Mise en place de projets de recherche en urgence en situation d'épidémie de MIE
Exemple des Antilles
CHIKV 2014 et ZIKV 2016

Pr Bruno Hoën
DFA: FWI and FG, an outlook

- Guadeloupe
  - Pop: 400,000

- Martinique
  - Pop: 380,000

- French Guiana
  - Pop: 255,000
Clinical research on Chikungunya in FWI and French Guiana

REACTing-driven projects
REsearch and ACTion targeting emerging infectious diseases (REACTing)

- First REACTing crisis
  - Chikungunya in the Caribbean, Dec. 2013
- First steps
  - 5 Dec 2103 : 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
Clinical research
4 projets prioritized

• Caribbean Arbovirosis Cohort (DAG 2)
• Extensive study of natural history of Chikungunya in a small sample of volunteers (CHIKITA)
• Prevention of Chikungunya infection in neonates: clinical evaluation of anti-CHIKV hyperimmune IVIG (CHIKIVIG-01, clinical trial)
• Assessment of seroprevalence of CHIKV infection in HIV-infected subjects after the end of the outbreak (CHIKVIH, cross-sectional study)
Prevention of Chikungunya infection in neonates: clinical evaluation of anti-CHIKV hyperimmune intravenous immunoglobulins

CHIKIVIG – 01
Day 6

DELIVERY = Day 0

Day 2

Clinical suspicion of acute CHIKV infection in a pregnant woman close to childbirth

Evaluation by an infectious disease specialist
Mother's written informed consent obtained

Dengue RDT

Positive

Mother exclusion

Negative

CHIKV RT-PCR results available before delivery

Yes

Probable maternal CHIKV infection

Definite maternal CHIKV infection

No

Negative CHIKV RT-PCR

Maternal CHIKV infection excluded

Delivery should happen within 6 days following first symptoms of maternal CHIKV infection. Otherwise, the neonate is not enrolled

Neonate administration of anti-CHIKV IVIG

Result of CHIKV RT-PCR in mother

Negative

Positive

Safety and tolerability evaluation of anti-CHIKV IVIG

Efficacy evaluation of anti-CHIKV IVIG
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
  • Ethics Committee 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 FWI and FG
  • 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
Research program on ZIKV infection in pregnant women and their offspring in French West Indies and French Guyana French Territories in America, FTA (DFA)
Preliminary data
Research on Zika in pregnant women in DFA

- Institutions, under the shield of AVIESAN/REACTing
  - Inserm Sponsor
  - CIC 1424 Antilles-Guyane Operator
  - CRB Bio-bank
  - REACTing Nord Methodology and Statistics
  - Institut Pasteur UEMI

- 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
Objectives of the ZIKA-DFA studies (1)

• ZIKA-DFA-FE
  – Measure the incidence of ZIKV infection during pregnancy
  – Describe clinical manifestations of the disease during pregnancy
  – Measure the incidence of microcephaly diagnosed in utero and at birth
  – Identify other complications not yet identified as possible complications of ZIKV
  – Measure relative risk of birth defects /other complications, with a focus on the role of
    • Gestational age at the time of ZIKV infection
    • Symptomatic ZIKV infection
Objectives of the ZIKA-DFA studies (2)

• ZIKA-DFA-BB
  - Describe abnormalities in and follow of apparently healthy children born to mothers infected with ZIKV during pregnancy (Cohort 1)
  - Follow-up children born with defects to mothers infected with ZIKV during pregnancy (Cohort 2)
  - Quantify the risks of complications in fetuses/children born to mothers infected with ZIKV, weighted by gestational age at the time of infection and exposure to cofactors. For this purpose, a cohort of healthy children born to uninfected mothers will be assembled (Cohort 3)
ZIKA – DFA – FE : 5 work packages

• **WP1**: identification and follow-up of pregnant women presenting with clinical symptoms of acute ZIKV infection, at any time of pregnancy

• **WP2**: follow-up of pregnant women in whom embryofetopathy is suspected during pregnancy ultrasound monitoring

• **WP3**: build up a serum collection from blood samples drawn once per trimester in any pregnant woman throughout the Zika outbreak

• **WP4**: build up a collection of mother and cord blood sampled the day of delivery in any delivering woman throughout the Zika outbreak

• **WP5**: build up a collection of maternal blood and fetal tissues in women in whom pregnancy, started during the Zika outbreak, would terminate with abortion, fetal death, or medical pregnancy termination
Observational studies of the consequences of ZIKV infection in the course of pregnancy during the 2016 outbreak of Zika in the FTA (ZIKA-DFA-FE)

<table>
<thead>
<tr>
<th>WP1</th>
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<tbody>
<tr>
<td>Clinical symptoms of acute ZIKV infection</td>
<td>Suspected embryofetopathy during ultrasound monitoring of pregnancy</td>
<td>Serum collection from blood samples drawn once per trimester in any pregnant woman</td>
<td>Collection of mother and cord blood sampled the day of delivery</td>
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<td>Blood and urine RT-PCR within 10 days of 1st symptoms</td>
<td>ZIKV serology (neutralization)</td>
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<tr>
<td>Prenatal monitoring: monthly fetal ultrasound until delivery</td>
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<td>Fetal ultrasound at GW12, GW22, GW28, GW32, GW36</td>
<td>In case of stillbirth, see WP5</td>
<td>Fetal autopsy, fetal tissue storage</td>
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<td>Placenta: ZIKC RT-PCR ZIKV &amp; histopathology</td>
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If abortion, fetal death, or medical termination of pregnancy, see WP5.

Clinical symptoms of acute ZIKV infection:
Blood and urine RT-PCR within 10 days of first symptoms of ZIKV serology.
Prenatal monitoring: monthly fetal ultrasound until delivery.

If abortion, fetal death, or medical termination of pregnancy, see WP5.

Suspicious embryofetopathy during ultrasound monitoring of pregnancy:
ZIKV serology (neutralization) Prenatal monitoring: monthly fetal ultrasound ± amniocentesis ± MRI at W30-34.

Suspected embryofetopathy during ultrasound monitoring of pregnancy.
ZIKV serology (neutralization)
Prenatal monitoring: monthly fetal ultrasound ± amniocentesis ± MRI at W30-34.

In case of stillbirth, see WP5.

Collection of mother and cord blood sampled the day of delivery:
ZIKV serology in mother + blood cord biobanking.

Collection of maternal blood and fetal tissues if abortion, fetal death, or medical pregnancy termination:
ZIKV serology (neutralization).
Fetal ultrasound at W12, W22, W28, W32, W36.

Collection of maternal blood and fetal tissues if abortion, fetal death, or medical pregnancy termination:
ZIKV serology (neutralization).
Fetal ultrasound at W12, W22, W28, W32, W36.

Expected numbers (3 FTA) over a 1-year period:
N=15,000
N=1,800
N=9,000
N=120
N=60

N=15,000 serum collection from blood samples drawn once per trimester in any pregnant woman.

WP3

WP4

WP5
Observational studies of the consequences of ZIKV infection in the course of pregnancy during the 2016 outbreak of Zika in the FTA (ZIKA-DFA-FE).

If abortion, fetal death, or medical termination of pregnancy, see WP5.

### WP1
Clinical symptoms of acute ZIKV infection during pregnancy:
- Blood and urine RT-PCR within 10 days of 1st symptoms
- ZIKV Serology

Prenatal monitoring: monthly fetal ultrasound until delivery.

If abortion, fetal death, or medical termination of pregnancy, see WP5.

### WP2
Suspected embryofetopathy during ultrasound monitoring of pregnancy:
- ZIKV serology (neutralization)
- Prenatal monitoring: monthly fetal ultrasound ± amniocentesis ± MRI at W30-34.

If abortion, fetal death, or medical termination of pregnancy, see WP5.

### WP3
Serum collection from blood samples drawn once per trimester in any pregnant woman:
- ZIKV serology q trimester
- Fetal ultrasound at W12, W22, W28, W32, W36

### WP4
Collection of maternal blood and cord blood sampled the day of delivery:
- ZIKV serology in mother + blood cord biobanking.

### WP5
Collection of maternal blood and fetal tissues if abortion, fetal death, or medical pregnancy termination:
- ZIKV serology (neutralization)
- Fetal autopsy, fetal tissue storage
- Placenta: ZIKV RT-PCR ZIKV & histopathology.

In case of stillbirth, see WP5.

N=1101
Mar 381
Guy 404
Gua 316

N=169
Mar 35
Guy 125
Gua 9

N=3244

N=2361
Mar 368
Guy 1080
Gua 913

N=154
Mar 34
Guy 91
Gua 29

Observed numbers (3 FTA), by March 27, 2017.
ZIKA-DFA-FE and ZIKA-DFA-BB, an outlook

**WP 1**
Symptoms of Zika
N=1,500

**WP 2**
Fetopathy
N=30

**WP 3**
Asymptomatic pregnant women
N=15,000

**WP 4**
Delivery
N=9,000 (biobank)

**WP 5**
IUFD
N=60

**Cohort 1: ZIKV + healthy neonates** (N=1,900)
- Born to SYMPTOMATIC mothers
- N=1,500
- Born to ASYMMPTOMATIC mothers
- N=400

**Cohort 2**
Birth defect
N=120

**Cohort 3**
ZIKV - healthy NN
N=200

**Cohort of healthy neonates – F/U up to 2 years of age**

**Specific clinical F/U**

Random extraction, according to serologic profile

ZIKV-  ZIKV+

ZIKA-DFA-FE

ZIKA-DFA-BB
ZIKA-DFA-BB: Follow-up schedule (Cohort 1)

• **At birth (before D4):**
  - Clinical examination by a pediatrician
    - Biometrics, including head circumference
    - Neurologic examination
    - Search for liver/spleen enlargement
    - Thorough skin exam in search for rash/purpura
  - If cord blood not sampled at birth, blood sampled by Day 3 (at the time of Guthrie's test) for Zika serology
  - Transfontanellar ultrasound
  - Brain MRI
  - Hearing test and retina digital imaging (RetCam®)

• **From Day 4 to 2 years of age**
  - Clinical examination focused on neurological development at 2nd, 4th, 9th, 18th, and 24th months
  - Brain MRI if needed
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: IRB to evaluate the project
Original aspects of ZIKA-DFA research program

- Prospective cohort of pregnant women assessed for ZIKV infection from the beginning of their pregnancy
- Strongly and effectively linked to
  - care
  - epidemiological surveillance
- Committed and open to collaborative research
  - ZIKALLIANCE
  - Other research teams
    - IRSET: identification of environmental cofactors
    - ...
Etude descriptive et pronostique des arboviroses endémiques, et émergentes dans les départements et régions d’outre-mer et en France métropolitaine menée dans une cohorte hospitalière d’enfants et d’adultes suspects d’arbovirose aiguë
Cohorte Arbovirose (CARBO)

- **Contexte**
  - Emergence des arboviroses en zone tropicales et subtropicales
  - Hyperendémie de la dengue aux Antilles et en Guyane
    - Formes graves
    - Complication spécifique: fuite plasmatique, dengue hémorragique
  - Emergence du Chikungunya sur le continent américain
    - Phase aiguë: formes graves et transmission périnatale
    - Phase post-aiguë et chronique: atteinte musculosquelettique invalidante
  - Emergence de l’infection à virus Zika sur le continent américain
    - Syndrome de Guillain-Barré
    - Embryofœtopathies
  - En France métropolitaine
    - Cas importés
    - Chaines de transmission locales
- **Hypothèses**
  - Etude de cohorte multicentrique
    - caractérisation des formes graves d’arbovirose,
    - recherche de facteurs prédictifs de survenue de ces formes graves
    - compréhension de la physiopathologie des arboviroses
Conclusion

• Les conditions de la réussite de projets de recherche clinique
  – Commencer tôt, dès le premier signal d'émergence (si possible avant…)
  – Avoir des outils de recueil prêts/actualisables rapidement (CARBO)
  – Multi-/trans-disciplinarité à envisager dès le début, avec des liens forts avec
    • Les soins
    • La surveillance épidémiologique
    • La recherche fondamentale
  – Une coordination précoce de la réflexion (REACTing, …)

• Ce qui n'est plus un problème
  – Les aspects administratifs : CPP, ANSM ont compris les enjeux de l'urgence

• Ce qui reste un problème
  – Le financement : on a besoin d'un budget de démarrage "tout de suite"…
AGNOWNLEDGMENTS

• 3 FTA
  – Clinical Investigation center (CIC) of Antilles-Guyane
  – Gynecologists-obstetricians and pediatricians
  – Biological Resource Centers (CRB) of Guadeloupe and Martinique

• Pôle recherche clinique INSERM

• Unité d'épidémiologie des maladies émergentes, Institut Pasteur

• REACTing