JNI 21es Journées Nationales d'Infectiologie
Poitiers
et la région Nouvelle Aquitaine
Palais des Congrès du Futuroscope
du mercredi 9 septembre 2020
au vendredi 11 septembre 2020

ST : Le point sur les MIE
Recherche clinique

Bruno Hoen

INSTITUT PASTEUR

Déclaration d'intérêts de 2014 à 2019

- **Intérêts financiers :**
- **Liens durables ou permanents :**
- **Interventions ponctuelles :**
- **Intérêts indirects :**

AUCUN

Les conditions de la réussite de projets de recherche clinique en situation d'émergence

- Commencer tôt, dès le premier signal d'émergence (et aller vite !)
- Avoir des outils de recueil prêts, actualisables rapidement
- Recherche trans-disciplinaire dès le début, avec des liens forts avec
  - les soins
  - la surveillance épidémiologique et les autorités de santé publique
  - la recherche fondamentale
- Une coordination précoce de la réflexion (REACTing)
  - Identifier les questions de recherche
  - Définir les priorités
- Être adossé à (intégré dans) une structure de recherche clinique

aviesan
alliance nationale
pour les sciences de la vie et de la santé

REACTing

Inserm

Clinical research on Chikungunya in FWI and French Guiana

REACTing-driven projects

CENTRE HOSPITALIER UNIVERSITAIRE POINTE-À-PITRE ABYMES

CIC
ANTILLES GUYANE

Université des Antilles

REsearch and ACTion targeting emerging infectious diseases (REACTing)

- First REACTing "crisis"
  - Chikungunya in the Caribbean, Dec. 2013
- First steps
  - 5 Dec 2013 : first cases identified in St Marteen
  - 20 Dec 2013 : first conf call of the REACTing steering committee, with field professionals (FWI and Réunion island)
  - End of January 2014 :
    - Working groups settled
    - Research priorities identified
    - Kick-off budgets secured

REACTing

Clinical research: 4 projects prioritized

- Caribbean Arbovirosis Cohort : DAG 2
- Extensive study of natural history of Chikungunya in a small sample of volunteers : CHIKITA
- Evaluation of anti-CHIKV hyperimmune IVIG in the prevention of Chikungunya infection in neonates: CHIKIVIG-01, clinical trial
- Assessment of attack rate of CHIKV infection in HIV-infected subjects : CHIKVIH, cross-sectional study

Prevention of Chikungunya infection in neonates: clinical evaluation of anti-CHIKV hyperimmune intravenous immunoglobulins

CHIKIVIG – 01

CHIKIVIG-01: progress of the trial

- Key dates
  - Study protocol completed by 30 April 2014 and sent to
    - French Research Agencies for funding,
    - Ethics committee for approval,
    - MoH for authorization

    } Fast-track processing requested to all
  - Ethics Committe approval 21 May 2014
  - Funding (MoH, PHRC) notified 28 May 2014
  - Agreement with LFB for providing CHIK IVIg signed 23 July 2014
  - Authorization MoH (ANSM) granted 12 August 2014
  - Study sites opening: 16 August – 5 September 2014
  - 1st enrollment: 17 September 2014
- Accrual in the FTAs
  - 4 inclusions between Sept 17 and Oct 18
  - December 2014: end of epidemics in FWI
- Future: enrollment in other areas with CHIKV
  - French Polynesia: hardly implementable and epidemics rapidly terminated
  - New Caledonia: paperworks OK, but waiting for the epidemics…
  - Mexico: implementation on its way
  - Brazil: preparation for enrollment in Rio de Janeiro

Am. J. Trop. Med. Hyg., 98(6), 2018, pp. 1819–1825
doi:10.4269/ajtmh.16-0719

Outbreak of Chikungunya in the French Caribbean Islands of Martinique and Guadeloupe: Findings from a Hospital-Based Surveillance System (2013–2015)

Frédérique Dorléans,[1*] Bruno Hoen,[3,10,13] Fatiha Najioullah,[4] Cécile Herrmann-Storck,[5] Kinda Maria Schepers,[10] Sylvie Abel,[2] Isabelle Lamaury,[10] Laurence Fagour,[4] Raymond Césaire,[4] Stéphanie Guyomard,[6] Ruth Troudard,[2] Yvette Adélaïde,[7] Marie-José Romagne,[7] Magguy Davidas,[7] Séverine Rochais,[7] Sylvie Boa,[8] Frédérique de Saint-Alary,[8] Annabel Preira,[8] Patrick Saint-Martin, Amandine Vaidie,[1] Mathilde Melin,[1] Elise Daudens-Vaysse,[1] Jacques Rosine,[1] Alain Blateau,[1] Luisiane Carvalho,[1] Alexandra Septfons,[9] Marie-Claire Paty,[9] Ghislain Leduc,[1] Sylvie Cassadou,[1] Martine Ledrans,[1] and André Cabié[11,12]

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Severe Sepsis and Septic Shock Associated with Chikungunya Virus Infection, Guadeloupe, 2014

Amélie Rollé, Kinda Schepers, Sylvie Cassadou, Elodie Curlier, Benjamin Madeux, Cécile Hermann-Storck, Isabelle Fabre, Isabelle Lamaury, Benoit Tressières, Guillaume Thiery, Bruno Hoen

During a 2014 outbreak, 450 patients with confirmed chikungunya virus infection were admitted to the University Hospital of Pointe-à-Pitre, Guadeloupe. Of these, 110 were nonpregnant adults; 42 had severe disease, and of those, 25 had severe sepsis or septic shock and 12 died. Severe sepsis may be a rare complication of chikungunya virus infection.

Emerging Infectious Diseases • www.cdc.gov/eid •

• Vol. 22, No. 5, May 2016

Am. J. Trop. Med. Hyg., 97(2), 2017, pp. 356–360
doi:10.4269/ajtmh.15-0753

Guillain–Barré Syndrome and Chikungunya: Description of All Cases Diagnosed during the 2014 Outbreak in the French West Indies

Stephanie Balavoine,[1] Mathilde Pircher,[2] Bruno Hoen,[1,3,4] Cecile Herrmann-Storck,[5] Fatiha Najioullah,[6] Benjamin Madeux,[7] Aissatou Signate,[8] Ruddy Valentino,[9] Annie Lannuzel,[3,10,11] Magali Saint Louis,[12] Sylvie Cassadou,[13] André Cabié,[2,3,4] and Kinda Schepers[1]*

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Clinical Infectious Diseases

BRIEF REPORT

Chikungunya, a Risk Factor for Guillain-Barré Syndrome

Sophie Stegmann-Planchard,[1,2] Pierre Gallian,[3,4] Benoit Tressières,[2] Isabelle Leparc-Goffart,[5] Annie Lannuzel,[6] Aissatou Signaté,[7] Cédric Laouénan,[8,9] André Cabié,[10] and Bruno Hoen[11]

Clinical Infectious Diseases 2019

Table 1. Chikungunya Virus Infections Among Cases and Controls

	Cases (n = 24)	Controls (n = 72)
Typical CHIKF before GBS, no. (%)	13 (54.2)	
Time from CHIKF to GBS, d		
Median [IQR]	8 [4–18]	
Min–max	1–22	
CHIKV infection, no. (%)		
Yes	15 (62.5)	16 (22.2)
No	0	56 (77.8)
Uncertain	9 (37.5)	0

	Conventional Analysis[a] (n = 60)		Maximal Bias Approach[b] (n = 96)	
CHIKV Infection	OR (95% CI)[c]	*P*[c]	OR (95% CI)	*P*
Yes	35.9 (7.5–infinite)	<.0001	8.3 (2.3–29.7)	.001
No	1		1	

Title

The attack rate of the Chikungunya virus infection was 61% in a French population-based cohort after the 2014 Caribbean outbreak.

Short Title

Attack Rate of Chikungunya

Keywords

Chikungunya, Chikungunya virus, Attack rate, Seroprevalence, French West Indies, Martinique, Guadeloupe

Authors

Elodie Curlier[1,5], Laurence Fagour[2], Cécile Herrmann-Storck[3], Adrien Staelen[4], Ingrid Vingadassalom[5], Sébastien Breurec[3], Sylvie Abel[4,6], Sandrine Pierre-François[4], Janick Jean-Marie[5], Cédric Laouénan[7], Raymond Césaire[2,6], Bruno Hoen[1,5,6]*, and André Cabié[4,5,6]*

Clinical research program on ZIKV infection in pregnant women and their offspring in French West Indies and French Guyana French Territories in America, FTA

Research on Zika in pregnant women in FTA

- Institutions, under the shield of AVIESAN/REACTing
  - Inserm — Sponsor
  - CIC 1424 Antilles-Guyane — Operator
  - CRB 3 FTA — Bio-bank
  - REACTing Nord — Methodology and Statistics
  - Institut Pasteur UEMI — Methodology and Statistics
- Ambition: implement the same research project in 3 FTA

ZIKV and birth defects: so many questions

- Assess the impact of ZIKV infection on the risk of adverse pregnancy
- When during pregnancy does ZIKV infection pose the highest risk to the fetus?
- Beyond microcephaly, identify and describe the spectrum of birth defects and other complications caused by in utero ZIKV infection
- Assess the impact of in utero ZIKV infection on child development
- Quantify absolute and relative risks of complications in fetuses/children born to mothers infected with ZIKV, weighted by gestational age at the time of infection
- Identify potential cofactors that might impact the risk of these different outcomes
  - Maternal
  - environmental

ZIKA-DFA: Regulatory and ethics issues

- ZIKA-DFA-FE
  - Jan 4: project writing starts
  - Feb 5: regulatory frame for research defined (noninterventional research, sponsor Inserm)
    - Authorizations to be obtained from national IRB, CCTIRS (Advisory committee on personal information management in the field of health research), and CNIL (Committee for information technology and freedom)
  - Feb 16: all application files completed and dispatched, along with a request by the Director General of Health (MoH) to expedite evaluation
  - Mar 4: all authorizations granted
- ZIKA-DFA-BB
  - Feb 29: project writing starts
  - April 10: regulatory frame for research defined (biomedical research, sponsor Inserm)
    - Authorizations to be obtained from national IRB and ANSM (French Medicines Agency)
  - April 20: all application files completed and dispatched
  - April 27: ANSM and IRB approval granted

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MARCH 15, 2018 VOL. 378 NO. 11

Pregnancy Outcomes after ZIKV Infection in French Territories in the Americas

Bruno Hoen, M.D., Ph.D., Bruno Schaub, M.D., Anna L. Funk, M.Sc., Vanessa Ardillon, M.D., Manon Boullard, M.Sc., André Cabié, M.D., Ph.D., Caroline Callier, M.Sc., Gabriel Carles, M.D., Sylvie Cassadou, M.D., Raymond Césaire, M.D., Ph.D., Maylis Douine, M.D., Ph.D., Cécile Herrmann-Storck, M.D., Philippe Kadhel, M.D., Ph.D., Cédric Laouénan, M.D., Ph.D., Yoann Madec, Ph.D., Alice Monthieux, M.D., Mathieu Nacher, M.D., Ph.D., Fatiha Najioullah, Ph.D., Dominique Rousset, M.D., Ph.D., Catherine Ryan, M.D., Kinda Schepers, M.D., Ph.D., Sofia Stegmann-Planchard, M.D., M.P.H., Benoît Tressières, M.Sc., Jean-Luc Voluménie, M.D., Samson Yassinguezo, M.D., Eustase Janky, M.D., Ph.D., and Arnaud Fontanet, M.D., Dr.P.H.

AMERICAN SOCIETY FOR MICROBIOLOGY | Journal of Clinical Microbiology®

LETTER TO THE EDITOR

Kinetics of Anti-Zika Virus Antibodies after Acute Infection in Pregnant Women

Bruno Hoen,[a,b,c] Mathieu Carpentier,[a] Stanie Gaete,[d] Benoît Tressières,[a] Cécile Herrmann-Storck,[e] Ingrid Vingadassalom,[a] Patricia Huc-Anaïs,[f] Anna Louise Funk,[g] Arnaud Fontanet,[g,h] Xavier de Lamballerie,[i] on behalf of the ZIKA-DFA-FE Study Group

Severe Thrombocytopenia after Zika Virus Infection, Guadeloupe, 2016

Timothée Boyer Chammard, Kinda Schepers, Sébastien Breurec, Thierry Messiaen, Anne-Laure Destrem, Matthieu Mahevas, Adrien Soulillou, Ludovic Janaud, Elodie Curlier, Cécile Herrmann-Storck, Bruno Hoen

Severe thrombocytopenia during or after the course of Zika virus infection has been rarely reported. We report 7 cases of severe thrombocytopenia and hemorrhagic signs and symptoms in Guadeloupe after infection with this virus. Clinical course and laboratory findings strongly suggest a causal link between Zika virus infection and immune-mediated thrombocytopenia.

Emerging Infectious Diseases • www.cdc.gov/eid •

• Vol. 23, No.4, April 2017

CORSER - Etude séro-épidémiologique du virus SARS-CoV-2 en France: constitution d'une collection d'échantillons biologiques humains

- Objectif principal : Détecter la présence d'anticorps spécifiques anti-SARS-CoV-2 chez des sujets
  - ayant effectué un séjour en Chine dans les semaines ayant précédé le début de l'épidémie (CORSER-1)
  - ayant présenté une suspicion d'infection à SARS-CoV-2 avec un résultat négatif de la recherche du virus par RT-PCR sur prélèvement respiratoire,
    ou contacts ou co-exposés de cas confirmés d'infection à SARS-CoV-2,
    ou ayant travaillé ou séjourné dans un hôpital où ont été pris en charge des cas confirmés d'infection à SARS-CoV-2 (CORSER-2a et 2b).
  - ayant été exposés à un risque d'infection par le SARS-CoV-2 dans un "cluster" de circulation de SARS-CoV-2 (CORSER-2c)
  - travaillant dans un établissement de santé (CORSER-2d)
  - soignés dans des unités de soins de long séjour (CORSER-2e)
- Objectifs secondaires
  - Estimer la prévalence des anticorps anti-SARS-CoV-2 dans les populations étudiées
  - Estimer la proportion d'infections asymptomatiques
  - Caractériser la cinétique des anticorps

CORSER - Etude séro-épidémiologique du virus SARS-CoV-2 en France: constitution d'une collection d'échantillons biologiques humains

	Inclusions réalisées	Prélèvements réalisés	Inclusions en cours
CORSER-1a/b	23	21	25
CORSER-2a/b	117	109	Terminé
CORSER-2c Crépy-1 Crépy-2 Crépy-3 Chorale ARIA	 209 661 1401 54	 209 661 1346 54	 Terminé Terminé Terminé Terminé
CORSER-2d			
- HU Strasbourg	168	168	Terminé
- CRAC Lille	393	393	Terminé
- IMM	769	769	Terminé
- Bichat-Dialyse			
- Gériatrie Nancy	272	272	Terminé
CORSER-2e	54	54	Terminé

ESSAI DE CHIMIOPROPHYLAXIE DE L'INFECTION A SARS-COV-2 (COVID-19) CHEZ LES SOIGNANTS EXPOSES :

ESSAI MULTICENTRIQUE RANDOMISÉ CONTROLÉ VERSUS PLACEBO EN DOUBLE AVEUGLE

COVIDAXIS

- Promoteur : CHU Saint-Etienne
- Investigateur coordonnateur : **Pr E. Botelho-Nevers**
  CHU Saint-Etienne
- Responsable Scientifique : **Pr B. Hoen**
  Institut Pasteur Paris

Institut Pasteur

CHU Saint-Étienne

L'essai COVIDAXIS-1 : les dates clés

Date	Action/événement
24/02	Rédaction du premier synopsis – Discussion avec REACTing
12/03	Début de rédaction du protocole – COPIL constitué – Promoteur identifié
23/03	Dossier complet déposé à CPP, ANSM et PHRC – DSMB identifié
28/03	Demande de révision du CPP
30/03	Protocole révisé soumis au CPP – 31/3 avis défavorable
01/04	Procédure d'appel et demande d'avis d'un 2ème CPP
07/04	Avis favorable CPP et ANSM
10/04	Ouverture du 1er centre investigateur
05/05	Résultats modèle macaque et 1ère réunion du DSMB : recommande la poursuite de l'essai (N=86)
22/05	Article Mehra et al dans Lancet
27/05	Avis en urgence du DSMB : poursuite de l'essai – ANSM : suspension de l'essai (N=117)
08/06	ANSM levée de la suspension envisagée – CS de l'essai : non reprise de COVIDAXIS-1

Long-term consequences of COVID-19: research needs

Persisting complaints after recovery

Extreme fatigue
Muscle weakness
Low grade fever
Inability to concentrate
Memory lapses
Changes in mood
Sleep difficulties
Headaches
Needle pains in arms and legs
Diarrhea and bouts of vomiting
Loss of taste and smell
Sore throat and difficulties to swallow
New onset of diabetes and hypertension
Skin rash
Shortness of breath
Chest pains
Palpitations

Questions to be answered by research

How can we help people with long term complaints? Physical therapy? Nutrition? Medications?
How many will need intensive reconditioning? Will it help?
How many will suffer from long term sequelae? Which sequelae?
How long will they suffer?
Can we predict during the acute disease which patients will develop long term consequences?
Are there features of the acute disease which predict long term consequences? Or underlying diseases which put patients at risk?
Are there management strategies of the acute disease related to the prevention (or exacerbation) of the long term consequences?
Will the people be infected again?
What is the contribution of social distancing and long isolation?
What is the time course of the immunological response in these patients? How does it differ from the time course in patients with no sequelae? Are there immunological patterns related to specific sequelae?
Is there an infectious or inflammatory explanation to the prolonged disease?
Are some of the manifestations explained by hypercoagulability?
Is there a genetic determinant to the prolonged disease?

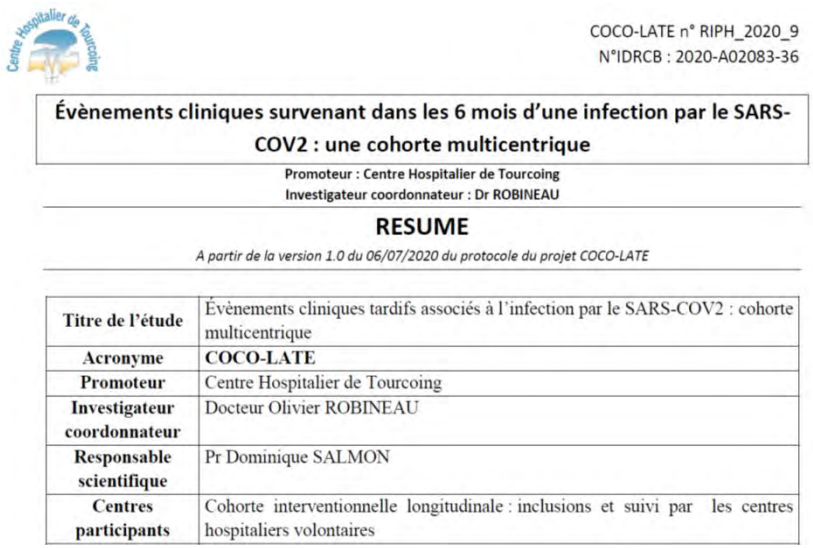
Yelin D, Lancet ID 2020
https://doi.org/10.1016/S1473-3099(20)30701-5

Long-term consequences of COVID-19: research needs

Requirements and design for research

Requirements
Multi-disciplinary approach
Common protocol of follow-up (time-points and evaluation)
Population and outcome definitions
Information on underlying conditions and the acute disease characteristics
Availability of biological samples collection
Multi-centre and multi-national approach
Information technology services support
Funding
Design of research
Cohorts of COVID-10 convalescents seen at regular intervals during 1-2 years after the acute disease: *Exposures:* Severity and management of the acute disease, people's characteristics and underlying disorders. *Outcomes:* Long term sequelae.
Nested case-control studies on severe long-term manifestations looking for explanatory mechanisms: *Cases:* Convalescents with a severe organ or system manifestation *Controls:* Convalescents without long term manifestations.
Randomized controlled trials on optimal treatment for specific complaints or for prevention of individual long-term consequences Multi-arm multi-stage designs Other adaptive designs

COCOLATE



COCO-LATE n° RIPH_2020_9
N°IDRCB : 2020-A02083-36

Évènements cliniques survenant dans les 6 mois d'une infection par le SARS-COV2 : une cohorte multicentrique

Promoteur : Centre Hospitalier de Tourcoing
Investigateur coordonnateur : Dr ROBINEAU

RESUME

A partir de la version 1.0 du 06/07/2020 du protocole du projet COCO-LATE

Titre de l'étude	Évènements cliniques tardifs associés à l'infection par le SARS-COV2 : cohorte multicentrique
Acronyme	**COCO-LATE**
Promoteur	Centre Hospitalier de Tourcoing
Investigateur coordonnateur	Docteur Olivier ROBINEAU
Responsable scientifique	Pr Dominique SALMON
Centres participants	Cohorte interventionnelle longitudinale : inclusions et suivi par les centres hospitaliers volontaires

Yelin D, Lancet ID 2020
https://doi.org/10.1016/S1473-3099(20)30701-5