les populations cibles sera cruciale. Le présent article explore les connaissances et les attitudes des adultes VIH-positifs au sujet de la vaccination contre la grippe saisonnière/pandémique, de même que les facteurs qui facilitent ou empêchent leur participation aux essais cliniques sur des vaccins.

MÉTHODE : Un questionnaire validé auto-administré de 70 éléments a été distribué à tous les patients VIH-positifs qui se présentaient pour un suivi de routine auprès de huit centres affiliés au Réseau canadien pour les essais VIH des Instituts pour la recherche en santé du Canada entre octobre 2008 et février 2009, de même qu'à tous les participants à l'étude CTN237 du Réseau. Cette étude regroupe des participants provenant de toutes les provinces canadiennes.

RÉSULTATS : En tout, 610 adultes VIH-positifs ont répondu (298 participants à l'étude CTN 237 et 312 autres participants). La plupart ont signalé avoir reçu le vaccin antigrippal la saison précédente (83 % des 237 participants du Réseau vs 83 % des autres participants, $p =$ non significatif) et la plupart se disaient prêts à recevoir le vaccin contre la grippe pandémique s'il leur était offert (76 % vs 73 %, $p =$ non significatif). Une majorité croyait important d'inclure les patients VIH-positifs dans les essais cliniques sur les vaccins (65 % vs 53 %, $p < 0,001$) et accepterait de participer à des essais sur le vaccin contre la grippe pandémique si elle y était invitée (86 % vs 51 %, $p \leq 0,0001$). Les prédicteurs de la volonté à participer à un essai sur un vaccin contre la grippe pandémique étaient le désir de s'en protéger soi-même, RR 4,5 (IC à 95 %, 2 à 8) et d'en protéger autrui, RR 2,3 (IC à 95 %, 1,3 à 4,5). La crainte des injections, RR 0,49 (IC à 95 %, 0,1 à 1,5) et la nécessité de devoir subir des tests sanguins supplémentaires, RR 0,49 (IC à 95 %, 0,2 à 1,4) ont été les principaux obstacles à une participation.

CONCLUSION : La plupart des adultes canadiens VIH-positifs interrogés reçoivent une vaccination antigrippale. La protection contre la grippe pandémique est jugée importante et constitue un argument en faveur de la vaccination antigrippale et de la participation à d'éventuels essais cliniques. Les obstacles modifiables qui s'opposent aux objectifs identifiés dans le cadre de la présente étude devraient être au centre des efforts visant à accroître l'immunisation antigrippale dans cette population.

susceptibility to both seasonal and pandemic influenza. Indeed, up to 40% of all febrile respiratory illnesses in HIV-positive patients are attributable to seasonal influenza (1). Moreover, the estimated rate of influenza-related death in persons with AIDS is 9.4 to 14.6 deaths/1000 patients – approximately double the rate in the general population (2). Several studies have demonstrated that seasonal influenza vaccination is

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efficacious in the HIV-positive population (3-5). One meta-analysis (6) found that three to seven vaccinations were needed to prevent one seasonal influenza infection. These studies were performed before the advent of highly active antiretroviral therapy and current studies are investigating whether alternative vaccine schedules or dosages will improve the immunogenicity of influenza vaccination in patients with HIV.

Despite the ongoing efforts to improve the effectiveness of influenza vaccines in persons with HIV, there is limited information available about the attitudes of HIV-positive patients toward vaccination and regarding participation in vaccine clinical trials. This information is critical to ensuring that immunization policy and supporting patient education campaigns are responsive to the needs of this growing population of high-risk patients, and to ensuring participation of this population in clinical trials of seasonal and pandemic influenza vaccines. We conducted a survey among Canadian adults with HIV infection to evaluate their knowledge, attitudes and behaviours regarding seasonal and pandemic influenza vaccine, and to explore facilitators and barriers to participation in vaccine clinical trials.

METHODS

Patient population

A self-administered questionnaire was administered at eight Canadian Institutes of Health Research (CIHR) Canadian HIV Trials Network (CTN) centres to all HIV-positive patients during their regularly scheduled clinic visits between October 2008 and February 2009. The questionnaire was also administered to all patients participating in CTN trial 237, which included four additional CTN sites for a total of 12 sites. CTN 237 is an ongoing clinical trial evaluating alternative seasonal influenza vaccine doses and schedules in patients with HIV. Patients participating in CTN 237 completed the survey instrument after providing informed consent for participation in the vaccine clinical trial. All patients received an information letter detailing the study. The research ethics boards of all participating centres approved the study.

Survey instrument

The survey instrument is a 70-item self-administered questionnaire based on the Theory of Planned Behavior, which has been described elsewhere (7-10). Seasonal influenza vaccination attitude items were adapted directly from a previously validated survey instrument examining attitudes of health care workers toward influenza immunization (11). Knowledge items were developed in consultation with a panel of three subject matter experts and were considered to be adequate indications of patient knowledge toward influenza and influenza vaccination. Content validity of individual items and the tool as a whole was evaluated using a standard content validity index (12).

Statistical analysis

Statistical analysis was performed using SPSS version 15.0 (SPSS Inc, USA). Sample size was calculated as the number of respondents required to generate a point estimate of willingness to receive seasonal or pandemic influenza vaccines or to participate in vaccine clinical trials with a 95% CI \pm 5%. Continuous data are presented as means with 95% CIs. Categorical data are presented as frequencies and percentages. Differences in categorical variables between trial and nontrial participants were calculated using χ^2 testing. Composite scores were created for global

attitudes toward influenza vaccination, perceived behavioural control and subjective norm. Internal consistency for each composite score was tested using Cronbach's alpha, a measure of overall reliability of the score. The three composite scores were entered into hierarchical binary logistic regression and corrected for age, sex and education differences. Univariate logistic regression was used to explore predictors of willingness to receive a vaccination and to participate in a pandemic influenza vaccine trial. Hierarchical binary logistic regression was used to find independent predictors of willingness to receive an influenza vaccination and willingness to participate in a future trial. The model examined trial and nontrial participants grouped together and separately.

RESULTS

All experts deemed the content of all items and the final survey instrument to be valid and no items required modification or elimination. A minimum of 400 participants was required to be powered to do the analysis and subgroup analysis. A total of 610 participants completed the survey. Trial and nontrial participants were similar and were represented by all Canadian provinces (Table 1). In both groups, self-reported prior receipt of influenza vaccination was 83%. Trial participants were more likely to report an intention to receive the current season influenza vaccine than nontrial participants (99% versus 89%; $P < 0.0001$).

Differences in attitudes and knowledge toward influenza vaccination, trial participation and pandemic influenza were compared between trial and nontrial participants. Overall, trial participants had better knowledge about influenza and influenza immunization than nontrial participants (mean knowledge score 74 versus 66, respectively, $P < 0.0001$) (Figure 1). However, more than 25% percent of respondents in both groups believed that influenza vaccine can cause influenza and over 50% of respondents believed that influenza is caused by bacteria and can be treated with antibiotics.

The attitudes of trial and nontrial participants toward seasonal and pandemic influenza vaccine, participation in clinical trials, and participation in a trial of a candidate pandemic influenza vaccine were compared using the χ^2 test (Table 2). Overall, the majority of participants in both groups reported that receiving influenza vaccine is important to them (76% trial versus 64% nontrial; $P < 0.001$) and that people with HIV should receive an influenza vaccine annually (71% trial versus 61% nontrial, $P = 0.01$). While both trial and nontrial participants agreed or strongly agreed that 'inventing a pandemic flu vaccine is important' (76% versus 73%; $P =$ nonsignificant [NS]), most do not believe that people with HIV are at higher risk of severe illness from pandemic influenza than people without HIV (43% trial versus 41% nontrial; $P =$ NS). Most respondents in both groups would receive a pandemic influenza vaccine if it were offered to them (69% trial versus 64% nontrial; $P =$ NS).

The majority of both trial and nontrial participants believed that HIV-positive patients should be included in studies of pandemic influenza vaccines (65% versus 53%; $P < 0.001$); most HIV-positive adults surveyed report willingness to participate in a clinical trial of a pandemic influenza vaccine (86% trial versus 51% nontrial; $P < 0.0001$). The group currently participating in a trial was less concerned about the need for extra blood tests, extra clinic visits or side effects than the nontrial group (16%, 16% and 38% versus 26%, 26% and 52%, respectively; $P < 0.005$). Both groups reported a strong desire to help other people and to be protected from pandemic influenza (Table 2).

TABLE 1
Demographics of participants from Canadian Institutes of Health Research Canadian HIV Trials Network (CTN) centres and from CTN trial 237

Demographic	Nontrial participants, %	Trial participants, %	P
Total, n	312	298	
Age, years			
18-24	2	2	NS
25-34	7	7	NS
35-44	32	30	NS
45-54	38	42	NS
55 or older	21	19	NS
Education			
Less than high school	10	8	NS
High school	43	46	NS
Bachelor's degree	23	22	NS
Master's degree	6	4	NS
PhD	0.60	3	NS
Other	18	16	NS
Sex			
Male	84	88	NS
Received flu shot			
Yes	83	83	NS
Plan to receive flu shot			
Yes	89	99	0.0001

NS Nonsignificant

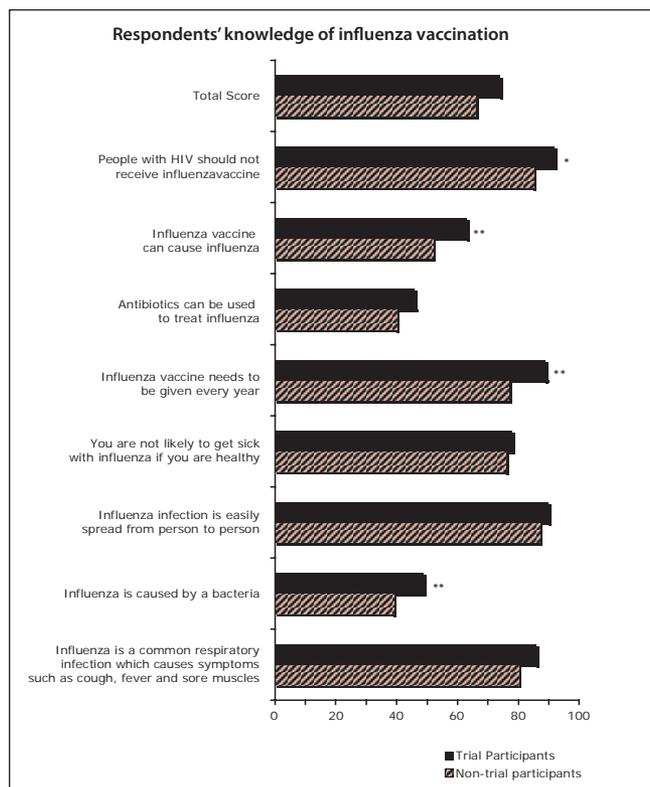


Figure 1 The percentage of respondents that answered the question correctly. *P<0.05 **P<0.01. Participants recruited from Canadian Institutes of Health Research Canadian HIV Trials Network (CTN) centres (nontrial participants) versus those from CTN trial 237 (trial participants)

Univariate (not shown) and hierarchical binary logistic regressions were performed to determine predictors of willingness to

TABLE 2
Percentage of respondents that agree or strongly agree with the question (selected questions only)

Question	Nontrial participants, %	Trial participants, %	P
Trial attitudes			
Will participate in a future trial	51	86	0.0001
Concern about side effects	52	38	0.001
Need for extra clinic visits	26	16	0.002
Need for extra blood tests	26	16	0.001
Fear of needles	12	7	0.03
Desire to protect myself from pandemic flu	57	72	0.0001
Desire to help other people	52	75	0.0001
Vaccine attitudes			
Receiving a flu shot is important to me	64	76	0.001
I can get seriously ill from the flu shot	8	2	0.003
I am able to decide whether or not I receive a flu shot	70	72	0.5
People with HIV should receive a flu shot every year	61	71	0.01
I can get seriously ill if I get influenza	45	42	0.5
Pandemic attitudes			
People with HIV are at higher risk of severe illness from pandemic flu than people without HIV	44	43	0.5
If I was offered a vaccine to prevent pandemic flu, I would receive it	64	69	0.1
Inventing a vaccine to prevent pandemic flu is important	74	76	0.2
People with HIV should be included in studies testing new flu vaccines	53	65	0.001
If there is not enough pandemic flu vaccine for everyone, people with HIV should be a priority to get it first	27	31	0.1

The χ^2 test was used to find differences between participants recruited from Canadian Institutes of Health Research Canadian HIV Trials Network (CTN) centres (nontrial participants) versus those from CTN trial 237 (trial participants)

receive seasonal influenza vaccine (Table 3). Self-reported prior receipt of influenza vaccine, willingness to receive a pandemic influenza vaccine, and the knowledge that influenza vaccine needs to be given every year were the strongest predictors of willingness to receive seasonal influenza vaccine. Overall, composite attitude scores and the perception that influenza vaccination was the norm were significantly associated with increased willingness to be vaccinated (Table 4).

Univariate (not shown) and hierarchical binary logistic models were built for willingness to participate in a pandemic influenza vaccine trial (Table 5). After adjustment for age, sex and level of education, desire to be protected from pandemic influenza, overall better knowledge, and participation in CTN 237 or in any past trial were the strongest predictors of willingness to participate in a future trial of pandemic influenza vaccines (Table 5).

DISCUSSION

Pandemic influenza is a major public health concern. On June 11, 2009, the World Health Organization declared a pandemic in response to the global spread of a novel swine-origin H1N1 influenza A virus. Since onset of the pandemic, the World

TABLE 3
Predictors of willingness to receive seasonal influenza vaccine

Item	OR	95% CI	P
Global influenza attitudes			
Composite score items (Cronbach's alpha value = 0.80)			
Receiving a flu shot is important to me			
It is best to avoid all vaccinations in people with HIV			
Getting a flu shot will protect me from getting the flu			
I can get seriously ill from the flu shot			
People with HIV should receive a flu shot every year			
As long as my CD4 count is good, I do not need a flu shot			
The flu shot poses a greater risk to people with HIV than natural infection with flu			
People with HIV are more likely to have side effects from the flu shot than people without HIV			
<i>Global attitude score</i>	16.9	6.8–41.9	0.0001
Subjective norm			
Composite score items (Cronbach's alpha value = 0.68)			
My family thinks it is important for me to receive a flu shot			
My doctor thinks it is important for me to receive a flu shot			
My friends think it is important for me to get the flu shot			
<i>Subjective norm score</i>	2.7	1.4–5.2	0.002
Perceived behavioural control			
Composite score items (Cronbach's alpha value = 0.52)			
I am able to decide whether or not I receive a flu shot			
It is my choice whether or not I get a flu shot			
<i>Perceived behavioural control score</i>	0.54	0.2–1.2	0.123

Hierarchical binary logistic regression using global attitude score, subjective norm score and perceived behavioural control score to predict willingness to receive an influenza vaccine. The model was adjusted for age, sex and education level. Internal consistency measures are provided in the table as the alpha value

TABLE 4
Perceived frequency of behaviour

Question	OR	95% CI	P
Perceived frequency of behaviour			
What percentage of people with HIV in this clinic do you think receive the flu shot each year	1.02	1.00–1.04	0.037
What percentage of people with HIV in Canada do you think receive the flu shot each year	0.99	0.97–1.01	0.58
Previous vaccine behaviour			
I got the flu shot last year	21.4	9.0–50.8	0.0001
Pandemic flu			
If I was offered a vaccine to prevent pandemic flu I would receive it	5.5	2.3–13.5	0.0001
Inventing a vaccine to prevent pandemic flu is important	1.2	0.5–2.8	0.6
If there is not enough pandemic flu vaccines for everyone, people with HIV should be a priority to get it first	2	0.6–6.1	0.23
Knowledge			
You are not likely to get sick with influenza if you are healthy	3.4	1.3–9.0	0.014
Influenza vaccine needs to be given every year	11.3	4.0–31.2	0.0001
Influenza vaccine can cause influenza	1.6	0.6–4.2	0.35
People with HIV should not receive influenza vaccine	3.9	1.4–11.0	0.01
% of correct answers	0.06	0.03–1.3	0.39

Hierarchical binary logistic regression shows significant predictors of willingness to receive the influenza vaccination. The regression was adjusted for age, sex and level of education

TABLE 5
Predictors of willingness to participate in a pandemic influenza vaccine trial

Question	OR	95% CI	P
Need for extra clinic visits	0.86	0.3–2.5	0.78
Need for extra blood tests	0.49	0.2–1.4	0.17
Time commitment	1.14	0.5–2.7	0.76
Extra cost (ie parking)	0.4	0.2–0.9	0.03
Fear of needles	0.49	0.1–1.5	0.19
Desire to be protected against pandemic flu	4.5	2.4–8.4	0.0001
Desire to please my doctor	1.6	0.5–5.0	0.37
Desire to help other people	2.3	1.3–4.3	0.005
Total knowledge	7.2	1.4–35.5	0.018
Previous trial behaviour			
Participating in CTN 237	5.5	3.2–9.4	0.0001
I participated in a past trial	7.1	2.9–16.9	0.0001
Pandemic influenza			
People with HIV are at higher risk of severe illness from pandemic flu than people without HIV	1.15	0.7–1.8	0.54
If I was offered a vaccine to prevent pandemic flu I would receive it	1.9	1.2–3.1	0.008
Inventing a vaccine to prevent pandemic flu is important	1.43	0.8–2.4	0.205
People with HIV should be included in studies testing new flu vaccines	2.1	1.3–3.2	0.002
If there is not enough pandemic flu vaccines for everyone, people with HIV should be a priority to get it first	1.2	0.7–2.0	0.422

Hierarchical binary logistic regression shows significant predictors of willingness to participate in a pandemic influenza trial. The regression was adjusted for age, sex and level of education. CTN Canadian Institutes of Health Research Canadian HIV Trials Network

Health Organization has reported 399,232 laboratory-confirmed cases of pandemic influenza H1N1 2009 and over 4735 deaths reported (13,14). At the time of writing, there have been 83 deaths reported in Canada. Notably, the majority of cases in the current pandemic have occurred in young adults with minimal comorbidities and the case fatality rate in this group has substantially exceeded previous seasons.

In Canada, prelicensure clinical trials of pandemic vaccines involved relatively small numbers of healthy children and adults. The rapid implementation of postmarketing vaccine clinical trials in special populations is an essential component of the Canadian government's pandemic preparedness plans.

Studying candidate pandemic influenza vaccines in immunocompromised patients will be essential, especially with the use of an adjuvant in the current H1N1 vaccine. Patients who are immunocompromised are at greater risk of morbidity and mortality from pandemic influenza, so understanding the efficacy of the vaccine in this group is critical (2). HIV-positive patients represent a prototypical immunosuppressed group that can serve as a model for studying the immunogenicity and efficacy of a pandemic influenza vaccine. The CIHR CTN, comprised of academic centres across Canada, in collaboration with pandemic vaccine research groups such as the CIHR/Public Health Agency of Canada Influenza Research Network is well positioned to rapidly implement pandemic influenza vaccine clinical trials in HIV-positive patients in the early postmarketing period. This study, conducted before the onset of the current pandemic, sought to better understand the

knowledge and attitudes of Canadian adults with HIV regarding seasonal and pandemic influenza and influenza vaccines, and to identify facilitators and barriers to participation of this group in vaccine clinical trials to inform the development and rapid implementation of pandemic influenza vaccine trials when needed. Clearly, with the subsequent declaration of a pandemic, this effort has become increasingly urgent.

Overall, our results suggest that influenza vaccine uptake among Canadian adults with HIV is quite high, with a self-reported immunization rate of 83% among trial participants. This uptake rate is considerably higher than that reported in the general population in Canada (34%) and in the over 65 year old population in Canada (74%) (14). As predicted by the Theory of Planned Behaviour, the theoretical framework upon which this survey was based, the strongest predictor of willingness to receive an influenza vaccine was having received it in the past (OR 21.4, 95% CI 9.0 to 50.8, $P < 0.0001$) (7-10). When composite scores were created for global attitudes towards influenza ($\alpha = 0.80$) and entered into a hierarchical binary logistic model, an overall positive attitude toward influenza was shown to be a predictor of willingness to receive the vaccine (OR 16.9, 95% CI 6.8 to 41.9, $P < 0.0001$). Participants who believed that the influenza vaccination was generally accepted among their peer group and generally accepted by most people (subjective norm score $\alpha = 0.68$) were more likely to report willingness to receive the vaccine (OR 2.7, 95% CI 1.4 to 5.2, $P = 0.002$). Important modifiable knowledge gaps were identified among participants, which are likely to impact vaccine uptake. The belief that influenza is a treatable bacterial infection and that the influenza vaccine can cause influenza were widely held, even among trial participants who had just participated in an informed consent discussion. Overall, poor knowledge scores were associated with less willingness to be vaccinated, suggesting that educational campaigns addressing these knowledge gaps could positively impact vaccine uptake in this population. Likewise, our data suggest that educational campaigns that recognize and capitalize on the strength of the perception of influenza vaccination as the subjective norm in this population could positively impact uptake rates.

Overall, more than one-half of respondents believed that HIV-positive patients should be included in trials of new vaccines, and two-thirds would receive a pandemic vaccine if offered one. Over 68% of respondents reported that they would be willing to participate in a clinical trial evaluating the safety and efficacy of a pandemic influenza vaccine. As expected, the strongest predictor of willingness to participate in a future trial of pandemic influenza vaccine was prior participation in a clinical trial (OR 7.1, 95% CI 2.9 to 16.9, $P < 0.0001$). Willingness to receive a pandemic influenza vaccine and belief that people with HIV should be included in clinical trials of new vaccines also independently predicted willingness to participate in a pandemic

vaccine trial. Interestingly, most respondents did not believe that people with HIV are at higher risk of severe illness due to pandemic influenza than people without HIV, and most did not believe that HIV-positive patients should receive priority if pandemic vaccine supplies are limited. Despite this, desire to be protected from pandemic influenza was also a strong motivator for participation in pandemic vaccine trials. Other studies have examined the risk perception of the public during and after major infectious outbreaks such as severe acute respiratory distress syndrome and avian influenza (H5N1) (15-18). It has been shown that perception of risk increases during an outbreak and is maintained even two years after the outbreak is over. Increased perception of risk during these outbreaks led to greater adherence to recommended disease prevention strategies (18). Given the current pandemic and media coverage of the impact of the pandemic, it is likely that HIV-positive Canadian adults may perceive themselves to be at more risk from pandemic influenza than when the study was performed, suggesting that desire for protection from infection might be an even stronger motivation now. Thus, our results may underestimate the proportion of individuals who would receive a pandemic vaccine if offered and the proportion that would be willing to participate in clinical trials of pandemic vaccines.

Several barriers to participation in a pandemic vaccine clinical trial were identified. More than one-third of participants reported concern about side effects to be a barrier to participate in a pandemic vaccine trial. Less frequently reported barriers included the need for extra clinic visits and blood tests, costs associated with participation, and fear of needles. Interestingly, only concern about extra costs associated with trial participation independently predicted unwillingness to participate. Ensuring pandemic vaccine trials require as few visits and extra blood tests as possible, ensuring that as much safety information as possible is made available to participants during the informed consent process and having systems in place to reimburse participants for out-of-pocket expenses is likely to improve willingness to participate among this population.

CONCLUSION

The H1N1 influenza A outbreak has been classified at level 6. Vaccines have been developed; thus, it is essential to be prepared to implement rapid clinical trials in key groups of patients. The CTN represents a system that is well positioned to implement these trials. The HIV-positive population is largely willing to participate in pandemic influenza vaccine trials. Several factors to increase vaccine uptake and trial participation in HIV positive patients have been identified.

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