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Protocolo

Development of vaccines for Chagas disease (CRUZIVAX): stakeholders' preferences and potential impacts on healthcare

Francesco Ramponi[a], Céline Aerts[a], Paula Sartor[b,c], María Jesús Pinazo[a], Héctor Freilij[d], Carlos A. Guzmán[e], Emilio Malchiodi[f,g], Elisa Sicuri[a,h,*]

[a] *ISGlobal, Hospital Clínic, Universitat de Barcelona, Barcelona, Spain*
[b] *Región Sanitaria 5, Ministerio de Salud del Chaco, Juan José Castelli, Chaco, Argentina*
[c] *Universidad Nacional del Nordeste, Facultad de Ciencias Exactas Naturales y Agrimensura, Corrientes Capital, Argentina*
[d] *Hospital de Niños Ricardo Gutiérrez, Buenos Aires, Argentina*
[e] *Department of Vaccinology and Applied Microbiology, Helmholtz Centre for Infection Research, Braunschweig, Germany*
[f] *Universidad de Buenos Aires, Facultad de Farmacia y Bioquímica, Cátedra de Inmunología, and Instituto de Estudios de la Inmunidad Humoral Ricardo A. Margni (IDEHU), UBA-CONICET, Buenos Aires, Argentina*
[g] *Universidad de Buenos Aires, Facultad de Medicina, Departamento de Microbiología, Parasitología e Inmunología, and Instituto de Microbiología y Parasitología Médica (IMPaM), UBA-CONICET, Buenos Aires, Argentina*
[h] *LSE Health, London School of Economics & Political Science, London, United Kingdom*

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ABSTRACT

A vaccine for Chagas disease does not currently exist. This study aims to inform the development of two vaccines for the prevention and treatment of *Trypanosoma cruzi* infection, and guide their pre-clinical phase up to clinical phase I. The three main objectives are: 1) to explore patients' and policy makers' preferences on the candidate vaccines in Argentina and Spain; 2) to investigate health-related quality of life of patients affected by Chagas disease; and 3) to assess the potential health provider savings associated with the vaccines, in terms of resource use and health care costs. Discrete choice experiments will be employed to estimate and characterize the theoretical demand for the vaccines and investigate patients' and policy makers' preferences. Health-related quality of life will be assessed using the EQ-5D-3L questionnaire. Resources use and costs associated with Chagas disease will be investigated using information from the databases of the Hospital Clínic of Barcelona.

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Desarrollo de vacunas para la enfermedad de Chagas (CRUZIVAX): preferencias de las partes interesadas y posibles impactos en la asistencia sanitaria

Palabras clave:
Enfermedad de Chagas
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Preferencias del paciente
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RESUMEN

No existen vacunas para la enfermedad de Chagas. Este trabajo pretende informar la fase preclínica de dos vacunas para la prevención y el tratamiento de la infección por *Trypanosoma cruzi*. Los objetivos principales son tres: 1) investigar las preferencias de los pacientes y de los responsables de políticas sanitarias en Argentina y España; 2) investigar la calidad de vida relacionada con la salud de los pacientes afectados por la enfermedad de Chagas; y 3) estimar los ahorros potenciales asociados con las vacunas para los proveedores de salud. Se usarán experimentos de elección discreta para estimar y caracterizar la demanda teórica de las vacunas e investigar las preferencias de los pacientes y de los responsables de las políticas sanitarias. La calidad de vida relacionada con la salud se evaluará mediante el cuestionario EQ-5D-3L. Se investigarán el uso de recursos y los costes asociados a la enfermedad de Chagas utilizando bases de datos del Hospital Clínic de Barcelona.

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Introduction

Chagas disease is caused by infection with the *Trypanosoma cruzi* parasite and it is one of the 20 neglected tropical diseases recognized by the World Health Organization.[1] Seventy million people worldwide are at risk of infection, and 6-8 million people are affected by Chagas disease.[2] Most of infected individuals

* Corresponding author.
E-mail addresses: elisa.sicuri@isglobal.org, e.sicuri@lse.ac.uk (E. Sicuri).

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live in Latin America, and have low access to prevention, diagnosis and treatment of the infection.[3] Currently available treatments have substantial limitations, and parasitological cure can only be achieved when treatment is delivered in the acute phase of the disease, or at early stages of its chronic phase.[4] A prophylactic vaccine against Chagas disease does not exist, and the most effective prevention strategies are vector control, and control of other routes of transmission. However, research is currently underway to develop a prophylactic and therapeutic vaccine for Chagas disease (CRUZIVAX^{TM}). Initial pre-clinical studies and results from laboratory studies are promising,[5,6] and work aimed at first-in-man studies is undergoing.

This study focuses on the Gran Chaco region, which spans in Argentina, Bolivia and Paraguay, and has a very high burden of Chagas disease. In many rural villages of this region, *T. cruzi* seroprevalence varies between 20% and 50% among children and adolescents under 15 years of age.[7,8] Because of migration, Chagas disease has become a public health problem also in non-endemic areas.[9–11] Therefore, this study focuses on Spain, which is the main destination of Latin American emigration to Europe.[12] Because of the migration flows, the number of cases of *T. cruzi* infection diagnosed in Spain has increased dramatically in the last decade.[11] For example, in a neighborhood of Barcelona, the prevalence of Chagas disease among primary care patients from Latin America reached 2.87% in 2011,[12] and a 3.4% infection prevalence in pregnant women and a 7.3% rate of transmission to their newborns were estimated in the maternity wards of two large hospitals.[13]

The costs associated with Chagas disease can very high,[14–16] and the development of a vaccine could help to reduce the substantial impact of Chagas disease on health system resources. However, few studies have attempted to estimate the economic value of potential vaccines.[17–19] Furthermore, little information is available on the preferences of the population affected by Chagas disease and their potential demand for technologies that are under development.[20] Evidence on health-related quality of life (HRQoL) of patients with Chagas disease is scarce.[21]

The aim of this work is to provide health economic evidence to inform the initial phase of the vaccine development. This study has three main objectives: 1) to estimate preferences and potential demand curve for the candidate vaccine CRUZIVAX^{TM} among individuals at-risk, infected population, and health policy makers; 2) to estimate the HRQoL of patients with Chagas disease and of people at risk of being infected in endemic and non-endemic areas; and 3) to assess lifetime costs of disease to estimate the potential savings generated by the CRUZIVAX^{TM} vaccine.

Method

Design

The theoretical demand will be characterized using a discrete choice experiment (DCE). The study will include four versions of the DCE: 1) DCE on the prophylactic vaccine, addressed to health policy makers; 2) DCE on the prophylactic vaccine, addressed to individuals at risk of infection or already infected; 3) DCE on the therapeutic vaccine, addressed to health policy makers; and 4) DCE on the therapeutic vaccine, addressed to individuals at risk of infection or already infected. The content of the DCE for the individuals at risk looks at the specific characteristics of the vaccine (*e.g.*, the way the vaccine is administered, the severity and duration of the adverse reaction, and the price per vaccine dose), and will be used to explore the relative importance of each attribute and its levels in the individual's decision of whether or not to get the vaccine for themselves, or for a family member. The content of the DCE targeted to health policy-makers focuses on characteristics of the health system and on financial issues (*e.g.*, the feasibility of adding the Chagas vaccine to national vaccination programs in endemic areas). Of note, the DCE for the preventive vaccine administered to policy makers refers only to Argentina. A therapeutic vaccine would be of interest in both Argentina and Spain.

To obtain information on HRQoL, the EQ-5D questionnaire will be used, which allows to estimate quality-adjusted life years. HRQoL data and DCE responses will be collected from the same patients.

Data on the use of health care resources by patients with Chagas disease over time will be obtained from the clinical databases of the Hospital Clínic of Barcelona (Spain). Unit costs and individual patient data on the use of healthcare resources will be used to estimate the costs of outpatient and inpatient interventions and total lifetime follow-up cost for patients.

Setting

Data collection will take place in Barcelona (Spain) and in two Argentinian provinces: San Juan (Cuyo region, west Argentina) and Chaco (Northeast region). Both provinces are categorized as being at high risk of vector transmission. Moreover, "urban triatomism" (*i.e.*, *T. cruzi* infection happening in urban areas) is reported in San Juan.[22]

Tools and materials for data collection

Vaccine attributes and levels for the DCE were chosen using the Delphi method. The most relevant attributes and levels of the vaccine were identified by a group of 16 experts. DCE were created using series of 12 sets of options regarding the characteristics of the vaccine, generated using a statistical software (STATA). For each set of options, two alternatives were created, which report different values for each of the vaccine characteristics. Respondents can choose their preferred alternative in each set. In the electronic version the DCE will be accompanied by drawings of each of the characteristics and their values.

In addition to the DCEs, the data collection tool for patients includes the EQ-5D-3L questionnaire, which assesses the following components of HRQoL: mobility; self-care; activities of daily living; pain/discomfort; and anxiety/depression.

Questionnaires including DCEs for both prophylactic and therapeutic vaccination and the HRQoL questionnaire are provided in online Appendices A and B. The questionnaires for patients in Argentina collect also socio-economic and demographic data, such as age, sex, level of education, occupation, and housing characteristics, as well as data on symptoms related to the progression of Chagas disease. Data collected in Spain can be linked to the hospital database, which contains clinical and socio-demographic information. The DCE survey for health policy makers in Spain is reported in online Appendix C; the survey for Argentinian and international policy makers is reported in online Appendix D.

Additional information on data collection and management is provided in online Appendix E.

Statistical analysis

The data collected with the DCEs for the therapeutic and the prophylactic vaccines will be analyzed separately, following good research practices in terms of the statistical models applied.[23] Statistical analyses will be conducted using Stata.

For the estimation of the HRQoL determinants of patients with Chagas disease and of people at risk of infection, a multivariate model based on a Beta distribution will be adopted.[24] In addition to clinical factors, the analysis will control for sociodemographic characteristics to isolate the impact of the disease on quality of

life. For example, we will explore differences between rural and urban settings, and we will investigate whether gender, ethnicity and socio-economic status are relevant factors affecting the HRQoL of patients affected by Chagas disease.

To estimate the lifetime costs of Chagas disease, the use of health care resources will be investigated using information from the clinical database of the Hospital Clínic of Barcelona. Clinical follow-up records of patients with *T. cruzi* infection will be retrieved from the Hospital Clínic database, which includes information on patients' use of resources from the time of positive diagnosis. Unit costs of the interventions will be obtained using costings list from the Hospital Clinic. The costs associated with each contact with the health facility will be estimated from the provider's perspective. The data analysis will follow the methods adopted by Basu and Manning[25] to estimate lifetime cost of illness by controlling for censoring cases.

Discussion

We acknowledge that the COVID-19 pandemic might affect the capability of conducting the planned interviews with patients, the duration of data collection and the minimum sample size targets. Further, we are aware that, to generalize the findings of the case study analysis conducted at the Hospital Clínic in Barcelona to endemic settings, additional information and assumptions on the different unit costs, health care practices, patients' access to the health system and disease prevalence will be required. However, we believe that this study will provide new and crucial information on preferences around the new potential vaccines, characteristics of the target population and potential impact on the health systems in endemic and non-endemic settings. The results of the study may be useful to guide the development of new technologies, with the aim of maximizing their coverage once they are ready and available on the market.

Ethics approval and consent to participate

The study protocol, tools for data collection and informed consents have been approved by the Ethics Committee of the Hospital Clínic de Barcelona (CEim Hospital Clínic) in Spain, and by the Ethics Committee of the Ministry of Public Health of San Juan and Facultad de Ciencias Exactas, Naturales y Agrimensura de la Universidad Nacional del Nordeste in Argentina (see online Appendix F).

Participants provided the informed consent to enter the study. Information and informed consent forms are provided in online Appendix G.

Consent for publication

Participants provided their consent for information about themselves to be published.

Availability of databases and material for replication

Not applicable to this article.

Related articles

No other publications containing the results of this study have already been published or submitted to any journal.

Study status

At the time of this submission participant recruitment was not completed.

Editor in charge

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Authorship contributions

E. Sicuri conceived the study. E. Sicuri, C. Aerts, H. Freilij, C.A. Guzmán, P. Sartor, M.J. Pinazo, F. Ramponi and E. Malchiodi contributed to the study design. E. Sicuri and C. Aerts designed the data collection tools and wrote the first draft of the protocol. F. Ramponi and E. Sicuri wrote the final version of the manuscript with substantial intellectual contribution and by incorporating the contribution from all the authors. All authors provided critical revision of the manuscript each one according to their respective expertise. All authors approved the final version of the protocol.

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Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.gaceta.2022.102275.

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