Déterminants à la participation ou non à un essai vaccinal préventif

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RESUME

La mise au point de nouveaux vaccins reste cruciale, notamment dans le contexte des épidémies dues à des pathogènes émergents et de la lutte contre la résistance aux antibiotiques. Malgré l'augmentation du nombre d'essais vaccinaux en cours de réalisation, le développement clinique des vaccins prend du temps et coûte cher. Optimiser le recrutement dans ces essais est donc primordial. Au sein du Centre d'Investigation Clinique axe Vaccinologie labellisé INSERM du CHU de ST ETIENNE, nous sommes confrontés aux difficultés à recruter dans ce type d'essais. Aux craintes liées à la participation à la recherche clinique, s'ajoute probablement le phénomène de défiance envers les vaccins. Le but de ce travail de thèse a donc été d'identifier les barrières et motivations à la participation à un essai clinique vaccinal. Dans un premier temps, les déterminants à la participation à un essai vaccinal préventif décrits dans la littérature ont été synthétisés. L'altruisme et l'indemnisation financière ont ainsi été identifiés comme facteurs motivants principaux et la peur des effets secondaires et le design de l'étude comme les principaux freins. Toutefois les études publiées portaient sur un petit nombre de vaccins, beaucoup étaient des vaccins hypothétiques et peu d'études se sont intéressées au rôle et aux attitudes des médecins référents.

Nous avons donc étudié l'attitude des praticiens référents face à leur patient qui s'est vu proposer de participer à un essai vaccinal préventif. Les médecins référents se révèlent être peu informés quant à la recherche clinique en général et aimeraient avoir plus d'informations au préalable afin de donner un avis objectif au patient. Nous avons aussi étudié les barrières et motivations des personnes approchées pour participer à un essai vaccinal préventif. Nous avons pu mettre en évidence que l'altruisme était la motivation principale à participer à un essai vaccinal et qu'un avis favorable aux vaccins en général était associé au fait d'accepter de participer à ce type d'essai, facteur assez logique mais non encore démontré. De plus, la peur des effets secondaires potentiels s'est révélée être le frein principal à la décision de participer.

L’incitation financière, motivation chez les plus jeunes, était un frein à la participation chez les personnes plus âgées. Enfin, la qualité de l’information donnée au participant potentiel par le médecin du centre de recherche est cruciale et renforce l’importance de partager l’information avec le médecin référent du patient.

Ce travail de thèse s’inscrit dans l’effort du CIC pour optimiser et augmenter le recrutement des participants dans les essais vaccinaux préventifs, champs dans lequel peu de données sont disponibles par rapport à la recherche clinique en général. De plus, ce travail est complémentaire de travaux amorcés par le CIC concernant l’étude des déterminants psycho-sociaux de la vaccination dans la population générale.

ABSTRACT

The development of new vaccines is crucial, notably in the context of epidemics due to emerging pathogens and the fight against antibiotic resistance. Despite the increase in the number of vaccine trials being conducted, clinical development of vaccines is time consuming and expensive. Optimizing recruitment in these trials is therefore essential. Within the Clinical Investigation Center Vaccinology axis INSERM certified of the University Hospital of ST ETIENNE, we are confronted to difficulties in recruiting in this type of trial. In fact recruitement is challenged by the fear in clinical research and defiance toward vaccines. The purpose of this work was therefore initially to summarize the determinants of participation in a preventive vaccine trial reported in the literature. Altruism and financial compensation were identified as the main motivating factors and fear of side effects and study design as the main obstacles. However, data focused in few types of vaccines, mainly hypothetical ones, and provide few data about the role and the attitude of primary physicians.

We therefore studied the attitude of practitioners towards their patients who were offered to participate in this type of trial. The primary physicians declared to be little informed about clinical research in general and would like to have more information in advance in order to give an objective opinion to the patient. We also studied barriers and motivators in people proposed to participate in a real vaccine preventive trial. We highlighted that altruism was the main motivation to participate in a vaccine trial and that a favorable opinion on vaccines was associated with acceptance to participate in this type of trial. In addition, fear of potential side effects was found to be the main reason for the decision to not participate. In addition, we noted that financial incentives, which were a motivation for younger people, were a barrier to participation for older people. Finally, the quality of the information given by the physician at the research centre is crucial and reinforces the importance of sharing information with the patient's referring physician. This work is in the same line that the CIC's effort to optimize

and increase the recruitment of participants in preventive vaccine trials, field rarely explored in clinical research in general This work is part of a desire to continue the work already initiated by the CIC on the study of the psycho-social determinants of vaccine acceptance in the general population.

LISTE DES ABREVIATIONS

CIC : Centre d'Investigation Clinique

OMS : Organisation Mondiale de la Santé

ROR : Rougeole - Oreillons - Rubéole

VHB : Virus de l'Hépatite B

VIH : Virus de l'Immunodéficience Humaine

LEEM : Les Entreprises du Médicament

i-REIVAC: Innovative Clinical Research Network In Vaccinology

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

VHC : Virus de l'Hépatite C

URPS : Union régionale des professionnels de santé

CONTEXTE

La vaccination est l'un des plus grand succès de Santé Publique. Selon l'OMS, 2 à 3 millions de vie sont sauvées chaque année grâce à ce procédé [1]. Du XVIIIème siècle à nos jours, les vaccins ont permis d'éradiquer ou de diminuer l'incidence de plusieurs pathologies dans le monde (Figure 1).

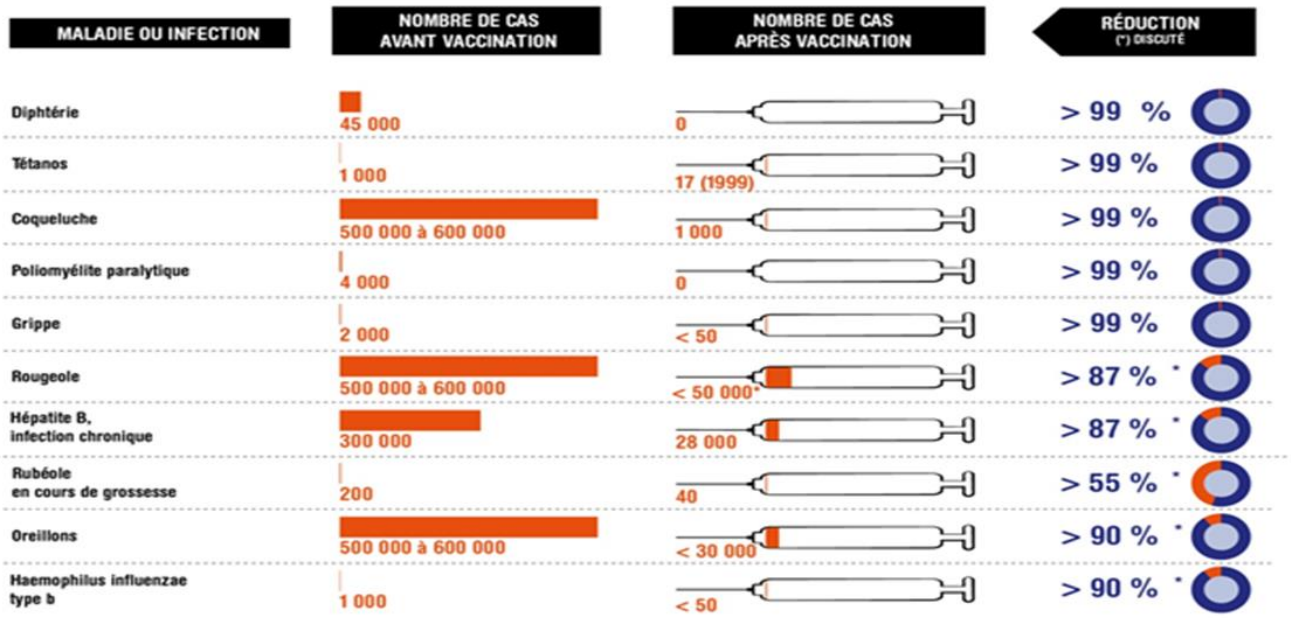

Figure 1: Impact de la vaccination sur les maladies évitables en France, Leem

Le plan d'action mondial pour les vaccins 2011-2020 établit par l'OMS a pour but de prévenir des millions de décès d'ici 2020 en assurant un accès équitable aux vaccins à travers le monde [2].

La mise au point de nouveaux vaccins reste nécessaire. C'est le cas pour lutter contre les maladies émergentes, telles que le Zika ou le Chikungunya, mais également des maladies extrêmement sévères telles que la maladie à virus Ebola [3]. L'élaboration de nouveaux vaccins est également cruciale pour combattre les maladies sans vaccin efficace à ce jour [4], et apparait comme une des stratégies intéressantes pour lutter contre l'antibiorésistance [5] et les infections associées aux soins [6]. La recherche actuelle se concentre également sur le

développement de nouveaux adjuvants, l'évaluation de nouvelles voies d'administration et de nouvelles stratégies vaccinales [7].

Cependant avant toute mise sur le marché, il est nécessaire et obligatoire de réaliser des essais cliniques [8]. Les différentes phases des essais sur des volontaires sains puis sur la population cible permettent de tester l'immunogénicité du vaccin testé, sa tolérance et son efficacité. Le succès de ces essais dépend bien sûr du vaccin lui-même mais également d'un recrutement suffisant de volontaires. En recherche clinique en général, un essai clinique sur cinq est interrompu avant la fin de l'essai et le principal motif d'interruption est l'échec du recrutement [9]. Or le temps et le coût associé au développement d'un vaccin [10] font qu'il est crucial d'atteindre un recrutement optimal dans ces essais. La France est au 4ème rang européen en termes de participation aux essais industriels mais on note une baisse de son attractivité depuis 2015 avec un déclin du nombre d'essais menés sur le territoire. Seulement 85% des centres ont atteint leur objectif de recrutement et 22% n'ont pas pu inclure de patients dans les essais (33% dans les essais de phase 1 et 2) quel que soit le domaine ou la spécialité [11].

Le recrutement de volontaires pour les essais cliniques représente ainsi un réél défi car les participants potentiels se méfient souvent des essais expérimentaux. En France, la récente polémique autour de l'affaire Biotrial de Rennes n'a fait qu'augmenter la méfiance vis-à-vis de la recherche clinique [12]. La population pense servir de « cobaye » en participant à un essai clinique, terme largement relayé par les médias [13,14]. L'histoire controversée de certaines expérimentations humaines a probablement joué un rôle [15]. Cependant, ces événements ont permis d'assurer l'itération des principes éthiques et des codes de bonne conduite pour la recherche clinique qui devrait rassurer les volontaires [8]. La difficulté à recruter, inclure et garder les patients dans les essais cliniques en général est bien connue [16,17], cependant pour les essais vaccinaux se rajoute possiblement une difficulté supplémentaire. En effet, face aux obstacles de recrutement dans les essais cliniques s'ajoute

la méfiance face aux vaccins. Dans le monde, ce geste simple de prévention est encore aujourd'hui un geste associé à bon nombre de polémiques (Rougeole-Oreillons-Rubéole (ROR) et autisme, Virus Hépatite B (VHB) et sclérose en plaques, etc…) [18,19] et on assiste à une recrudescence des mouvements anti-vaccins [20]. Les vaccino-sceptiques inondent la sphère médiatique et en particulier les réseaux sociaux. Le phénomène d'hésitation vaccinale défini comme étant le fait de retarder ou de refuser une vaccination sûre malgré sa disponibilité [21] a une influence indéniable sur les actes de vaccination dans les groupes dits hésitants [22]. Cette méfiance est également présente dans la communauté médicale et chez les professionnels de santé [23,24] et fragilise d'autant plus la couverture vaccinale dans le pays. En France, la crise de confiance vaccinale n'a donc jamais été autant d'actualité, avec en 2016, une défiance vis-à-vis de la sécurité des vaccins chez plus de 40% des français [25]. Le ministère de la santé a, depuis le 01 Janvier 2018, rendus obligatoire 11 vaccins chez l'enfant de moins de 2 ans afin de tenter rétablir la confiance en la vaccination. Les premiers résultats montrent un impact positif de l'extension de la vaccination obligatoire sur les couvertures vaccinales du nourrisson et sur l'opinion des mères quant à la vaccination [26]. Cependant il est très probable qu'il faille du temps pour rendre totalement confiance dans les vaccins.

Une étude de Cobb et coll. a évalué le niveau d'intérêt du public pour la participation à la recherche médicale en fonction du type d'étude et que les personnes soient volontaire sain ou patient. Si le public semblait intéressé pour participer à la recherche médicale, ils l'étaient d'autant plus en tant que patients plutôt que volontaires et ils semblaient être plus enclins à participer à une recherche non invasive [27]. Dans cette même étude, les patients auraient accepté à hauteur de 70 % de participer à un essai clinique sur un médicament contre seulement 59 % si le produit évalué était un vaccin [27].

En effet, le patient, dans le cadre d'un essai thérapeutique (médicament), peut avoir un avantage individuel direct (avec accès à un nouveau traitement, un suivi médical plus poussé), avec un objectif de guérison ou d'amélioration de son état de santé. En revanche, dans les essais vaccinaux préventifs, le bénéfice pour la santé individuelle n'est pas au premier plan, l'objectif premier étant de prévenir une maladie. Par conséquent, les volontaires sains et les patients pourraient avoir plus de difficultés à voir les avantages potentiels et ne s'attendent pas à améliorer leur état de santé. S'ajoute à cela l'appréhension liée aux effets secondaires potentiels dus à l'administration du vaccin expérimental et aux procédures liées au suivi des effets du vaccin en particulier au cours de la phase 1 [28].

Le CIC1408, axe vaccinologie labellisé INSERM du CHU de SAINT ETIENNE est une structure dédiée à la recherche clinique vaccinale qui, depuis 2008, participe via le réseau i-REIVAC (Innovative Clinical Research Network In Vaccinology) à de nombreux essais vaccinaux académiques et industriels nationaux et internationaux. Mieux inclure et inclure plus de patients ou volontaires sains dans ces essais fait partie des principaux objectifs du CIC. Toutefois, comme dans tous les centres ayant cette activité, il s'agit d'un défi quotidien [29]. Avoir une vision plus nette des déterminants à la participation aux essais vaccinaux nous a donc semblé nécessaire afin *in fine* d'optimiser le recrutement. Pour cela nous avons conduit une revue de la littérature et 2 travaux originaux. En effet dans un ouvrage qui traite des essais de prévention et de vaccination impliquant des volontaires sains dans le contexte du VIH, Fillieule *et coll.*, souligne que l'étude des modalités et difficultés de recrutement est « le parent pauvre du processus de mise en place d'un essai » et qu'il y a « un vrai travail à faire pour comprendre comment recruter au mieux » les volontaires » [30].

REVUE

Barriers and motivations to volunteers' participation in preventive vaccine trials: a systematic review

Revue publiée dans Expert Review of Vaccines, Mai 2017

Nous avons réalisé une revue de la littérature qui a permis de synthétiser les déterminants à la participation à un essai clinique vaccinal préventif décrits dans la littérature. Nous avons donc réalisé une recherche documentaire selon la procédure prescrite par les directives PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [31], sans limite de temps, en faisant référence aux termes suivants : « recrutement », « vaccin » et « essais ». Pour l'affiner, nous avons également utilisé les termes « barrières », « motivations », « participation », « volonté », « volontaires » avec différentes combinaisons. Sur les 50 articles sélectionnés, 39 portaient sur des essais cliniques de vaccins contre le VIH. L'identification de ces facteurs est ayant été largement examinée dans les études vaccinales contre le VIH [32–34], nous avons donc choisi de n'utiliser que les revues sur le sujet et les derniers articles publiés. Nous avons pu extraire des raisons communes mais aussi spécifiques à certaines pathologies.

Ce travail montre que les motivations principales communes étaient l'altruisme et l'incitation financière et les causes de refus communes principales étaient la peur des effets secondaires et le design de l'étude (nombre de visites, durée de l'étude, examens prévus…). En revanche, nous avons pu extraire des déterminants spécifiques à certaines pathologies dites « controversées » comme la peur de contracter le virus par le vaccin et la peur d'être discriminé dans les études contre le VIH, le VHC ou encore le papillomavirus.

EXPERT REVIEW OF VACCINES, 2017
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REVIEW

Barriers and motivations to volunteers' participation in preventive vaccine trials: a systematic review

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ABSTRACT

Introduction: The recruitment of volunteers in preventive vaccine trials (PVT) is a challenge, since vaccine hesitancy and debates on vaccines are combined to usual difficulties of enrollment in clinical trials.

Areas covered: Current knowledge of the reasons leading to the volunteers' participation or non-participation in PVT mainly focuses on data from preventive HIV vaccine trials. A systematic PubMed search was conducted using PRISMA guidelines to identify articles or reviews that reported barriers and motivations to participation in PVT regardless of the targeted disease or population.

Expert commentary: In view of the barriers and motivations reviewed here, improvements in recruitment could be made through a better explanation of the prevented disease, of the expected individual and collective benefit and of all ethical protective principles associated to the trials. Use of decision aids as well as patient and public involvement may improve given information and may enhance comprehension of participants and their participation in PVT. Further prospective and interventional studies are needed to analyze if these leads may improve acceptation level in PVT.

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KEYWORDS
Vaccine; clinical trials; motivations; barriers; participation; recruitment

1. Introduction

Immunization against infectious diseases has saved more lives than any other public health intervention and is therefore one of the greatest and cost-effective successes in modern medicine [1]. While vaccines have provided benefits, the primary effectiveness of new vaccination programs depends on the public acceptance of vaccines [2]. Indeed, the history of vaccination has created social issues since the eighteenth century with variolation detractors [3]. More recently, the hepatitis B immunization programs in 1995 [4], the measles vaccination in the United Kingdom [5,6], and the 2009 influenza A(H1N1) episode have contributed to the increase of negative attitudes toward vaccination globally [7], and notably in France [8]. Nowadays, the media play a large role in disseminating and sensationalizing objections to vaccines [9]. This excessive media coverage of the supposed side effects of vaccines probably overshadows the risk posed by vaccine preventable infectious diseases.

The development of new vaccines is, however, crucial to prevent infectious diseases from remaining a leading cause of mortality [10]. For this purpose, the achievement of clinical trials in human volunteers followed by studies in the target population is necessary prior to vaccine licensure [11]. The recruitment of volunteers in clinical trials is nevertheless challenging, as potential subjects are frequently suspicious about experimental testing. They fear being considered as guinea pigs by participating in clinical research. Controversial historical human experimentations such as the Tuskegee experiment [12] or the tuberculosis vaccine experiment in Lübeck have probably had a role. However, these events have ensured the iteration of ethical principles and codes of good practice for clinical research that may reassure volunteers.

If the public seems to remain interested in participating in medical research, this appears to be preferably for non-invasive studies [13] and by patients rather than by healthy people. Indeed, the patient, in a therapeutic trial (drug or vaccine), may have a direct individual benefit (with access to a new treatment, a greater medical monitoring), with an objective of cure or improvement of their health condition. By contrast, in preventive vaccine trial (PVT), individual health benefit is not at the forefront, the primary objective is to prevent from a disease. Therefore, healthy volunteers may have more difficulty in seeing the potential benefit for themselves and do not expect to improve their health condition. Moreover, local side effects due to needle administration of tested vaccine are present and inconvenient procedures are required (multiple blood samples, several visits, and test for adverse effects) particularly in phase 1 studies [14]. In vaccine trials, general suspicion against vaccines is added to the usual mistrust of clinical research and contributes to difficulties in finding volunteers to participate in clinical vaccine trials [15] beyond usual difficulties and challenges experienced in clinical trials for recruitment, enrollment, and retention of study participants [16,17].

We will review here the barriers and motivations to volunteers' participation in PVT. All but one article deal with vaccine trials completed before marketing authorization. Therefore, most of them are based on the willingness to participate in a hypothetical trial rather than an actual trial. Our aim, without

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focusing on HIV vaccine trials though, is to identify the common and specific barriers as well as the motivations which influence potential volunteers whether to take part or not in PVT. Through this research, we aim to facilitate recruitment in this type of clinical trial.

2. Methods

With the aim of identifying which reasons affect whether volunteers participate in PVT, we first conducted a literature search according to the procedure prescribed by the PRISMA guidelines [18], with no time limit, cross-referencing the following terms: 'recruitment', 'vaccine', and 'trials'. Our method of research is outlined in Figure 1. In 2016, M.D. and E.B.N. independently searched in the PubMed database and Google Scholar to identify articles that reported barriers and motivations to participation in PVT in various populations. This search yielded 195 references. To refine it, we also used the terms 'barriers', 'motivations', 'participation', 'willingness', 'volunteers' with different combinations. Inclusion criteria were: (1) PVT in Organization for Economic Co-operation and Development (OECD) and non-OECD countries; (2) articles containing information on motivators or barriers to participation in hypothetical or actual vaccine trials; (3) hypothetical or actual willingness; (4) all phases for actual vaccine trials; (5) participants over 15 years old; (6) English or French. For articles dealing with both adults' and children's responses, only adults' data were considered. Reference lists in the first set of articles were also scanned to identify potentially relevant papers that could be included in our review. Using this second search strategy, 50 articles matching our subject were identified. In order to avoid misunderstandings, two people (M.D. and A.G.B.) studied the papers and an extraction was compiled. Out of the 50 articles retrieved, 39 dealt with vaccine trials about immunization against HIV. Willingness to participate in HIV PVT has been widely investigated, and motivations and barriers in this context largely reviewed. We chose to use reviews about the subject rather than the original articles. In order to be up-to-date with motivations and barriers to participate in HIV PVT, articles published after the reviews were included only if they brought new elements about willingness to participate in HIV vaccine trials. We extracted information about motivations and barriers and in order to summarize findings, the term 'shared' will be used here to present barriers or motivations common to different studies and vaccines.

3. Motivations and barriers to participation in PVT

We included in this review 17 articles (see Figure 1). For HIV PVT, three reviews [19–21] and three articles were included [22–24]. The remaining articles referred to preventive vaccines against human papillomavirus (HPV) [16,25,26], hepatitis C virus (HCV) [27–30], influenza virus [31–33], and dengue [34]. Exhaustive research was performed to retrieve references about the motivations or barriers to participation in vaccine clinical trials for other diseases such as hepatitis B, zoster, malaria, and yellow fever but no relevant reference was found. Analysis of the common and specific vaccine trial barriers and motivations will be presented here.

3.1. Shared barriers to participation in PVT

Table 1 shows the barriers to participation in vaccine trials according to the type of vaccine, geographical area in which the studies were performed and the study phase [19,21,23–30,32–34]. We focused on the common barriers found in different studies regardless of the type of vaccine and we summarized them in Table 2.

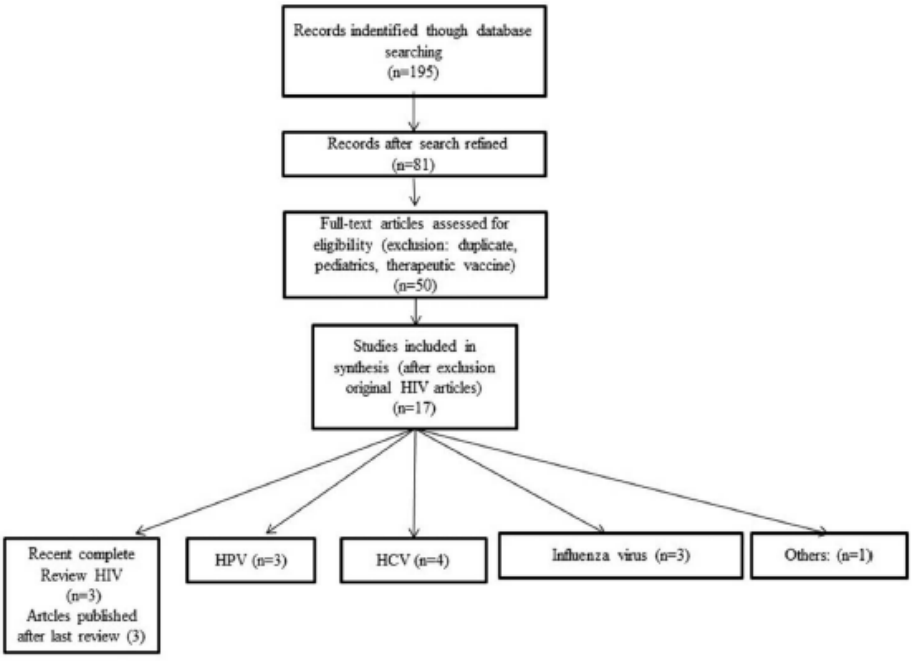

Figure 1. Prisma study selection.

Table 1. Barriers cited in the review.

Ref.	Review/article	Disease	Population Location	Phase Type of questionnaires Amount of remuneration	Barriers
[34]	Pérez-Guerra *et al.*	Dengue	Adults and Children Porto Rico	Hypothetical efficacy vaccine trial Key informant interview Not available	Lack of trust in new vaccines and vaccine trials procedures Fear of developing dengue and side effects from the vaccine Lack of information about candidate dengue vaccines
[25]	Gudmundsdottir *et al.*	Human papillomavirus (HPV)	Women 18–23 years old Island	Hypothetical vaccine trial Pilot interviews and 163 mailed questionnaires Not available	Dislike gynecologic examination Vaccine is being testes Do not consider themselves at risk Do not think their participation makes any difference
[26]	Hoover *et al.*	HPV	60 Women 15–28 years old U.S.A.	Hypothetical vaccine trial Interviewers Not available	Study design Time commitment Gender of pelvic examiner, comfort of/embarrassment about pelvic exams Opinions of participant's network members
[33]	Allsup *et al.*	Influenza	Healthy individuals aged 65–74 years U.K.	Phase 3 1173 postal questionnaires Not available	Do not want to be involved in a research project Concerned about side effects. Egg allergy Do not require the vaccine (If required, would rather the general practitioner gave the vaccine) Already received the vaccine this year. Illness requiring vaccination out of the study Previous bad reaction to the vaccine Unable to attend any of the sessions, Unable to get to general practice surgery Already involved in a clinical trial Fear of needles/dislike of injections Doubts about vaccine efficacy
[32]	Kiberd *et al.*	Influenza	610 Adults VIH positive Canada	Hypothetical vaccine trial Self-administered questionnaires Not available	Fear of needles/dislike of injections Need for extra clinic visits or blood tests Concerned about side effects
[27]	Park *et al.*	Hepatitis C virus (HCV)	113 PWID[a] seronegative for HCV Australia	Hypothetical vaccine trial Structured interview $30AUD to respond	Vaccine safety, side effects; e.g. contracting HCV from the candidate vaccine Time constraints, home duties, travel time
[29]	Levy *et al.*	HCV	67 participants, <30 years, high risk HCV seronegative drug users U.S.A.	Vaccine efficacy trial Interviewer-administered questionnaires $10 at screening $20 at results visit	Study length Trust to explain safety, trust to side effects
[30]	Maher *et al.*	HCV	Negative VHC People who inject drugs Australia	Feasibility study Ethnographic fieldwork $30–$50 per visit (proposed remuneration for trial participation)	Pragmatics obstacle: fear of needles, venipuncture and collection of sera. Distance Lack of remuneration for screening (not for all participants = screening procedures not clear) Uncomfortable with being asked for several forms of follow-up information, particularly home or mailing addresses Recent cessation of injecting drug Being adamant about injecting drugs again
[28]	Treloar *et al.*	HCV	26 PWID[a], 20–61 years old Australia	Vaccine efficacy trial Interview $30AUD to respond	Distrust of pharmaceutical companies Concerns of being surveyed and perceived as expendable 'guinea pigs' for experimental purposes

(*Continued*)

Table 1. (Continued).

Ref.	Review/article	Disease	Population Location	Phase Type of questionnaires Amount of remuneration	Barriers
[19]	Dhalla *et al.*	HIV	Compared OECD and non-OECD	Phase 3 Not available Not available	Personal risks: vaccine safety, 'guinea pigs', distrust of institutions Social risks: discrimination Personal costs: fear needles, logistic Social costs: family commitments Misconceptions: contracting HIV by vaccine, 'injury/death secondary to an HIV vaccine'
[21]	Hurley-Rosenblatt *et al.*	HIV	Not available	Phase 1, 2, 3 Not available Not available	Safety concerns: contracting HIV from the vaccine, vaccine safety, potential harm, negative side effects Fear or mistrust, concerns or misunderstandings about study design Discrimination and/or social risks Opposition to animal testing, not being a believer in modern medicine Social consequences relating to trial participation, the vaccine might not work, developing a positive HIV test Unpleasant experience. increasing high-risk behaviors
[23]	Yoon *et al.*	HIV	Male to female transgender, 18–55 years, HIV negative or unknown U.S.A.	Hypothetical vaccine trial Two hour focus group held (semi-structured open-ended questions) $30 for their time to respond	Stigma Unaware and misinformed Perceived themselves as being excluded from research Mistrust of the scientific community (pervasive fear and myths about scientific research) Perceived possible vaccine side effects
[24]	Chakrapani *et al.*	HIV	82 participants, low socioeconomic MSM and MSM community leaders in Chennai and Mumbai, 18 years and above	Hypothetical vaccine trial Focus group, semi-structured interview guide	Stigma, discrimination, family rejection, financially dependent family members Level of confidentiality Difficulties in comprehension Concern about excessive compensation Fear of side effects, concerns about vaccine-induced infection

[a]PWID: people who inject drugs.

Table 2. Common barriers to participating in a vaccine trial.

	References
Research	[25,32,33]
Do not consider themselves at risk	
Do not want to participate in a research program	
Medical procedures	[19,21,25,26,30,32,33]
Fear of needles/injections, dislike blood samples, dislike gynecologic exam	
Study design	[21,25,26,29,32,33]
Numbers of exams/extra visits, duration of the study	
Pragmatic obstacles	[19,21,26,27,30,33]
Time commitment, travel time, home duties, distance	
Vaccine safety/efficacy concerns	[19,23–25,29,32–34]
Side effects short and long-terms, vaccine safety and efficacy, risk contracting pathogenic agent from the vaccine	

3.1.1. Fear or dislike of medical procedures

Seven out of 13 articles reported fear or dislike of medical procedures as barriers. Indeed, medical procedures (blood samples or medical exams) included in trials caused concerns to many volunteers. Potential participants seemed reluctant to participate in a study in where clinical and biological examination could induce discomfort or embarrassment. For example, in HPV vaccine trials, women stated that they disliked pelvic examination, which might cause them discomfort or embarrassment [25,26]. In the same way, the fear of needles in blood sampling and vaccination was frequently reported [19,21,30,32,33]. This last barrier was also reported in studies about vaccination acceptability in general [16]. Surprisingly, it was the main reason for reluctance given by intravenous drug users in HCV vaccine trials [30], though it appears to be a paradox.

These reasons have also been reported, in other non-vaccine types of clinical trials, to decrease participation in the trials [35,36].

3.1.2. Study design, pragmatic obstacles

Six studies reported that study design was also a barrier. For example, the length of study is frequently reported as a barrier [19,29]. The degree of acceptation also depended on the frequency of examinations [19,26,32,33]. In the same way, pragmatic obstacles can limit recruitment; most people did not want their participation in a clinical trial to impact on their personal lives and become a restriction. Therefore, logistical factors such as time commitment [19,21,26,27], home duties [27], travel time [27], or distance between home and hospital [30] represented deterrents for enrollment. These latter factors were also found to contribute to non-participation in non-vaccine clinical trials [36–38].

3.1.3. Fear about side effects and safety

The literature showed mixed degrees of concern about side effects in whether people participated in studies or not. Eight papers reported fear of side effects as an obstacle to participation in vaccine clinical trials. Regarding the influenza vaccine, the fear in healthy older people was usually related to a previous adverse reaction [33]. Fear of side effects was mentioned as a reason for not participating in most clinical immunization trials except for the HPV vaccine. In Chakrapani *et al.*'s paper, some participants expressed willingness to participate only with assurance of no side effects [24]. A possible lack of efficacy of the studied vaccine was also mentioned as a reason for non-participation [19,21,23,25,33].

General safety concerns (regarding side effects in the short- and long-term, safety, and efficacy of the product …) were reported too as barriers in cancer trials [39] and in early phase non-vaccine clinical trials [40].

3.1.4. 'I don't consider myself at risk'

Curiously, this reason was rarely reported. It was only in HPV and influenza vaccine trials that medically eligible persons said they did not want to participate in the research project and were not concerned with the subject [25,32,33]. Indeed, women who did not want to participate in HPV vaccine trials did not consider themselves at risk or did not believe that their participation could make a difference [25]. Some older people felt that they did not need the influenza vaccine or preferred to be vaccinated by their GP [33].

3.2. Shared motivations among volunteers participating in PVT

Eleven papers reported on the motivations for participating in vaccine trials, and are detailed in Table 3 [20,22,24–28,30–32,34]. One article reported motivations about actual vaccine trials [20] while the others were based on hypothetical vaccine trials.

We identified three types of motivations that were shared regardless of the type of vaccine, and we summarized them in Table 4.

3.2.1. Altruism

Altruism was the most cited motivation for participation [20,22,24–28,30–32]. In these studies, a strong desire to help other people and cooperate for research was frequently found. In Spain, 42.6% of people were willing to collaborate with scientists [31]. In Canada, HIV positive adults agreed to receive the pandemic influenza vaccine because of a desire to help other people [32]. In Iceland, eligible women accepted the HPV vaccine in order to allow other people to benefit from it [25] and this was also cited as a key-motivating factor for HPV clinical trial participation in the United States [26].

Altruism was cited as the main motivation regardless of surveyed population groups. Indeed, it was the most important motivation in the OECD as well as in non-OECD countries [24] although with some differences whatever phase of the trial (early vs. phase 3) was considered [20]. In OECD countries, altruism was described as an interest to help medical research whereas a desire to help the world and society in general was prevalent in non-OECD countries [20]. During an avian influenza vaccine trial, contributing to the progress of science was found to be a stronger motivation for people over 60 than in younger people [31]. Altruism was also reported as a major motivator for participation in non-vaccine trials [35] as well as in blood donations that relied on volunteers [41].

3.2.2. Financial benefits

Eight studies reported that financial compensation was a real motivation for becoming volunteer. 'Cash payment' was a great motivator [20,24,26–28,30,31,34]. In poorer populations,

Table 3. Motivations reported in the literature.

Ref.	Review/article	Disease	Population Location	Phase Type of questionnaire Amount of remuneration	Motivations
[34]	Pérez-Guerra *et al.*	Dengue	Adults and children Porto Rico	Hypothetical vaccine trial Key informant interview Not available	Altruism Protection from dengue Free medicine intention Compensation for transportation and participation
[25]	Gudmundsdottir *et al.* [24,25]	HPV	Women 18–23 years old Island	Hypothetical vaccine trial Pilot interviews and 163 mailed questionnaires Not available	Other young people may benefits for their own benefit Fear of later acquiring cervical cancer Fear of later acquiring HPV infection Fear of later acquiring genital warts Fear of already being infected by HPV
[26]	Hoover *et al.*	HPV	60 Women 15–28 years old U.S.A.	Hypothetical vaccine trial Interviewers Not available	Monetary payment altruism
[31]	Costas *et al.*	Influenza	364 Healthy subject ≥18 years	Phase 3 Self-administered questionnaires 100€ per visit	Collaboration with science, obtaining information on the studied disease Economic reasons Protection against influenza, health benefits Influence of other people related with the study, trusting if specific physicians
[32]	Kiberd *et al.*	Influenza	610 Adults VIH positive Canada	Hypothetical vaccine trial Self-administered questionnaires Not available	Desire to protect myself from pandemic flu Desire to help other people Will participate in a future trial
[27]	Park *et al.*	HCV	113 PWID seronegative for HCV Australia	Hypothetical vaccine trial Structured interview $30AUD to respond	Altruism Health benefits Financial benefits Knowledge benefits Depending on the trial design and vaccine characteristics
[30]	Maher *et al.*	HCV	Negative VHC PWID[a] Australia	Feasibility study Ethnographic fieldwork $30–$50 (proposed remuneration for trial participation)	Financial remuneration Altruism Access to screening
[28]	Treloar *et al.*	HCV	26 PWID[a], 20–61 years old Australia	Vaccine efficacy trial, phase 3 Interview $30AUD to respond	Financial incentives Appeals to altruism Addressing concerns about trust and surveillance
[20]	Dhalla *et al.*	HIV	OECD and non-OECD countries	Early phase, 2b and 3 Several types: interviewer, mailed, hand-delivered, face-to-face, etc. Not available	Macrosocial motivators in common = altruism Personal motivators (psychological in OECD, psychological and physical in non-OECD) Financial benefits
[22]	Tarimo *et al.*	HIV	Police officers recruited after a series of sensitization meetings and general education sessions about HIV/AIDS and HIV vaccine trials Tanzania	Phase 1/2 Paper questionnaires (two parts) Not available	Altruism To be a role model to others Explanations about nature of the HIV vaccine studies provided by researchers To get more knowledge and education about HIV/AIDS or vaccine trials Medical check-ups, opportunity to know their health status To cooperate with research team (men) To get personal protection against HIV infection through the trial Overwhelming HIV epidemic Experiencing death of a close member of the family due to AIDS Others: free medical treatment, insurance, testing the strength of the vaccine in their body

(*Continued*)

Table 3. (Continued).

Ref.	Review/article	Disease	Population Location	Phase Type of questionnaire Amount of remuneration	Motivations
[24]	Chakrapani *et al.*	HIV	82 participants, low socioeconomic MSM and MSM community leaders in Chennai and Mumbai, 18 years and above	Hypothetical vaccine trial	Altruism
				Focus group, semi-structured interview guide	Monetary compensation Confidence in any government sponsored vaccine trial

*PWID: people who inject drugs.

Table 4. Common motivations to participating in a vaccine trial.

	References
Altruism	[20,22,24–28,30–32,34]
Help research, protect other people	
Financial benefits	[20,24,26–28,30,31,34]
Monetary payment	
Personal benefits	[20,22,25,27,31,32]
Health benefits, protect from virus	

financial assistance was essential [20,24,28,31] and a stronger motivation for young people than older people [31]. For others, compensation was legitimate in view of the procedures or the length of the study [26]. As described in Table 3, financial compensation was not always specified in studies. When available, amounts ranged between USD 10 and USD 110 per visit. These data were in accordance with average amounts offered in clinical trials in general [42]. Financial reward is also a frequent motivator reported in other non-vaccine trials [40] and is the main motivator for participation in phase 1 studies, although less frequent in healthy volunteers with a higher income and education level [14].

3.2.3. Personal benefits

One motivator to participation in a PVT could be fear of the disease potentially prevented by the vaccine. A study in Sierra Leone just after epidemic Ebola virus showed that 60% of the people interviewed were willing to be study subjects if Ebola vaccine trials were conducted in their communities [43]. In our review, six papers reported that participation in a PVT trial was considered as personal benefit. Despite not being top priority for participation, it was cited as a motivation in a HPV trial [25], as well as getting protection against pandemic influenza [31,32] and dengue [34]. Participants though they would be protected from the targeted disease. In this case, motivation is similar to what we can witness with patients who participate in a therapeutic trial [44]. However, social benefits and money outweighed the personal benefit of immunization [20,26–28,30,31,34]

3.3. Specific motivations and barriers by vaccine

Beyond the shared motivations and barriers, there are also specific motivations and barriers related to some target diseases such as HPV, HCV, or HIV.

3.3.1. Specific barriers

In HIV vaccine trials, fear of contracting HIV from the vaccine was mentioned as a barrier to participation [19,21,24]. The same fear of developing the disease from the vaccine was also reported in HCV [27] and dengue vaccines [34]. This fear stemming from long-standing distrust of medical research and correlated with controversial experiment [45,46] emphasizes that safety issues were predominant concerns, also present in HIV therapeutic vaccine trials [47]. Such fear is generated by misunderstanding, theories and mental models of vaccines like, for instance, including a small dose of a pathogen to train the immune system [46], and it can prove hard to vanish. In the same way, it is also difficult to explain and to reassure people about the risk that 'vaccine induces seropositivity' for HIV [19] as described in OECD and in non-OECD countries [24].

Indeed, fear of becoming anti-HIV positive after participation to a HIV trial is also a barrier that needs to be addressed by the sponsor and communicated to insurance companies, social welfare, and health companies in order to avoid problems with the volunteers. Social risks such as discrimination or stigmatization [19,21,23,24] were reported by volunteers in HIV vaccine trials, who had concerns about psychological reactions from their family, friends or others. People fear stigmatization because of enrollment in a trial and likelihood of being viewed as high-risk by their partners.

In HCV vaccine trials, previous intravenous drug users feared that they would be reminded of their past drug history [30]. Moreover, people who inject drugs did not feel comfortable in providing a phone number or several forms of follow-up information, particularly home or mail addresses, at the first visit [30].

3.3.2. Specific motivations

Most-at-risk populations for HIV contamination (men having sex with men, drug users …) seemed more likely to feel how useful it was to contribute personally to a vaccine development [21,28,30]. People at high-risk of contracting preventable diseases seemed to be interested in participating in vaccine research in order to get knowledge of the current advance in this specific area of research [20,21,27]. Altruistic reasons for participation could be motivated by family or friends, who have either lived with or died from AIDS [20]. In a study dealing with willingness to participate in a hypothetical HCV vaccine trial, 48% were very likely to encourage their drug-using peers to participate in the trial [48]. In an HCV vaccine trial for intravenous drug users, the cost of drugs led volunteers to consider the amount of compensation as a great motivation [30].

The findings of our review should be read with some caution. In particular, several sources of potential bias are inherent to the material that has been included. The majority of articles dealt with HIV vaccine trials, and it could over-represent reasons that are, in fact, specific and not common to all vaccine trials. Second, the methodology of this review was systematic rather than comprehensive, and is therefore subject to the bias of publishing and reporting. Third, only opinions of adults were considered, including the study of Pérez-Guerra *et al.* [34] (parents' opinion). Barriers related to consent and availability of parents or caregivers for dependent elderly [49] were, therefore, not studied. Motivations and barriers found in the dengue vaccine trial were however similar to adult PVT. It would be interesting to review the opinion of children in the participation in a PVT. Finally, most articles published and included in the review reported willingness to participate in potential PVT, yet not in real PVT.

4. Expert commentary

In this systematic review, we aimed to examine for the first time the shared motivations and barriers to participation in vaccine trials, without focusing on a specific vaccine. A better knowledge of these barriers and motivations will help in the recruitment of volunteers and probably in the conception of studies.

Surprisingly, the trial phase was not clearly mentioned as a barrier (early phases) or motivator (more advanced phases) in the articles reviewed here. It is, however, evident that the phase plays an important role in recruitment, and challenges raised at each trial phase influence participation in later phases [46]. Indeed, as in drug clinical trials [40], early phases of PVT are associated with more safety preoccupations [20]. It seems then necessary to inform participants and targeted population that trials need to be approved of by regulatory authorities before study initiation and are in accordance with all ethical protective principles [11]. Complete transparency in side effects is crucial to maintain confidence in volunteers [46,50]. In early phases, personal benefits might seem scarce to participating volunteers and physicians. But in advanced phases of PVT (phase 3), emphasizing personal benefits and explaining to volunteers that the trial is proposed to them because they are at risk may improve enrollment. Recently, we proposed a preventive phase 3 vaccine trial against *Clostridium difficile* to an at-risk volunteer. She refused because of her 'fear of the vaccine'. One month later, as she experienced *C. difficile* colitis, we asked her to participate in a *C. difficile* therapeutic drug trial and she accepted [personal data]. We cannot assume what decision she would have made had it been a *C. difficile* therapeutic vaccine trial. However, based on HIV vaccine trials, the willingness to participate in PVT, seems to be different to those in therapeutic vaccine trials. Despite these kinds of trials both deal with vaccines, therapeutic vaccine trials are rather similar to drug therapeutic trials, with an objective of cure for participants, i.e. patients. Personal health benefits then represented the top motivation in HIV therapeutic vaccine trial (to reduce antiretroviral treatment, avoid ART side effects, delay disease progression, etc.) [47]. This illustrates the importance of clarifying to the subject all expected personal benefits of prevention so he or she can make up their mind whether to participate or not. Similarly, the vaccine acceptability rate seems to be correlated with the rate of vaccine efficacy. Indeed, Cameron *et al.* show respondents are more than twice likely to accept a vaccine with 99% efficacy than a vaccine with 50% efficacy [51].

Another way to improve recruitment of participants in PVT is probably to explain the protocol better, to allow dialog between potential participants and investigators to ensure comprehension of the goals of the study and the targeted disease. Therefore, it is crucial to deliver optimum information about the experiment in order to gain trust in the medical team. Taking into account cultural sensitivity of targeted population seems also important, notably for a better communication as suggests by Rubicam *et al.* in HIV field [52].

Researchers involved in clinical trials should make an extra effort to confirm the volunteers' level of understanding regarding the trial and to guarantee that each of them has sufficient time to make an informed decision before participating in a clinical trial [44]. A well-known barrier to participation in trials, not only PVT but also therapeutic vaccine [47] or non-vaccine trials [53] is lack of knowledge about the trial. Fear of participation may be alleviated through extended discussion where accessible explanations of the study procedures, risks, and benefits are given; conflicting representations and

questions raised by volunteers are negotiated and answered [54]. Thus, informed consent should be kept as simple as possible, notably for elderly people [49].

The use of focus groups or patient and public involvement (PPI) makes it possible to improve both study design and feasibility, and to provide clearer information [55]. The use of PPI should probably increase in PVT. The use of multimedia resources may also improve the volunteers' comprehension of consent forms and study procedures as proposed in other area of clinical research [56]. These decision-making tools, also named decision aids (DA), supplement verbal guidance from clinicians by presenting clear-written and graphical protocol information that could help patients by clarifying the information before they make a decision. Although Stacey *et al*. found that the use of DA is more effective than standard information to support the informed consent process for treatment and screening [57], in the context of clinical trials it remains equivocal and requires more research [58]. The first study evaluating the use of DA in clinical trials suggested, however, that it is an effective way to optimize the informed consent process so as to increase knowledge and reduce decisional regret about trial participation [59]. In PVT, the use of DA in the informed consent process is however uncommon.

A barrier that has not appeared in this review is the one linked to mistrust of vaccines. Since more and more people are reluctant to vaccines [60], it will probably impact on the participation in PVT. This safety concern is, therefore, specific to vaccine trials. Further studies are needed to evaluate the impact of vaccine mistrust on PVT recruitment, notably in countries like France where confidence in vaccines is at the lowest.

Limits to the major motivators need to be stressed. Altruism, defined as 'acting with an unselfish regard for others', has been identified as a major factor in patients' decision-making to whether or not participate in trials such as PVT. This motivator is also associated to a higher retention of participants in trials. In other settings that rely on volunteers such as blood donations, a decrease in number of donors has been observed in recent years in most of European countries [61]. A decline in altruism has, therefore, been suggested to contribute to the threat of diminishing blood supplies [61], and it might also be associated with a decrease in participation in clinical trials. Since altruism is a major determinant to participate in PVT on incurable, threatening, emerging, or more mediatized diseases, a decline in this motivator probably impacts negatively on the recruitment. It is, therefore, crucial to arouse and maintain this willingness among participants.

Financial incentives, which are another important motivator, set a limit in volunteering. Indeed, some low income volunteers see it as a complementary income. In this case, we can wonder if this is truly voluntary participation. Financial compensation might be considered as bait. Unlike clinical trials, for blood donors, a study showed that a financial reward would be a minimal incentive for volunteers [62] and offering money or cash-equivalent incentives could have a negative effect on blood safety and blood donor contribution [63]. If in PVT, an increase of financial incentives can probably increase the recruitment of volunteers, ethical limits appear clearly and in our opinion it should not be recommended, notably in PVT-targeting specific populations (drug users …).

5. Five-year view

Motivations and barriers in participation in a real PVT may be different from those reviewed in this work which includes mainly hypothetical studies. In order to improve dramatically the participation in PVT, further studies about motivations and barriers accounting for participation in current PVT are warranted. In fact, issues associated with screening, inform consent and enrollment could, therefore, become available. Methods identified in a Cochrane review as useful to recruit participants in real clinical trials (telephone reminders, financial incentives at trial invitation …) should be implemented in PVT [64].

Improving public confidence in vaccines and vaccination is crucial. The use of media to inform participants, in a positive way, about the vaccine clinical research (flyers, advertising campaigns, dedicated pages on social networks, television reports, etc.) could possibly contribute to democratizing clinical research, reduce ignorance or fears, spark motivators as altruism in the general population. Implementation of DA for participants will probably increase, reinforcing the knowledge about PVT and raising some of the barriers to participation. In the same way, the generalization of focus groups or PPI in study design will probably increase, optimizing the acceptability of the study protocol in PVT.

Key issues

- There are common and specific motivations and barriers for participating in PVT
- Altruism is a major determinant to participate in PVT on incurable, threatening, emerging or more mediatized diseases. A decline in this motivator probably impacts negatively on the recruitment. It is therefore crucial to arouse and maintain this willingness among participants.
- Financial incentives, which are another important motivator, set a limit in volunteering.
- The main specific barriers are fear of contracting the preventable disease and of social discrimination due to participation in PVT trials such as HIV and HCV.
- Vaccine mistrust may complicate PVT recruitment. Improving public confidence in vaccines and vaccination is crucial.

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ARTICLE 1

Primary physicians' attitudes toward their patients receiving a proposal to participate in a vaccine trial

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Nous avons pu constater au quotidien, au sein du CIC Vaccinologie, l'influence des praticiens impliqués dans le suivi des personnes approchées pour être inclues, concernant leur décision de participer à un essai clinique vaccinal préventif. En effet, lorsque l'avis du médecin référent était pris, il était très souvent suivi. De plus, le médecin traitant est l'interlocuteur privilégié et la pierre angulaire du parcours vaccinal et a donc un rôle crucial dans le respect du calendrier vaccinal [35]. Il est considéré comme la source d'information la plus fiable pour le patient [36] en particulier dans le domaine de la vaccination. Leurs recommandations se sont avérées être le facteur le plus important dans les décisions des patients quant à leur participation aux essais cliniques, en particulier en oncologie [37,38]. Par contre, leur attitude à l'égard du patient qui reçoit une proposition de participation à un essai clinique a rarement été étudiée [39,40] et aucune étude n'a porté sur les essais vaccinaux. De ce fait, il nous a paru intéressant de connaître l'attitude des médecins référents (généralistes et autres spécialités suivant des patients avec pathologie chronique) face à un patient venant leur faire part de la proposition à participer à un essai vaccinal préventif qui leur a été faite par le CIC. Nous avons ainsi mené une étude mixte, quantitative et qualitative, en collaboration avec le département de médecine générale de l'Université Jean Monnet, afin de mettre en relief cet aspect peu exploré dans la littérature. Les médecins référents, c'est-à-dire des médecins généralistes et d'autres spécialistes qui suivent régulièrement des patients atteints de maladies chroniques, ont été invités par e-mail à répondre à une enquête anonyme en ligne (GoogleDrive®).

Entre mai et octobre 2017, le questionnaire a été envoyé par l'Union régionale des professionnels de santé (URPS Auvergne-Rhône-Alpes) à ses 4232 membres médecins généralistes et par le conseil d'administration de l'hôpital à ses 400 médecins pour les autres spécialités. Nous avons obtenu 521 réponses.

Le volet qualitatif, réalisé par Camille Touche, interne de médecine générale et formée au recueil de données qualitatives, a consisté en la réalisation de 15 entretiens en face à face, entre décembre 2017 et juin 2018, avec des médecins généralistes et d'autres spécialités installés en Loire ou en Haute-Loire. La collecte des données a été arrêtée à saturation des données comme recommandé dans ce type de travail [41]. Cet aspect qualitatif a permis d'aller en profondeur et d'illustrer les données obtenues par le travail quantitatif.

Les résultats ont révélé que les médecins référents aimeraient émettre un avis concernant la participation potentielle de leur patient à des essais vaccinaux, mais qu'ils manquent d'information au préalable. Nous avons constaté que les médecins français n'avaient pas une bonne connaissance des essais cliniques et qu'ils regrettaient de ne pas avoir reçu suffisamment d'information de la part des investigateurs sur le protocole en question.

Primary physicians' attitudes toward their patients receiving a proposal to participate in a vaccine trial

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Abstract

A trustworthy relationship between primary physicians (PPs) and their patients is crucial for vaccine acceptance. Little is known about attitudes of PPs toward participation of their patients in a preventive vaccine trial (PVT) proposed by investigation sites.

A cross-sectional study was conducted in Auvergne-Rhône-Alpes region (France) including an anonymous questionnaire for general practitioners (GPs) and other specialists as well as face-to-face interviews. A scenario of a patient, with chronic medical conditions, invited to participate in a PVT and reporting this situation to his/her PP was drawn up. PPs' attitudes were assessed in quantitative approach by a 5-point Likert scale and in qualitative approach by semi-directed individual interviews.

Among the 521 respondents to the questionnaire, 429 (82.3%) were GPs and 92 (17.7%) were other specialists. Only 7.5% (39/521) of respondents regularly practice clinical research. Confronted with the scenario, 312 respondents (59.8%) declared they would give their opinion spontaneously. Before giving their opinion, PPs would like more information about the trial (91.4%, n=476). Whatever their attitude, 488 (93.7%) would be influenced by available safety data. Face-to-face interviews confirmed that PPs lack of knowledge about clinical research, and would like to obtain information from investigators, particularly about safety.

PPs seem to be concerned by the decision of their patients to participate or not in a PVT but would like more information about the trial and clinical research before giving their opinion. Getting PPs to be more involved in the enrollment of patients in PVT may improve recruitment.

Keywords

Primary physicians, attitudes, recruitment, patient, preventive vaccine, vaccine trials, clinical trials

Introduction

The development of new vaccines continues to be needed[1,2] in order to fight emerging infectious diseases and healthcare-associated infections [3]. Prior to licensure of new vaccines, it is necessary to carry out clinical trials on healthy volunteers and the target population[4]. The success of clinical trials depends on the recruitment of a sufficient number of volunteers. Real difficulties exist in recruiting, including and retaining volunteers or patients in clinical trials[5,6]. In a US study, people were asked if they were interested in medical research participation[7]. Though as diagnosed volunteers - if diagnosed with the disease being studied- 70% of the responders agreed to participate in a medication clinical trial, only 59% agreed to participate if the evaluated product was a vaccine[7]. Consequently, recruitment for trials evaluating candidate vaccines probably meets more difficulties. It is possible that vaccine hesitancy may affect the recruitment of patients or volunteers in preventive vaccine trials (PVT) [8].

Factors influencing participation in clinical trials have been studied and have shown the importance of the primary physician's attitude [9,10]. The primary physician (PP), i.e. the physician following the patient on a regular basis, has a trustworthy relationship with the patient and is the most trusted source of information [9]. Their recommendations have been found to be the most important factor in patients' decisions about participation in clinical trials, specifically in oncology [11–13]. By contrast, the attitudes of PPs to the patient receiving a proposal to participate in a clinical trial have rarely been studied [14] and no study has focused on vaccine trials. In order to identify such attitudes and determine the factors that could influence them, we conducted a mixed-methods study of GPs and other specialists to evaluate PP attitudes toward patient participation in vaccine clinical trials.

Results

Characteristics of the participants in the quantitative study and the participants in the qualitative study. A total of 521 PPs (429 GPs and 92 other specialists) answered the quantitative questionnaire, corresponding to a response rate of 10% for GPs and 23% for other specialists. The main characteristics of respondents are summarized in Table 1. Of the 521 PPs who answered to the question, only 39 (7.5%) practice clinical research regularly (daily, weekly). This regular activity was more frequent among other specialists (6/33 among GPs vs 33/69 among other specialists, p=0.004). For qualitative study all solicited physicians accepted to participate. Characteristics of the 15 physicians (9 GPs and 7 other specialists) who agreed to participate in the qualitative study are summarized in Table 2. The interviews lasted between 9 to 41 minutes.

Table 1: Demographical characteristics of the panel population (n=521) * (infectiologists=6, cardiologists=3, pediatrics=5, internal medicine=4, surgery=11, dermatologists=1, endocrinologists=2, gastroenterologists=2, pneumologist=1, anaesthetists=6, geriatrics=1, gynaecologists=2, emergency physicians=7, urologists=3, rheumatologists=6, oncologists=3, ophtalmologists=2, neurologists=6, nephrologists=1, vascular physicians=5, oto-rhino-laryngologists=1, reproductive physicians=3, rehabilitation physician =3, psychiatrists=1, addictologist=1, nuclear physicians=1, not reported=5)

Characteristics	All respondents	
	n	%
Specialty		
General practitioners (GP)	429	(82.3)
Others specialties*	92	(17.7)
Age		
< 30 years	5	(0.9)
30 to 39 years	156	(29.9)
40 to 49 years	131	(25.1)
50 to 59 years	130	(24.9)
> 60 years	99	(19)
Gender		
Sex ratio (male/female)		0.98
Male	258	(49.5)
Place of practice		
Private practice	424	(81.4)
Hospital center	97	(18.6)
Clinical research activity		
Yes	102	(19.6)
No	419	(80.4)

Table 2: Qualitative case table (n=15)

Doctor	Gender	Age (years)	Specialty	Exercise place	Clinical research activity	Length of interview (min)
A	M	65	GP	Private practice	No	25
B	M	49	GP	Private practice	No	9
C	F	32	GP	Private practice	No	17
D	F	49	GP	Private practice	No	12
E	F	54	GP	Private practice	No	41
F	M	60	GP	Private practice	No	27
G	M	57	GP	Private practice	No	19
H	F	59	GP	Private practice	Yes	26
I	F	38	GP	Private practice	No	27
J	M	49	Nephrologist	University hospital	Yes	15
K	M	46	Rheumatologist	University hospital	Yes	17
L	F	43	Cardiologist	Hospital	No	17
M	M	31	Pneumologist	Private practice	No	16
N	F	51	Gastroenterologist	Both	Yes	12
O	M	56	Rheumatologist	Both	Yes	31

The attitudes of PPs to their patients who were offered participation in a vaccine trial.

Table 3 summarizes quantitative and qualitative data on enrolled physicians. Confronted with this situation, 312 physicians (59.8 %) declared they gave an unsolicited opinion. This declaration was independently associated with male gender and age ≥50 years old (see Table 4). When the opinion was solicited by the patient, 186 physicians (35.7%) did not wish to give an opinion. This attitude tends to be more frequent in physicians who do not have any clinical research activity (see Table 4) and qualitative data confirmed this reticence to give an opinion among GPs (see Table 3). Among all respondents, 476 (91.4%) declared they wanted more information before giving their opinion; this attitude was independently associated with female gender (see Table 4). Among 424 responding GPs, 397 (93.6%) declared that they wanted more information before giving their opinion, this proportion was significantly lower in other responding specialists ((79 out of 92 - 85.7%), p=0.012 in univariate analysis) (see Table 4). The qualitative data reflected the physicians' unease concerning this lack of information about the vaccine trial and lack of knowledge about clinical research (see Table 3). Of the 521 physicians who answered to the question, 367 (72%) were in favor of having a prior contact with the investigator to receive information as well as the study protocol. In both

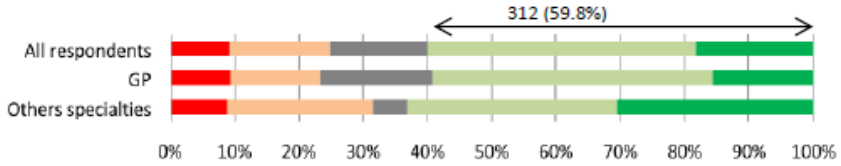
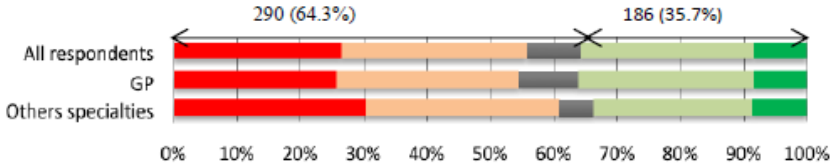
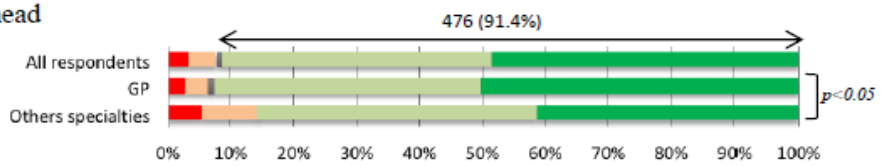
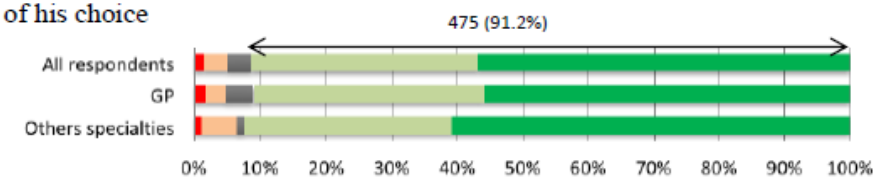
qualitative and quantitative analyses, the great majority of physicians declared they respected the patient's decision and left them to make up their mind independently (see Table 3).

Factors influencing the attitudes of PPs.

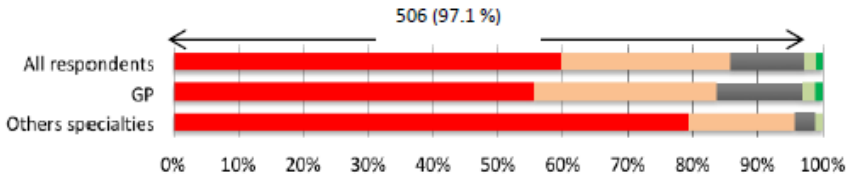
These factors based on the quantitative and qualitative results are shown in Table 3. The first factor that influenced the attitude of physicians was the availability of previous safety data, declared by 93.7% of respondents (n=488). Qualitative data also brought insight into the fact that physicians considered "old" vaccines safer than "new" ones and that vaccine under study could have long-term side effects (see Table 3). In multivariate analysis, female physicians and physicians over 50 are more concerned with safety data (see Table 5). The availability of safety data tends to be more important for physicians who did not have clinical research activity (Table 5). The patient's clinical condition was a factor influencing physicians for 459 of respondents (88%). Constraint for the patient (number of visits, vaccine schedule administration, study procedures…) was a factor that influenced 377 of them (72.4%) in their attitude. Qualitative data suggested that physicians made sure that the study design was not associated with too many invasive procedures for the patient. However physicians considered these procedures as a good point associated with a more complete follow-up for their patients (see Table 3). Benefit expected for the patient was the third factor influencing their attitude for 87.7% of respondents (n=457). All these factors were spontaneously declared in qualitative interviews (see Table 5). The infection targeted by the vaccine was also a frequent factor influencing their responses in 85.2% of cases (n=444). Interviews also showed that for physicians, some infections seemed to be more serious than others (see Table 5). For 77% of respondents (n=401), the patient's initial decision influenced their attitude. It was all confirmed by qualitative data, which also revealed that physicians checked if their patient was well-informed and able to understand what was being offered (see Table 3). Among respondents, 21.2% (n=110) did not consider the vaccine to be a drug like others since they

stated their opinion would have been different for a medicine trial (Table 3). The fact that the study was a placebo-controlled study influenced 55.6% of physicians (n=290). In qualitative data, physicians declared that it was difficult to explain what a placebo-controlled study is, as written in informed consent form (ICF) (Table 3). As reported in Tables 3 and 5, the importance of some factors varied significantly between GPs and other specialists.

Table 3:

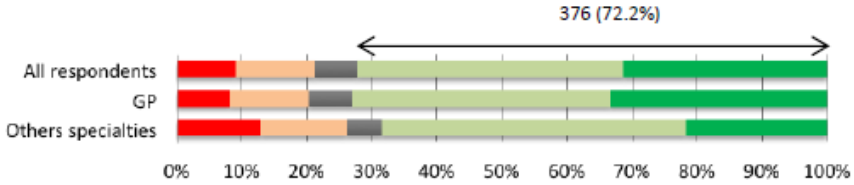
Attitudes of attending physicians when one of their patients is approached by clinical center of research to participate in a preventive vaccine trial	
Quantitative responses (n = 521) Lickert scale representation	**Qualitative verbatim sentences related**
Strongly disagree ■ Tend to disagree ■ Do not know ■ Tend to agree ■ Strongly agree	
Do you spontaneously give your opinion? 	-
If the patient asked your opinion, you do not wish to give an opinion 	*"If patients ask me for my opinion, I can eventually determine myself." (Doctor F)* *"You can't give advice if you don't know what you're talking about at all" (Doctor I)*
If the patient asked your opinion, you want more information before you go ahead 	*"In order to give an opinion in a field, it is necessary to be informed and you have to be initiated"(Doctor A)* *"To give an advice, maybe there's a need for more information for GPs" (Doctor I)*
If the patient asked your opinion, you give him your opinion but leave him free of his choice 	*"I push them to accept if they are really excited but on the other hand I let them make their decision alone"*(Doctor E)

If the patient asked your opinion, you discourage him from participating



"Often I encourage them to follow these protocols, for me it is an interesting method of analysis that must be maintained" (Doctor G)
« If they have been asked to be included it is because they fit the profile so there is no reason why I can advise them against it. » (Doctor N)

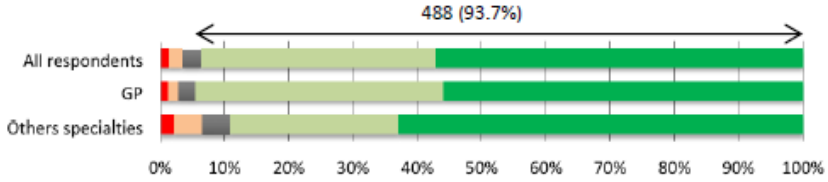
You would have preferred that your colleague contact you in advance to present the study and send you the protocol in question



"I should be able to contact the doctor who sets up the trial to find out what he is expecting, because I know absolutely nothing at all' (Doctor I)
"Indeed, there are always difficulties often because the inform consent form (ICF) for patients are often extremely poorly written with terms not always understandable to the non-specialist " (Doctor J)
"Very often they do not ask the questions to the investigators, they ask them to us (attending physicians)."(Doctor D)

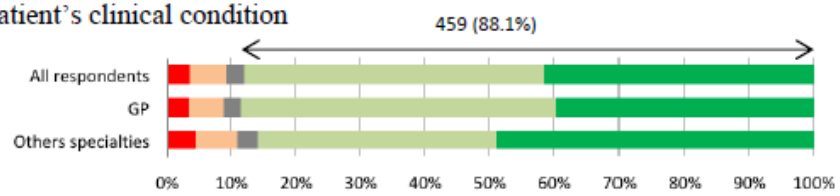
What factors could influence your opinion?

Available safety data



" What might come into play in my decision to recommend or not to recommend participation is the progress of the study. To know if there had already interesting data and lead to an improvement". (Doctor B)
" I have no fear about the old vaccines that we know about or those that are being put on the market. But participating in tests and it seems really complicated to me. Vaccinations you will often have a fallout at 20, 30 or 40 years old and I think it is more dangerous so you have to be more careful." (Doctor E)

Patient's clinical condition



" My patient's health condition is a factor I will consider" (Doctor B)
« My opinion will depend on my patient's health condition » (Doctor I)

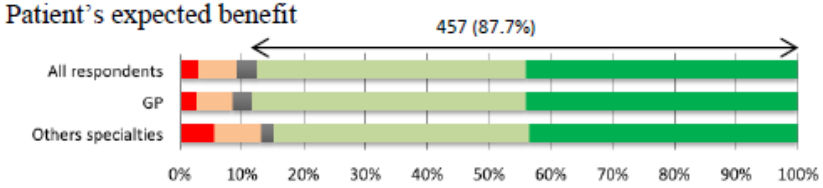
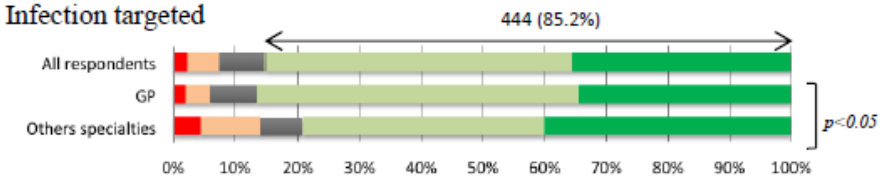
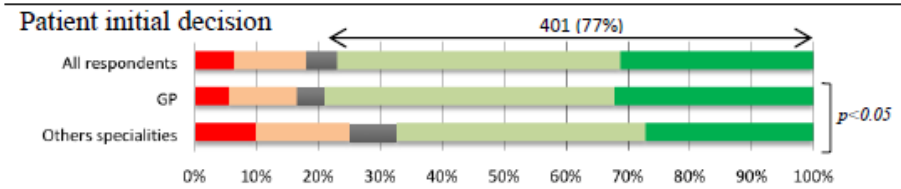
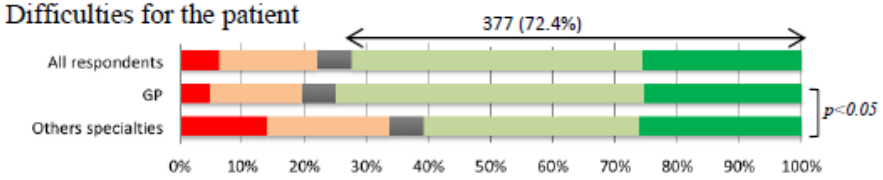
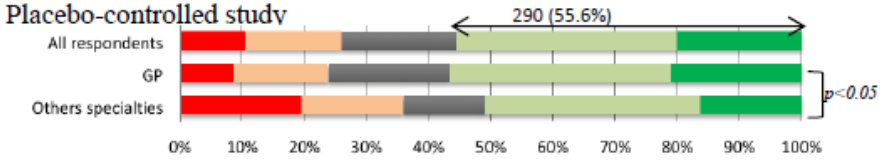
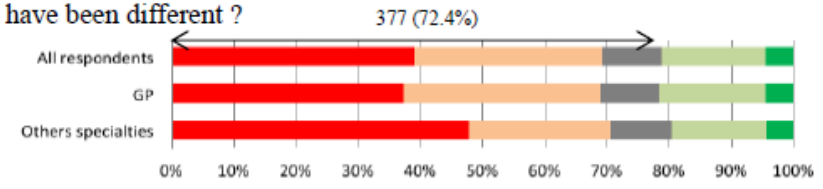
Patient's expected benefit 	*"One element is the individual benefit that it could have a posteriori" (Doctor B).* *"The potential gain, the potential benefit for the patient will be an element that will guide my recommendation" (Doctor F)*
Infection targeted 	*"First element will be the usefulness of the vaccine (depending on the pathogenicity of the virus or bacteria involved). If we are dealing with a pathology that does not kill, I would say to myself that it would be less important to offer it to my patients" (Doctor C)*
Patient initial decision 	*« I will check that the patient is really aware of what he is making as a decision and why he has made it. The rest, no, in my opinion it wouldn't concern me, it's the patient's decision! » (Doctor E)*
Difficulties for the patient 	*"If it doesn't require too many invasive tests for them, I think it advances science"(Doctor D)* *"They had the right to an electrocardiogram, a chest x-ray and a biological assessment. That's why I told them it was good to participate, because it came in addition to what we could do as a GP."(Doctor D)*
Placebo-controlled study 	*"The terms used in the ICF are anxious and you have to try to make him understand that there will be a random draw and that maybe he will end up in the placebo arm. So in the majority of cases, his participation in clinical research does not directly benefit him." (Doctor J)*
If the trial proposed was a drug trial, not a vaccine trial, would your opinion have been different ? 	*"It seems to me that a vaccine is a drug!"*(Doctor K) *"Oh no, it's not invasive for me. A sting does not hurt that much." (Doctor L)* *"So I do not have the fear about old vaccines we know."(Doctor E)* *" I think the drug trial seems a little less dangerous to me than the vaccine trial because in a vaccine trial we're going to have a very long-term impact"(Doctor E)*

Table 4: Univariate and multivariate analysis of physicians' attitudes when one of their patients is approached by clinical center of research to participate in a preventive vaccine trial - Odds-ratio [IC]

			If patient asked for your opinion,					
	Spontaneous opinion		Do not wish give your opinion		Want more information		Patient free of choice	
	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate	Univariate	Multivariate
Male gender	1.97 [1.29, 2.99]***	1.58 [1.02, 2.44]**	0.68 [0.47, 0.99]**	0.76 [0.51,1.11]	0.44 [0.22, 0.88]**	0.47 [0.23, 0.95]**	0.91 [0.42,1.99]	-
Age ≥ 50	3.26 [2.07, 5.11]***	2.90 [1.82,4.60]**	0.69 [0.47, 1.00]*	0.75 [0.51,1.10]	0.76 [0.40, 1.44]	-	1.65 [0.73, 3.76]	-
Hospital center practice	0.70 [0.43, 1.17]*	0.80 [0.47,1.34]	0.87 [0.53, 1.42]	-	0.45 [0.22, 0.94]**	2.2 [0.21,23.16]	0.74 [0.29, 1.90]	-
GP	1.27 [0.77, 2.10]		1.19 [0.74, 1.94]	-	2.42 [1.20, 4.90]**	3.34 [0.302, 36.98]	1.31 [0.51, 3.34]	-
Have a clinical research activity	1.16 [0.69, 1.93]		0.60 [0.37, 0.97]**	0.62 [0.38,1.01]	0.37 [0.19, 0.73]**	0.53 [0.21, 1.35]	1.06 [0.39, 2.86]	-

	If patient asked for your opinion,			
	Discourage patient		Prior contact	
	Univariate	Multivariate	Univariate	Multivariate
Male gender	1.99 [0.67, 5.92]	-	0.79 [0.52, 1.22]	-
Age ≥ 50	0.86 [0.30, 2.46]	-	1.67 [1.08, 2.60]**	1.67 [1.08, 2.60]**
Hospital center practice	0.65 [0.14, 2.96]	-	0.75 [0.44, 1.29]	-
GP	3.43 [0.44, 26.45]	-	1.37 [0.81, 2.32]	-
Have a clinical research activity	0.96 [0.27, 3.49]	-	0.72 [0.43, 1.20]	-

*$p < 0.2$

**$p < 0.05$

***$p \leq 0.001$

Table 5: Univariate and multivariate analysis of the opinion's influencing factors when one of their patients is approached by clinical center of research to participate in a preventive vaccine trial - Odds-ratio [IC]

	Patient initial decision		Patient clinical condition		Difficulties for patient		Expected benefit	
	Univariate	**Multivariate**	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**	**Univariate**	**Multivariate**
Male gender	0.76 [0.49, 1.20]	-	0.88 [0.49, 1.60]	-	0.83 [0.54, 1.25]	-	1.27 [0.70, 2.31]	-
Age ≥ 50	0.75 [0.48, 1.18]	-	0.91 [0.50, 1.65]	-	0.92 [0.60, 1.40]	-	0.76 [0.42, 1.37]	-
Hospital center practice	0.50 [0.29, 0.86]**	0.99[0.00, ∞]	0.76 [0.36, 1.60]	-	0.52 [0.31, 0.86]**	4.08 [0.38, 43.74]	0.60 [0.30, 1.20]*	0.42 [0.01, 13.32]
GP	1.77 [1.03, 3.04]**	0.99[0.00, ∞]	1.26 [0.60, 2.65]	-	2.11 [1.28, 3.49]**	7.53 [0.68, 83.43]	1.62 [0.81, 3.25]*	0.60 [0.02, 22.04]
Have a clinical research activity	0.54 [0.32, 0.91]**	0.69 [0.34, 1.38]	0.55 [0.28, 1.07]*	0.55 [0.28, 1.07]*	0.57 [0.35, 0.94]**	0.88 [0.45, 1.71]	0.81 [0.40, 1.65]	-

	Vaccine targeted		Available safety data		Placebo-controlled study	
Male gender	0.92 [0.48, 1.78]	-	0.26 [0.08, 0.79]**	0.22 [0.07, 0.70]**	1.00 [0.67, 1.52]	-
Age ≥ 50	0.77 [0.40, 1.49]	-	2.09 [0.73, 5.98]*	3.03 [1.02, 9.00]**	0.96 [0.63, 1.44]	-
Hospital center practice	0.39[0.19, 0.79]**	0.43[0.09, 20.51]	0.39 [0.14, 1.07]*	0.51 [0.01, 38.7]	0.61 [0.36, 1.00]*	1.07 [0.14, 8.18]
GP	2.54 [1.24, 5.18]**	1.06 [0.02, 50.85]	2.47 [0.90, 6.77]*	0.6 [0.01, 44.6]	0.67 [1.01, 2.76]**	1.48 [0.19, 11.50]
Have a clinical research activity	0.51 [0.25, 1.06]*	0.93 [0.34, 2.51]	0.29 [0.10, 0.73]**	0.33 [0.10, 1.12]*	0.61 [0.38, 0.99]**	0.76 [0.39, 1.46]

**p <0.1*
***p<0.05*

Discussion

This study described for the first time attitudes of PPs toward their patients receiving a proposal to participate in a vaccine trial. Our mixed methodology allows us to explore their attitudes thoroughly. The role of the physician-patient relationship in clinical research in general has been previously described in literature [9–11] and has revealed how the PPs' attitudes and opinions influence the participation of patients in therapeutic drug trials [10,15]. Concerning vaccine trials, data are lacking about the attitudes of PPs as well as their role in the patient's decision process. Among older adults interviewed about their willingness to participate in a vaccine clinical trial, 55% considered that their PP should be comfortable with their participation in the trial [16]. This observation highlights the potential role of PPs in whether a patient decides to participate in a vaccine trial. The present study presents data on the attitudes and factors influencing the reaction of PPs in this situation.

Firstly, we reported that PPs confronted with a scenario where one of their patients said he/ she was approached to participate in a PVT have a mixed reaction. In fact, although a large majority of physicians would like to make a recommendation to their patients regarding their potential participation, they often lack knowledge on clinical research. This poor knowledge of PPs was previously observed in oncology, despite the fact that PPs showed interest in training on clinical trials [17,18]. Chen et al, recommended that all physicians receive an education about clinical trial design and learn how to advise patients as far as research participation is concerned. They also suggested that it could be part of courses on the patient–physician relationship [14]. In our qualitative study, physicians recognized that research is an unknown domain for physicians who were not involved in this field (Doctor I, Table 3). It would be interesting to understand the nature and types of misconceptions about clinical research among physicians in order to accurately inform and re-educate them as suggested by Walsh et al. for potential participants [10]. We demonstrated that the attitudes of PPs were not

directly correlated with their specialty but tend to be correlated with the fact they have research activity or not. Therefore it could be beneficial to create continuing medical education sessions about clinical research or to implement training in medical schools. In this sense, recommendations were issued to develop a real education for non-professionals in the clinical trial in France [19].

Physicians also deplored that ICF given to the patients was the only source of information they had about the proposed clinical trial. As pointed out by Doctor J (Table 3) and highlighted by Pandiva et al., terms used in ICF are not always easy to understand for people not interested in clinical research such as patients [20] or even some physicians. They also regret the absence of previous communication with the investigator. Thus it seems crucial to improve communication between investigational centers and PPs, and that the investigator who approached the patient should inform the PP directly. In the US, a patient's reference guide suggests that patients may consult their PP to explore options about entering a clinical trial, and to use this guide to discuss the decision to participate or not in a clinical trial with their PP. This better communication is probably beneficial to the patient, to the PP who is the trusted physician for the patient, and to the investigator, and this could increase enrollment in the PVT.

Secondly, we observed that the most important factor influencing their attitude is the availability of safety data of the trial. This concern was frequently reported in the general population who want to be informed of any medication adverse reaction, however rare it may be [21]. It is notably the fact with vaccines, safety being the primary concern in Europe [22]. Among elderly people interviewed about their willingness to participate in a PVT, 75% of participants considered that safety precautions should be taken [16]. Physicians shared this concern with their patients. This observation emphasizes that general population and

physicians not involve in clinical research are not conscious that trials are stopped at the slightest safety problem.

Although the majority of respondents considered vaccines as a drug like any other, 20% of the physicians still declared they would think differently if the experimental product was not a vaccine. We cannot conclude from that whether they would be keener to recommend a medicine rather than a vaccine trial. However, in the qualitative study, some physicians reported concerns about long-term side effects of these new vaccines in development, as they have concerns about vaccines recently licensed. Vaccine hesitancy among physicians has been described [23–25]. We may hypothesize that hesitant physicians could discourage patients to participate in a PVT; however the influence of vaccine hesitancy on their attitude cannot be measured here. In the same way, if PPs do not perceive in-development vaccines as of interest, they possibly deter their patients from entering a vaccine trial. We observed that the type of infection targeted by the vaccine would influence their opinion. This point needs to be studied further as some vaccines in development will target diseases rarely managed by PPs [3]. If these vaccines seem less useful to them they could negatively influence their patients. Fortunately the great majority of medical doctors remain favorable to vaccines [26] and most physicians recognize that new strategies need to be developed to protect or cure patients [27].

Our study has several limits. Firstly we have a limited sample of PPs and a low response rate for the questionnaire. However, the panel was representative of the physician population in France when compared to official data [28]. The responding physicians were probably more concerned about vaccination matters or clinical research either positively or negatively, but this could not be verified in the absence of data about the refusing PPs for quantitative data. The panel was limited to Auvergne-Rhône-Alpes region. However, this region is the second bigger administrative one of France and it is a region with a great activity around vaccine development [29] and two vaccinology clinical investigation centers. For the qualitative study,

the sample was recruited according to guidelines [30] and as interviews were all face-to-face there were conducted in Loire and Haute Loire counties as a matter of practicality. The number of participants was stopped at data saturation [30]. Results from this first work could probably not generalized but bring data in a field not previously well explored. Secondly, we do not explore attitudes of PPs toward vaccination in general. Vaccine hesitancy exists among physicians in France and may affect up to 10% of GPs[31]. However a great majority of them recommend the most of vaccines to their patients [23]. The impact of hypothetical vaccine hesitancy among the panel could not be explored. Thirdly it was a majority of GPs who participated in both the qualitative and quantitative studies. This could underestimate possible differences between GPs and other specialists who accounted for a smaller sample. However, in France, GPs continue to have a crucial role in the follow-up and vaccination of patients including those also managed by other specialists [32]. It was a GP (CT) who conducted the interviews. It undoubtedly allowed closer contact with the others GPs, our larger category in the study. Qualitative data shed light on trends observed in the questionnaire results.

In conclusion, these results revealed that PPs would like to make a recommendation to their patients regarding their potential participation in vaccine trials but would like more information beforehand. We found that French physicians lacked knowledge of clinical trials and regretted not receiving enough information from investigators. Developing training and decision-making tools on vaccine trials to empower PPs (GPs or other specialists) may help investigators to enrol new patients. Decision aids (DA) featuring a clearly-written aim of the study, available safety data and graphical protocol presentations could clarify information and help PPs before they give their patients an opinion. DAs have proven to be an effective means of optimizing the informed consent process; they increase knowledge and reduce decisional regret about trial participation [33]. It would also be interesting to test these tools with PPs when they are confronted with patients asking for an opinion on a vaccine trial proposal. Further

studies are also needed to better evaluate among patients the role of the PPs in their decision to participate or not in a PVT.

Methods

We have conducted a descriptive cross-sectional study based on both quantitative (on-line survey) and qualitative methods (face-to-face interviews) among PPs, i.e. General practitioners (GPs) and others specialists following patients with chronic medical conditions on a regular basis. GPs from the Auvergne-Rhône-Alpes region, France and others specialists at the University Hospital of Saint-Etienne were invited via email to answer an anonymous Web-based survey (GoogleDrive®). All questions were previously validated and tested by general medicine and infectious diseases specialists involved in the study. Between May and October 2017, the questionnaire was sent by the regional union of healthcare professionals (URPS Auvergne-Rhône-Alpes) to their 4232 GP members. For the other specialists, the questionnaire was sent by the Hospital Board to their 400 physicians. The quantitative questionnaire featured fourteen questions about the attitudes of PPs to their patients who were offered participation in a vaccine trial. The scenario presented to the physicians was as follows: "A colleague of yours from the clinical research center of vaccinology offered one of your patients' participation in a PVT. The patient comes to you with a copy of the information consent form and informs you of the proposal made to him/her". The PPs' attitudes and the factors that influence their answers were determined based on a 5-category Likert scale (rating for each question was: strongly disagree, tend to disagree, do not know, tend to agree, strongly agree). The answers to each question were dichotomized into positive versus non-positive (including: don't know or no answer).

For the qualitative study, the method followed the COnsolidated criteria for REporting Qualitative research (COREQ) Reporting Guidelines [30]. Semi-directed individual interviews were held with GPs and other specialists settled in Loire or Haute-Loire -French counties located in Auvergne-Rhône-Alpes region- and working in private healthcare centers or in public-sector hospitals. Recruitment was based on reasoned sampling, by seeking maximum

variation according to the following criteria: age, gender, specialty, clinical or non-clinical research activity, and working in urban, rural or semi-rural areas[30]. The study was carried out between December 2017 and June 2018. First contacted by phone, the PP who accepted received the interviewer for a face-to-face interview by appointment in their office. The meetings were conducted following on interview guidelines developed according to the researchers' questions, literature data and the first results of the quantitative survey. The guide of face-to-face interviews is available as supplemental material. The interviews were recorded after consent by the respondents. Data collection was stopped when redundancy was observed (data saturation) [30]. Interviews were transcribed word per word on an anonymous data computer file. Data were inductively analyzed using a non-blind open manual coding, descriptive then thematic also using a constructivist grounded theory approach [34]. Grounded theory allows to evaluate the interrelationship between meaning in the perception of the subjects and their action[34]. In fine, the results were reworked with a team in the clinical trial center of the University Hospital of Saint-Etienne, with validation proofreading by a dozen interviewees.

Statistics. We used Microsoft Excel for the collection of recorded quantitative data, SPSS® IBM SPSS Statistics 24.0 (NY, USA) software for statistical analysis, and chi2 or Fisher's exact test to compare quantitative data. An univariate analysis was first conducted to determine factors associated to PPs attitudes. A p-value ≤ 0.05 was considered to be statistically significant. To adjust for confounding factors, we conducted a multivariate analysis to test associations between attitudes and the explanatory variables with a p-value ≤ 0.2 significance level obtained in the univariate analysis.

Ethics. Questionnaires were validated by the French National Commission for Data Protection and Liberties (Commission Nationale Informatique et Libertés). The study was received favorably by the local ethics committee (IRBN742017 / CHUSTE).

Author's contributions

MD, EBN designed the quantitative study and the questionnaire, and collected quantitative data. MD, AGB and EBN carried out analysis of data. CT held the interviews, collected qualitative data and analyzed them with a non-blind open annual coding (CT, RC, MD, EBN). MD and CT drafted this manuscript. EBN, AGB, RC, FL critically reviewed this manuscript. All authors read and approved the final manuscript.

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Conflict of interest

The authors declare that they have no conflict of interest.

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ARTICLE 2

Barriers and motivations for participation in preventive vaccine clinical trials: experience of 5 clinical research centers

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La revue de la littérature a révélé un manque de données sur les barrières et motivations à participer aux essais vaccinaux en général, quel que soit la pathologie ciblée par le vaccin à l'étude. Par ailleurs, elle a aussi montré que beaucoup de travaux étaient faits sur des vaccins hypothétiques ce qui pouvait avoir un impact sur les barrières et motivations à participer. Le but de ce travail était donc de tester les facteurs retrouvés dans la littérature, en France, en vie réelle au sein des centres d'investigation clinique du réseau F-CRIN i-REIVAC auquel nous appartenons. Comme nous l'avons vu, les facteurs recensés étaient essentiellement liés à des essais cliniques vaccinaux contre le VIH [32–34]. Il nous a donc paru nécessaire d'éprouver ces facteurs de manière plus globale en réalisant une étude prospective multicentrique étudiant les déterminants à la participation à un essai clinique vaccinal.

Nous avons donc diffusé un questionnaire papier à toutes les personnes qui se sont vues proposer de participer à un essai vaccinal préventif dans 4 CIC du réseau i-REIVAC et un centre participant à un essai du i-REIVAC. Nous avons récolté 341 questionnaires : 210 de personnes ayant accepté de participer à l'essai vaccinal proposé et 131 de personnes ayant refusé cette proposition.

Les résultats ont montré que l'altruisme était la motivation principale à participer à un essai vaccinal. La peur des effets secondaires s'est révélée être le principal frein à la décision de participer. De plus, cette étude a révélé que l'incitation financière était un frein à la participation chez les personnes plus âgées. D'autre part, avoir un avis favorable aux vaccins

en général était associé indépendamment au fait d'accepter de participer à ce type d'essai, ce qui n'avait pas été mis en évidence auparavant bien que paraissant naturel. Enfin, la qualité de l'information donnée au participant potentiel par le médecin du centre de recherche est ressortie comme un facteur clef pour la prise de décision. Notre étude confirme également qu'il est important d'informer le médecin traitant de la proposition faite à son patient puisque lorsque les patients ont demandé l'avis de leur médecin généraliste sur leur participation, plus de 50% l'ont suivi.

Expliquer le protocole au médecin traitant en amont pourrait permettre un échange plus constructif dans le processus de prise de décision du patient et avoir un impact positif sur sa participation potentielle.

Barriers and motivations for participation in preventive vaccine clinical trials: experience of 5 clinical research sites

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Abstract

Recruitment in preventive vaccine trials (PVT) is challenging due to common barriers to clinical research and lack of vaccine confidence. Identifying determinants of participation can help to improve recruitment. A prospective survey was conducted in 5 French clinical investigational sites. People with a proposal to participate in a PVT were asked to answer a survey, whatever their decision to participate or not in the trial. A total of 341 persons answered the survey: 210 accepting and 131 declining to participate in a PVT. Accepting people were significantly younger (38.5 vs 54.9 years old), more likely involved in early phases trials, had a higher level of education ($p<0.005$) and had a significantly better general opinion toward vaccines (92.3 % versus 72.3 %, $p<0.005$) compared to declining people. Factors associated with acceptance or with refusal were evaluated in 224 people in the 4 sites where both accepting and declining people were included. In a multivariate analysis, older age, having heard about PVT through multiple sources and financial incentives were significantly associated with refusal to participate in the PVT. To have a general favorable opinion on vaccines was associated with acceptance. The main motivation to participate was altruism (93.2%) whereas fear of side effects was at the forefront of the barriers (36.6%). Information given by the physician was key point for decision-making in 70.2% accepting people. In brief, vaccine defiance may negatively impact recruitment in PVT; reinforcing altruism and quality of information given are key points to accepting participation in PVT.

Introduction

Vaccination is one of the greatest successes in modern medicine, resulting in more than 2 to 3 million deaths per year prevented thanks to vaccines [1]. Development of new vaccines remains crucial in the context of outbreaks due to emerging pathogens [2] and is part of promising strategies to fight antimicrobial resistance and healthcare associated infections [3]. Despite an increase in vaccine pipeline [4] with more than 7 300 vaccine trials registered in clinical trial.gov [5], vaccine clinical development remains time -and cost- consuming [6]. Despite lack of data of preventive vaccine trials (PVT), recruitment failure is the primary reason for discontinuation in clinical drug trials, occurring in one out of five trials [7]. Due to the cost associated with the clinical development of a vaccine and the public health benefits expected, reaching optimal recruitment in PVT is crucial.

In a web survey conducted in the US, likelihood to participate in a vaccine trial was found lower compared to a trial for a new medication or a medical device among diagnosed volunteers [8], suggesting that participation in a PVT and therefore recruitment for these trials may be associated with specific factors that need to be studied more. In fact, vaccine hesitancy and doubts about vaccine safety in the general population [9] might have a negative impact on recruitment of volunteers in PVT. Therefore, investigative teams working in PVT may face to common challenges to clinical trials in general such as mistrust in research, difficulties in recruitment, enrollment, and retention of study participants [10–12]. These teams may also be confronted to specific concerns about vaccines not yet well studied. To date barriers and motivators to participate in a vaccine trial were poorly evaluated and published studies mainly deal with HIV, HCV and HPV vaccines [13].

To identify motivators and barriers to participate in a PVT may help investigators to address potential participants' concerns and to improve recruitment in these trials. In the present study, we aimed to identify factors associated to the acceptance or refusal to participate

in PVTs (phases 1 to 4) among healthy and diagnosed volunteers seen in five clinical vaccine investigational sites in France.

Material and methods

The study took place from September 2016 to March 2018 in 5 investigational sites among which 4 are part of I-Reivac "Innovative Clinical Research Network In Vaccinology" [14]. Consecutive potential participants, who received a proposal to participate in a PVT in these centers, whatever their decision regarding participation in the trial, were proposed to answer a survey. Eligible trials were PVT of all study phases with *(i)* Institutional Review Board approval, *(ii)* ongoing recruitment, and *(iii)* whatever the infectious disease targeted by the vaccine studied. Early-phase studies were defined as phase's 1 and 2a trials and later-phase studies as phases 2b and 3 (See Table 1).

Potential participants in a PVT who accepted to answer this survey received a self-administered questionnaire with six demographical questions and sixteen questions that would differ slightly different according to their decision regarding participation in the PVT. Demographical data and motivations or barriers to participate in the proposed PVT were asked. Willingness to participate in a hypothetical experimental preventive vaccine against HIV, HBV or influenza virus was also assessed. All questions were previously validated and tested by volunteers and infectious diseases specialists involved in the study.

Ethics. The local ethics committee of the University Hospital of Saint-Etienne approved these anonymous surveys in February 2016 (number IRBN732015/CHUSTE). A declaration to the French National Commission for Data Protection (**C**ommission **N**ationale **I**nformatique et **L**ibertés) was performed.

Statistics. To compare characteristics of accepting and declining people, differences between proportions were analyzed by the chi-squared test or Fisher's exact test. To identify factors associated with acceptance or refusal to participate, we did not use data of people from site number 2, as the latter could only collect questionnaires from accepting people. A p-value below 0.05 was considered to be statistically significant. To adjust for confounding factors,

we conducted a multivariate analysis to test association between the explanatory variables and the decision to accept participation in a PVT with a p-value below 0.2 significance level in the univariate analysis. The software used for collecting recorded data was Microsoft Excel and SPSS software (NYC 24.0) was used for statistical analysis.

Results

Table 1 summarized the population repartition between each clinical research sites and features of the proposed PVTs. Nine different PVTs were active at the time of the survey in the 5 sites (see Table 1). During the study period, approximatively five hundred individuals were approached to participate in a PVT in the 5 sites.

Respondents to the survey and their characteristics

Table 2 summarized the main characteristics of survey respondents. A total of 341 potential participants to a PVT answered the survey: 210 accepted the proposal to participate in a PVT (accepting people) and 131 declined the proposal (declining people). For site 2, only accepting people replied to the questionnaire. The majority was female (68.9%, 235 out of 341) and the mean age was 45.1 years ±18.2. Repartition of trials was balanced between early and late phases. Two hundred and twenty-four respondents (66.9%) were aware about clinical research and 69 (20.4%) had previously participated in a clinical trial. Fifty-nine respondents (17.4%) asked their general practitioner (GP)'s opinion regarding their participation in the PVT and 67.8 % (40/59) followed it. Declining people were significantly older, had a lower level of education and had generally more children than accepting people (See Table 2). Accepting people's general opinion on vaccines was significantly more favorable than declining people (92.3% vs 72.3%, p=<0.005) (See Table 2). A greater number of accepting people were proposed to participate in a trial with financial incentives (62.9% vs 28.2%, p<0.005).

Table 1: Design of proposed vaccine trials (PVT)

Microorganism targeted	Phase	Healthy volunteers accepted	Sexe eligible for study	Age	Site visit number	Vaccine Injection number	Financial compensation	Status of study vaccine	Sites of investigation	Number of acceptating people (n=210)	Number of declining people (n=131)
*Clostridium difficile***	3	No	All	50 years and older	4 or 11 depends arm and phone contact every two weeks	3	Yes	Experimental	1, 3	n=8 (3.8%)	n=36 (27.5%)
Streptococcus pneumoniae	2b	No	All	18 years and older	9	2 or 3 (depends arm)	No	Marketed	3	n=21 (10%)	n=5 (3.8%)
Staphylococcus aureus	2b	No	All	18 years to 85 years	5 and 1 contact phone	1	No*	Experimental	4, 5	n=48 (22.9%)	n=30 (22.9%)
Respiratory Syncytial Virus	2	Yes	Female	18 years to 45 years	5	1	Yes	Experimental	1, 2	n=90 (42.9%)	n=37 (28.2%)
Ebola virus**	2	Yes	All	18 years to 65 years	11 or 12 depends arm	2	Yes	Experimental	4	n=2 (1%)	n=0
Pneumococcal	2b	No	All	18 years to 75 years	10	2	No	Marketed	3	n=1 (0.5%)	n=0
Malaria	1	Yes	Female	18 years to 35 years	9 and 6 contact phone	3	Yes	Experimental	2	n=15 (7.1%)	n=0
Shigella sonnei	1	Yes	All	22 years to 50 years	5	1	Yes	Experimental	2	n=25(14.9%)	n=0
Clostridium difficile	3	No	All	50 years and older	6	3	No*	Experimental	3	n=0	n=23 (17.6%)

* Reimbursement of travel costs

** Study was suspended during 1 year due to investigation on potential adverse events

Table 2: Demographical characteristics of the panel population

n (%)	**Panel population (n=341)**	**Accepting people (n=210)**	**Declining people (n=131)**	**P**
Site				<0.005
1	73 (21.4)	34 (16.2)	39 (29.8)	
2	96 (28.2)	96 (45.7)	0 (0.0)	
3	92 (27)	30 (14.3)	62 (47.3)	
4	58 (17)	35 (16.7)	23 (17.6)	
5	22 (6.5)	15 (7.1)	7 (5.3)	
Age	45.1 ± 18.2 (n=320)	38.5 ± 14.5 (n=192)	54.9 ± 18.9 (n=128)	<0.005
Gender				0.204
Female	235 (68.9)	150 (71.4)	85 (64.9)	
Male	106 (31.1)	60 (28.6)	46 (35.1)	
Level of education				<0.005
High level	176 (51.6)	128 (61)	48 (36.6)	
To have children	217 (63.6)	113 (53.8)	104 (79.4)	<0.005
Distance between clinical trial center and home (n=207)				0.259
<10 km	133 (39.3)	89 (43)	44 (33.6)	
Between 10 and 30 km	83 (24.6)	51 (24.6)	32 (24.4)	
Between 30 and 50 km	29 (8.6)	15 (7.2)	14 (10.7)	
>50 km	93 (27.5)	52 (25.1)	41 (31.3)	
Clinical research awareness				0.621
Yes	224 (66.9)	135 (65.9)	89 (68.5)	
Prior participation to a clinical trial	69 (20.4)	48 (23.2)	21 (16)	0 .112
Study awareness by…				
Physician of the clinical center team	135 (39.9)	65 (31.4)	70 (53.4)	<0.005
Other physician	60 (17.8)	34 (16.4)	26 (19.8)	0.422
Poster	8 (2.4)	6 (2.9)	2 (1.5)	0.419
Media	10 (3)	10 (4.8)	0 (0)	0.011
Word of mouth	29 (8.6)	24 (11.6)	5 (3.8)	0.013
Internet	23 (6.8)	17 (8.2)	6 (4.6)	0.196
Postal letter	37 (10.9)	30 (14.5)	7 (5.3)	0.009
More than one source of information (physician and other)	17 (5)	6 (2.9)	11 (8.4)	0.022
Study compensated	213 (62.5)	140 (66.7)	73 (55.7)	0.042
Study phase				<0.005
Phases 1 and 2a (early)	169 (49.6)	132 (62.9)	37 (28.2)	
Phases 2b, 3 (late)	172 (50.4)	78 (37.1)	94 (71.8)	
Vaccination opinion				
Positive opinion	286 (84.6)	192 (92.3)	94 (72.3)	<0.005
Treating physician opinion requested	59 (17.4)	37 (17.8)	22 (16.8)	0.814
Opinion followed	40 (67.9)	28 (75.7)	12 (54.4)	
Opinion of those around you requested	140 (41)	82 (39.2)	60 (46.5)	

Factors associated with acceptance to participate in a PVT

Only participants on sites 1, 3, 4 and 5 were included in this analysis (n=224). People included in this analysis were approached to participate mainly in late-phase trials. In the univariate analysis presented in Table 3, for one year increase in age (p<0.005, OR= 0.97 (95% IC: 0.95-0.98)), having heard about PVT through multiple sources (p=0.006, OR=0.09 (95% IC=0.01-0.75)), and proposal for a financially compensated study (p<0.005, 0.48 (95% IC=0.28-0.80)) were associated with declining participation to the PVT. In the multivariate analysis (after adjustment on age, clinical research awareness, asking for advice from GP, having children, having heard about PVT through multiple sources, and financially compensated studies), these confounding factors were also associated with declining the proposal.

In the univariate and multivariate analyses, having a favorable opinion about vaccines was the only factor associated with acceptance to participate in the PVT (p<0.005, OR: 4.98 (95% IC=1.88-13.2)).

Table 3: Univariate and multivariate analysis of factors associated with acceptance

Only participants on sites 1, 3, 4 and 5 were included in this analysis (n=224). In site 2, only accepting participants were included.

Explanatory variables	Univariate analysis OR (95 % CI)	p	Multivariate analysis aOR (95%CI)	p
Age OR for one year increase in age	0.97 (0.95-0.98)	*<0.005*	0.94 (0.91-0.96)	<0.005
Male gender	1.25 (0.74-2.09)	*0.399*	-	-
Having Children	0.66 (0.37 – 1.20)	*0.173*	1.89 (0.77-4.69)	0.165
Prior participation in a PVT	0.92 (0.46 – 1.85)	*0.818*	_	-
Clinical research awareness	0.64 (0.38-1.10)	*0.111*	0.71 (0.38-1.38)	0.317
Asking treating physician's opinion	1.60 (0.85 – 3.00)	0.137	1.24 (0.53-2.88)	0.619
Favorable opinion about vaccines	3.04 (1.49 – 6.23)	0.002	4.98 (1.88-13.2)	<0.005
Multiples source of information	0.09 (0.01 – 0.75)	0.006	0.09 (0.01-0.77)	0.028
Higher level of education	1.18 (0.7-1.99)	0.535	-	-
Information by the physician of the clinical research team	0.72 (0.43-1.20)	*0.206*	-	-
Early Phase	1.10 (0.63-1.92)	0.726	-	-
Financial incentives	0.48 (0.28 – 0.80)	<0.005	0.16 (0.07-0.37)	<0.005

Accepting people's motivations

Two hundred and six accepting people (98%) from the five research sites answered the specific questionnaire about their reasons to participate in a PVT. They are depicted in Table 4. Altruism was the main reason to encourage 192 of them (93.2%) to consent a participation in a PVT for Financial incentives encouraged 118 of them (57.3%) to accept the proposal, including 110 people in early phase trials. The direct potential benefit of being protected by the vaccine was a reason to consent to participate for 81 respondents (39.3%). The fact to feel concerned about the targeted disease in the study was declared by 80 of them (38.8%). Points that helped them to accept enrollment were the quality of the information provided by the physician for 145 respondents (70.4%), the subject of trial for 124 (60.2%), the medical follow-up for 120 (58.2%) of them, financial incentives for 98 (47.6%), and GP's opinion for 63 out of the 206 respondents (30.6%).

Barriers for declining people

The reasons for declining the offer to participate in a PVT given by the 131 declining people are depicted in Table 3. Key factors to decline the proposal were the fear of side effects for 48 participants (36.6%), difficulties to attend protocol appointments for 38 of them (29%) and distance from the clinical research center for 30 of them (23%).

Attitudes according to different proposed scenarios.

Declining people were asked if their answer would be different had the targeted disease affected them: it was the case in 27.3% (35/128) of respondents that would have agreed to participate in the PVT. The same proportion would have agreed to participate in the clinical trial if the drug tested was not a vaccine. Among accepting people, 29% (59/195), 44.5% (90/202), 42.4% (86/ 203) would have declined to participate if the evaluated vaccine was

respectively against influenza, HIV and HBV. Among the declining people 9.2 % (12/130), 16% (21/130), 26.4% (34/129) would have agreed to participate if the evaluated vaccine was respectively against HIV, HBV, flu.

Table 4: Motivations and barriers to participate in a PVT

Motivations for accepting people	**Respondents (n=206)**
Reasons that would encourage you to consent to participate in a preventive vaccine trial were…	
…To help research/to do advance science	192 (93.2)
…To help neighbors/to protect others	135 (65.5)
...Because the study is compensated	118 (57.3)
…Because I feel concerned about the disease/the topic	81 (39.3)
…To protect myself from the disease prevented by the vaccine	80 (38.8)
Points that helped me make my decision to participate in a PVT were…	
Quality of information provided by the physician	145 (70.4)
Theme of the clinical trial	124 (60.2)
Medical follow-up planned for this study	120 (58.2)
Financial incentives if such were the case	98 (47.6)
Possibility to withdraw at any time	92 (44.6)
Opinion of my general practitioner or referent physician	63 (30.6)
Opinion of my entourage/relatives	59 (28.6)
Barriers for declining people	**Respondents (n=131)**
Reasons that would discourage you to consent to participate in a PVT were…	
I'm afraid about side effects	48 (36.6)
I don't have time to come to appointments	38 (29.0)
I live too far away	30 (22.9)
I'm afraid about components of the vaccine	26 (19.85)
I'm not sure how effective the vaccine is	19 (14.50)
My entourage advised me against it	15 (11.45)
I don't trust studies promoted by pharmaceutical companies	15 (11.45)
I've been scared since trial drug in Rennes (France)	13 (9.92)
I'm not a guinea pig	9 (6.87)
I have a bad experience in the past	5 (3.82)
I do not want to participate in a research project	12 (9.16)
I'm against vaccination	13 (9.92)
I don't want to be injected with the product	13 (9.92)
My treating physician advised me not to participate	5 (3.82)
I'm afraid of needles	3 (2.29)
I feel that my interest comes after that of the realization of the study	3 (2.29)
I don't think I'm at risk of getting the disease affected by this vaccine	0 (0.00)
The study is not adequately compensated	0 (0.00)
Beliefs/Religion/Culture	0 (0.00)
Others	24 (18.32)

Discussion

Our survey identified motivations and barriers to participation in a PVT among people proposed to participate in trials studying real vaccines in development. These factors have been rarely studied in PVT in general. A recent study explored barriers to enrollment in PVT through feelings of investigators [15], not among people approached for participation in PVT. Previous studies that evaluated these factors among potential participants usually focused on a unique vaccine trial and in young adults or were conducted considering hypothetical vaccine trial [13]. People interviewed in our study, were potential participants in an actual PVT seen in 5 French clinical research sites. Nine PVT with different targeted diseases and different phases of development were proposed.

Factors and motivators associated with acceptance to participate in a PVT have been identified in this large survey. Our study showed that having a favorable opinion about vaccines was the only independent factor associated with acceptance to participate in PVT, emphasizing that the opinion about vaccines impact on recruitment in a PVT. Vaccine hesitancy was in fact listed as one top barrier with "some effect" on PVT recruitment by researchers in Belgium [15]. In addition, Rikin *et al.* observed in 191 elderly Hispanic people that being vaccinated against seasonal flu the year before increased by 2.6 times the acceptance of participation in a PVT [16]. In the same way, we also observed that a third of the declining people declared they would accept to participate in a trial if the drug tested was not a vaccine. This difference in willingness to participate in a trial according to the type of product tested was previously reported in a US study [8]. Therefore to gain a better understanding about opinion on vaccines by people approached to participate in a PVT may help to target favorable people and increase recruitment.

Altruistic motivation was shown to play an important role in vaccination decisions [17]. In clinical research, whether in non-vaccine trials [18] or in PVT [13], altruism was shown to be

a major motivation to participate in trials, a fact we also observed here. To target people with altruistic motivation may improve recruitment. Promoting altruistic participation in PVT could prove effective strategy to promote clinical research vaccination as observed in blood donations [19].

We also identified factors and barriers associated with refusal to participate in PVT. Older age being the major independent factor associated to refusal. Recruiting elderly in PVT may then be challenging as also reported by researchers in vaccine field [15]. This point seems therefore crucial since among all 9 trials conducted during our study period, 4 included elderly participants. Some vaccine-preventable diseases affect particularly older people and many vaccines in development target the elderly [3]. Older people who considered they were good health were more likely to participate in a PVT than who those considered their health condition as bad [20]. Regardless of age, the way older people see their health condition may influence their participation in PVT and it should be taking into account before enrollment in PVT.

Financial incentives for participating in a PVT showed negatively associated with acceptance in our survey, as frequently and previously reported [13]. This observation may be due to inclusion of participants > 40 years-old in our analysis whereas financial incentives are a stronger motivation for young people [21]. Indeed, in a study with elderly Hispanic people where different scenarios were proposed to potential participants in a PVT against seasonal influenza [16], when a $80 financial incentive was proposed, the proportion of people that agreed to participate decreased by 12.2% compared to no incentive. However, when we included accepting people, enrolled mainly in early-phase studies, in the analysis, financial incentives help 49% of them to make a decision. This is probably linked to the fact that only early-phase studies received financial incentives [22] and in these phases participants are frequently healthy volunteers.

Having heard about the PVT through multiple sources was found as the third independent factor for refusal here. It may be due to the fact that people interviewed were approached to participate mainly in late phase trials and were not coming spontaneously to the center. By contrast in other settings, using multiple recruitment sources simultaneously was found beneficial to recruitment [23].

Fear about side effects was at the forefront of the barriers to participate in a PVT as we previously reviewed [13] and it was pointed out by more than 30% of declining people. Safety concerns about vaccines were also reported for over 40% of French participants in the vaccine confidence project [9]. It seems then very important that investigators be transparent and clearly describe available safety results to participants [24,25].

The purpose of the PVT was also found to be a key factor for decision-making (See Table 3), as highlighted by the fact that accepting or declining people would change their mind if the proposed trial was related to an HIV, HBV or influenza trials. These data are concordant to previous results summarized by our team [13]. These findings make echo to the role of knowledge on disease and the perceived risk for the acceptance of a vaccine [26]. Indeed, the acceptance of a possible vaccine is associated to the knowledge of vaccines usefulness [27]. So it would be important during study presentation to patient to insist on available safety data and to explain with details the targeted diseases.

Most of the accepting people got information from the medical staff in the research site, and the quality of given information helped 70% of the accepting people to make their decision. The research clinic staff is the major source of information for potential participants, particularly in the elderly as previously shown [20]. In our panel, 20% of respondents requested their GP's opinion on their participation in a PVT and followed it in more than 50% of cases. In the US, 55% of the participants aged over 60 years in an influenza PVT, considered that their physician needs to be comfortable with their participation [20]. In

parallel to this study, we conducted a study in primary care physicians and treating specialists and around 60% of them wanted to be involved in the decision making by their patients about participation in PVT [28]. However, physicians considered to be undertrained about on clinical research, and would like more information about the PVT to participate in the decision-making process [28]. It would be important to inform the patient's GP of the proposal made to his or her patient. Explaining the protocol to them could allow a more constructive exchange in the decision making process.

Our study has several limitations. Due to the study design, the population of participants was quite heterogeneous. We chose to include potential participants for different type of PVT (Phases 1 to Phases 3) as well as healthy and diagnosed volunteers to bring insights in motivations and barriers to participate in PVT in general. In fact previous data only focused on a specific vaccine. Moreover our study was performed in the real-life setting of investigational sites and reflected the challenges that investigators involved in vaccinology have to cope with. One of the sites did not have access to participants who refused because their proposed trial mainly involved healthy volunteers who presented spontaneously came to them. To reduce this potential bias we did not integrate their observations in the analysis of factors associated with acceptance.

In conclusion, in this study that interviewed potential participants in real PVTs, we observed that the general opinion vaccine has an impact on recruitment. To foster vaccine-confident participants may improve recruitment in PVT. Financial incentives and multiplication of information sources are not suitable for all types of potential participants, particularly in trials including the elderly. The quality of the information given by the medical staff in the clinical research center is a crucial issue, and the possibility for shared decision with primary care physicians reinforces the need for a specific training of all physicians on clinical research.

Conflict of interest

The authors declare that they have no conflict of interest.

Author's contributions

MD, EBN conceived the study and the questionnaire. MD, AGB and EBN carried out analysis of data. All authors critically reviewed this manuscript. All authors read and approved of the final manuscript.

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CONCLUSIONS GENERALES

Notre analyse de la littérature nous a montré le manque de données concernant les attitudes des médecins face à la participation d'un de leur patient à un essai vaccinal préventif et que peu de données était disponibles concernant les déterminants à participer ou non à un essai de ce type. Au cours de ce travail de thèse, nous avons pu ainsi apporter des éléments de réponse concernant les déterminants à la participation ou non à un essai vaccinal préventif. Nous avons ainsi pu évaluer les déterminants du point de vue des individus mais également du point de vue des médecins traitants dont l'avis semblait, d'après notre expérience sur le terrain, un élément décisionnel pour le patient.

Dans un premier temps, nous avons donc voulu étudier, à travers une étude à méthodologie mixte, qualitative et quantitative, comment se positionne le médecin référent face à un patient venant lui faire part de la proposition qui lui a été faite par le CIC. En effet un sondage IFOP de 2010, montrait que 59% des Français se tourneraient en premier lieu vers leur médecin traitant pour avoir des informations sur la recherche et les essais cliniques et que 79% le ferait au total mais peu de données plus complètes étaient disponibles. Grâce à cette étude, nous avons pu mettre en lumière un manque de connaissance et un besoin de formation globale en recherche clinique, notamment chez les médecins généralistes. Cela s'explique probablement en partie par le manque de temps des médecins et le manque de formation à la recherche au cours des études médicales françaises. Le manque d'information les met mal à l'aise pour émettre une recommandation, pourtant souhaitée, à leur patient. Via le volet qualitatif, nous avons constaté que les médecins non impliqués déclarent que la recherche est un domaine finalement inconnu. Nous avons cependant démontré que cela n'était pas directement lié à leur spécialité, mais avait tendance à être lié au fait qu'ils aient ou non une activité de recherche. De plus, ils regrettaient l'absence de communication préalable avec

l'investigateur. Deuxièmement, nous avons observé que le facteur le plus important qui influençait leur attitude était la disponibilité des données sur l'innocuité des vaccins à l'essai. Cette préoccupation est partagée par la population générale qui souhaite être informée de tout effet indésirable médicamenteux, aussi rare soit-il [42]. C'est notamment le cas des vaccins, la sécurité étant la première préoccupation en Europe [43]. Les médecins interrogés dans notre panel ont partagé cette préoccupation. Cette observation souligne donc que la population générale et les médecins qui n'ont pas d'activité de recherche ne sont pas conscients que les essais sont interrompus au moindre problème de sécurité. Bien que la majorité des répondants considèrent les vaccins comme un médicament comme un autre, 20 % des médecins ont admis qu'ils penseraient différemment si le produit expérimental n'était pas un vaccin. Nous ne pouvons cependant pas en conclure qu'ils seraient plus enclins à recommander un médicament plutôt qu'un essai vaccinal. Toutefois, dans l'étude qualitative, certains médecins nous ont fait part de leurs préoccupations au sujet des effets secondaires à long terme de ces vaccins expérimentaux, comme pour les vaccins récemment homologués. Cette crainte est constitutive du phénomène d'hésitation vaccinale présente chez les professionnels de santé [23,24,44] mais également dans la population générale [25]. Cette étude avait plusieurs limites : nous avions un échantillon limité dû à un faible taux de réponse mais cet échantillon était représentatif de la population des médecins en France [45]. Les résultats ne peuvent ainsi pas être généralisés mais apportent des données dans un domaine peu exploré auparavant. Nous n'avons pas examiné les attitudes des médecins référents à l'égard de la vaccination en général car nous ne voulions pas « cliver ». Cependant nous savons que l'hésitation vaccinale existe chez les médecins en France et peut toucher jusqu'à 10 % des généralistes [46] bien qu'une grande majorité d'entre eux recommandent la plupart des vaccins à leurs patients [23].

Dans un second temps, nous avons donc évalué les motivations et les freins à la participation à ce type d'essai chez les personnes approchées pour participer à un essai vaccinal préventif. Nous avons ainsi interrogé des personnes en situation de vraie vie face à

des vrais vaccins à l'essai, éléments qui manquaient dans la littérature. Notre étude a confirmé que la peur des effets secondaires était au premier rang des obstacles à la participation, ce qui est déjà largement décrit dans la littérature (Revue). Il semble donc très important que les investigateurs fassent preuve de transparence et pédagogie et synthétisent clairement les résultats préalables disponibles aux participants.

L'altruisme s'est confirmé être une motivation majeure pour participer aux essais vaccinaux préventifs, ce que nous avions pu relever dans la littérature (Revue) également. Dans le cas des dons de sang, une diminution de l'altruisme a été suggéré comme contribuant à la menace d'une diminution de l'approvisionnement en sang [47] et elle pourrait également être associée à une diminution de la participation aux essais cliniques. L'altruisme étant au centre des motivations, il est crucial de maintenir cette motivation qui pourrait comme chez les donneurs de sang avoir une influence négative sur le recrutement.

Avoir une opinion favorable sur les vaccins était le seul facteur indépendant associé à l'acceptation de participer observé dans notre étude, soulignant que l'opinion sur les vaccins a un impact sur le recrutement. L'hésitation à l'égard d'un vaccin a en fait été citée comme l'un des principaux obstacles, avec "un certain effet" sur le recrutement dans ce type d'essais par des chercheurs en Belgique [29] mais sans confirmation par les volontaires eux-mêmes avant notre travail. A contrario, l'âge avancé était le principal facteur indépendant associé au refus. En effet, le recrutement de personnes âgées dans les essais vaccinaux peut alors s'avérer difficile, comme l'ont également signalé Harrington et coll.[29]. Ceci pose donc souci car certaines maladies évitables par la vaccination touchent particulièrement les personnes âgées et de nombreux vaccins en développement ciblent cette population [6].

L'indemnisation pour la participation était associée négativement à l'acceptation dans notre enquête qui dans cette analyse n'a pas inclus les volontaires sains. Les incitations financières sont au contraire une motivation forte chez les jeunes [48]. Cette étude a également montré

l’importance donnée à la maladie prévenue par le vaccin. Ces données concordent avec les résultats antérieurs résumés par notre équipe (Revue). Ces résultats font également écho au rôle des connaissances sur la maladie et le risque perçu pour l’acceptation d'un vaccin [49]. En effet, l'acceptation d'un éventuel vaccin est associée à la connaissance de l'utilité des vaccins [50]. Il semble ainsi donc important, lors de la présentation de l'étude, d'insister auprès du patient sur les données de sécurité disponibles et d'expliquer en détail les maladies ciblées.

PERSPECTIVES

Ce travail de thèse soulève beaucoup de points de réflexion à approfondir.

La relation de confiance du patient envers son médecin référent étant à prendre en considération, il semble crucial que les investigateurs améliorent l'échange avec les médecins référents en les impliquant davantage dans la proposition faite au patient. En pratique, afin de pallier l'inconfort de certains médecins lors de la consultation quant à fournir au patient une recommandation face à un sujet qu'il ne maîtrise pas totalement, une meilleure communication entre centres investigateurs et praticiens serait bénéfique. La question de la recherche arrivant souvent en plus de la consultation initiale, une information synthétique sur le protocole de recherche dédié au médecin, sous forme de plaquette par exemple, leur permettrait d'avoir une vision rapide et globale de l'essai proposé à son patient. Il serait par la suite intéressant, à travers une étude prospective, randomisée de comparer l'influence de cette stratégie auprès des médecins sur le recrutement dans les essais vaccinaux. Une autre solution serait de développer un outil d'aide à la décision qui permettrait aux médecins de discuter plus aisément avec son patient de la décision de participer ou non à un essai clinique. Il a été montré que l'utilisation de ces outils est plus efficace que l'information standard pour appuyer le processus de consentement éclairé pour le traitement et le dépistage [51], mais dans le contexte des essais cliniques, elle demeure équivoque et nécessite plus de recherche [52]. La première étude évaluant son utilisation dans les essais cliniques a toutefois suggéré qu'il s'agit d'un moyen efficace d'optimiser le processus de consentement éclairé afin d'accroître les connaissances et de réduire les regrets décisionnels concernant la participation aux essais [53] mais cela reste à montrer dans les essais vaccinaux préventifs.

Par ailleurs, comme l'ont recommandé Chen et coll. dans les essais en général, il serait primordial que tous les médecins reçoivent une formation sur la conception des essais cliniques et apprennent comment conseiller les patients en ce qui concerne la participation à la recherche [40]. Il y aurait donc un intérêt certain à créer des sessions de formation médicale continue sur la recherche clinique ou de mettre en place une période de stage dans une structure de recherche clinique au cours de l'externat ou de l'internat. C'est ce que nous faisons pour les étudiants passant dans notre service depuis 2016. Cela permettrait aux futurs médecins d'avoir eu connaissance des termes spécifiques à la recherche et des aspects pratiques de la conduite d'un essai clinique. Des mises en situation de proposition de participation aux patients, sous forme de jeux de rôle par exemple, leur permettraient d'apprendre à développer un argumentaire salutaire quand la situation se présentera au cours de leur carrière. Pour autant, il serait intéressant d'étudier au préalable, à travers une étude qualitative, les connaissances réelles et les probables idées fausses sur la recherche clinique des médecins qui n'ont pas d'activité dans le domaine afin de leur fournir une information et une formation adaptée à leur demande. Les médecins sont conscients des limites de leurs connaissances et une meilleure communication sur les enjeux de la recherche vaccinale améliorerait probablement les choses.

Parallèlement, les déterminants du côté des individus approchés pour participer aux essais sont aussi très révélateurs et ouvrent beaucoup de perspectives d'amélioration dans l'approche des participants. Premièrement, face à l'association forte entre l'opinion favorable sur les vaccins et l'acceptation de participer, il serait important de s'attacher à mieux connaitre l'opinion sur les vaccins des personnes approchées. Cela permettrait de cibler les personnes plus enclines à accepter et donc à améliorer sur le long terme le recrutement, mais également à préserver du temps médical. Il est fort probable que présenter un essai clinique vaccinal à un patient « hésitant » voire « anti-vaccin » soit peu efficace en termes de recrutement. Le travail de fond engagé par les autorités de santé et les médecins au quotidien

pour lutter contre l'hésitation vaccinale pourrait dans le futur avoir un impact positif sur l'acceptation à participer aux essais vaccinaux.

L'altruisme étant au centre des motivations à la participation aux essais vaccinaux, cibler également les personnes altruistes peut améliorer le recrutement. Il est crucial pour cela de faire un effort de communication en valorisant les actions autour de la recherche vaccinale ou en mettant en place des ateliers de sensibilisation et d'information pour le public. La promotion de la participation altruiste pourrait s'avérer une stratégie efficace pour promouvoir la participation en recherche clinique en général et en vaccinologie en particulier, comme on l'observe pour les dons de sang. En ce sens nous aimerions à terme développer et tester avec les équipes de sciences humaines de PRESAGE (institut de Prévention en SAnté GlobalE), dirigé par le Pr Chauvin, l'impact de panneaux d'affichage pour le CIC et le CHU pour promouvoir la participation à la recherche clinique comme acte de civisme.

LISTE DES PUBLICATIONS ET COMMUNICATIONS

PUBLICATIONS

Articles en lien avec la thèse:

1. **M. Detoc**, A. Gagneux-Brunon, F. Lucht & E. Botelho-Nevers (2017) Barriers and motivations to volunteers' participation in preventive vaccine trials: a systematic review, Expert Review of Vaccines, 2017, 16:5, 467-477

2. **M. Detoc**, C. Touche, A. Gagneux-Brunon, F. Lucht, R. Charles and E. Botelho-Nevers (2019) Primary physician's attitudes toward their patients receiving proposal to participate in a vaccine trial
   Accepté avec révisions mineures dans Human Vaccines and Immunotherapeutics, Mai 2019

3. **M. Detoc** *et al.* Barriers and motivations for participation in preventive vaccine clinical trials: experience of 5 clinical research sites
   Soumis à Vaccine – Avril 2019

Articles en lien avec la vaccination:

1. Killian M, **Detoc** M, Berthelot P, Charles R, Gagneux-Brunon A, Lucht F, Pulcini C, Barbois S, Botelho-Nevers E.Vaccine hesitancy among general practitioners: evaluation and comparison of their immunisation practice for themselves, their patients and their children.Eur J Clin Microbiol Infect Dis. 2016 Nov;35(11):1837-1843

2. Fanget-Sagnes L, Charles R, Boyer B, Berthelot P, **Detoc M**, Botelho-Nevers E. Vaccins dans la prévention des infections nosocomiales : avis des patients hospitalisés avant pose d'une prothèse orthopédique. Hygiènes 2019; 1: 21-26.

3. Amandine Gagneux-Brunon, Pascale Morineau-Houssine, Cécile Janssen, Véronique Ronat, **Maëlle Detoc**, Amélie Valran, Solène Secher, François Raffi, Elisabeth Botelho-Nevers
   Low vaccine Coverage against diphtheria, tetanus, poliomyelitis, invasive pneumococcal diseases and seasonal influenza in French HIV-infected patients
   En cours de rédaction

COMMUNICATIONS ORALES

Communications en lien avec la thèse

1. **Médecins référents : un appui pour améliorer le recrutement dans les essais cliniques vaccinaux.**
   Maëlle Detoc, Camille Touche, Frédéric Lucht, Amandine Gagneux-Brunon, Rodolphe Charles, Elisabeth Botelho-Nevers

   - RICAI 2018 (38ème réunion inter-disciplinaire de chimiothérapie anti-infectieuse, Paris), Décembre 2018

2. **Motivations et freins à la participation à un essai clinique vaccinal**
   Maëlle Detoc, Odile Launay, Christian Dualé, Frédéric Lucht, Jean-Charles Le Huec, Catherine Mutter, Elisabeth Botelho-Nevers, Amandine Gagneux-Brunon

   - RICAI 2018 (38ème réunion inter-disciplinaire de chimiothérapie anti-infectieuse, Paris), Décembre 2018

Communications en lien avec la vaccination

1. **Vaccins chez l'immunodéprimé : point de vue des patients**
Anne Pouvaret, Nicolas Maillard, Xavier Roblin, Hubert Marotte, **Maëlle Detoc**, Amandine Gagneux-Brunon, Elisabeth Botelho-Nevers

   - Communication orale acceptée aux Journées Nationales d'Infectiologie, Lyon Juin 2019

COMMUNICATIONS SUR PANNEAUX

Communications en lien avec la thèse

1. **Barrières et motivations de volontaires à participer à un essai clinique vaccinal préventif**
   M. Detoc, A. Gagneux-Brunon, F. Lucht, E. Botelho-Nevers

   - Journée de la recherche, IFRESIS, Saint-Etienne, Juin 2017

Communications en lien avec la vaccination

1. **Les politiques vaccinales des médecins généralistes (MG): pour eux-mêmes, leurs enfants, leurs patients**
   S. Barbois, R. Charles, A. Gagneux-Brunon, **M. Detoc**, F. Lucht, E. Botelho-Nevers

   - Journées Nationales d'Infectiologie, Nancy Juin 2015

2. **Connaissances et croyances sur les infections associées aux soins chez les patients allant bénéficier d'une pose de prothèse articulaire**
   M.Hoyon**, M.Detoc**, B.Boyer, P.Berthelot, P.Verhoeven, E.Botelho-Nevers

   - Journées Nationales d'Infectiologie, Nantes Juin 2018

AUTRES COMMUNICATIONS

1. **Human papillomavirus and medically assisted reproduction : a multicenter prospective study**
   M. Detoc, S. Charaoui, J. Jacquet, M. Ghazi, L. Mery, A. Papaxanthos-Roche, I. Garrigue, B. Pozzetto, M. Cottier, C. Chauleur, I. Aknin, J.P. Klein, T. Bourlet

   - EUROGIN 2018 (International Multidisciplinary HPV Congress) – Lisbonne Décembre 2018

2. **La pratique du don du sang du point de vue de l'âge : expérience au sein de l'EFS Auvergne-Rhône-Alpes (St Etienne)**
   Elyès Ben Khalifa, **Maëlle Detoc**, Alain Lefebvre, Julie Huet, Sophie Titoulet, Dominique Legrand, Fabrice Cognasse, Pascal Vallet

   - Communication orale acceptée au XXIXe congrès de la Société Française de la Transfusion Sanguine - Nantes du 18 au 20 septembre 2019

3. **Vers une écologie du stress en application au don de sang : expérience au sein de l'EFS Auvergne-Rhône-Alpes (St Etienne)**
   Elyès Ben Khalifa, **Maëlle Detoc**, Alain Lefebvre, Julie Huet, Sophie Titoulet, Dominique Legrand, Fabrice Cognasse, Pascal Vallet

   - Communication orale acceptée au XXIXe congrès de la Société Française de la Transfusion Sanguine - Nantes du 18 au 20 septembre 2019

4. **Analyse du discours des donneurs : expérience au sein de l'EFS Auvergne-Rhône-Alpes (St Etienne)**
   Elyès Ben Khalifa, **Maëlle Detoc**, Alain Lefebvre, Julie Huet, Sophie Titoulet, Dominique Legrand, Fabrice Cognasse, Pascal Vallet

   - Communication orale acceptée au XXIXe congrès de la Société Française de la Transfusion Sanguine - Nantes du 18 au 20 septembre 2019

5. **Le stress lié au don de sang : expérience au sein de l'EFS Auvergne-Rhône-Alpes (St Etienne)**
   Elyès Ben Khalifa, **Maëlle Detoc**, Alain Lefebvre, Julie Huet, Sophie Titoulet, Dominique Legrand, Fabrice Cognasse, Pascal Vallet

   - Communication orale acceptée au XXIXe congrès de la Société Française de la Transfusion Sanguine - Nantes du 18 au 20 septembre 2019

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ANNEXES

Questionnaire destiné aux médecins généralistes

Ce questionnaire est entièrement anonyme. Nous vous remercions par avance pour le temps consacré à y répondre

Pour un patient, la décision de participation à un essai clinique dépend de plusieurs paramètres. A ce titre, l'avis du médecin traitant s'avère souvent crucial.
Aussi, nous aimerions connaitre votre attitude face à la situation suivante :
L'un de vos confrères du **C**entre d'**I**nvestigation **C**linique **(CIC)** Vaccinologie du CHU de ST ETIENNE a proposé à l'un de vos patients de participer à un **essai clinique portant sur un vaccin préventif**.
Le patient vient vous voir avec la notice d'information et vous informe de la proposition qui lui a été faite….

A/ Données générales vous concernant

1. Genre
   - ☐ Féminin
   - ☐ Masculin

2. Age :
   - ❑ <30 ans
   - ❑ 30-39 ans
   - ❑ 40-49 ans
   - ❑ 50-59 ans
   - ❑ > 60 ans

3. Quel est votre lieu d'exercice ? (une ou plusieurs réponses possibles)
   - ❑ Centre Hospitalo-Universitaire
   - ❑ Centre Hospitalier
   - ❑ Cabinet libéral

B/ Vous et la vaccination de vos patients

1. Vous considérez que vacciner vos patients ayant une pathologie chronique et suivis par un spécialiste fait partie de vos missions :
   - ❑ Pas du tout d'accord
   - ❑ Plutôt pas d'accord
   - ❑ Plutôt d'accord
   - ❑ Tout à fait d'accord
   - ❑ Je ne sais pas

2. Quand un patient est suivi à l'hôpital pour une pathologie chronique, laissez-vous le service s'occuper des vaccins: ❑ Oui ❑ Non

Si non, Intervenez-vous dans le programme vaccinal :

4.1. Pour vacciner vous-même le patient : ❑ Oui ❑ Non
4.2. Pour limiter ou contrôler les choix proposés à votre patient : ❑ Oui ❑ Non

C/ Mise en situation : L'un de vos patients vous informe que le **C**entre d'**I**nvestigation **C**linique en Vaccinologie lui a proposé de participer à un essai clinique vaccinal préventif, quelle est votre attitude ?

1. Vous donnez **spontanément** votre avis sur sa future participation ?
   - ❑ Pas du tout d'accord
   - ❑ Plutôt pas d'accord
   - ❑ Plutôt d'accord
   - ❑ Tout à fait d'accord
   - ❑ Je ne sais pas

2. Si le patient vous demande votre avis,
   2.1. Vous ne souhaitez pas émettre un avis
   - ❑ Pas du tout d'accord
   - ❑ Plutôt pas d'accord
   - ❑ Plutôt d'accord
   - ❑ Tout à fait d'accord
   - ❑ Je ne sais pas

   2.2. Vous souhaitez plus d'informations avant de vous avancer
   - ❑ Pas du tout d'accord
   - ❑ Plutôt pas d'accord
   - ❑ Plutôt d'accord
   - ❑ Tout à fait d'accord
   - ❑ Je ne sais pas

   2.3. Vous lui donnez votre avis mais le laissez libre de son choix
   - ❑ Pas du tout d'accord
   - ❑ Plutôt pas d'accord
   - ❑ Plutôt d'accord
   - ❑ Tout à fait d'accord
   - ❑ Je ne sais pas

   2.4. Vous le dissuadez de participer
   - ❑ Pas du tout d'accord
   - ❑ Plutôt pas d'accord
   - ❑ Plutôt d'accord
   - ❑ Tout à fait d'accord
   - ❑ Je ne sais pas

   2.5 Vous auriez préféré que votre confrère vous contacte au préalable pour vous présenter l'étude et vous envoie le protocole en question
   - ❑ Pas du tout d'accord
   - ❑ Plutôt pas d'accord
   - ❑ Plutôt d'accord
   - ❑ Tout à fait d'accord
   - ❑ Je ne sais pas

3. Quelles sont les raisons qui pourraient influencer votre décision ?
   3.1 La volonté initiale du patient
   - ❑ Pas du tout d'accord
   - ❑ Plutôt pas d'accord
   - ❑ Plutôt d'accord
   - ❑ Tout à fait d'accord
   - ❑ Je ne sais pas

3.2 L'état clinique du patient
- ❑ Pas du tout d'accord
- ❑ Plutôt pas d'accord
- ❑ Plutôt d'accord
- ❑ Tout à fait d'accord
- ❑ Je ne sais pas

3.3 La pénibilité pour le patient (nombre de visites, mode d'administration du vaccin, procédures de l'étude etc…)
- ❑ Pas du tout d'accord
- ❑ Plutôt pas d'accord
- ❑ Plutôt d'accord
- ❑ Tout à fait d'accord
- ❑ Je ne sais pas

3.4 Le bénéfice attendu pour votre patient
- ❑ Pas du tout d'accord
- ❑ Plutôt pas d'accord
- ❑ Plutôt d'accord
- ❑ Tout à fait d'accord
- ❑ Je ne sais pas

3.5 L'infection ciblée par le vaccin
- ❑ Pas du tout d'accord
- ❑ Plutôt pas d'accord
- ❑ Plutôt d'accord
- ❑ Tout à fait d'accord
- ❑ Je ne sais pas

3.6 Les données de sécurité disponibles
- ❑ Pas du tout d'accord
- ❑ Plutôt pas d'accord
- ❑ Plutôt d'accord
- ❑ Tout à fait d'accord
- ❑ Je ne sais pas

3.7 Le fait que l'étude soit contre placebo
- ❑ Pas du tout d'accord
- ❑ Plutôt pas d'accord
- ❑ Plutôt d'accord
- ❑ Tout à fait d'accord
- ❑ Je ne sais pas

4 Si l'essai proposé était un essai médicamenteux et non vaccinal, votre avis aurait-il été différent ?
- ❑ Pas du tout d'accord
- ❑ Plutôt pas d'accord
- ❑ Plutôt d'accord
- ❑ Tout à fait d'accord
- ❑ Je ne sais pas

D/ Votre lien avec la recherche clinique

1. Avez-vous une activité de recherche clinique ? ❑ Oui ❑ Non

   Si oui,

   1.1. De manière :

   - ☐ Régulière (quotidienne, hebdomadaire)
   - ☐ Fréquente (mensuelle, trimestrielle)
   - ☐ Occasionnelle (semestrielle, annuelle)

   1.2 Faites-vous de la recherche ? (une ou plusieurs réponses possibles)

   - ❑ Epidémiologique
   - ❑ Médicamenteuse
   - ❑ Sur des dispositifs médicaux

Questionnaire destiné aux médecins référents

Ce questionnaire est entièrement anonyme. Nous vous remercions par avance pour le temps consacré à y répondre

Pour un patient, la décision de participation à un essai clinique dépend de plusieurs paramètres. A ce titre, l'avis du médecin référent s'avère souvent crucial.
Aussi, nous aimerions connaitre votre attitude face à la situation suivante :
L'un de vos confrères du **C**entre d'**I**nvestigation **C**linique **(CIC)** en Vaccinologie du CHU de ST ETIENNE a proposé à l'un de vos patients de participer à un **essai clinique vaccinal préventif**.
Le patient vient vous voir avec la notice d'information et vous informe de la proposition qui lui a été faite….

A/ Données générales vous concernant

1. Genre
   - ☐ Féminin
   - ☐ Masculin

2. Age :
   - ❑ <30 ans
   - ❑ 30-39 ans
   - ❑ 40-49 ans
   - ❑ 50-59 ans
   - ❑ > 60 ans

3. Quel est votre lieu d'exercice ? (une ou plusieurs réponses possibles)
   - ❑ Centre Hospitalo-Universitaire
   - ❑ Centre Hospitalier
   - ❑ Cabinet libéral

4. Quelle est votre spécialité ? : _____

B/ Vous et la vaccination de vos patients

1. Vous considérez que vacciner vos patients fait partie de vos missions :

❑ Pas du tout d'accord
❑ Plutôt pas d'accord
❑ Plutôt d'accord
❑ Tout à fait d'accord
❑ Je ne sais pas

2. Vous ne vous occupez que des vaccins spécialement recommandés aux types de patients que vous suivez (ex : patients immunodéprimés et vaccin anti-pneumocoque, etc…)

❑ Pas du tout d'accord
❑ Plutôt pas d'accord
❑ Plutôt d'accord
❑ Tout à fait d'accord
❑ Je ne sais pas

C/ Mise en situation : L'un de vos patients vous informe que le **C**entre d'**I**nvestigation **C**linique en Vaccinologie lui a proposé de participer à un <u>essai clinique vaccinal préventif</u>, quelle est votre attitude ?

1. Vous donnez **spontanément** votre avis sur sa future participation ?
   - ❑ Pas du tout d'accord
   - ❑ Plutôt pas d'accord
   - ❑ Plutôt d'accord
   - ❑ Tout à fait d'accord
   - ❑ Je ne sais pas

2. Si le patient vous demande votre avis,
   2.1. Vous ne souhaitez pas émettre un avis
   - ❑ Pas du tout d'accord
   - ❑ Plutôt pas d'accord
   - ❑ Plutôt d'accord
   - ❑ Tout à fait d'accord
   - ❑ Je ne sais pas

   2.2. Vous souhaitez plus d'informations avant de vous avancer
   - ❑ Pas du tout d'accord
   - ❑ Plutôt pas d'accord
   - ❑ Plutôt d'accord
   - ❑ Tout à fait d'accord
   - ❑ Je ne sais pas

   2.3. Vous lui donnez votre avis mais le laissez libre de son choix
   - ❑ Pas du tout d'accord
   - ❑ Plutôt pas d'accord
   - ❑ Plutôt d'accord
   - ❑ Tout à fait d'accord
   - ❑ Je ne sais pas

   2.4. Vous le dissuadez de participer
   - ❑ Pas du tout d'accord
   - ❑ Plutôt pas d'accord
   - ❑ Plutôt d'accord
   - ❑ Tout à fait d'accord
   - ❑ Je ne sais pas

   2.5 Vous auriez préféré que votre confrère vous contacte au préalable pour vous présenter l'étude et vous envoie le protocole en question
   - ❑ Pas du tout d'accord
   - ❑ Plutôt pas d'accord
   - ❑ Plutôt d'accord
   - ❑ Tout à fait d'accord
   - ❑ Je ne sais pas

3. Quelles sont les raisons qui pourraient influencer votre décision ?
   3.1 La volonté initiale du patient
   - ❑ Pas du tout d'accord
   - ❑ Plutôt pas d'accord
   - ❑ Plutôt d'accord
   - ❑ Tout à fait d'accord
   - ❑ Je ne sais pas

3.2 L'état clinique du patient
- ❑ Pas du tout d'accord
- ❑ Plutôt pas d'accord
- ❑ Plutôt d'accord
- ❑ Tout à fait d'accord
- ❑ Je ne sais pas

3.3 La pénibilité pour le patient (nombre de visites, mode d'administration du vaccin, procédures de l'étude etc…)
- ❑ Pas du tout d'accord
- ❑ Plutôt pas d'accord
- ❑ Plutôt d'accord
- ❑ Tout à fait d'accord
- ❑ Je ne sais pas

3.4 Le bénéfice attendu pour votre patient
- ❑ Pas du tout d'accord
- ❑ Plutôt pas d'accord
- ❑ Plutôt d'accord
- ❑ Tout à fait d'accord
- ❑ Je ne sais pas

3.5 L'infection ciblée par le vaccin
- ❑ Pas du tout d'accord
- ❑ Plutôt pas d'accord
- ❑ Plutôt d'accord
- ❑ Tout à fait d'accord
- ❑ Je ne sais pas

3.6 Les données de sécurité disponibles
- ❑ Pas du tout d'accord
- ❑ Plutôt pas d'accord
- ❑ Plutôt d'accord
- ❑ Tout à fait d'accord
- ❑ Je ne sais pas

3.7 Le fait que l'étude soit contre placebo
- ❑ Pas du tout d'accord
- ❑ Plutôt pas d'accord
- ❑ Plutôt d'accord
- ❑ Tout à fait d'accord
- ❑ Je ne sais pas

4 Si l'essai proposé était un essai médicamenteux et non vaccinal, votre avis aurait-il été différent ?
- ❑ Pas du tout d'accord
- ❑ Plutôt pas d'accord
- ❑ Plutôt d'accord
- ❑ Tout à fait d'accord
- ❑ Je ne sais pas

D/ Votre lien avec la recherche clinique

1. Avez-vous une activité de recherche clinique ? ❑ Oui ❑ Non

   Si oui,

   1.1. De manière :

   - ☐ Régulière (quotidienne, hebdomadaire)
   - ☐ Fréquente (mensuelle, trimestrielle)
   - ☐ Occasionnelle (semestrielle, annuelle)

   1.2 Faites-vous de la recherche ? (une ou plusieurs réponses possibles)

   - ❑ Epidémiologique
   - ❑ Médicamenteuse
   - ❑ Sur des dispositifs médicaux

JE SUIS D'ACCORD POUR PARTICIPER A UN ESSAI CLINIQUE VACCINAL

MERCI DE BIEN VOULOIR COMPLETER CE QUESTIONNAIRE.
Une fois complété, merci de bien vouloir le mettre dans l'enveloppe jointe.

*Ce **questionnaire anonyme** s'adresse aux personnes sélectionnées pour participer à un essai clinique vaccinal préventif et qui ont accepté d'y participer. Nous aimerions connaître les facteurs influençant votre participation à un essai clinique vaccinal. Ceci permettra d'optimiser notre activité et de vous apporter des réponses adaptées. Nous vous remercions pour vos réponses.*

A. Vous

1/ Genre
- ☐ Féminin
- ☐ Masculin

2/ Age: _____

3/ Quel est votre niveau d'études ?
- ☐ Brevet des collèges (ou certificat d'études)
- ☐ CAP/BEP
- ☐ Baccalauréat
- ☐ Bac +2
- ☐ Bac +3/+4
- ☐ Bac +5 et plus

4/ Quelle est votre catégorie socio-professionnelle ?
- ☐ Agriculteur
- ☐ Artisan, commerçant, chef d'entreprise
- ☐ Profession libérale
- ☐ Enseignants
- ☐ Cadre
- ☐ Profession intermédiaire
- ☐ Employé
- ☐ Ouvrier
- ☐ Etudiant
- ☐ Retraité
- ☐ Sans emploi
- ☐ En congé parental
- ☐ Autre : _____

5/ A combien de kilomètres du centre de recherche clinique habitez-vous?
- ☐ < 10 km
- ☐ 10 et 30 km
- ☐ 30 et 50 km
- ☐ > 50 km

6/ Avez-vous des enfants ?
- ☐ Oui, nombre d'enfants : _____
- ☐ Non

B. L'étude clinique proposée

1/ Comment avez-vous eu connaissance de l'étude ?

- ☐ Par le médecin du centre de recherche
- ☐ Par un autre médecin (votre médecin traitant, votre médecin spécialiste…)
- ☐ Affiche
- ☐ Presse
- ☐ Bouche à oreille
- ☐ Annonce sur Internet
- ☐ Courrier postal/mail
- ☐ Autres, précisez : _____

2/ Avez-vous déjà participé à une étude de recherche médicale dans le passé ?

- ☐ Oui
- ☐ Non

3/ Avant que l'on vous propose cette étude, étiez-vous sensibilisé à la recherche médicale ?

- ☐ Oui
- ☐ Non

Si oui, pourquoi ?_____

4/ Quelle a été votre réaction lorsque l'on vous a proposé de participer à cette étude:

Avez-vous été surpris ? ❑ Oui ❑ Non
Avez-vous été choqués ? ❑ Oui ❑ Non
Avez-vous considéré cela comme « naturel » ? ❑ Oui ❑ Non
Vous êtes-vous senti obligé de dire « oui » ? ❑ Oui ❑ Non
Pensez-vous avoir eu assez de temps pour prendre votre décision ? ❑ Oui ❑ Non
Aviez-vous des craintes particulières du fait que ce soit un vaccin qui soit à l'essai ? ❑ Oui ❑ Non

5/ Avez-vous pensé que vous preniez un risque en donnant votre accord pour participer ? ❑ Oui ❑ Non

6/ Si l'on vous dit « recherche médicale » quel mot vous vient immédiatement à l'esprit ?

_____

7/ Quelles ont été les raisons principales qui ont motivé votre décision? *(Une ou plusieurs réponses possibles. **Numérotez la raison de la plus importante à la moins importante si plusieurs raisons ont motivées votre choix)***
Par ordre :

[ ] ❑ Pour aider la recherche/faire avancer la science
[ ] ❑ Pour aider mon prochain/protéger les autres
[ ] ❑ Pour me protéger de la maladie prévenue par le vaccin
[ ] ❑ Parce que je me sens concerné(e) par ce sujet/cette maladie
[ ] ❑ Parce que l'étude est indemnisée
[ ] ❑ Autres, précisez : _____

8/ Quels ont été les points qui ont contribué à prendre votre décision? *(Plusieurs réponses sont possibles)* ***Numérotez la raison de la plus importante à la moins importante si plusieurs raisons ont motivées votre choix***
Par ordre :

[ ] ❑ Qualité de l'information donnée par le médecin
[ ] ❑ La thématique de l'essai
[ ] ❑ L'avis de votre entourage
[ ] ❑ L'avis de votre médecin traitant ou médecin spécialiste
[ ] ❑ Le suivi médical prévu pour cette étude
[ ] ❑ L'indemnisation si telle était le cas
[ ] ❑ La possibilité de se rétracter à tout moment

9/ Concernant cette étude, avez-vous demandé son avis à votre médecin traitant ?

- ☐ Oui
- ☐ Non

Si oui, en avez-vous tenu compte pour prendre votre décision ?

- ☐ Oui
- ☐ Non

10/ Concernant cette étude, avez-vous demandé son avis à une autre personne ?

- ☐ Oui
- ☐ Non

Si oui, laquelle ? _____

11/ De manière générale, êtes-vous plutôt pour ou contre la vaccination ?

- ☐ Plutôt pour
- ☐ Plutôt contre

12/ Etes-vous à jour de vos vaccins ?

- ☐ Oui
- ☐ Non
- ☐ Je ne sais pas

13/ Accepteriez-vous de participer à un essai clinique pour tester un vaccin expérimental contre le VIH ?

- ☐ Oui
- ☐ Non

Quelle que soit la réponse,
pourquoi ?_____
_____

14/ Accepteriez-vous de participer à un essai clinique étudiant un nouveau vaccin contre l'hépatite B ?

- ☐ Oui
- ☐ Non

Quelle que soit la réponse,
pourquoi ?_____
_____

15/ Accepteriez-vous de participer à un essai clinique étudiant un nouveau vaccin contre la grippe ?

- ☐ Oui
- ☐ Non

Quelle que soit la réponse,
pourquoi ?_____
_____

16/ Accepteriez-vous de participer à un essai clinique étudiant un nouveau vaccin contre HPV (Human Papillomavirus) ?

- ☐ Oui
- ☐ Non

Quelle que soit la réponse,
pourquoi ?_____
_____

17/ Etes-vous d'accord pour répondre à une enquête rétrospective à la fin de l'étude afin de connaître votre ressenti après votre participation?

- ☐ Oui
- ☐ Non

18/ Qu'est ce qui aurait pu vous faire **refuser** de participer à l'essai proposé ?

_____
_____
_____

JE NE SOUHAITE PAS PARTICIPER A UN ESSAI CLINIQUE VACCINAL

MERCI DE BIEN VOULOIR COMPLETER CE QUESTIONNAIRE.
Une fois complété, merci de bien vouloir le mettre dans l'enveloppe jointe.

*Ce **questionnaire anonyme** s'adresse aux personnes sélectionnées pour participer à un essai clinique vaccinal préventif et qui, après information, n'ont finalement pas souhaité y participer. Nous aimerions connaître les facteurs influençant votre non-participation à un essai clinique vaccinal. Ceci permettra d'optimiser notre activité et de vous apporter des réponses adaptées.*
Nous vous remercions pour vos réponses.

A. Vous

1/ Genre
- ☐ Féminin
- ☐ Masculin

2/ Age: _____

3/ Quel est votre niveau d'études ?
- ☐ Brevet des collèges (ou certificat d'études)
- ☐ CAP/BEP
- ☐ Baccalauréat
- ☐ Bac +2
- ☐ Bac +3/+4
- ☐ Bac +5 et plus

4/ Quelle est votre catégorie socio-professionnelle ?
- ☐ Agriculteur
- ☐ Artisan, commerçant, chef d'entreprise
- ☐ Profession libérale
- ☐ Enseignants
- ☐ Cadre
- ☐ Profession intermédiaire
- ☐ Employé
- ☐ Ouvrier
- ☐ Etudiant
- ☐ Retraité
- ☐ Sans emploi
- ☐ En congé parental
- ☐ Autre : _____

5/ A combien de kilomètres du centre de recherche clinique habitez-vous?
- ☐ < 10 km
- ☐ Entre 10 et 30 km
- ☐ Entre 30 et 50 km
- ☐ > 50 km

6/ Avez-vous des enfants ?
- ☐ Oui, nombre d'enfants : _____
- ☐ Non

B. L'étude clinique proposée

1/ Comment avez-vous eu connaissance de l'étude ?

- ☐ Par le médecin du centre de recherche
- ☐ Par un autre médecin (votre médecin traitant, votre médecin spécialiste…)
- ☐ Affiche
- ☐ Presse
- ☐ Bouche à oreille
- ☐ Annonce sur Internet
- ☐ Courrier postal/mail
- ☐ Autres, précisez : _____

2/ Avez-vous déjà participé à une étude clinique dans le passé ?

- ☐ Oui
- ☐ Non

3/ Avant que l'on vous propose cette étude, étiez-vous sensibilisé à la recherche médicale ?

- ☐ Oui
- ☐ Non

Si oui,
pourquoi ?_____
_____

4/ Si l'on vous dit « recherche clinique » quel mot vous vient immédiatement à l'esprit ?
_____

5/ Quelle(s) ont été la(les) principale(s) raison(s) de votre refus? (***Si plusieurs réponses merci de numérotez de la raison la plus importante à la moins importante)***
Par ordre :

- [ ] ❑ Je ne veux pas participer à un projet de recherche
- [ ] ❑ J'ai peur suite à l'essai médicamenteux de Rennes
- [ ] ❑ Je ne suis pas un cobaye
- [ ] ❑ J'ai eu une mauvaise expérience dans le passé
- [ ] ❑ J'ai peur des effets secondaires
- [ ] ❑ Je suis contre les vaccins
- [ ] ❑ J'ai peur des éléments constituants le vaccin
- [ ] ❑ Je ne suis pas certain de l'efficacité du vaccin
- [ ] ❑ Je ne veux pas que l'on m'injecte un produit
- [ ] ❑ J'ai peur des piqûres/des aiguilles
- [ ] ❑ Je pense que je ne risque pas d'attraper la maladie concernée par ce vaccin
- [ ] ❑ L'étude n'est pas assez bien indemnisée
- [ ] ❑ Je n'ai pas le temps de venir aux rendez-vous
- [ ] ❑ J'habite trop loin
- [ ] ❑ Mon médecin traitant me l'a déconseillé
- [ ] ❑ Mon entourage (Famille/amis) me l'a déconseillé
- [ ] ❑ Croyances/Religion/Culture
- [ ] ❑ Je me méfie des études promues par les firmes pharmaceutiques
- [ ] ❑ J'ai l'impression que mon intérêt passe après celui de la réalisation de l'étude

6/ Concernant cette étude, avez-vous demandé son avis à votre médecin traitant ?

- ☐ Oui
- ☐ Non

Si oui, en avez-vous tenu compte pour prendre votre décision ?

- ☐ Oui
- ☐ Non

7/ Concernant cette étude, avez-vous demandé son avis à une autre personne ?

- ☐ Oui
- ☐ Non

Si oui, laquelle ? _____

8/ De manière générale, êtes-vous plutôt pour ou contre la vaccination ?

- ☐ Plutôt pour
- ☐ Plutôt contre

9/ Etes-vous à jour de vos vaccins ?

- ☐ Oui
- ☐ Non
- ☐ Je ne sais pas

10/ Auriez-vous accepté de participer si l'étude ne concernait pas un vaccin mais un médicament expérimental?

- ☐ Oui
- ☐ Non

Si oui, pourquoi ?

_____
_____
_____

11/ Auriez-vous accepté de participer à un essai clinique pour tester un vaccin expérimental contre le VIH ?

- ☐ Oui
- ☐ Non

Si oui,
pourquoi ?_____
_____

12/ Auriez-vous accepté de participer à un essai clinique étudiant un nouveau vaccin contre l'hépatite B ?

- ☐ Oui
- ☐ Non

Si oui,
pourquoi ?_____
_____
_____

13/ Auriez-vous accepté de participer à un essai clinique étudiant un nouveau vaccin contre la grippe ?

- ☐ Oui
- ☐ Non

Si oui,
pourquoi ?_____
_____
_____

14/ Pensez-vous que votre décision aurait été différente dans le cas où vous auriez été personnellement concerné par la maladie ciblée ?

- ☐ Oui
- ☐ Non
- ☐ Peut-être

Pourquoi ?_____
_____
_____

15/ Qu'est ce qui aurait pu vous faire **accepter** de participer à l'essai proposé ?

_____
_____
_____