Global Forum on Bioethics in Research

Theme 5

Public health Emergencies

The World Health Organization Ethics Review Committee experience Ebola Virus & Zika Virus

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2012-2016

World Health Organization

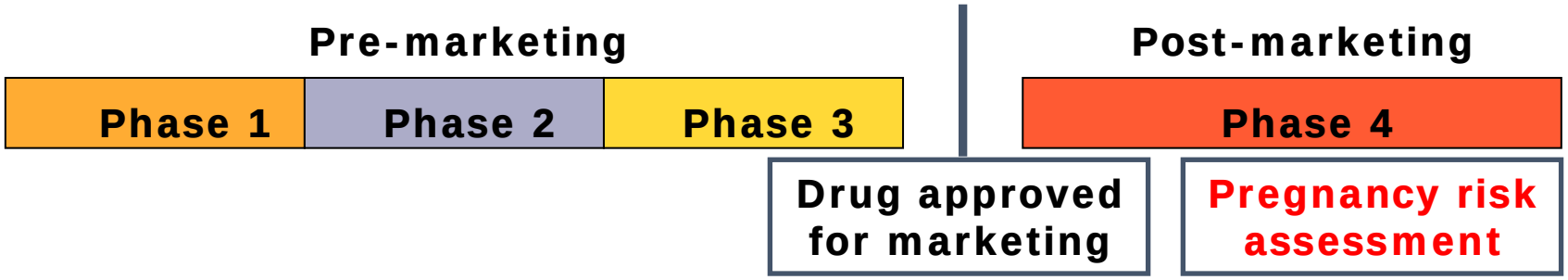
Ebola Virus (EBV):
Ethical considerations for unregistered interventions:
Report of an Advisory Panel to WHO, Aug 2014

- Research on investigational drugs or vaccines authorized - first time within a lethal outbreak
- Ethical imperative - offer available experimental interventions to patients on condition that:
  - Safety data in non-human primates available
  - Criteria for compassionate use met
  - Information on product uncertainty shared
  - Fair distribution, informed consent, confidentiality protected

Ebola Virus (EBV): Ethical considerations for unregistered interventions: Report of an Advisory Panel to WHO, Aug 2014

- "…because of higher mortality rates, children and *pregnant women* should be considered particularly vulnerable to EBV *and given special protection* in interventions.."
- IRBs looked at these considerations in their review
- Were children & pregnant women given special protection in research?

Standard drug development process:
Medicines affecting general population + pregnant women



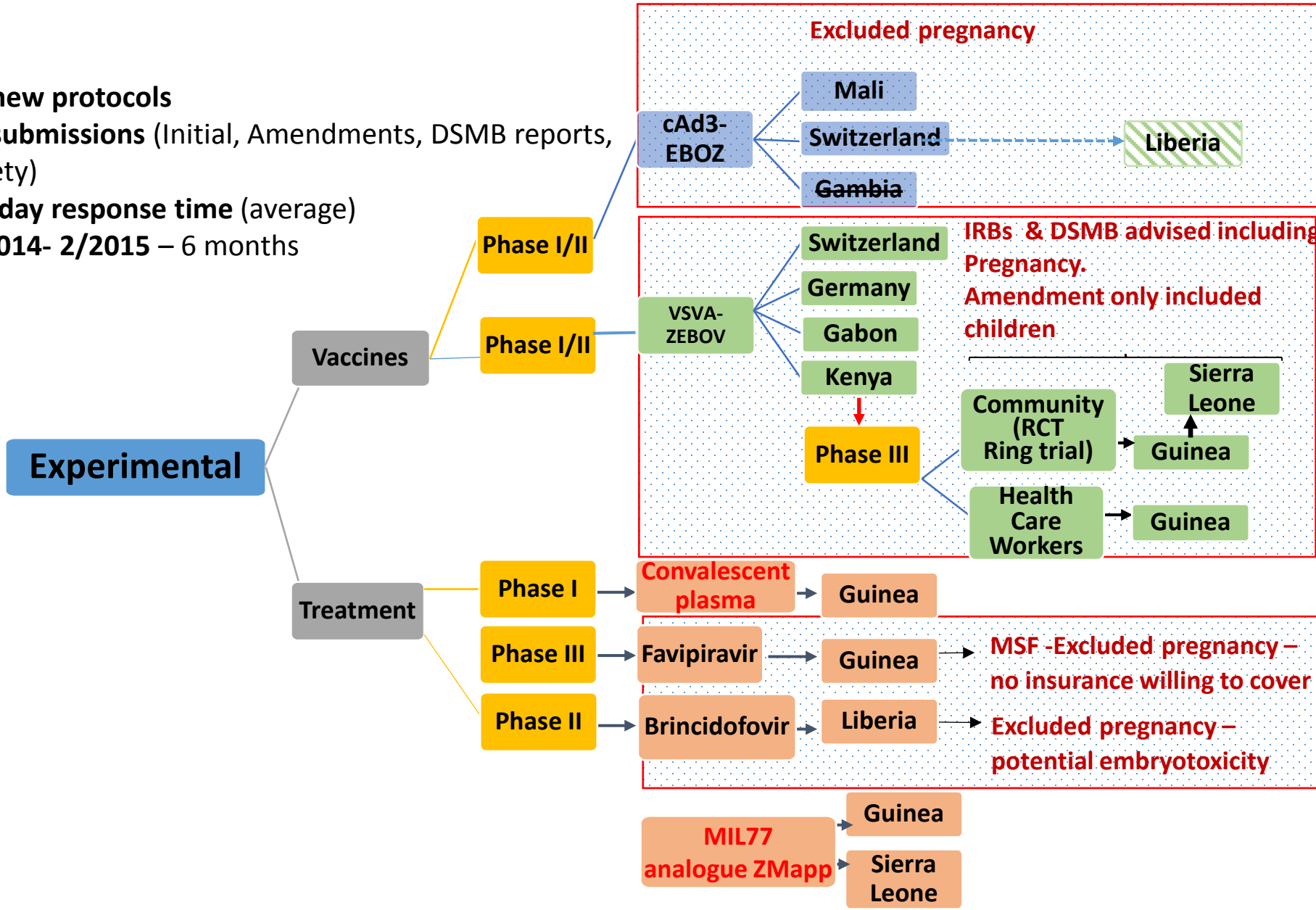
- Safety assessment delayed until product tested in non-pregnant groups:
  - Most risk-averse course of action
    - Wait until existing data suggest no problem; principle of "do no harm"
    - Supported by physician responsibility to woman & fetus
    - Drive to reduce legal liability - potential harm to fetus ($3-4 billion lawsuits DES, $80-100m thalidomide) first generation lawsuits
  - Economic considerations part of drug development process, but liability costs stifle research to identify new, beneficial drugs
  - Increasing efforts argue that women should be "presumed eligible" for participation in biomedical research.
    - CIOMS guidelines
    - FDA – Office of Women's Health & analyses of data by sex

What rules apply in life threatening infection: >50% mortality, 100% fetal death, no available treatment?

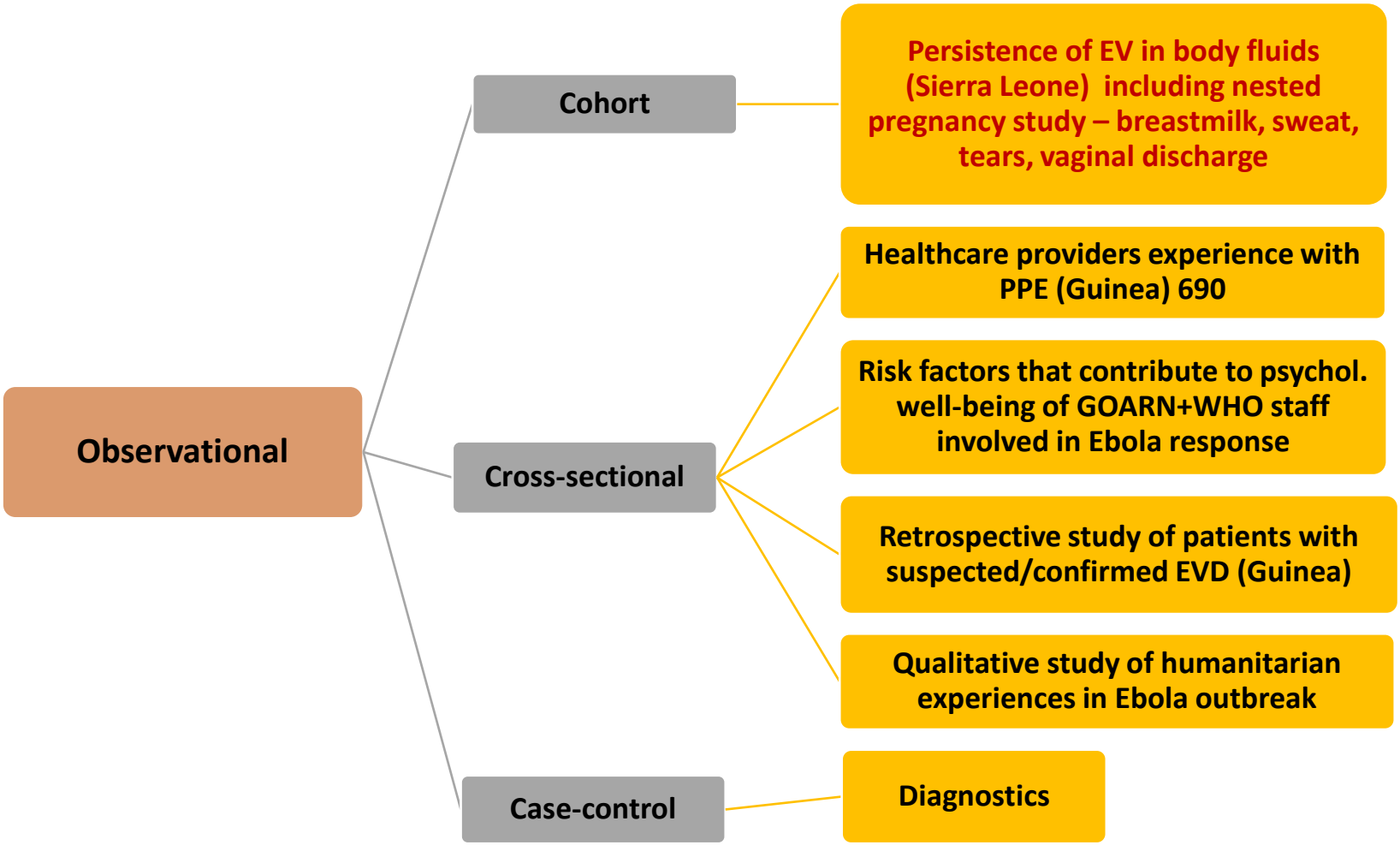
- EBV concentrates in placenta & amniotic fluid around fetus
- Fetus becomes concentrated ball of virus in woman's body
- Prior evidence - pregnant women at increased risk of:
  - Death – 7-11% survival: EBV = hemorrhagic fever – woman can bleed to death
  - High stillbirth rate, 100% fetal mortality
  - High neonatal mortality -
- After viraemia has resolved & woman still pregnant, EBV test positive are positive > 1 month
- High neonatal mortality reported – 100% so far
- Routine pregnancy testing not Standard of Care (SoC) – therefore reproductive status unknown
- 2014 outbreak- very little data on pregnancy or fetal outcomes

Research reviewed by ERC (1) Interventions

19 new protocols
36 submissions (Initial, Amendments, DSMB reports, Safety)
4.5 day response time (average)
9/2014- 2/2015 – 6 months



Research reviewed- (2) Observational



Inclusion vs Exclusion of Pregnant women

- Treatment protocols attempted to include pregnancy
  - Depended on insurance cover
  - Excluded if reproductive toxicity data indicated risk
- All vaccine protocols excluded pregnancy
  - Exclusion applied in initial phase – Phase I/II
  - Continued in each amendment
  - Even when IRBs advised inclusion with IC
  - Even when DSMCs advised inclusion

IRB Dilemma

- In an emergency – 50-70% mortality in EBV patients
  - Halt /delay implementation of a protocol for EBV while arguing for inclusion of specific groups – SPEED vs JUSTICE
  - IRBs had no recent data to argue risk-benefit:
    - number of pregnancies EBV+ coming to care
    - mortality risk in pregnancy
    - Fetal mortality risk
  - Researchers needed approval from pharma & legal representatives; would lengthen time to implementation

OR

  - Approve protocol, excluding pregnancy

Basic Principles: ethics & science

An opportunity to assess safety/efficacy under rigorous scientific conditions – when both women and their fetuses – with 50-100% risk of death – was lost.

This leaves the next epidemic with NO data in pregnancy.

What level of mortality needs to be reached for pregnant women to be included?

Zika virus (ZIKV)

- Mosquito-borne virus first identified 1947
- 2015 – linked to Guillain-Barré syndrome & microcephaly
- Lab diagnosis - blood or urine, saliva or semen. Negative PCR test not always reliable
- No treatment available
- In research:
  - How reliable is the diagnosis?
  - What are participant expectations?
  - How /what information is conveyed to participants?

Cohort studies planned…

- Case-control – for risk factors for microcephaly
- Prospective longitudinal cohort of newborns & infants born to ZIKV exposed pregnancies
- Prospective longitudinal cohort – persistence of ZIKV in body fluids
- Sero-prevalence of ZIKV in general population
- Clinical characterization protocol

ethics…

- What is the standard of care?
- Does standard of care (SoC) include:
  - ultrasound, diagnostic tests?
  - therapeutic abortion?
  - Is abortion legal?
- If SoC does not include ultrasound but research includes it, what happens when abnormalities are identified?
- If ZIKV identified, no abnormalities identified?
- Who bears responsibility & for how long?
- Does a ZIKV focus take away resources from routine care?

Reflections: What mortality rate needs to be reached for pregnant women to be included?

- We had a clear mandate to provide pregnant women with “special protection”
- As long as product (drug or vaccine) involves pharma, protocols become risk averse
- Timelines are tight, research is delayed if IRBs insist
- Requirements for inclusion & exclusion must be agreed with regulatory authorities & pharma, in advance - before the next epidemic