Mise en place de projets de recherche en urgence en situation d'épidémie de MIE
Expérience 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

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

Maladies infectieuses Inserm
Institut national
de la santé et de la recherche médicale

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)

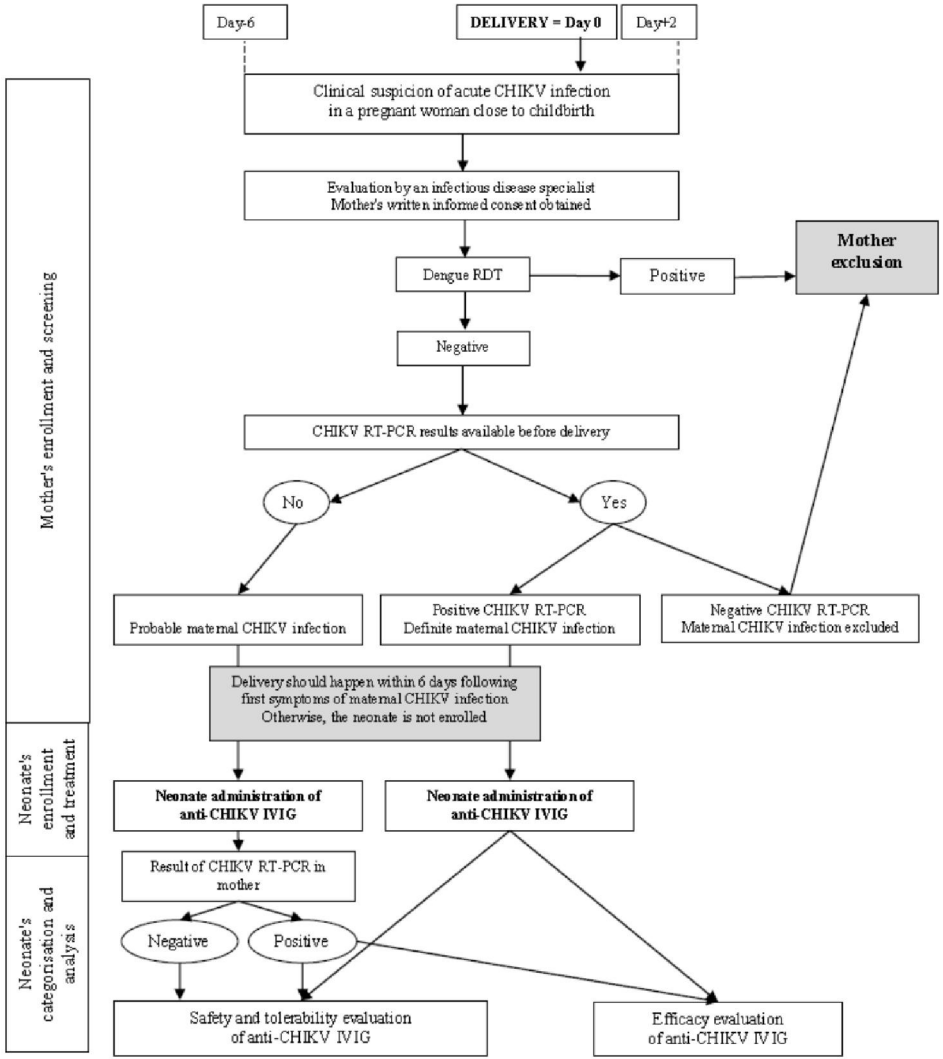
- First REACTing crisis
  - Chikungunya in the Caribbean, Dec. 2013
- First steps
  - 5 Dec 2103 : first cases identified in St Marteen
  - 20 Dec 2013 : first conf call of the REACTing steering committee, with field professionals (FWI and Réunion island)
  - End of January 2014 :
    - Working groups 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
No
Yes
Probable maternal CHIKV infection
Positive CHIKV RT-PCR
Definite maternal CHIKV infection
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
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
Mother's enrollment and screening
Neonate's enrollment and treatment
Neonate's categorisation and analysis

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 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

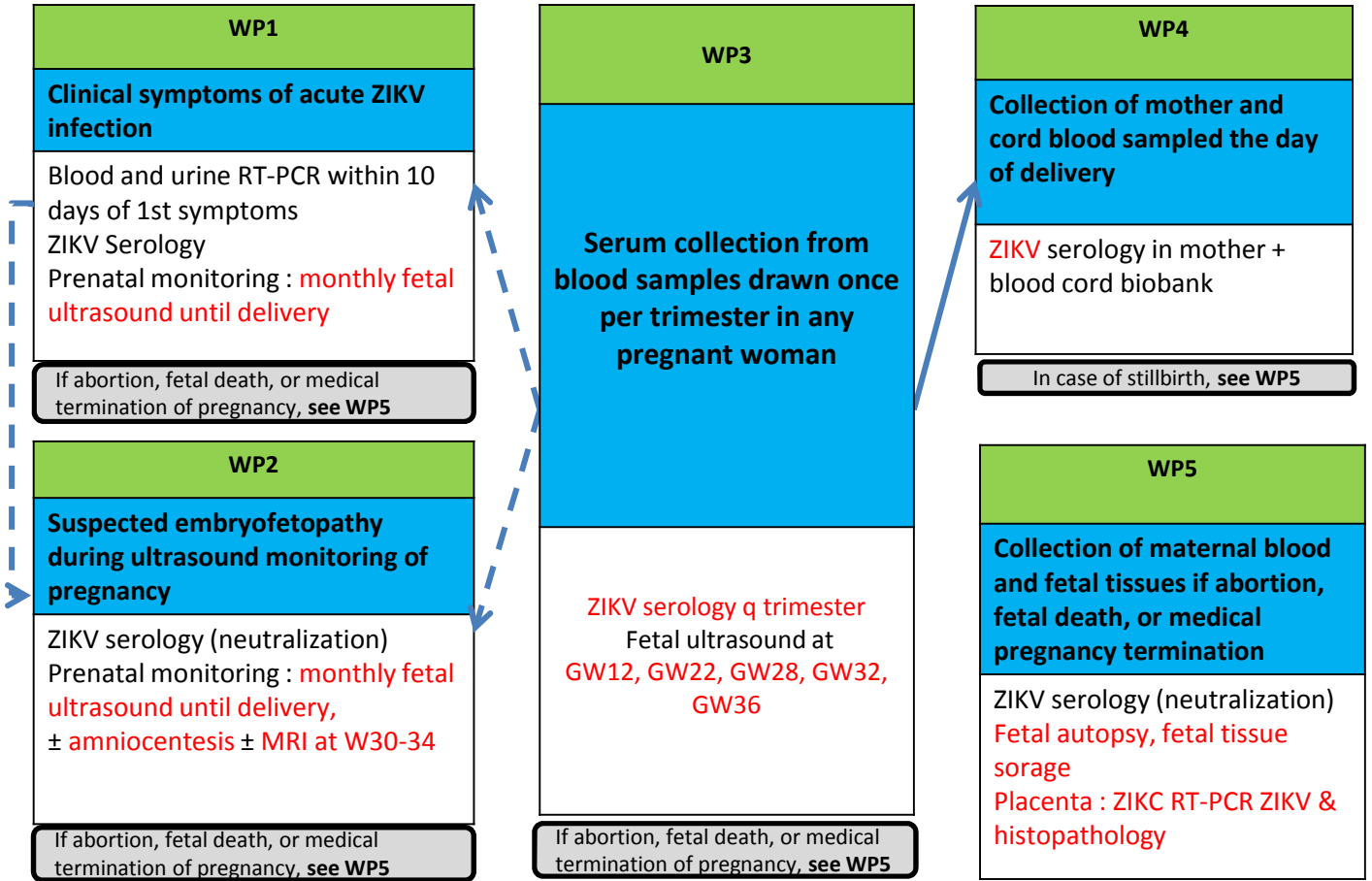
Objectives of the ZIKA-DFA studies (2)

- **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 pregancy (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)

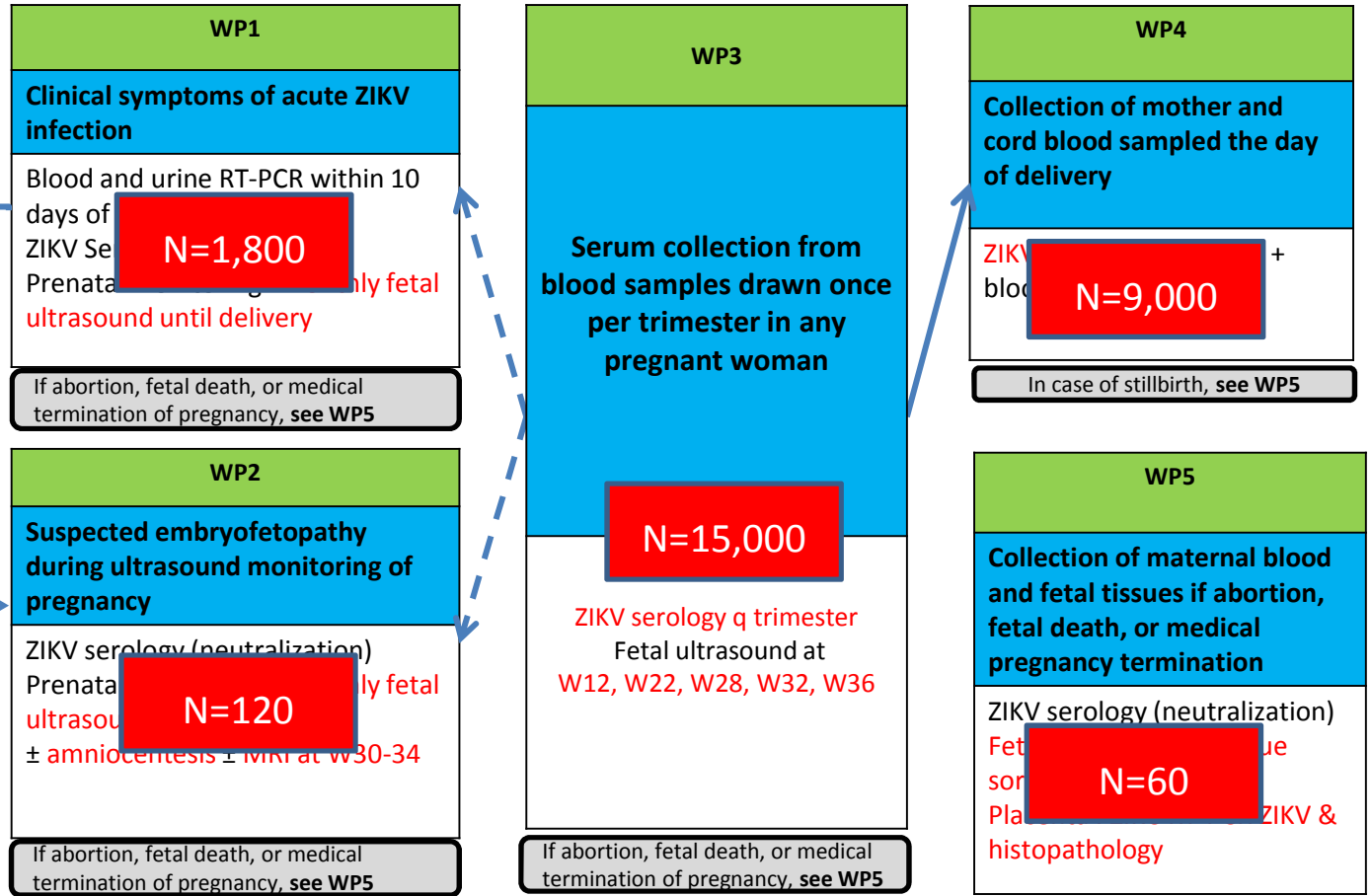
ZIKA – DFA – FE : 5 work packages

- **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

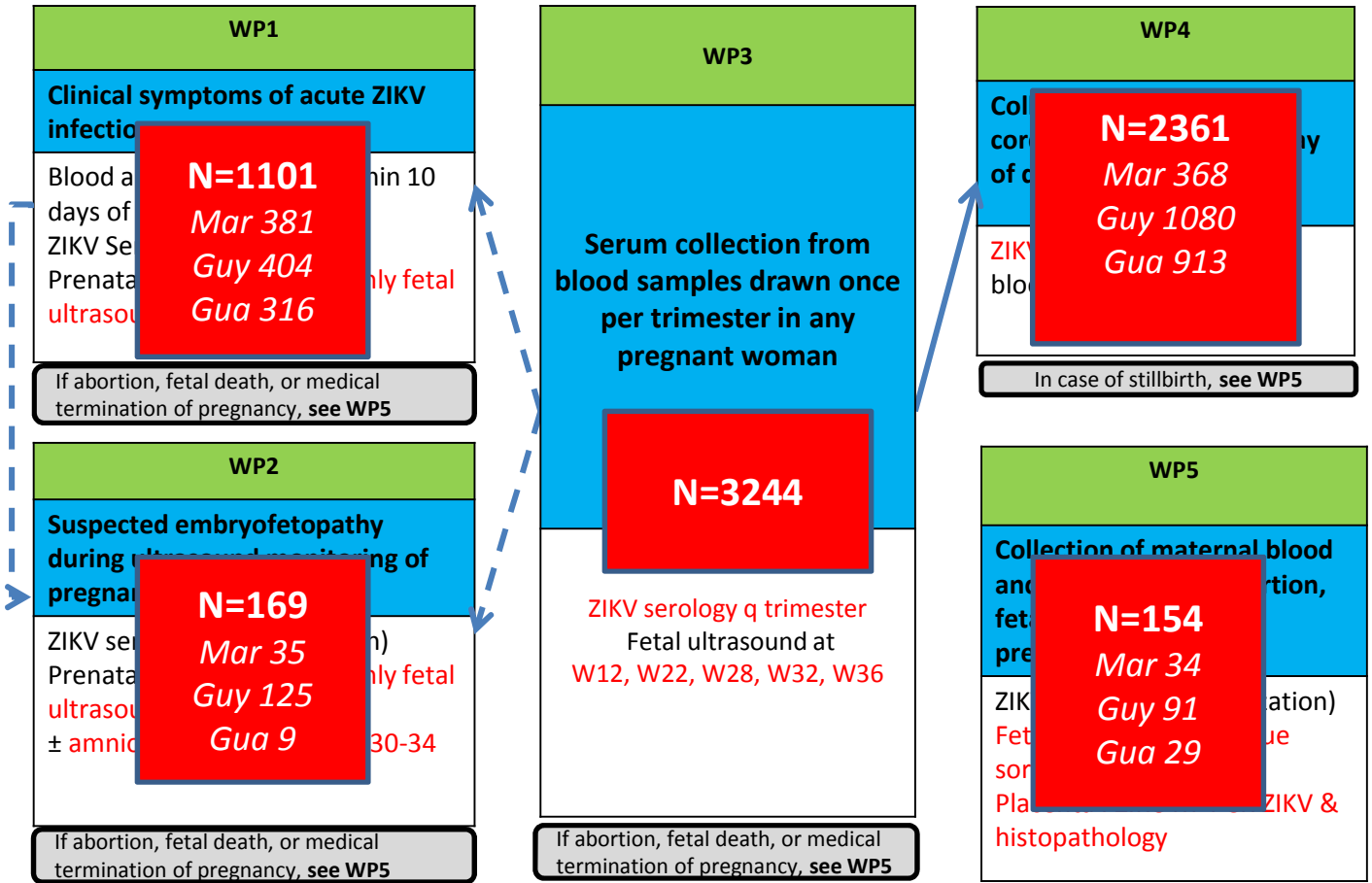
Observational studies of the consequences of ZIKV infection in the course of pregnancy during the 2016 outbreak of Zika in the FTA (ZIKA-DFA-FE)



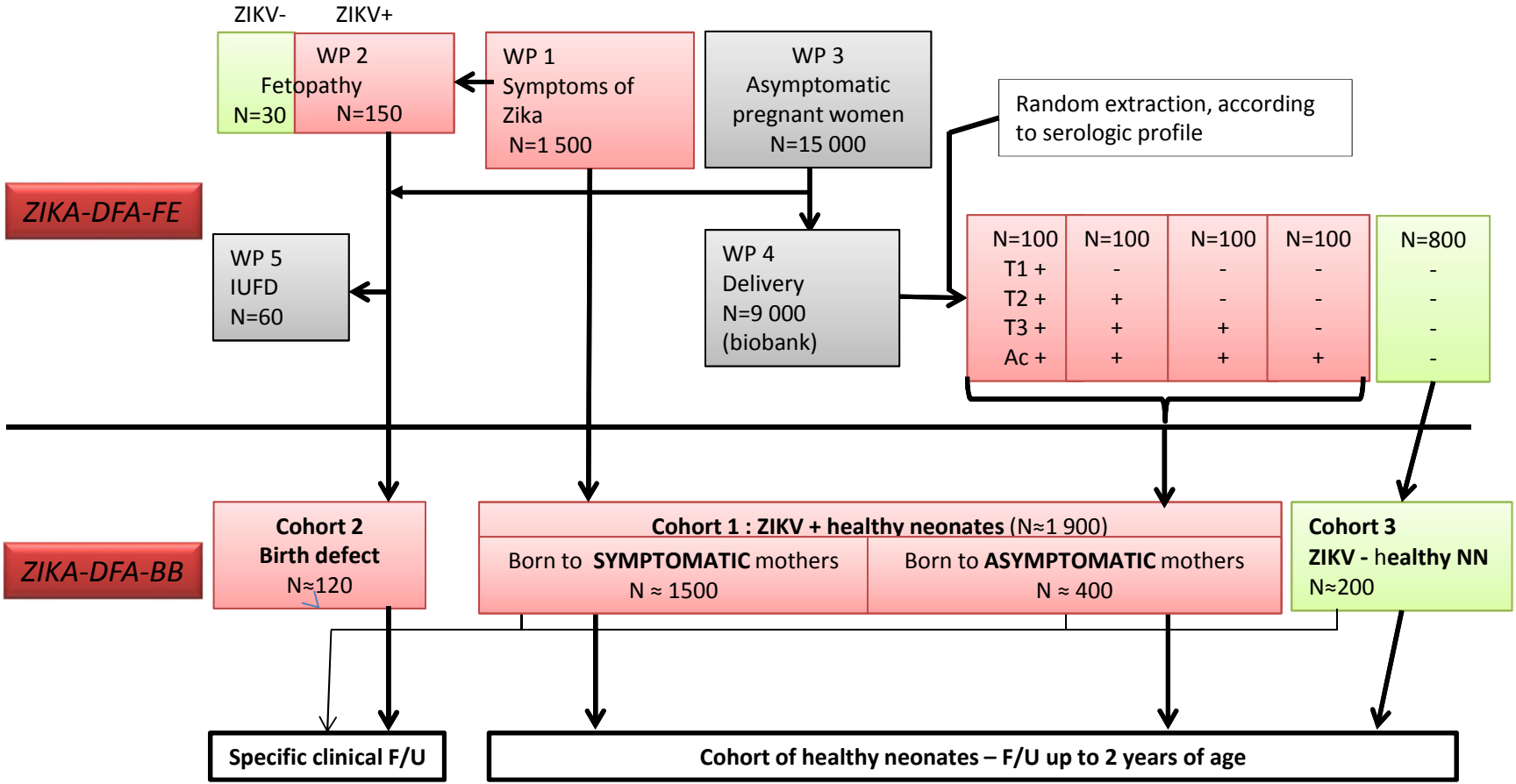
Expected numbers (3 FTA) over a 1-year period



Observed numbers (3 FTA), by March 27, 2017



ZIKA-DFA-FE and ZIKA-DFA-BB, an outlook



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

- **At birth (before D4) :**
  - Clincal examination by a pediatrician
    - Biometrics, including head circumference
    - Neurologic examination
    - Search for liver/spleen enlargement
    - Thorough skin exam in search for rash/purupura
  - 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
    - …

CHU de Martinique

CIC ANTILLES GUYANE

Instituts thématiques

Inserm

Inserm CIC1424

Institut national de la santé et de la recherche médicale

REACTing

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"…

AGNOWLEDGMENTS

- 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