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HABILITATION A DIRIGER DES RECHERCHES

Ecole doctorale Sociétés, Politiques, Santé Publique (SP2)
Spécialité Santé Publique

Approches statistiques intégratives et développements méthodologiques pour optimiser la recherche clinique vaccinale

Statistical approaches and methodological developments to optimize clinical vaccine research

Présentée et soutenue publiquement
Presented and defended in public

Le 17 décembre 2019
On 17 December 2019

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Née le 22 février 1979 à Munich, Allemagne
Born on 22 February 1979 in Munich, Germany

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I am very grateful and honoured that you accepted to judge my research and HDR thesis as one of the main examiners. This is a particular pleasure for me, since you also judged my PhD thesis in 2013. Thank you very much for travelling to Bordeaux for the defence. I am looking forward to benefitting from your expertise in clinical trial methodology and biostatistics and to discussing my work with you.

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Je vous exprime mes plus sincères remerciements d'avoir accepté de juger mon HDR en tant que rapportrice et de faire le déplacement à Bordeaux pour la soutenance. Votre grande expérience dans l'épidémiologie clinique me fournira assurément des éléments de réflexion et discussion.

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Je tiens à te remercier vivement d'avoir accepté d'être rapportrice de mon HDR. Ton expertise en épidémiologie clinique contribuera à améliorer mon projet hospitalo-universitaire. Je te témoigne aussi ma grande reconnaissance pour tes conseils concernant mes autres activités hospitalo-universitaires.

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Je tiens à te remercier vivement d'avoir accepté de présider mon jury d'HDR. Ta vision scientifique et analytique en épidémiologie et santé publique et tes conseils sur mon parcours hospitalo-universitaire me sont précieux.

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Je te remercie chaleureusement de ta confiance et pour tout ce que tu m'as appris depuis que nous travaillons ensemble. Ton grand enthousiasme quotidien pour la recherche est une source de motivation pour moi. Tes compétences et les discussions que nous pouvons avoir ensemble restent primordiales pour mon travail et mon projet hospitalo-universitaire.

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Je vous suis profondément reconnaissante du savoir-faire et de la rigueur méthodologique que vous m'avais transmis. J'ai énormément appris sur le plan scientifique et stratégique en travaillant étroitement avec vous depuis mon arrivée à l'ISPED en 2007. Je vous remercie de votre soutien dans ma carrière académique et de votre confiance. Je vous souhaite le meilleur pour votre nouvelle fonction à Santé Publique France.

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To my family, with fond memories of my mother Hella Richert

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PREAMBLE

In this preamble, I propose to briefly present my professional background and to evoke the key elements that guided my choices and led me to develop my current research themes. My detailed curriculum vitae and research activities are presented later in this document.

After my medical studies at the University of Freiburg in Germany, including one exchange year at the University of Bordeaux and hospital internships in Italy and Bordeaux, I obtained my medical degree and medical thesis in Germany in 2005.

I then began my professional career at the University Hospitals of Geneva in Switzerland, where I worked in the team of Professor René Rizzoli (Bone Disease Division, Department of Geriatrics) from January 2006 to September 2007. This is a hospital division with a strong research focus on metabolic bone diseases (osteoporosis and abnormalities of phosphocalcic metabolism), covering both basic and clinical research projects. During this period, I carried out hospital medical consultations as an M.D. In addition, I was in charge of coordinating observational clinical studies and clinical trials as a research project manager, and I also had a role as a clinical co-investigator in the department. This experience very much influenced my choice to pursue my further path in clinical epidemiology, and I remain grateful to Professor Rizzoli that he gave me the opportunity to discover this research field.

For both professional and personal reasons I moved to Bordeaux in October 2007 and have been working at the School of Public Health (ISPED) of the University of Bordeaux since then. I was first a clinical trial project manager at the Clinical Trials Unit (head: Professor Geneviève Chêne) of the Bordeaux Inserm Research Centre and the ANRS (French National Agency for Research on AIDS and hepatitis) until September 2010. In this position, I was responsible for the coordination of academic multicenter clinical trials of HIV treatments, in particular a large European randomized phase III multicenter trial comparing two antiretroviral strategies. In parallel, thanks to the support of Geneviève Chêne who has always encouraged and supported me to continue my academic training and career, I obtained a Master 2 Research degree in Public Health, option clinical epidemiology, in 2010 at ISPED.

I then did my PhD in Public Health and Epidemiology at the University of Bordeaux from 2010 to 2013 under the supervision of Professor Geneviève Chêne and Professor Rodolphe Thiébaut, both of whom I closely work with until today. My PhD research, which was funded by a young researcher grant from the non-governmental organisation Sidaction, focused on trial design and analysis of endpoints in HIV vaccine trials. This gave me the chance to specialize in clinical vaccine research at a time when this research topic started emerging within the Inserm Research Center thanks to a strong collaboration with the French « Labex » Vaccine Research Institute (VRI) that was created in 2011.

After obtaining my PhD degree in 2013, I had the opportunity to take on a position as an assistant professor (« AHU ») in Public Health and then be tenured as an associate professor in Public Health and Biostatistics (« MCU-PH », subsection 46.04 in the French university system) since 2016. This

position, which is affiliated with both the University of Bordeaux and the University Hospital, comprises teaching and research as well as hospital activities.

In the last years, my hospital activities in the Public Health Department of the University Hospital of Bordeaux were devoted to my role as co-head (together with Professor Geneviève Chêne until October 2019) of the international clinical trials platform EUCLID/F-CRIN at the Clinical Investigation Center (CIC 1401) and as a methodologist at the Clinical Epidemiology Unit (« USMR ») in the Medical Information Division (head of division: Professor Rodolphe Thiébaut). I have taken over the responsibility of interim team head of the USMR unit in October 2019 and will take over the coordination of the Clinical Epidemiology module of the Clinical Investigation Center as well as the role of the head of the EUCLID/F-CRIN platform starting from November 2019. All three structures are dedicated to clinical research activities, in particular to study methodology and statistics.

I teach statistics and epidemiology at the Faculty of Medicine and at the School of Public Health, where I am responsible for two teaching units at the Master's degree level (teaching unit "Principles of clinical trials" in the Master 2 Epidemiology and teaching unit « Omics data » in the Master 2 Public Health Data Science) and co-responsible of the university diploma (« DU ») in clinical research.

For my research activities, I am affiliated with the SISTM team ("Statistics In System Biology and Translational Medicine") at the Inserm Research Center U1219 and Inria (team head: Professor Rodolphe Thiébaut), where I lead a research axis on translational vaccinology that was created 2019. Pursuing my research on methodological and statistical aspects in vaccine clinical development since my PhD, I have extended it to cover systems vaccinology approaches, which combine statistical methods for high dimensional immunogenicity data with biological knowledge to better understand the immune response to vaccines. My research, which is situated at the interface between biostatistics, clinical epidemiology, immunology, and vaccinology, is currently mainly applied to trials evaluating HIV and Ebola vaccines conducted in collaboration with the VRI or within international research consortia. As part of my research activities, I am also a clinical trial methodologist at the Clinical Trials Unit of the Inserm U1219 Research Center in Bordeaux, particularly for vaccine and immunotherapy trials of the VRI and ANRS, as well as for the vaccine trials of the international clinical trials platform EUCLID/F-CRIN.

To gain a better understanding of immunological mechanisms and the relevant laboratory assay methods I spent two times six months as a visiting researcher in the team "Virus Immunology" of Professor Marcus Altfeld at the "Heinrich Pette Institute", Leibniz Institute for Experimental Virology (Hamburg, Germany) in 2016 and 2018, which has resulted in a fruitful and durable collaboration between our teams.

In terms of research supervision, I have been supervising the PhD thesis of Edouard Lhomme, who did his PhD research on the modelling of the immunological response to HIV and Ebola vaccines and who will defend his PhD in November 2019. In addition, I have directed four Master 2 research projects in

epidemiology since 2013, I have been the academic referent for two Master 1 theses in Public Health and I supervise public health interns and research engineers on a daily basis.

Although my research development has brought me now to dedicating considerable portions of my research time to disentangle immune response mechanisms at the cell level by using appropriate statistical methods, I have not lost sight of the public health perspective that is embodied by the development of new vaccines. Indeed, I am deeply convinced that safe and efficacious vaccines can very much contribute to improving population health, although I do not neglect that large challenges for successful vaccine implementation also reside in social and communication science and vaccine acceptability. Like many other research fields, current vaccine research is intricate, and interdisciplinary collaborations are necessary to move towards the aim. I am proud to be a small part of this endeavor, and my enthusiasm for this research persists during my every-day work.

I am very much grateful to all those who have helped and comforted me in this journey, in particular my mentors, Professor Rodolphe Thiébaut and Professor Geneviève Chêne. I am also thankful to my colleagues and collaborators locally, at the VRI, and beyond, who make my research activities a rich learning experience every day, both in terms of science and in terms of personal encounters.

CURRICULUM VITAE

CIVIL STATUS

Born on 22 February 1979 in Munich, Germany

Professional address: Inserm U1219 « Bordeaux Population Health Research Center », ISPED, University of Bordeaux, F-33076 Bordeaux cedex, France

E-mail: laura.richert@u-bordeaux.fr

CURRENT POSITION

Since September 2016: **Associate Professor in Public Health (Maître de conférences des universités – praticien hospitalier), University and University Hospital of Bordeaux, France** (sub-section CNU 46.04: biostatistics, medical information and communication technologies)

- Researcher in the SISTM team ("Statistics In System Biology and Translational Medicine", head: Pr R. Thiébaut), Inria and Inserm UMR U1219 Bordeaux Population Health Research Center; coordinator of the research axis "Translational Vaccinology" since July 2019
- Lecturer at the Medical Faculty and at the Bordeaux School of Public Health (ISPED), University of Bordeaux
- Clinical Epidemiologist, Clinical Epidemiology Unit ("USMR"), Medical Information Division, Public Health Department, Bordeaux University Hospital (Pr. R. Thiébaut); interim team head since October 2019
- Head of the EUCLID/F-CRIN clinical trials platform (University Hospital Bordeaux, Inserm, University of Bordeaux, Institut Bergonié, University Hospital Limoges), Clinical Investigation Center CIC 1401, University Hospital Bordeaux (head since November 2019; co-head from 2014 to 2019)
- Coordinator of the Clinical Epidemiology module of the Clinical Investigation Center (CIC1401), University Hospital Bordeaux, Inserm, University of Bordeaux and Institut Bergonié (since November 2019)

PROFESSIONAL EXPERIENCE

2016, 2018 Visiting researcher, Department of Virus Immunology, Heinrich Pette Institute, "Leibniz Institute for Experimental Virology", Hamburg, Germany (Prof. M. Altfeld); two times 6 months full-time

2013-2015 Assistant Professor in Public Health, University of Bordeaux and University Hospital of Bordeaux

2010- Clinical trial methodologist, Inserm U897 (later U1219) Research Center, University of Bordeaux, France (methodological coordination of clinical trials evaluating antiretroviral therapies or HIV vaccines; ANRS, Vaccine Research Institute)

2010-2013 PhD student in Public Health, Inserm U897 Research Center, University of Bordeaux

2007-2010 Clinical trials project manager, Clinical Trials Unit of the Inserm U897 Research Center, Bordeaux (national and international clinical trials in the field of HIV treatment; ANRS)

2006-2007 Physician and clinical study project manager, Bone Disease Division, WHO Collaborating Centre for the Prevention of Osteoporosis, Department of Geriatrics, University Hospitals of Geneva, Switzerland (coordination of clinical research studies in metabolic bone diseases; clinical trial co-investigator; medical consultations)

DIPLOMAS

28/10/2013 PhD in Public Health - epidemiology option, PhD school "Societies, Politics, Public Health", University of Bordeaux, France (PhD thesis: "Trial design and analysis of endpoints in HIV vaccine trials"; supervisors: Pr G. Chêne and Pr R. Thiébaut)

24/06/2010 MSc (Master 2) in Public Health, Clinical Epidemiology option, Bordeaux School of Public Health (ISPED), Université Bordeaux Segalen, France (Master's thesis: "Prevalence and determinants of poor locomotor performance in HIV-infected patients in the ANRS CO3 Aquitaine Cohort", supervisor: Pr G. Chêne)

02/06/2005 Doctor of Medicine (Dr.med), University of Freiburg, Germany (medical thesis: "Analysis of the costs of hospital care at the Dermatology University Hospital Freiburg in the context of performance-based payments and diagnosis-related groups", supervisor: Prof. M. Augustin)

10/05/2005 Full accreditation (licence to practice) as a Medical Doctor (MD), Medical Association of Baden-Württemberg, Germany

04/05/2005 Medical State Examination, University of Freiburg, Baden-Württemberg, Germany

ADDITIONAL TRAINING COURSES

Training in clinical research methodology

09/2015 Atelier Inserm 236: “Big data in clinical research”, Bordeaux, France (2 days)

07/2014 University of Vienna: “Symposium on Small Populations”, Vienna, Austria (2 days)

10/2012 French Society of Statistics (SFdS): “Statistical Approaches for Adaptive Designs”, Paris, France (2 days)

10/2012 University Medical Center Rotterdam: “Bayesian Adaptive Methods for Clinical Trials”, Rotterdam, The Netherlands (2 days)

06/2011 Atelier Inserm 209: “Recent statistical advances in causal analysis”, Bordeaux, France (2 days)

10/2009 Atelier Inserm 198: “Recent protocols in epidemiology”, Saint Raphaël, France (2 days)

Pedagogical training

2013-2014 “Séminaires de formation à l’enseignement” (teacher training seminars), CRAME, University of Bordeaux (11 days)

Regulatory and good clinical practice (GCP) training

09/2018 Sunnikan Consulting: “Les bonnes pratiques cliniques ICH E6 (R2)” (GCP training), Bordeaux, France (1 day)

09/2016 IFIS Consulting: “Les essais cliniques de phase I” (phase I trials), Bordeaux, France (1 day)

03/2015 IFIS Consulting: “Bonnes pratiques en essais cliniques” (GCP training), Bordeaux, France (1 day)

09/2012 Sunnikan Consulting: “Protection des données à caractères personnel appliquée à la recherche clinique” (data protection training), Bordeaux, France (1 day)

09/2010 Sunnikan Consulting: “Aller au-delà des Bonnes Pratiques Cliniques” (GCP training), Bordeaux, France (1 day)

05/2009 Sunnikan Consulting: “Bonnes pratiques cliniques françaises et Bonnes pratiques de data management” (GCP training), Bordeaux, France (3 days)

01/2007 Geneva University Hospital: « Les bonnes pratiques des essais cliniques », Geneva, Switzerland (3 days)

RESEARCH ACTIVITIES

Affiliation with a labelled research structure

- Inria and Inserm: SISTM team ("Statistics In System Biology and Translational Medicine", head Pr R. Thiébaut) of Inria and Inserm "Bordeaux Population Health" Research Center, UMR U1219, University of Bordeaux
    - Coordinator of the research axis “Translational Vaccinology” since July 2019
        - Vaccine trial design and methodology
        - Data science for vaccine trials: integrative statistical analyses and modelling of immune responses to vaccines and immunotherapies
    - Co-head of the Data science division (head Pr R. Thiébaut) of the French Vaccine Research Institute (Labex VRI) since September 2019; http://vaccine-research-institute.fr/en/

Involvement in research grants and clinical trials

- Data science in vaccinology: integrative statistical analyses and modelling of immune responses to vaccines and immunotherapies:
    - Work package co-leader of the WP “Data Science”, H2020 IP-Cure-B project (Immune profiling to guide host-directed interventions to cure HBV infections, project coordinator: Pr. F. Zoulim, Inserm U1052 CRCL)
- Coordination of multicenter vaccine clinical trials
    - Work package co-leader “WP Clinical Trials”, H2020 IMI-2 EBOVAC2 project (Ebola vaccine research, Ebola+ programme; project coordinator: Pr. R. Thiébaut, Inserm U1219), including the conduct of two international phase II trials assessing heterologous two-dose vaccine strategies against Ebola (clinicaltrials.gov identifiers: NCT02416453 and NCT02564523)
    - Partner in the H2020 IMI-2 EBOVAC3 project, “WP Clinical Trials” (Ebola vaccine research, Ebola+ programme; project coordinator: Pr. D. Watson-Jones, London School of Hygiene and Tropical Medicine), including the conduct of a phase II trial assessing a heterologous two-dose vaccine strategy against Ebola in infants in Africa
- Methodologist and co-investigator of national and international vaccine clinical trials
    - Phase II Ebola vaccine trial PREVAC (NCT02876328) and PREVAC-UP, legal sponsors Inserm, NIH and London School of Hygiene and Tropical Medicine, funded by the sponsors and by EDCTP2, coordinating investigator Pr. Y. Yazdanpanah, AP-HP
    - Phase I pregnancy-associated malaria vaccine trial PRIMALVAC (NCT02658253), legal sponsor Inserm, funded by the German Federal Ministry of Education and Research, and Irish Aid (via the European Vaccine Initiative), Inserm and INTS, coordinating investigators Pr. O. Launay, AP-HP, and Dr. S. Sirima, CNRFP, Burkina Faso
    - Phase I single-center pertussis vaccine trial BPZE-1 (NCT02453048), legal sponsor Inserm, funded by Iliad Biotechnologies, coordinating investigator Dr N. Al-Tawil, Karolinska University Hospital, Stockholm
    - Phase II pneumococcal vaccine trial PNEUMOVAS (NCT03069703), legal sponsor AP-HP, funded by “PHRC-N” 2015, coordinating investigator Pr. B. Terrier, AP-HP
    - Phase I/II HIV vaccine trial ANRS VRI01 (NCT02038842), legal sponsor Inserm-ANRS, funding VRI, coordinating investigator Pr. J.D. Lelievre, AP-HP/VRI

- Phase I/II therapeutic HIV vaccine trial ANRS VRI04 (set-up ongoing), legal sponsor Inserm-ANRS, funding VRI, coordinating investigators Pr. Y Lévy and Pr. J-D. Lelièvre, AP-HP/VRI
- Phase I HIV vaccine trial ANRS VRI06 (set-up ongoing), legal sponsor Inserm-ANRS, funding VRI, coordinating investigators Pr. Y Lévy and Pr. J-D. Lelièvre, AP-HP/VRI

Research valorisation, scholarships and awards

- Public/private partnerships for clinical trial coordination and conduct: Johnson and Johnson/Janssen Prevention and Vaccines (IMI-2 Ebola + programme; and PREVAC Ebola vaccine trial); Merck (PREVAC Ebola vaccine trial); Iliad Biotechnologies (BPZE-1 pertussis vaccine trial); Gilead Sciences and Spring Bank Pharmaceuticals (clinical trial within the H2020 IP-Cure-B project)
- Sidaction "Young Researcher" grant for the research work done during my PhD thesis (2010-2013)
- Award for the oral communication "Optimization of a randomized Phase I-II trial design to evaluate the safety and efficacy of different HIV vaccine strategies", 7è Conférence Francophone d'Epidémiologie Clinique (EPICLIN), Paris, France, 16-17 May 2013

TEACHING ACTIVITIES

Teaching volume: approximately 80 hours/year ("HETD")

Medical Faculty, University of Bordeaux

- PACES (first year of medical, paramedical and pharmaceutical studies)
  2013- T.U. – Epidemiology and Statistics (practical tutorials/ED)

- DFASM1-3 (4th to 6th year of medical studies)
  2017- Practical tutorials and conferences for critical article reading (LCA)

Bordeaux School of Public Health (ISPED), University of Bordeaux

- Master 2 in Epidemiology
  2013- T.U. "Experimental designs" (formerly: "Principles of Clinical Trials")
  2016- T.U. "Synthesis and design of epidemiological studies"

- Master 2 in Biostatistics
  2016- T.U. "Analyses of clinical trials"

- Master 2 in Public Health Data Science (in English)
  2019- T.U. "Basics"
  2019- T.U. "Omics data"

- University Diplomas (DU) – distance learning
  2013-2015 University diploma in epidemiology: tutorials
  2016- University diploma in clinical research: teaching module "Clinical Trials"

- Summer school
  2014-2017 Course "Clinical Trials – Methodological and operational aspects"
  2017- Course "Big data in immunology" (in English)

2019- Course “Fundamentals of clinical research”

Administrative responsibilities

2013-2015 Co-coordination of the T.U. “Principles of Clinical Trials”, Master 2 in Epidemiology, ISPED, University of Bordeaux

2013-2015 Co-coordination of the summer school course “Clinical Trials – Methodological and operational aspects”, ISPED, University of Bordeaux

2013-2015 Co-coordination of continuous training courses (DPC mixte): “Réunion de concertation pluridisciplinaire (RCP) : Forum méthodologique en épidémiologie clinique (EPP 282)”; and “Groupe d'analyse des pratiques (GAP) : Analyse des pratiques méthodologiques en épidémiologie clinique (EPP 283)”, Bordeaux University Hospital

2016- Coordination of the T.U. “Experimental Designs”, Master 2 in Epidemiology, ISPED, University of Bordeaux (6 ECTS)

2016- Co-coordination of the university diploma in clinical research (distance learning), ISPED, University of Bordeaux

2017- Member of the local committee of the medical specialty diploma in Public Health (DES de Santé Publique), University of Bordeaux

2019- Coordination of the T.U. “Omics data”, Master 2 in Public Health Data Science, EUR Digital Public Health, ISPED, University of Bordeaux (8 ECTS)

2019- Coordination of the summer school course “Big data in immunology”, ISPED, University of Bordeaux

Pedagogical supervision activities

- Academic tutor at ISPED for Master 1 students in Public Health doing their internship in another institution

  2015- E. Sewu: “HIV prevalence and associated factors among men having sex with men inTogo in 2015”

  2015- M. LeGoff: “The worldwide economic impact of hearing loss “

- Supervision of tutored projects for Master 1 students in Public Health, ISPED, University of Bordeaux (2019)

Participation in thesis evaluations and juries

- Main examiner for Master 1 and Master 2 theses in Public Health, ISPED, University of Bordeaux (2014, 2015, 2017, 2019)

- Member of the jury for the Master 2 theses in Epidemiology, ISPED, University of Bordeaux (2015, 2017, 2019)

- President of a jury for the Master 1 theses in Public Health, ISPED, University of Bordeaux (2015)

- Main examiner and jury member for medical theses (2018)

Invited teaching

2015 "Big data in epidemiology", XIth national training seminar for public health residents, Lyon, France, 23 April 2015

2016 "Big data in epidemiology", Webinar "Quantitative Methods and Medical Information Processing" (QuanTIM), UMR 912, Sciences Economiques & Sociales de la Santé et Traitement de l'Information Médicale (SESSTIM), INSERM/IRD/Aix-Marseille Université, INSERM/IRD/Aix-Marseille University, France, 20 May 2016

2016 "Everything you always wanted to know about statistics", Department of Virus Immunology, Heinrich Pette Institute, Leibniz Institute for Experimental Virology, Hamburg, Germany, series of 6 seminars, May - July 2016

2018 "Statistics seminars", Department of Virus Immunology, Heinrich Pette Institute, Leibniz Institute for Experimental Virology, Hamburg, Germany, series of 5 seminars, April- June 2018

2019 Advanced module "Biostatistics", medical specialty training (DES) in Public Health, France (1 course; distance learning at the national level)

2016, 2019 Master 2 "Vaccinology": T.U. "Clinical Trials", UPEC, Paris, France (2 courses)

HOSPITAL ACTIVITIES

Public Health Department, Bordeaux University Hospital

EUCLID/F-CRIN clinical trials platform (Bordeaux University Hospital, Inserm, University of Bordeaux, Institut Bergonié, Limoges University Hospital), Clinical Investigation Center CIC 1401, Bordeaux University Hospital

- Platform coordination

  2014-2019 Co-head of the platform (with Pr Geneviève Chêne)

  2019- Head of the platform (since November 2019)

  - Research facility for international or complex clinical trials, certified by F-CRIN (French Clinical Research Infrastructure Network, https://www.fcrin.org/) following a selection through a competitive call for candidates in 2013 (funding obtained: 2 million euros over 5 years, starting 1st January 2014, PIA-1)
  - Co-chair (and chair since 1st November 2019) of the executive committee of the platform
  - Structuring and monitoring of all the platform's activities (consortium of 5 institutions; involving 9 local and regional clinical research units)
  - Obtention of the "ECRIN Data Center" certification (2 research units; 2015) and "University of Bordeaux research platform" label (2019)
  - Development of a sustainability plan ("business plan")
  - Organisation and animation of an annual scientific seminar on clinical research methods (duration 1 day; approximately 70 participants)

- Methodology and coordination of complex or international clinical trials
  - Contribution to the preparation of applications for calls for funding at the European (H2020, IMI-2, EDCTP) or national level (PHRC, RHU)
  - Methodology and coordination of funded clinical trial projects
  - Between 2014 and 2019: solicitation of the platform on 59 complex European or national projects; 27 applications submitted for European or national funding, 11 of which were accepted (3 H2020 projects, 2 IMI2 projects, 1 EDCTP project, 5 national PHRC projects)

- 19 projects conducted by EUCLID/F-CRIN (mainly in Europe and in Africa), including 9 vaccine trials; total budget obtained on projects: approximately 12 million euros.

- Supervision of research/study engineers for the coordination of the platform and the conduct of the clinical trials

Clinical Epidemiology Unit (« Unité de Soutien Méthodologique à la Recherche Clinique et Epidémiologique », USMR), Medical Information Division, Bordeaux University Hospital

- Interim team head since Oct 14, 2019
  - Management of the team: 3 M.D.s, 1 assistant professor, 1-3 residents in Public Health, 1 quality and risk manager, 1 secretary, 14 clinical research staff (statisticians, data managers, informatician)

- Methodological consultations for application to national or local calls for funding (national or interregional calls "PHRC"; internal calls at the Bordeaux University Hospital)

- Methodology, biostatistics and data management of funded clinical research projects with the Bordeaux University Hospital as legal sponsor

- Supervision of residents and assistant professors in Public Health

Clinical Epidemiology module, Clinical Investigation Center (CIC1401), University Hospital Bordeaux, Inserm, University of Bordeaux and Institut Bergonié

- Coordinator of the module since November 2019
  - "Meta-platform" acting as transfer structure between public health research and hospital or out-patient care structures or health decision-makers
  - Coordination and structuration of the existing methodological resources for clinical and public health research (epidemiology, biostatistics, data management, medical informatics, economics for medico-economic evaluation) at the University and University Hospital environment in Bordeaux

SUPERVISION OF STUDENTS, INTERNS AND ENGINEERS

Supervision of PhD students in Public Health, University of Bordeaux

- E. Lhomme: "Analysis of the determinants and modelling of the post-vaccination immune responses in experimental vaccine strategies" (start of thesis: 2016, defense planned: 25/11/2019)

Supervision of Master's students in Public Health, ISPED, University of Bordeaux

- A. Herteau: Modeling the dose effects of prophylactic vaccines: example of an experimental vaccine against the Ebola virus (2019)
- N. Lafosse: Study of the determinants of the variability of the cellular immune response after prophylactic HIV vaccination with the MVA HIV-B vaccine in the ANRS VRI01 phase II trial (2017)

- A. Tsaranazy: Development of a cumulative index of chronic exposure to immunosuppression in HIV-infected patients (2015)
- E. Lhomme: Modelling the dynamics of immune responses to a prophylactic HIV-1 vaccine in a vaccine clinical trial (2014; co-supervision with Pr R. Thiébaut)

Supervision of research/study engineers and interns in the SISTM team

- H. Lorenzo, study engineer: Systems vaccinology analyses of the phase I rVSV ZEBOV vaccine trial (co-supervision with R. Thiébaut; 2015-2016)
- S. Delahaye, study engineer: various statistical analyses; in particular, systems vaccinology analyses of the ANRS VRI01 trial; and micro-RNA systems vaccinology analyses of the phase I rVSV ZEBOV vaccine trial (2017-2019)
- V-H. Tran, research engineer: statistical analyses of deep immune receptor profiling data by flow cytometry (2019)
- A. Herteau, resident in public health: critical methodological appraisal of the statistical analysis pipeline for targeted metabolomics data; and statistical analyses of the immunometabolomics data from a yellow fever vaccine trial (6-months internship in 2019)
- E. Reiner, trainee: statistical analyses of the Luminex data of the EBOVAC2 EBL2001 trial (4-months internship in 2019)
- M. Durand, study engineer: statistical analyses of immune profiling data of the EBOVAC2 EBL2001 trial (since 2019)

Supervision of research/study engineers for the set-up, conduct, and analysis of vaccine clinical trials (EUCLID/F-CRIN platform and Inserm U1219 Research Center CTU)

- Supervision of a project team comprised of 2 to 8 persons for each trial (with eight trials between 2013 and 2019)

PEER-REVIEW ACTIVITIES AND EXPERTISES

Reviewer of applications for funding

- French National Research Agency (ANR), France: reviewer (2019)
- Clinical research programme for hospitals (PHRC), France
    - National PHRC: annual methodological expertise
    - Interregional PHRC
        - Reviewer for “GIRCI AURA” (2019)
        - Examiner and jury member for “GIRCI SOOM” (2014)
- Call for interregional projects in the French overseas departments (DOM): reviewer (2015)
- Internal call of the University Hospital of La Reunion Island, France: reviewer (2013, 2014, 2017)
- Call for "HIV Clinical Trials Units", NIH, United States: reviewer (2013)
- National Research Foundation, South Africa: reviewer (2013)

Peer reviewer for scientific journals

AIDS, Biostatistics, Bone, JAIDS, JAMA, Plos One, Scientific Reports, Trials

Other contributions as scientific expert

- Participation in Delphi consensus groups for extensions of the Consort recommendations (extension for outcome reporting; extensions of adaptive trials)

RESPONSABILITIES IN THE SCIENTIFIC COMMUNITY

- Member of a Steering Committee appointed by the General Directorate of Health (DGS) to analyse the potential adverse effects of aluminium vaccine adjuvant, Paris, France (2013)
- Member of the Steering Committee of the French Clinical Research Infrastructure Network F-CRIN, France (since 2014)
- Member of the Organizing Committee of the "8ème conférence francophone d'épidémiologie Clinique" (EPICLIN, 2014)
- Elected staff member of the Council of the Inserm U897 Research Center, Bordeaux, France (2014-2015)
- Member of the working groups "Methodology" (since 2016) and "Hemorrhagic Viral Fevers" (since 2019), Inserm-REACTing network, France
- Member of the Independent Data Monitoring Committee (IDMC) ANRS 12345 TA-PROHM clinical trial (since 2018)
- Co-coordinator of the F-CRIN working group on data base quality, France (2019)
- Member of the methodological working group "Early-stage clinical trial designs", RECaP network (CIC), France (since 2019)

MEMBERSHIP IN SCIENTIFIC SOCIETIES

Member of the International Society of Clinical Biostatistics (ISCB) since 2013

COLLABORATIONS

Vaccine research

- Labex Vaccine Research Institute, Université Paris Est-Créteil, France
- Inserm-REACTing network, France
- F-CRIN I-REIVAC network, AP-HP and Inserm, Paris, France
- IMI-2 Ebola+ programme: London School of Hygiene and Tropical Medicine, UK; University of Oxford, UK; University of Antwerp, Belgium; Centre Muraz, Burkina Faso
- MRC Clinical Trials Unit, University College London, UK
- Heinrich Pette Institute, « Leibniz Institute for Experimental Virology », Hamburg, Germany

- Bernhard-Nocht-Institut and UKE University Hospital, Hamburg, Germany
- NIH, Bethesda, Washington, USA
- School of Public Health, University of Minnesota, USA
- Statistical Center for HIV/AIDS Research & Prevention (SCHARP, HVTN), University of Washington, USA
- Baylor Institute for Immunology Research, Dallas, USA

Clinical trial methodology and coordination

- European Research Infrastructure Network ECRIN, France/Europe
- European FP7 network NEAT (European AIDS Treatment Network)
- French Clinical Research Infrastructure Network F-CRIN, France
- Clinical Research Department (PRC), Inserm, France
- Inserm-ANRS, France
- RECaP network (network of Clinical Epidemiology modules of the Clinical Investigation Centers), France

SUMMARY OF MY RESEARCH

1. Context

1.1. Scientific background

Vaccines are one of the most efficient tools to prevent and control infectious diseases, and there is a need to increase the number of safe and efficacious vaccines against various pathogens (Mehand et al, 2018). However, clinical development of vaccines - and of any other investigational product - is a lengthy and costly process. Considering the public health benefits of vaccines, their development needs to be supported and accelerated.

As is the case for therapeutic drugs or other biomedical interventions, clinical vaccine research is classically performed in a development plan with clinical trials from phase I and II to phase III. Phase I and II trials are early- to mid-stage trials conducted to assess safety and explore immunogenicity (i.e. vaccine-elicited immune responses that are measured in the blood or tissue of vaccinated individuals) in a limited number of participants. Phase IIB (for preliminary efficacy testing) and phase III trials (for confirmatory efficacy testing) are mid-to-late-stage trials that are very costly and often challenging to conduct. The challenges in late-stage trials with efficacy testing reside in the low incidence of the disease to prevent and thus huge required sample sizes, e.g. for HIV vaccine efficacy evaluation, or in the constraint to conduct such trials during sporadic outbreaks and emergency situations, e.g. efficacy evaluations of Ebola vaccines or vaccines against other potential emerging diseases.

The use of adaptive trial designs has been proposed to optimize mid- and late-stage clinical development of HIV vaccines (Gilbert et al, 2011). For efficacy testing during an outbreak, a ring vaccination cluster-randomized trial has been conducted successfully for the rVSV Ebola vaccine (Henao-Restrepo et al, 2017).

Efficient early-stage clinical development and respective decision making are also crucial aspects in vaccine research and even more important than in other applications. In this regard, several methodological challenges exist in early-stage clinical vaccine research:

First, the number of possible candidate vaccine strategies against a given pathogen that needs to be down-selected in early clinical development is potentially very large. Indeed, thanks to the use of recombinant technologies for vaccine generation, several different vaccine platforms and strategies now often co-exist in clinical development. Many properties of a vaccine strategy have become modifiable, such as the vaccine vector, antigen inserts, doses, time intervals between injections, etc (Figure 1). The use of heterologous prime-boost strategies, combining two different candidate vaccines sequentially, increases even more the spectrum of potential strategies that could in principle be evaluated in clinical trials.

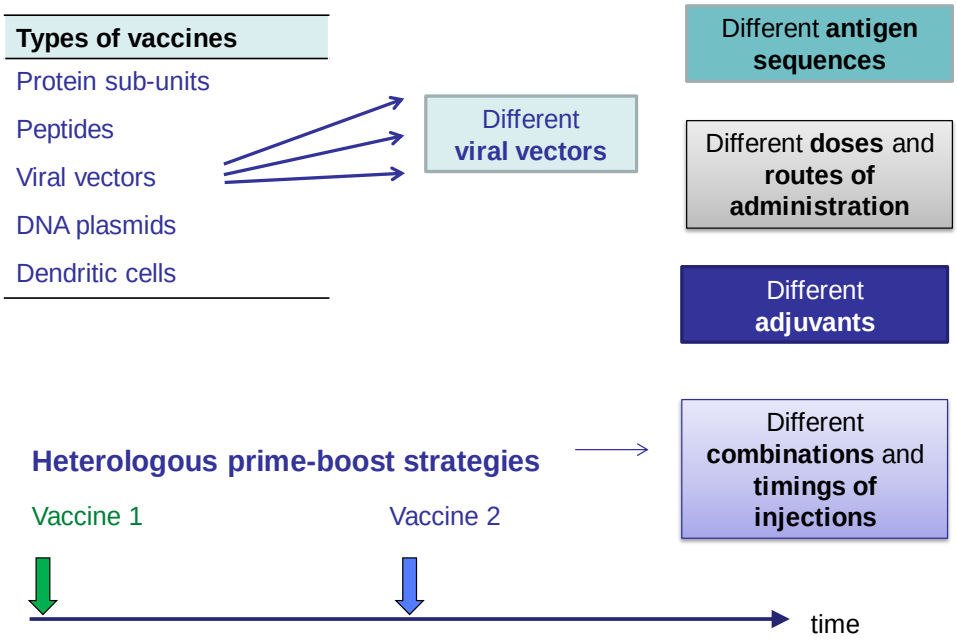


Figure 1. Modifiable properties of vaccine strategies

This results in a very large theoretical number of candidate vaccine strategies that is untestable within the current clinical development paradigm. Prioritisation of the most promising strategies as well as "no-go" decisions to leave place for a next potential candidate strategy are thus essential in the overall development process.

Second, in early clinical development of new vaccines, there is in general no validated correlate of protection, i.e. a surrogate marker predictive of clinical efficacy (Plotkin & Gilbert, 2012), that could be used as a consensus immunogenicity endpoint and down-selection criterion. Although this is inherent to many investigational products that have not yet undergone efficacy testing, vaccine development is often additionally hampered by the absence of immune correlates of risk (or of natural protection). For instance, for HIV, although studies in HIV controllers are informative, there is so far no validated correlate of virus control nor of natural protection from infection. For new emerging diseases, there are in general too little observational data on natural immunity available when vaccine clinical development starts. This implies considerable uncertainty about the interpretation of immunogenicity results and about the potential value of a vaccine strategy as it transits through early clinical development. Given the complexity of the immune system and the many unknowns in the generation of a protective immune response, early vaccine clinical development nowadays thus takes advantage of high throughput (or "omics") methods allowing to simultaneously assess a large number of response markers at different levels ("multi-omics") of the immune systems. Omics measurements in general can range from genomics, transcriptomics, to proteomics and metabolomics, etc. This has induced a paradigm shift towards early-stage and translational vaccine clinical trials including fewer participants but with thousands of data points collected on every single individual. For instance,

typical examples of data generated in early-stage vaccine trials include the measurements of antibodies, with their type and functions, of functional cellular responses and cytokine secretion, of various phenotypic cell populations by flow or mass cytometry, and of gene expression levels by RNA-seq (Figure 2).

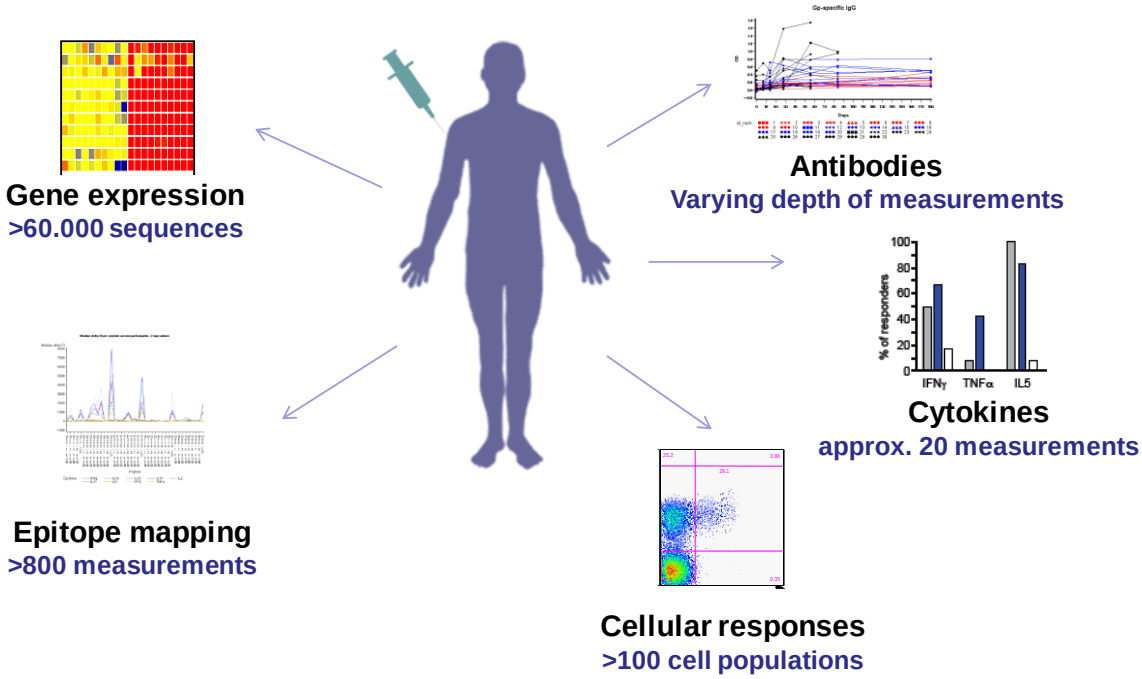


Figure 2. Immunogenicity data typically generated in early-stage vaccine trials

The acquisition of huge amounts of immune response data in each participant of a clinical trial is expected to contribute to acceleration of vaccine development thanks to a broader search for immunogenicity signals and a better understanding of the mechanisms induced by each vaccine strategy. This constitutes the foundations of systems vaccinology (Pulendran et al, 2010; Pezeshki et al, 2019). Although initial results obtained by analysing multi-omics data to disentangle vaccine effects in humans have been promising (Querec et al, 2009), this remains a difficult research field, both from the immunological as well as from the statistical perspective. The different omics assays used result in large amounts of complex and diverse data that are characterized by their multidimensionality, i.e. the number of parameters p measured is much greater than the sample size n ($p >> n$). The statistical analysis of such multidimensional data requires careful considerations related to the large numbers of variables, measured at different levels of the system, and the correlations between them. Thus, extracting meaningful information from these multi-omics data and transferring it towards an acceleration of vaccine development requires adequate statistical methods and thoughtful interpretation of the results.

Third, the immune responses to a given vaccine can vary largely between individuals. For instance, women tend to have a better response to the Flu vaccine, and measles and mumps immune responses

wane at different rates between males and females (Klein et al, 2010). Deep assessments of the immune response with multi-omics data measured at different levels of the immune system together with sociodemographic and clinical characteristics should contribute to a better comprehension of inter-individual variability. This could then help to better design vaccine strategies or to tailor personalized or stratified vaccine strategies to specific individuals or population subgroups. However, design factors such subtle differences in the administered vaccine strategy or in the assays used also need to be considered to understand variability observed between different studies.

In summary, in order to optimize early vaccine clinical development in the absence of validated correlates of protection on the one hand, and in the presence of multidimensional immunogenicity data assessed at different levels of the immune systems on the other hand, the following methodological questions arise:

- Which trial designs and immunogenicity endpoints should be used in early-stage vaccine trials (phase I and II)?
- Which statistical analysis methods are appropriate?
- How to integrate and interpret these multi-omics data?
- What decision criteria should be used to continue or not the development in a larger trial?

In addition, given the large number of potential candidate strategies to be tested:

- Can statistical and mathematical modelling contribute to a better understanding of relevant mechanisms of actions and determinants of immune responses to vaccines?
- Can in-silico modelling be used to predict and narrow down the most promising vaccine strategies prior to a clinical trial?
- Can modelling contribute to better inform trial design?

1.2. Overall objective of my research project

The main objective of my research is to accelerate the early clinical development of vaccines and immunotherapies, by

- elucidating the potential effects and mechanisms of action of vaccines and immunotherapies in integrative statistical analyses of the induced responses at various levels of the immune system
- better informing future trial designs and statistical analysis methods by means of modelling and methodological developments

To reach this objective, I propose using integrative analyses and modelling to better understand vaccine mechanisms and to improve the selection of candidate vaccine strategies to be tested in clinical trials. Thus, I seek to combine statistical methods for multidimensional data, immunological knowledge and modelling of the interrelationships of these markers over time to guide vaccine clinical

development. This methodological research is at the interface between biostatistics, clinical epidemiology, immunology, and vaccinology and therefore requires knowledge in each of these fields as well as interdisciplinary collaborations. The main current areas of application of my work are early-stage trials of HIV and Ebola vaccine strategies.

1.3. Research environment and responsibilities

For my research activities at the University of Bordeaux, I have been affiliated since 2010 with the SISTM team ("Statistics In System biology and Translational Medicine"; head Pr Rodolphe Thiébaut) of the Inserm Centre U1219 "Bordeaux Population Health Research Center" and of Inria. This team develops statistical methods for high dimensional biomedical data and for mechanistic modelling, mainly applied to immunology. Within the SISTM team, I am responsible for the coordination of the research axis “Translational Vaccinology”, which was created in July 2019 and currently includes five persons (1 PhD student, 1 Master student, 1 resident in Public Health, 1 study engineer and myself). This research axis works in close collaboration with the other two axes of the team that are dedicated to the development of new statistical methods (axis “High Dimensional Statistical Learning”, coordinated by Boris Hejblum; and axis “Mechanistic Learning”, coordinated by Mélanie Prague; see Figure 3).

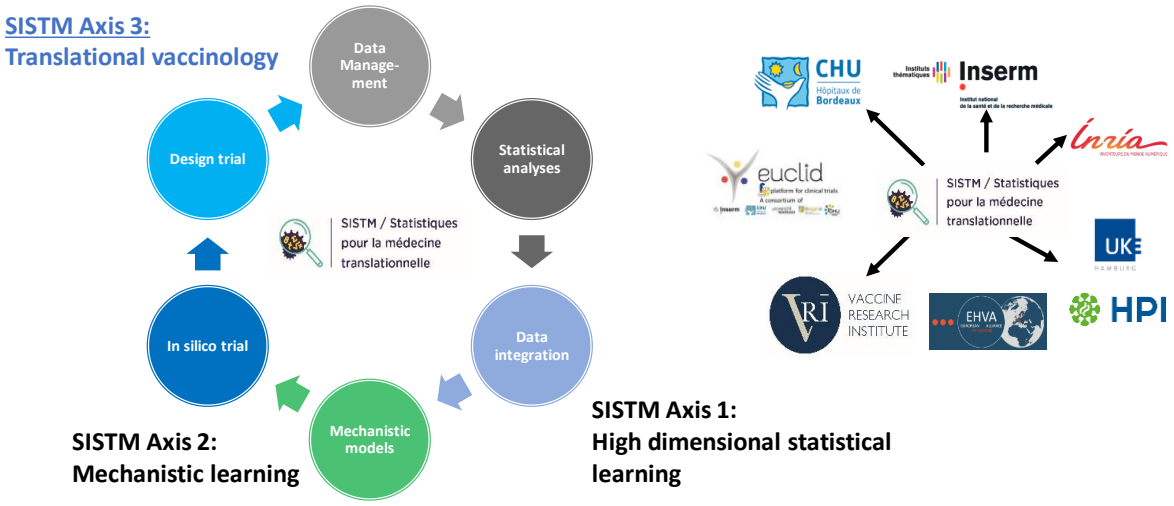


Figure 3. Research axes of the SISTM team (left part) and major collaborations (right part)

Since September 2019, I am also co-head (together with Rodolphe Thiébaut) of the Data Science division of the French Vaccine research institute (VRI; vaccine-research-institute.fr/), which has largely overlapping objectives and activities with my research axis in the SISTM team.

Furthermore, as co-head since 2014 and future head of the EUCLID/F-CRIN clinical trials platform as well as a methodologist of trials conducted at the Clinical Trials Unit (CTU) of the Inserm U1219

Research Center in Bordeaux (head: Dr Linda Wittkop), I am strongly involved in design, set-up, conduct, analysis and valorisation of vaccine clinical trials.
The EUCLID/F-CRIN platform is a clinical trial research facility, established by a consortium of five institutions (Bordeaux University Hospital, Inserm, University of Bordeaux, Institut Bergonié, Limoges University Hospital) that was accredited by F-CRIN (French national infrastructure funded by the "Plan d'Investissements d'Avenir") in 2014. The success of this platform, which performs all activities of a Clinical Trials Unit (CTU) for international or complex trials, is reflected in its growing activity in projects with high national and international visibility. Vaccine trials are a major activity of this platform, with ten vaccine projects taken on since 2014, corresponding to a cumulative project-specific funding of more than 7 million euros for the platform activities related to these trials. I am directly involved as co-PI in the funding applications and conduct of eight of these vaccine projects, the remaining two being managed by Edouard Lhomme as co-PI, an assistant professor in Public Health, whose activities I co-supervise.
The Clinical Trials Unit of the Inserm U1219 Research Center is the CTU coordinating the vaccine trials conducted by the VRI, mainly for HIV vaccine research, and I have the role of trial methodologist for these trials.

Overall, all my research activities are performed in stable interdisciplinary collaborations at the local, national and international levels with research teams in immunology, vaccinology and infectious diseases as well as with institutions and clinical trials units for clinical trial conduct and coordination.

2. Vaccine trial design and methodology

My role as methodologist for vaccine trials at the Inserm U1219 Research Center CTU (vaccine and immunotherapy trials of the ANRS and the VRI) since 2010, and at the EUCLID/F-CRIN clinical trials platform since 2014 allows me to contribute to vaccine clinical trials from the design, trial planning, and set-up, to trial conduct and final analyses. The national and international vaccine trials for which I was or currently am methodologist and co-principal investigator are summarized in Table 1.

Table 1. Overview of national and international vaccine clinical trials in which I am involved as methodologist and co-prinicipal investigator

PROJECT NAME AND NCT IDENTIFIER	TOPIC	DESIGN CHARACTERISTICS	LEGAL SPONSOR	FUNDING SOURCE	COORDINATOR/ COORDINATING INVESTIGATOR	COUNTRIES AND TOTAL NUMBER OF SITES	TRIAL STATUS	MAIN ROLES AND RESPONSIBILITES OF LAURA RICHERT
PRIMALVAC NCT02658253	Pregnancy-associated malaria vaccination	Phase I dose escalation (n=68)	Inserm	BMBF and Irish Aid, (via EVI); Inserm, INTS	O. Launay, AP-HP, Paris S. Sirima, CNRFP, Burkina Faso	France, Burkina Faso 2 sites	Terminated ; publication submitted	Trial methodology, coordination of CTU activities
BPZE1 NCT02453048	Pertussis vaccination	Phase I dose escalation (n=54)	Inserm	Iliad Bio-technologies	N. Al-Tawil, Karolinska Univ. Hosp., Stockholm	Sweden 1 site	Terminated; publication draft ongoing	Trial methodology, coordination of data and statistics center actitivites
EBOVAC2 NCT02416453 NCT02564523	Ebola vaccination	2 randomized Phase II trials - n=612 - n =1188	Janssen Vaccines & Pre-vention	IMI-2	R. Thiébaut, Inserm and Inria	- France, UK (9 sites) - Burkina Faso, Côte d'Ivoire, Kenya, Uganda (6 sites)	Terminated; publication draft ongoing	Co-lead of WP "Clinical trials"; trial methodology
ANRS VRI01 NCT02038842	HIV vaccination	Randomized Phase I/II (n=92)	Inserm-ANRS	VRI	J.-D. Lelièvre, AP-HP and VRI, Créteil	France 4 sites	Terminated; publication draft ongoing	Trial methodology, coordination of CTU activities
PREVAC and PREVAC-UP NCT02876328	Ebola vaccination	Randomized Phase II (n=4300)	Inserm, LSHTM, NIH	Inserm, LSHTM, NIH, EDCTP-2, IMI-2	Y. Yazdanpanah, AP-HP, Paris	Guinea, Liberia, Sierra Leone, Mali 6 sites	Follow-up ongoing	Chair of TMT, coordination of activities of coordinating CTU and of data center for the whole trial; member of methodology group
PNEUMOVAS NCT03069703	Pneumococcal vaccination	Randomized Phase II (n=120)	AP-HP	PHRC-N	B. Terrier, AP-HP, Paris	France 49 sites	Recruitment ongoing	Trial methodology, coordination of statistics center activities
ANRS VRI04/ DALIA-2 NCT pending	Therapeutic HIV vaccination	Randomized Phase II (n=50)	Inserm-ANRS	VRI	Y. Lévy and J.-D. Lelièvre, AP-HP and VRI, Créteil	France 10 sites	Set-up	Trial methodology, coordination of CTU activities
ANRS VRI06 NCT pending	HIV vaccination	Phase I dose-escalation (n=72)	Inserm-ANRS	VRI	Y. Lévy and J.-D. Lelièvre, AP-HP and VRI, Créteil	France, Switzerland 2 sites	Set-up	Trial methodology, coordination of CTU activities

ANRS: National Agency for Research on AIDS and hepatitis, France; AP-HP: Assistance Publique – Hôpitaux de Paris, France; BMBF: Bundesministerium für Bildung und Forschung, through Kreditanstalt für Wiederaufbau, Germany; CNRFP: Centre National de Recherche et de Formation sur le Paludisme, Burkina Faso; EDCTP: European & Developing Countries Clinical Trials Partnership; EVI: European Vaccine Initiative; IMI: Innovative Medicines Initiative; INTS: Institut National de Transfusion Sanguine, France LSHTM: London School of Hygiene and Tropical Medicine; UK; NCT: clinicaltrials.gov identifier; NIH: National Institutes of Health, USA; TMT: Trial Management Team; VRI: Vaccine Research Institut, France; WP: work package

For each of these clinical trials, I supervise the activities of a research project team at the EUCLID/F-CRIN platform or Inserm CTU consisting of two to eight persons (research project managers, clinical research associates, data managers, biostatisticians). Depending on the size and risk of the project, this most often involves weekly internal meetings for project management and supervision, in addition to more formal staff meetings (in general on a monthly basis).

I also contribute to the overall scientific trial governance of these trials, by sitting on the Trial Steering Committees/Scientific Committees and by interacting closely with the legal sponsor and with other involved partner teams.

Beyond their primary results and the associated publications, these trials also provide datasets of interest for further statistical analyses in my research program (see chapter 3).

2.1. Trial design

When aiming at accelerating vaccine clinical development, the selection of an appropriate and efficient trial design is one important aspect. My research project does not necessarily have a strong focus on the de-novo development of new trial designs, but the goal is to make an informed choice about the best available design for a given research question and context. When no such design can be identified in the literature, we consider making extensions or adaptations of designs for our research context.

In the literature, phase I and II designs and methodological discussions for choosing an early-stage design for a specific clinical context were predominantly driven by cancer research (Brown et al, 2011; Doussau et al, 2012). These designs are not necessarily directly applicable to vaccine trials in healthy volunteers, due to the differences in trial populations, in safety and surrogate efficacy endpoint definitions, and in the underlying hypotheses (such as acceptable toxicity rates for example). Likewise, the application of adaptive designs to earlier development stages in vaccine research is difficult since these designs require a validated endpoint for transition between stages, and no such immunogenicity endpoint has been identified so far. Nevertheless, vaccine trials focussing on immunogenicity could benefit from other features of design optimization, not necessarily relying on adaptive designs. Few authors have so far addressed design considerations in early-stage vaccine trials beyond endpoint definitions (Moodie et al, 2006; Huang et al, 2016; Huang et al, 2017). Application of optimized trial design to early-stage vaccine development therefore remains a relevant méthodological challenge.

The following works illustrate my contributions to this research field. I have performed a review and methodological discussion of existing design options for HIV vaccine trials in 2015 (Richert et al, 2015). More recently, a collaborative work regarding the application of a multi-arm multi-stage (MAMS) adaptive design to a therapeutic HIV vaccine phase II trial with a virological endpoint has been published (Moore et al, 2019). I have also given thorough thoughts to existing phase I dose-escalation designs and their applicability to vaccinology. Although this has not been subject to a specific methodological paper, the results of these considerations are reflected in the protocols of these

trials (see Table 1), and their design will be described as part of the methods section of the publication of the trial results.

During my PhD thesis, for which I obtained a Young Research Grant from the French non-governmental organisation Sidaction funding my three-year PhD work, I worked on the design of a randomized phase I/II HIV vaccine trial to evaluate four prime-boost strategies combining different candidate vaccines. One of the candidate vaccines (vaccine 1 in Figure 4) had not been evaluated in humans before with this specific HIV antigen insert and thus required a phase I safety evaluation. After a review of potential design options, we did not identify any adequate existing design for a phase I/II randomized vaccine trial in the literature. We thus developed an open-label four-arm randomized design combining phases I and II assessments with two binary primary endpoints for safety and immunogenicity (Richert et al, 2014).

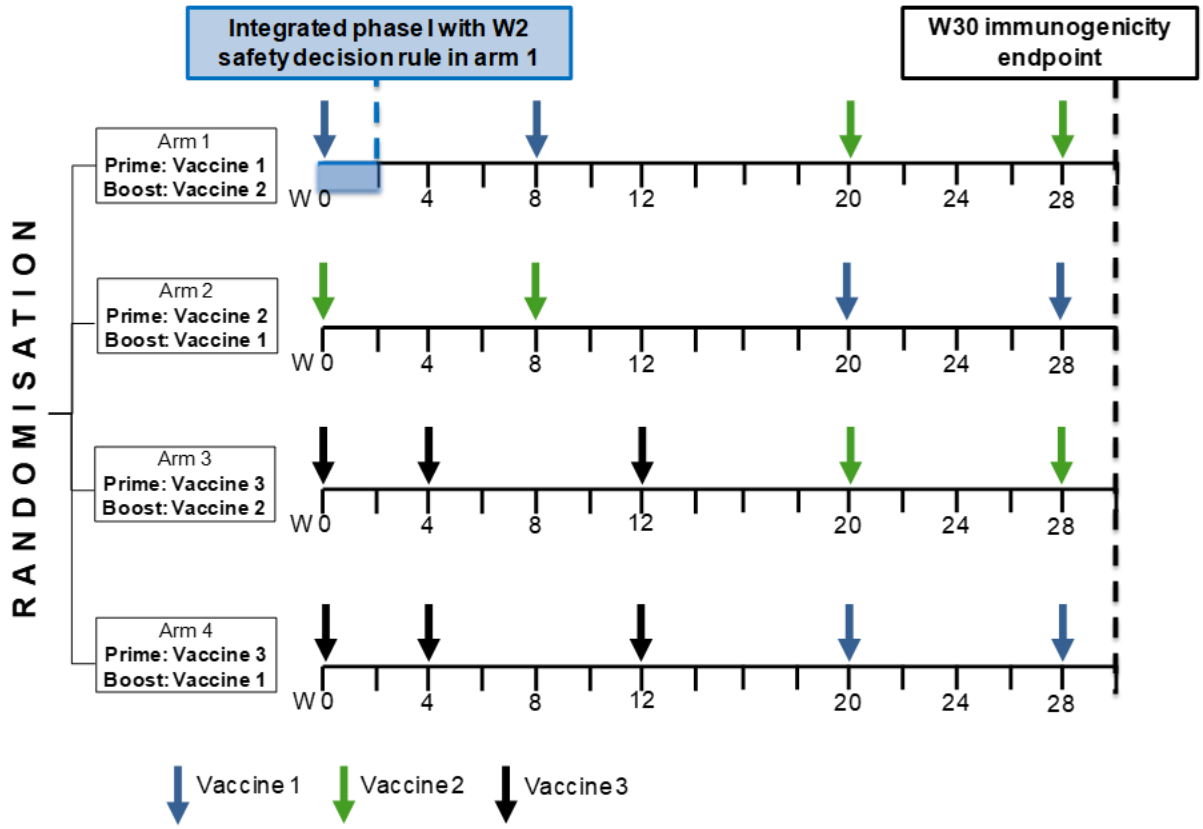


Figure 4. Overview of the ANRS VRI01 study design (n=23 per randomized arm)

The operating characteristics of this design including a sequential Bayesian stopping rule for the safety endpoint were assessed in simulations (in particular assessment of type I and II errors and expected sample sizes under various scenarios) and compared to two sequential frequentist methods. We projected the trial timelines with high accrual rates. The results showed that the different sequential methods had satisfactory properties, but the Bayesian approach has the advantage of greater flexibility.

Unlike frequentist methods, its interpretation does not depend on the trial design. This can be an advantage, especially if the recruitment dynamics in the trial deviate from the initial projections.
This design has been implemented in the trial protocol (ANRS VRI01 trial, clinicaltrials.gov NCT02038842), which was successfully conducted. I was the methodologist during the whole course of this trial, which is now terminated (conference communication: Lelièvre et al, 2017; publication in preparation).

2.2. Quality by design in clinical trials

Conducting clinical trials at the highest possible standards and reducing waste in research (Ioannidis et al, 2014; Moher et al, 2016) requires constant surveillance of the methodological integrity during the whole course of the trial. Indeed, a well-selected initial trial design is important but not sufficient by itself to achieve high scientific evidence, since bias during trial conduct can be introduced even in "gold standard" randomized double-blind parallel arm trials.
The term "Quality by Design" (QbD) relates to the concept that quality can be built into a process or product. The concept is used by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) based on the International Conference on Harmonization (ICH) Q8 guideline on pharmaceutical development, with a focus on drug manufacturing. There, it reflects a systematic approach that starts with predefined objectives, an understanding of the pharmaceutical product and manufacturing processes along with a knowledge of the risks involved and how best to mitigate those risks (ICH, 2009).
Application of the quality by design principles to clinical research itself (considering the clinical trial as the "product") has to our knowledge not yet been formalized in the literature. Under the impetus of Geneviève Chêne, although we do not use the detailed steps of the QbD approach, we aim to apply the overarching principle to clinical trials conducted at the EUCLID/F-CRIN platform and at the Inserm Research Center CTU. This implies anticipating (and proactively preventing or resolving) methodological problems instead of managing them retrospectively when the trial is terminated. This goes beyond using a formalized quality and risk management system (such as the ISO9001 norm, for which more and more academic CTUs are now certified), as it involves a strong focus on methodological aspects in interrelationship with operational aspects of trial conduct. Constant involvement of the trial methodologist together with experienced CTU project teams is important for success of this strategy.
The coordination of the PREVAC trial, which I supervise at the EUCLID/F-CRIN platform, exemplifies this. Briefly, PREVAC (Partnership for Research on Ebola VACcination) is an ongoing randomized phase II prophylactic vaccine clinical trial evaluating the safety and immunogenicity of three different vaccine strategies against Ebola in four West African countries (NCT02876328, Table 1 and Figure 5). I was involved in the writing of the different versions of the protocol and resolution of the methodological issues that have been encountered over time. I am chairing the Trial Management

Team meetings, am a member of the Trial Steering Committee and contribute to weekly coordination meetings with the site staff, meetings of the methodology working group (in collaboration with the University of Minnesota) and of the lab working group and the FANG assay group that has been put in place biweekly to monitor the analysis progress and quality of the antibody response measured by FANG assay (primary endpoint of the trial). At the CTU level, I supervise the project team, with a particular focus on overall methodological and operational aspects as well as data management.

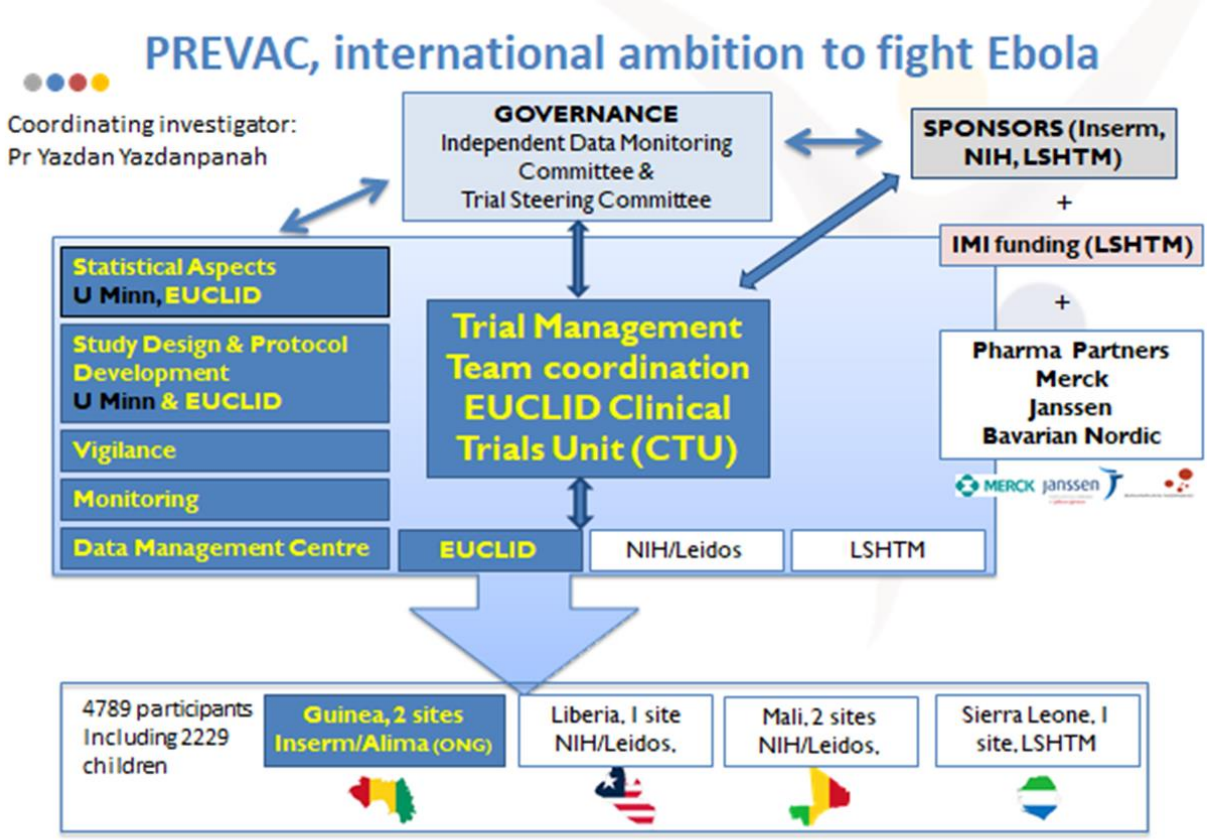


Figure 5. Governance and trial management of the PREVAC trial

Although the PREVAC trial itself is still ongoing, the methodological considerations of this complex trial and their interrelationships with trial operations and logistics have started to been published (Lhomme et al, 2019) or communicated in conferences (conference communications: Colin et al, 2017; Campion et al, 2019). A manuscript on the protocol considerations (writing group co-lead is Edouard Lhomme from our team, under my supervision) and a second one on the clinical data management system used (lead author: Monique Termote, under my supervision) are currently under preparation.

2.3. Primary results of vaccine trials

Progressing from the initial research question and design of a clinical trial to the publication of the primary results is in general a process that lasts several years. Therefore, it is not unforeseen that among the vaccine trials I have set-up as a methodologist so far, only the first ones are reaching their publication stage now (Table 1).

The primary results of the ANRS VRI01 phase I/II HIV vaccine trial, the design of which I have outlined in chapter 2.1, have been presented at the Conference of the International AIDS Society in 2017, and preliminary results of exploratory endpoints at the Research for Prevention (R4P) conference in 2018 (conference communications: Lelièvre et al, 2017; Richert et al, 2018). The trial assessed the safety and immunogenicity of of three candidate vaccines used as prime or boost: MVA HIV-B (coding for Gag, Pol, Nef); LIPO-5 (5 lipopeptides from Gag, Pol, Nef); and DNA GTU-MultiHIV B (coding for Rev, Nef, Tat, Gag, gp160 clade B). Healthy adult volunteers were randomized to four parallel arms: Arm 1 received MVA at weeks 0 and 8 and LIPO-5 at weeks 20 and 28; Arm 2 received LIPO-5 at weeks 0 and 8 and MVA at weeks 20 and 28; Arm 3 received DNA at weeks 0, 4 and 12, and LIPO-5 at at weeks 20 and 28; and Arm 4 received DNA at weeks 0, 4 and 12 and MVA at weeks 20 and 28. MVA was the vaccine that had not previously been tested in humans with this HIV antigen insert and was thus the focus of the phase I safety evaluation.

Ninety-two participants were randomized in the trial (Figure 6).

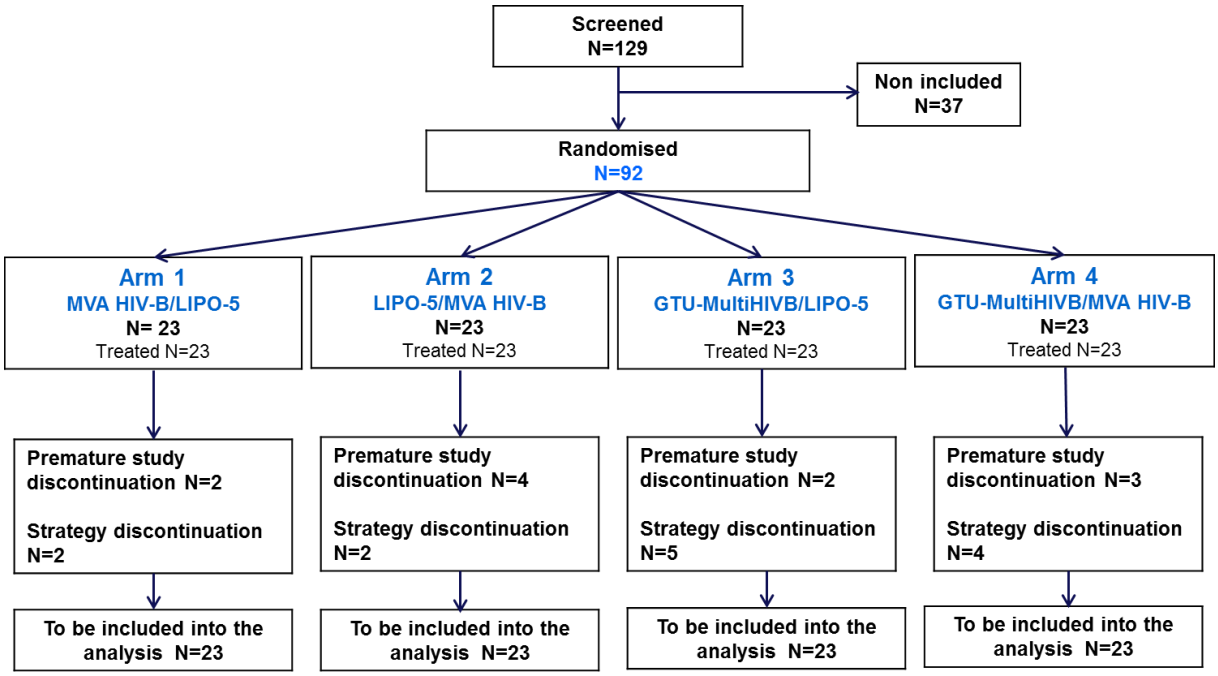


Figure 6. Participant flow chart of the ANRS VRI01 trial

This optimized phase I/II trial design with an unbiased evaluation of four heterologous prime-boost HIV vaccine strategies in parallel arms helped to identify MVA HIV-B as a safe and immunogenic T-cell vaccine given as either prime or boost in various combinations. The IFN-ELISpot responses, which were the primary immunogenicity read-out, are shown in Figure 7.

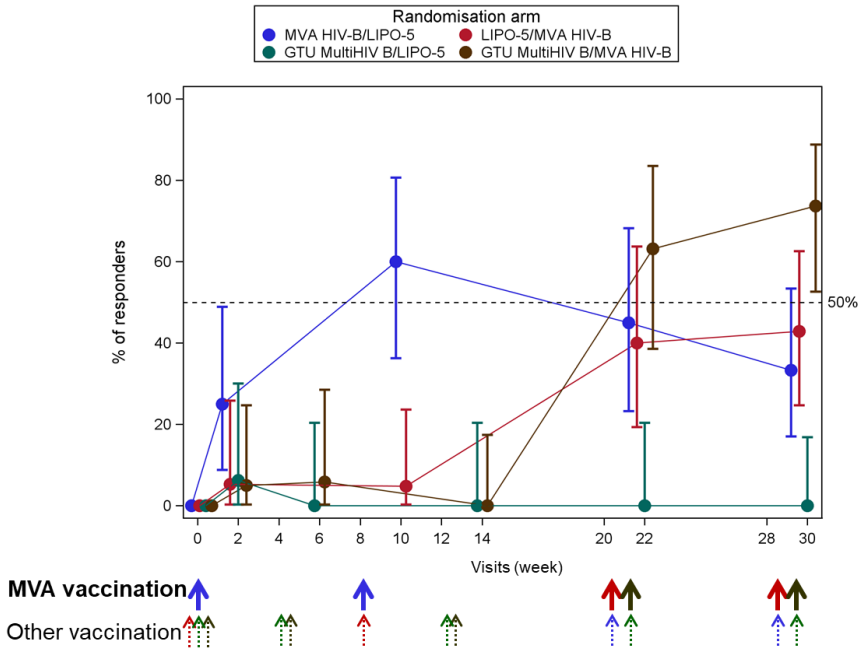


Figure 7. Proportion of IFN-g-ELISpot responders per arm and time point in the ANRS VRI01 trial

Two-sided 95% confidence intervals shown for W0, W2, W6, W14 and W22 (secondary endpoints) and two-sided 90% confidence interval for W30 (primary endpoint). Results of per protocol analysis.

The strategy combining GTU-MultiHIV B prime and MVA HIV-B boost (Arm 4) met the pre-defined minimum immunogenicity criterion to pursue clinical development in per-protocol analyses of the primary endpoint with 74% of responders, p=0.02 for superiority to 50% threshold (mITT results: 67% of responders, p=0.06 for superiority to 50% threshold).

Given the very low ELISpot responses in Arm 3, only blood samples from participants in arms 1, 2 and 4 were further analysed for secondary and exploratory immunogenicity objectives (n=62). We found that these three prime-boost vaccine strategies induced CD4+ and CD8+ T cell responses, primarily due to their MVA component. This vaccine component also drove changes in whole blood gene expression equilibrium assessed by microarray (Figure 8).

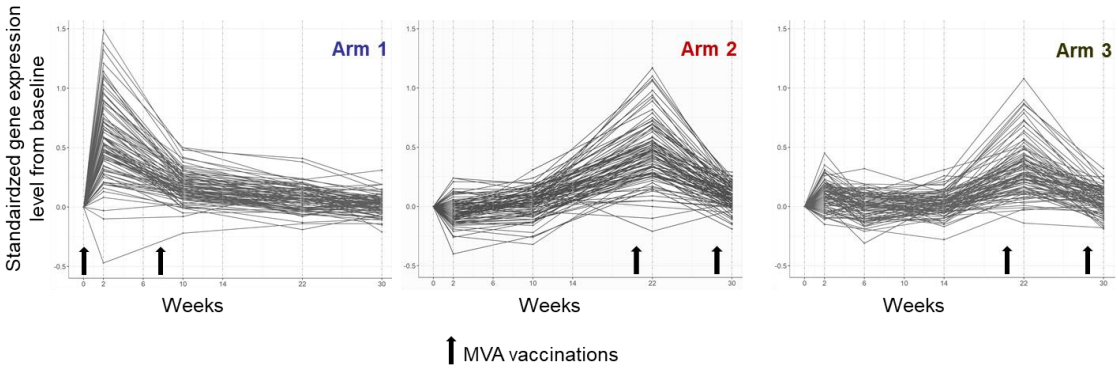


Figure 8. Changes in gene expression after MVA vaccination as prime or boost in the ANRS VRI01 trial

Gene expression was measured on full blood by microarray, and statistical analyses for time-course gene expression analyses were performed using mixed effect regression models with a random intercept and random slopes, and a variance component score test for significance testing. Eighty-six genes varied significantly after the 1st MVA injection (as prime or boost) compared to week 0. The graphs on this figure show the dynamics of these 86 genes per arm, which were mainly related to cell cycle pathways. Each line corresponds to the mean dynamics of a given gene.

The drafting of the paper of this trial, led by the coordinating clinician investigator (Jean-Daniel Lelièvre) and myself, is currently ongoing.

For the other terminated trials listed in Table 1, their main results and publication status are briefly summarized below.

- Primalvac trial (phase I dose-escalation trial of a pregnancy-associated Malaria vaccine) : the primary safety and immunogenicity results of this trial showed that the vaccine (VAR2CSA PRIMVAC vaccine) adjuvanted with Alhydrogel® or GLA-SE presented an acceptable safety profile and was immunogenic in both women never exposed to P. falciparum in France and nulligravid women living in a malaria-endemic area in Burkina Faso. Seroconversion was observed in all PRIMVAC-vaccinated women and the combination with GLA-SE tends to increase PRIMVAC-specific IgG levels and duration of the response. However, only the higher dosage was able to induce cross-reactive antibodies against other VAR2CSA variants, and no cross-inhibition was observed. These results have been presented at international conferences (conference communication: Konate et al, 2018) and the manuscript is currently under revision for the Lancet Infectious Diseases (*Sirima SB, Richert L, et al. Safety and Immunogenicity of PRIMVAC adjuvanted with Alhydrogel or GLA-SE, a vaccine candidate to prevent placental malaria: a first-in-human randomised, double-blind, placebo-controlled, dose-escalation study in non-pregnant French and Burkinabe women. In revision for Lancet Inf Dis*).
- Ebovac 2 trials (two randomized phase II trials – EBL2001 in Europe and EBL2002 in Sub-Saharan Africa – of a heterologous two-dose anti-Ebola vaccine strategy with Ad26.ZEBOV and MVA-BN-Filo): the primary results, showing the safety and humoral immunogenicity of the two-dose vaccine strategy, have been presented at international conferences (conference

communications: Barry et al, 2019; Thiébaut et al, 2019) and the preparation of the manuscripts is currently ongoing.

- BPZE-1 trial (phase I dose-escalation trial of a nasal pertussis vaccine): a manuscript of the primary results of showing the safety and humoral immunogenicity of this vaccine at different dose levels is currently in preparation (*Jahnmatz M, Richert L et al. Live attenuated intranasal pertussis vaccine BPZE1: Safety, colonization and serum antibody responses in humans in a phase Ib randomized placebo-controlled dose-escalation study*).

Given the substantial contributions and huge efforts provided unitedly by several research teams to conduct these vaccine trials, the author lists of the publications are results of consensus decisions among all partners.

3. Data science for vaccine trials

Statistical analyses of the immunogenicity data recorded in vaccine trials require a comprehensive data science approach, combining

- a sound understanding of assay specificities and of the nature of the acquired data,
- appropriate statistical methods for multidimensional data,
- and immunological knowledge to make a meaningful interpretation of the data.

The selection of adequate and efficient bioinformatics tools for the pre-treatment of high throughput omics data is also an important aspect in the overall analysis pipeline but is not a focus of my own research (since this is done in Boris Hejblum's research axis of the SISTM team).

3.1. Statistical analyses per assay and marker

3.1.1. Immune assay specificities and their methodological consequences

Many laboratory assays used in early-stage vaccine studies (be it high throughput omics assays or other immunological assays) are technically complex and have methodological specificities with an impact on the statistical analysis methods.

During my PhD thesis, I delved into the methodological aspects of the Luminex (multiplex bead array) assay, of cellular immune response assays (IFN-γ ELISpot assay and intracellular cytokine staining (ICS) assay), and their endpoint definitions in vaccine trials (Richert & Thiébaut, 2013; Surenaud et al, 2016).

My PhD student Edouard Lhomme (from 2016 to 2019) who has terminated his thesis and will defend it on November 25, 2019, has pursued and extended this methodological work with a focus on functional T-cell assays (in particular the ICS assay). The ICS assay relies on flow cytometry to

characterize T lymphocytes producing cytokines after specific antigenic stimulation. Non-stimulated cells from the same blood sample serve as a control condition. The common statistical approach currently used for the analysis of such data is to i) first subtract the response observed in non-stimulated cells from each stimulated sample; ii) then perform an inter- or intra-arm comparison of the percentages of cells producing cytokine(s) of interest. Step i) aims at capturing the antigen-specific response, but the subtraction may induce biased estimates and compromise type-I-error and statistical power. We propose using a bivariate linear model for the analysis of cellular immune responses to obtain accurate estimations of the vaccine effect. This bivariate model allows modelling simultaneously both response variables (non-stimulated and stimulated) depending on the vaccine effect. The stimulated response is adjusted on the non-stimulated response to take into account their correlation (Figure 9).

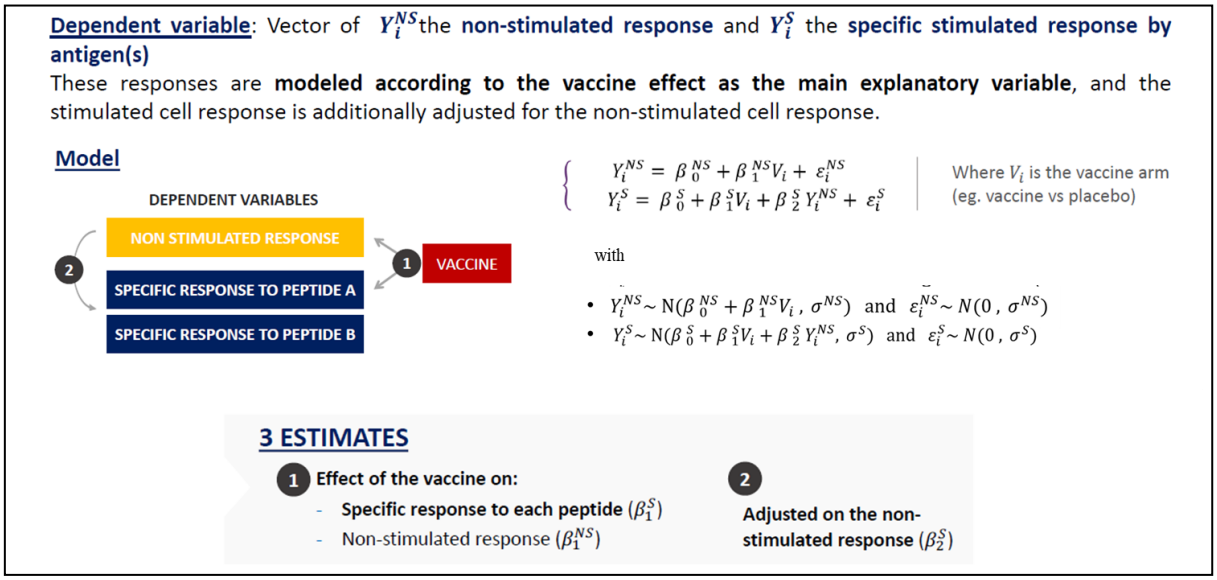


Figure 9. Bivariate model for estimating the vaccine effect on functional T-cell responses – overview of modelling principles and detailed equation for an inter-arm comparison

Edouard benchmarked the model's statistical performances in comparison to conventional approaches (t-test of background-subtracted response or of raw response) through numerical simulations. The results of these simulation studies showed that the new method allows modelling the vaccine effect while taking into account a linear relationship between the non-stimulated response and the antigenic responses and incorporating their measurement errors. The model always controlled type-I error in all simulation scenarios, while its statistical power was always at least as good as in the conventional approach. By contrast, the conventional analysis approach with background subtraction did not control type-I error and had very low statistical power in case of vaccine effect on non-stimulated response. Edouard applied this new approach to analyze data from two HIV vaccine trials, ANRS VRI01 (NCT02038842) and VRI02 ANRS 149 LIGHT (NCT01492985). The novel method has the advantage of taking into account all available information with more flexibility than the conventional

approach, leading to more accurate and more detailed results, and thus enabling a better interpretation of the vaccine effect. Edouard has presented this work in several conferences, targeting different audiences this year (conference communications: Lhomme et al, 2019a, Lhomme et al, 2019b, Lhomme et al, 2019c), and his paper on this method is currently under revision for the Journal of Immunological Methods (*Lhomme E, .., Richert L. Analyzing cellular immunogenicity in vaccine clinical trials: a new statistical method including non-specific responses for accurate estimation of vaccine effects; In revision for J Immunol Methods*).

This method is now used in the SISTM team as the standard method for analyses of functional cellular data with non-stimulated control conditions, for instance in the currently ongoing analysis of cellular proliferation data from the EBOVAC2 EBL2001 trial (see Table 1 and chapter 2.3). The latter is conducted by Mélany Durand, the study engineer (biostatistician) in the Translational Vaccinology axis under my supervision. In addition, together with our colleague Boris Hejblum, we have established an online interface based on R Shiny to make this analysis method available for use by immunologists without specific training in statistical modelling (https://shiny-vici.apps.math.cnrs.fr/).

My strong collaborations with the immunology monitoring platform (head: Christine Lacabaratz) of the VRI on the one hand, and with the team "Virus Immunology" (head: Marcus Altfeld) at the Heinrich-Pette-Institut, Leibniz Institute for Experimental Virology, in Hamburg, Germany, on the other hand, allow me to be confronted with the latest developments in assay technologies. I have spent two six-month periods as a full-time visiting researcher in Marcus Altfeld's team in 2016 and 2018. This gave me the opportunity not only to deepen my immunological knowledge but also to acquire solid understanding of state-of-the-art assay technologies, such as flow cytometry (FACS) and its extensions, bulk RNA sequencing and single-cell qPCR (Fluidigm technology) (Schommers et al, 2016; Martrus et al, 2017; Rechtien et al, 2017; Lunemann et al, 2018: Salzberger et al, 2018; Ziegler et al, 2018; Niehrs et al, 2019; van Stigt Thans et al, 2019). I am currently supervising Solenne Delahaye, a study engineer in the SISTM team, for the statistical analyses of data generated with the Fluidgim technology. Recently, the collaboration with the Altfeld lab has also paved the way for me to become acquainted with immunometabolomics measurements. Alice Herteau, a resident in public health and intern in the SISTM team under my supervision, has taken on the critical methodological assessment of this type of data and its statistical analysis pipeline.

3.1.2. Statistical analyses methods per marker

The statistical analysis plan for immunogenicity data from vaccine trials usually starts with separate analyses for each assay, and with separate statistical testing for each measured marker within the assay. Due to the many markers assessed simultaneously in an assay (e.g. hundreds of cell populations in flow cytometry data, or thousands of transcribed gene sequences in RNA Seq), test multiplicity must be taken into account when performing statistical analyses at the "individual marker level". Since

early-stage vaccine trials and their high-throughput immunogenicity readouts are primarily of an exploratory nature, false discovery rate (FDR) methods are used for multiplicity adjustment. The choice of the most appropriate FDR adjustment method depends on the analyzed immunogenicity data. For instance, in some immunogenicity assays, such as Luminex assays of cell supernatants after stimulation, test statistics may be correlated, since a) the peptides used for the stimulation of the cells can be overlapping or grouped by their belonging to the vaccine sequence, and b) responses of different cytokines are not independent of each other. Thoughtful selection of the FDR adjustment method is thus warranted. Such an analysis approach has for instance been chosen for the statistical analyses of Luminex and gene expression data of the ANRS VAC18 HIV vaccine trial (Richert et al, 2013), and is still part of the team's current statistical analysis plan for such data.

In addition, dimension-reduction and development of summary statistical variables for a given assay and immune response type (or even across several assays) can facilitate the interpretation of immunogenicity signals in vaccine trials. Different methods for geneset analyses (analyzing gene expression information at the geneset or pathway level instead of at the individual gene level) are widely used for transcriptomic data (Hejblum et al, 2015). However, methodological research published in the literature is scarce regarding methods to statistically summarize immunogenicity data with lower dimensionality, such as cellular assays, and is largely focussed on polyfunctionality of ICS data (Lin et al, 2015). In the analysis of a therapeutic HIV vaccine trial (DALIA trial), I used statistical methods to summarize information from quantitative multidimensional data across one or more immunological tests. I explored a non-parametric method, allowing to establish a score ("U-score") from the partial rankings of an individual's multivariate data within the study population (Wittkowski et al, 2004). With this method, all variables are treated equally, without weighting. As a second dimension reduction approach, we used a principal component analysis (PCA) with a Spearman correlation matrix. The construction of the U-scores showed an increase in the multivariate post-vaccination scores compared to pre-vaccination. In addition, correlations between post-vaccination immunogenicity markers and virological outcomes in these HIV-infected patients were found and summarized using a PCA (Lévy et al, 2014). These methods for dimension reduction were also useful for secondary analyses of the DALIA 1 data set (Brezar et al, 2015; Thiébaut et al, 2019). Since then, these analysis approaches have been also used for other vaccine trial analyses done by my PhD student Edouard Lhomme.

3.2. Systems vaccinology analyses

A systems biology approach allows combining statistical methods for data integration and down-selection together with a priori biological knowledge. When applying this approach to data from different high dimensional assays that measure different levels of the immune responses to a vaccine, this is termed "systems vaccinology". If appropriate, this follows in the overall analysis pipeline after

the “per assay” statistical analyses have been performed. My research in this field is done in close collaboration with Boris Hejblum’s axis in the SISTM team, which develops statistical methods for multidimensional data and for their down-selection, while my axis brings in the applied knowledge of translational vaccinology.

We have conducted systems vaccinology analyses of data from a phase I trial of rVSV-ZEBOV Ebola vaccine in healthy volunteers (clinicaltrials.gov NCT02283099) in collaboration with the Altfeld lab and with Marylyn Addo’s team (UKE University Hospital, Hamburg, Germany). For this, we used linear methods based on sparse Partial Least Square (sPLS) regression to investigate the interrelationships between the early innate immune responses after vaccination (characterized by cell subpopulations and cytokines) and later antibody production. We then also integrated early gene expression changes in the full blood after vaccination into the analyses. We found an early innate signature comprised of five markers that correlated with later antibody responses. This signature included plasma IP-10 levels, measured on day 3 after vaccination, as a correlate of antibody induction. Gene expression analyses by RNA Seq also identified an early gene expression signature linked to IP-10 and thus corroborated the potential relevance of serum IP-10 as an early determinant of antibody responses (Figure 10).

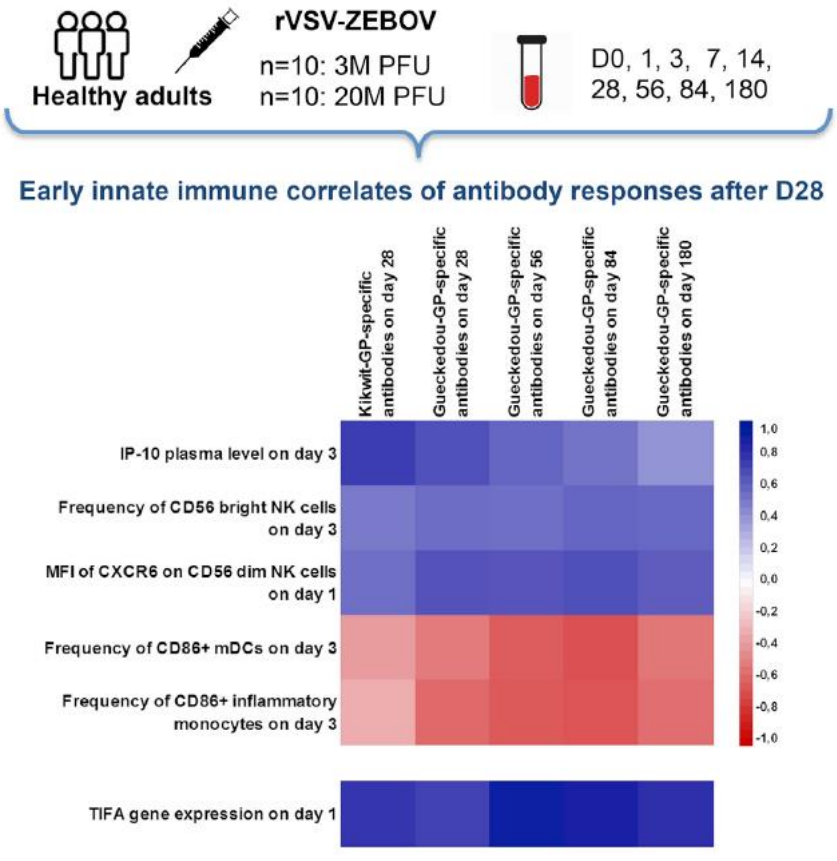


Figure 10. Overview of the study design and workflow and heatmap of early innate signature correlating with later antibody responses, phase I trial of rVSV ZEBOV vaccine (NCT02283099)

These results have been published with a shared first authorship in Cell Reports (Rechtien et al, 2017). My research stay in Hamburg in 2016 has been greatly beneficial for this collaborative project, during which I co-supervised Hadrien Lorenzo who was at that time the study engineer in the SISTM team performing the analyses. This work also illustrates the nurturing impact that this kind of applied vaccinology project can have on the other research axes of the SISTM team: Hadrien Lorenzo has since then continued his work as a PhD student in the axis on High Dimensional Statistical Learning (under the supervision of R. Thiébaut and J. Saracco) to develop improved statistical analysis methods for this type of data. Since then, and notably during my second research stay in Hamburg in 2018, I have also pursued the systems vaccinology analyses of this phase I Ebola vaccine trial in collaboration with Marylyn Addo's team: we are integrating microRNA changes as an additional "level" into the analyses (ongoing work, for which I supervise Solenne Delahaye, a study engineer in the SISTM team).

The data generated in the IMI-2 Ebovac2 projet (see table 1 and chapter 2.3), in particular an extensive immune monitoring by various assays that was performed in subgroups of participants enrolled in the EBL2001 trial in Europe, provide the opportunity to perform systems vaccinology analyses for a different Ebola vaccine strategy (heterologous two-dose strategy with Ad26.ZEBOV and MVA-BN-Filo). The analyses of these data, for which I am the task leader in the IMI-2 consortium, are currently in the preparatory phases ("per assay" analyses are ongoing, see chapter 3.1). For these, I have supervised Eva Reiner, a biostatistics trainee in my research axis from March to June 2019, and Mélany Durand (study engineer) who has taken over the analyses since Eva's departure.

We have also applied a systems vaccinology approach to the immunogenicity data from the ANRS VRI01 trial (see chapter 2.3). The statistical analyses were performed by Solenne Delahaye (study engineer under my co-supervision). We identified a gene expression signature that correlates with later functional T-cell responses across the three different prime-boost association in which the MVA HIV-B vaccine was used. These results have been presented as an oral presentation at the R4P conference in 2018 (conference communication: Richert et al, 2018) and will be part of the primary paper of this trial.

A currently ongoing systems vaccinology project (in collaboration with the Altfeld lab in Hamburg) concerns the integrative analyses of immune responses after yellow fever vaccination, with a particular focus on integrating immunometabolomics data in addition to more common systems vaccinology data (such as innate responses and gene expression).

3.3. Modelling of determinants of immune responses to vaccines

Specific statistical methods for multi-dimensional analyses allow integrating and down-selecting the massive data from several high-throughput assays in early-stage vaccine trials. Nevertheless, classical regression methods are still useful when the interest lies in assessing a small number of (non-omics)

determinants of immune responses to vaccines. The sample sizes in early-stage vaccine trials are most often relatively small for classical multivariable regression modelling. However, these trials usually generate repeated longitudinal data of the immune response measurements after vaccination. This allows a) to model the dynamics of the immune responses over time (which is a research question in itself) and b) to make use of the repeated observations to increase the feasibility of multivariable modelling and model fitting without over-parametrization (which is a methodological advantage when studying immune response determinants).

The longitudinal dynamics of a given immune response marker are often non-linear and become particularly complex in case of repeated vaccinations (e.g. prime-boost strategies). They thus require careful consideration of the adequate model.

A modelling work carried out by Edouard Lhomme under my co-supervision when he was a Master's student in our team (2015) concerned the dynamics of immune responses and the relationships between them in a phase II prime-boost HIV vaccine trial (HVTN 068 trial). We used mixed-effect regression models with spline functions for time effects to model the response dynamics of cytotoxic CD8+ T-cells and their dependence on the responses of CD4+ T-helper cells after vaccination with an adenovirus vector vaccine. This modelling project, conducted in collaboration with the SCHARP/HVTN team (Prof. Steve Self and Dr. Steve de Rosa, University of Washington, USA), showed a significant association between the response of CD4+IL-2+ T-cells on day 14 post-prime vaccination and the subsequent CD8+IFN-γ+ responses, including post-boost time points (Lhomme et al, 2016). This result highlighted the role of the early CD4+ T-helper response in stimulation and maintenance of the cytotoxic CD8+ response to the vaccine.

The Master's theses of two other students I supervised also focused on modelling the immune responses after vaccination: Nicolas Lafosse (2017) used mixed-effects regression models to assess the determinants associated with the variations in IFN- y ELISpot response after MVA HIV-B vaccination in the ANRS VRI01 phase II HIV vaccine trial. His work showed that MVA HIV-B vaccination had an effect on non-stimulated IFN- y ELISpot response, which in turn was associated with the total stimulated IFN- y ELISpot response. This contributed to the arguments in favour of developing the bivariate model for the analysis of functional T-cell responses (Edouard Lhomme's PhD work, see chapter 3.1). Alice Herteau (2019) modelled the dose-response relationship of the antibody dynamics after rVSV-EBOV-GP Ebola vaccination in a phase I trial, using mixed-effects regression models with a change in the antibody response slope over time.

My further contributions regarding the modelling of immune response determinants are the following:

- Edouard Lhomme, as a PhD student under my supervision, and I contributed substantially to a meta-regression conducted in the SISTM team to assess the determinants of antibody response variability to Ebola vaccines (Gross et al, 2018).
- I supervised as senior author the modelling of the association between vitamin D levels and immune responses to hepatitis B and Streptococcus pneumoniae vaccinations in datasets from two ANRS vaccine trials in HIV-infected patients (Viard et al, 2016).

I have not yet started working on model-based in-silico trials to narrow down the most promising vaccine strategies to be tested in real clinical trials, which is one of the objectives of my current research project. Indeed, given the complex interrelationships of immune responses and their underlying mechanisms, mechanistic models based on ordinary differential equations are more appropriate than classical regression models to capture the causal relationships between markers mobilized after vaccination. Establishing an adequate mechanistic model and fitting it to observed data from vaccine trials is a crucial step in understanding the response mechanisms and predicting the long-term response. Such a model could then be used to make in-silico simulations and predictions of the effects of different refinements of a given vaccine strategy (i.e. varying the timing of vaccination, adding a booster dose, or personalizing the strategy according to individual characteristics). The best strategies identified by such an in-silico approach could then be tested in a real vaccine clinical trial. The research axis on mechanistic learning led by Melanie Prague in the SISTM team has a strong focus on methods for mechanistic modelling. I plan to intensify research projects at the interface between the two axes, where Melanie's axis will bring in the theoretical knowledge and developments for model fitting and my research axis the translational, immunological knowledge about immune responses to vaccines.

Also of note, the overall analysis pipeline before modelling selected immune response markers currently relies on a step-by-step approach: down-selection methods for multidimensional data are used in systems vaccinology analyses, and the results of these analyses and/or prior immunological knowledge are used for modelling the non-linear relationships of a smaller number of markers or their determinants. A combination of a multidimensional down-selection approach simultaneously with longitudinal or mechanistic modelling of vaccine immunogenicity data is not yet practicable and is a future development focus of the two other research axes in the SISTM team (axis "Mechanistic Learning" and axis "High Dimensional Statistical Learning").

4. Interrelationships between trial design and analysis methods

Beyond the inherent dependency between the statistical methods used for the primary endpoint analysis and the sample size calculation, there are various examples illustrating the impact of our data science and analysis projects on subsequent protocol designs.

Below, I provide some precise examples based on the research activities described in chapter 3:

- Systems vaccinology approaches can allow for down-selection of the most relevant immunogenicity markers to be measured in future trials (for instance our analyses of the phase I rVSV-ZEBOV data suggested the importance of plasma IP-10 levels measured early after vaccination, see chapter 3.2).

- The statistical analyses done by Edouard Lhomme on the HVTN 068 trial data (see chapter 3.3) showed the contribution of modelling to better inform measurement time points in future clinical trials in order to better capture and understand the cellular immune responses to certain types of vaccines (in particular, by performing measurements of the CD4+IL-2+ T-cell response at day 14 post-prime, which are not systematically included in trial protocols so far)
- The modelling of the antibody responses in a phase I vaccine trial done by Alice Herteau (see chapter 3.3) provided an estimation of the dose-response relationship. However, it also corroborated that the vaccine trial field is far away from a scenario where model-based phase I dose-escalation designs, such as continuous reassessment methods (CRM), could be reasonably applied. This is mainly due to the unknowns about the underlying dose-effect relationships for vaccines and to a gap in the literature regarding the description of such relationships.

Overall, our data science approach aims to contribute to a better understanding of the dynamics and interrelationships between the immunogenicity markers after injections of different vaccines. In turn, this would make it possible a) to better target the measurement of non-redundant markers at key follow-up times in future clinical trial protocols; and b) to pre-select the most promising vaccine strategies to be tested in clinical trials.

My role as a trial methodologist in long-term collaborations allows me to transfer the results of my methodological research directly to new clinical trial protocols in order to increase the efficiency of vaccine clinical development.

5. Summary of the overall research project and of my supervision activities

The overarching principles of my research project with the axis on “Translational Vaccinology” in the SISTM team, which were described in the preceding chapters, are summarized in Figure 11.

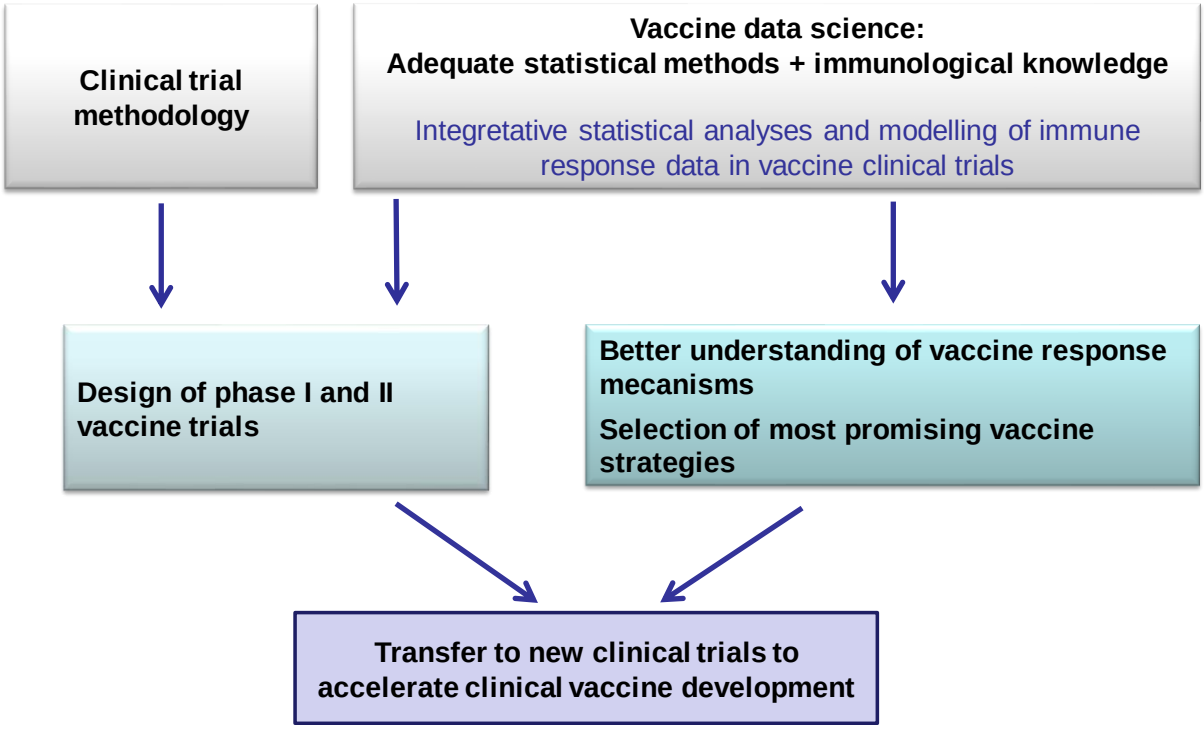


Figure 11. Overview of main principles of the research project

My efforts in supervising research activities are summarized below:

Supervisor for PhD thesis in Public Health, University of Bordeaux:

- E. Lhomme: "Analysis of the determinants and modelling of the post-vaccination immune responses in experimental vaccine strategies” (start of thesis: 2016, defense planned: 25/11/2019)

Supervision of Master’s theses in Public Health, option Epidemiology, ISPED, University of Bordeaux:

- A. Herteau: Modeling the dose effects of prophylactic vaccines: example of an experimental vaccine against the Ebola virus (2019)
- N. Lafosse: Study of the determinants of the variability of the cellular immune response after prophylactic HIV vaccination with the MVA HIV-B vaccine in the ANRS VRI01 phase II trial (2017)

- A. Tsaranazy: Development of a cumulative index of chronic exposure to immunosuppression in HIV-infected patients (2015) *[work not detailed in this document]*
- E. Lhomme: Modelling the dynamics of immune responses to a prophylactic HIV-1 vaccine in a vaccine clinical trial (2014; co-supervision with Pr R. Thiébaut)

Supervision and coordination of research activities in the SISTM team:

- Supervision of research/study engineers and interns:
    - H. Lorenzo, study engineer: Systems vaccinology analyses of the phase I rVSV ZEBOV vaccine trial (co-supervision with R. Thiébaut; 2015-2016)
    - S. Delahaye, study engineer: various statistical analyses; in particular, systems vaccinology analyses of the ANRS VRI01 trial; and micro-RNA systems vaccinology analyses of the phase I rVSV ZEBOV vaccine trial (2017-2019)
    - V-H. Tran, research engineer: statistical analyses of deep immune receptor profiling data by flow cytometry (2019)
    - A. Herteau, resident in public health: critical methodological appraisal of the statistical analysis pipeline for targeted metabolomics data; and statistical analyses of the immunometabolomics data from a yellow fever vaccine trial (6-months internship in 2019)
    - E. Reiner, trainee: statistical analyses of the Luminex data of the EBOVAC2 EBL2001 trial (4-months internship in 2019)
    - M. Durand, study engineer: statistical analyses of immune profiling data of the EBOVAC2 EBL2001 trial (since 2019)
- Coordination of the research axis “Translational Vaccinology” of the SISTM team since July 2019
- Co-head (together with Rodolphe Thiébaut) of the Data Science division of the French Vaccine Research Institute (VRI) since September 2019

Supervision of research/study engineers for the set-up, conduct, and analysis of vaccine clinical trials (EUCLID/F-CRIN platform and Inserm U1219 Research Center CTU):

- Supervision of a project team comprised of 2 to 8 persons for each trial
- Eight national or international vaccine trials (2013-2019)

6. Outlook

Given the relatively recent creation of my research axis “Translational Vaccinology” in the SISTM team, I plan to strengthen the work of this axis over the next years. Recruitment of an additional study engineer is planned, and I will take on the supervision of a new PhD student in early 2020 (Hélène

Savel, see details further below). It is also planned that Edouard Lhomme continues as a permanent hospital-university researcher (he is candidate to a position of associate professor) in this axis after obtaining his PhD. More and more datasets of terminated vaccine trials are now available in our team or will become available in the near future, which will allow us to use them for research projects in this axis (data science projects).

Close collaborations with experts in infectious diseases, vaccinology and immunology are crucial for the success of our interdisciplinary approach. I am therefore dedicated to actively pursue strong research collaborations, in particular with:

- The French Labex Vaccine Research Institute (VRI), in my role as co-head of the « Data Science » division and, in collaboration with Inserm U1219 Research Center CTU, as methodologist of the vaccine trials initiated by the VRI and its partners (currently mainly HIV and Ebola vaccine research);
- The research team led by Marylyn Addo (UKE University Hospital, Hamburg, Germany), which provides the opportunity to collaborate on systems vaccinology analyses in early-stage vaccine trials against emergent pathogens (such as MERS-CoV, for instance);
- The research team led by Marcus Altfeld (Heinrich-Pette-Institute, Hamburg, Germany), which allows me to work on new types of complex experimental immunological data (technological advances) and to improve my knowledge in fundamental and translational immunology (e. g. immunometabolomics).

New collaborations for the SISTM research axis are also upcoming. For instance, Edouard Lhomme plans to do his post-doc in a team in the U.S. specialized in systems serology, i.e. in deep assessments of vaccine-induced antibody responses and their functions. We hope that this will not only increase our expertise but also further improve the visibility and impact of our research contributions to vaccine research.

I also plan to continue my strong involvement in vaccine trial coordination and methodology within the EUCLID/F-CRIN clinical trials platform. As head of the platform, I intend to make this platform a leading clinical trials unit for vaccine trials.

In the following paragraphs, I will briefly outline the major research projects I am committed to for the next years:

We will perform further systems vaccinology analyses to elucidate the potential effects and mechanisms of action of Ebola vaccine strategies: Ad26.ZEBOV + MVA-BN®-Filo (in the H2020 IMI-2 EBOVAC2 project) and rVSV-ZEBOV (in the PREVAC and PREVAC-UP projects). The development of mechanistic models of the immune responses to the different Ebola vaccines is also planned within these projects.

Furthermore, a new H2020-funded project (IP-Cure-B; coordinator: Fabien Zoulim, Inserm U1052 CRCL) will start in 2020 to assess new concepts of immune therapy against chronic hepatitis B. I am leader of the work package “Data Science”, which is funded with 374,000 Euros over 5 years and has

the following objectives: i) to better understand the effect of the tested cure strategies on different components of the immune system and the virus, and the interrelations between them; and ii) to propose in-silico models predicting the viro-immunological responses to treatment and to optimally define cure strategies. For the SISTM research axis, this project provides an opportunity to extend our applications to immunotherapies and therapeutic vaccinations against hepatitis B.

Hélène Savel, my new PhD student starting in 2020, will work on a research project in a public-private partnership with the industrial partner Ipsen (French "Cifre" PhD funding mechanism). She will carry out methodological research on the integration of "omics" data into in-silico modelling of early-stage clinical trials in cancer. Although no long-term orientation of my research towards cancer research is planned, the supervision of this PhD thesis provides an excellent occasion to be confronted with and learn from in-silico approaches in a different, well advanced, application field.

I have already described some of the broader scientific perspectives of my research activities related to in-silico modelling in chapters 3.3 and 4. In addition to the in-silico down-selection of the most promising vaccine strategies, this could also allow exploring the personalization of vaccine strategies. For instance, the vaccine regimen could be adapted according to the age or the sex of the vaccine recipient. Moreover, an early immunogenicity assessment (in hours or days following a first vaccine injection) could inform the decision to administer an additional injection to a given individual. Indeed, this "precision vaccinology" framework could become a standard approach in the future, because of the observed heterogeneity in immune responses to various vaccines including routine vaccines. Hence, identification of determinants of this variability and adaptations of vaccine strategies according to individual characteristics may considerably improve the prevention of these infectious diseases.

In conclusion, I hope that my research project will contribute to optimizing vaccine clinical development in order to establish safe and efficacious vaccine strategies to prevent infectious diseases and improve population health. Moreover, the overall methodological approach as well as some of the specific developments could also be transposable to other application domains in clinical epidemiology with complex data.

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Lévy Y, Thiébaut R, Montes M, Lacabaratz C, Sloan L, Harrod C, **Richert L**, Chêne G, Banchereau J, Palucka K. Vaccination of HIV-1 infected patients with dendritic cells loaded with HIV-1 lipopeptides elicits broad T cell immunity associated to a reduced peak of HIV-1 viral load following HAART interruption. 19th Conference on Retroviruses and Opportunistic Infections, Seattle, USA, 5-8 March 2012, and AIDS Vaccine 2012, Boston, USA, 9-12 Sept 2012

Hue S, **Richert L**, Hocini H, Surenaud M, Tisserand P, Lacabaratz C, Salmon D, Raimbault M, Lelièvre JD, Liquet B, Lévy Y, Thiébaut R. Characterization of ANRS HIV LIPO-5 vaccine in healthy volunteers combining cytokine multiplex and transcriptomic analyses. AIDS Vaccine 2011, Bangkok, Thailand, 12-15 Sept 2011

Richert L, Bonnet F, Mercié P, Dauchy FA, Bruyand M, Greib C, Dabis F, Chêne G, Dehail P. High Prevalence of Locomotor Disorder in HIV Infected Patients, ANRS CO3 Aquitaine Cohort, 2007 to 2009. 17th Conference on Retroviruses and Opportunistic Infections. San Francisco, USA, 16-19 Feb 2010

Trombetti A, **Richert L**, Hadaya K, Graf JD, Martin PY, Rizzoli R. FGF-23 and post-transplant hypophosphatemia: evidence for a causative link. 30th Annual meeting of the American Society for Bone Mineral Research. Montreal, Canada, 12-16 Sept 2008

Richert L, Trombetti A, Herrmann FR, Triponez F, Meier C, Robert JH, Rizzoli R. Age and gender distribution of primary hyperparathyroidism in a European country with a particularly high life expectancy. 35th European Symposium on Calcified Tissues, Barcelone, Spain, 24-28 May 2008, and Annual European Congress of Rheumatology, Paris, France, 11-14 June 2008

Communication in the general public press

Chêne G, **Richert L**. Vieillir avec le VIH et les trithérapies. Biofutur 2011; 327:42-43

LIST OF APPENDICES: FULL TEXT OF SELECTED PUBLICATIONS

The appendices contain one selected publication for each of the chapters described for my research activities.

Appendix 1: Trial design
Richert L, Doussau A, Lelièvre JD, Arnold V, Lévy Y, Chêne G, Thiébaut R. 2014. Accelerating clinical development of HIV vaccine strategies – methodological challenges and considerations in constructing an optimized multi-arm phase I/II trial design. Trials. 15:68

Appendix 2: Quality by design in clinical trials
Lhomme E, Modet C, Augier A, Faye S, Dabakuyo-Yonli TS, Levy-Marchal C, D'Ortenzio E, Yazdanpanah Y, Chêne G, Beavogui AH, **Richert L;** PREVAC study team. 2019. Enrolling study personnel in Ebola vaccine trials: from guidelines to practice in a non-epidemic context. Trials. 20(1):422

Appendix 3: Primary results of vaccine trials
Sirima SB, **Richert L**, Chêne A, Konate AT, Campion C, Dechavanne S, Semblat JP, Benhamouda N, Bahuaud M, Loulergue P, Ouédraogo A, Nébié I, Kabore M, Kargougou D, Barry A, Ouattara M, Boilet V, Allais F, Roguet G, Havelange N, Lopez-Perez E, Kuppers A, Konaté E, Roussillon C, Kanté M, Belarbi L, Diarra A, Henry N, Soulama I, Ouédraogo A, Esperou H, Leroy O, Batteux F, Tartour E, Viebig NK, Thiébaut R, Launay O, Gamain B. Safety and Immunogenicity of PRIMVAC adjuvanted with Alhydrogel or GLA-SE, a vaccine candidate to prevent placental malaria: a first-in-human randomised, double-blind, placebo-controlled, dose-escalation study in non-pregnant French and Burkinabe women. *In revision for Lancet Inf Dis*

Appendix 4: Immune assay specificities and their methodological consequences
Lhomme E, Hejblum B, Lacabaratz C, Wiedemann A, Lelièvre JD, Levy Y, Thiébaut R, **Richert L.** Analyzing cellular immunogenicity in vaccine clinical trials: a new statistical method including non-specific responses for accurate estimation of vaccine effects. *In revision for J Immunol Methods*

Appendix 5: Statistical analyses per marker
Richert L, Hue S, Hocini H, Raimbault M, Lacabaratz C, Surenaud M, Wiedemann A, Tisserand P, Durier C, Salmon D, Lelièvre JD, Chêne G, Thiébaut R, Lévy Y; for the ANRS Vaccine Network / Vaccine Research Institute. 2013. Evaluation of cytokine and gene transcription profiles of immune responses to an HIV lipopeptide vaccine in HIV-negative volunteers. AIDS. 27(9):1421-1431.

Appendix 6: Systems vaccinology analyses
Rechtien A*, **Richert L***, Lorenzo H, Martrus G, Hejblum B, Dahlke C, Kasonta R, Zinser M, Stubbe H, Matschl U, Lohse A, Krähling V, Eickmann M, Becker S; VEBCON Consortium, Thiébaut R, Altfeld M, Addo MM. 2017. Systems Vaccinology Identifies an Early Innate Immune Signature as a Correlate of Antibody Responses to the Ebola Vaccine rVSV-ZEBOV. Cell Rep. 20(9):2251-2261. *equal contribution.

Appendix 7: Modelling of determinants of immune responses to vaccines
Lhomme E, **Richert L,** Moodie Z, Pasin C, Kalams SA, Morgan C, Self S, De Rosa SC, Thiébaut R. 2016. Early CD4+ T cell responses are associated with subsequent CD8+ T cell responses to a rAd5-based prophylactic prime-boost HIV vaccine strategy. Plos One. 11(4):e0152952