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Research with pregnant women

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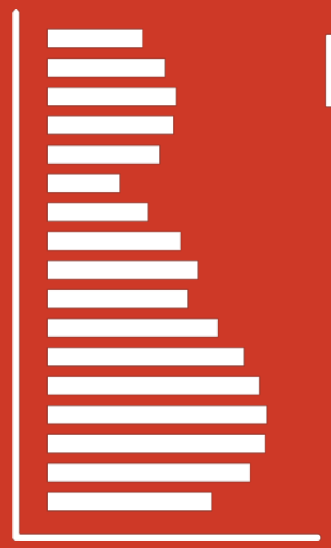
PHASES

PREGNANCY + HIV/AIDS

SEEKING EQUITABLE STUDY

NIH



Pregnancy Research Ethics for Vaccines, Epidemics, and New Technologies

PREVENT

wellcome trust

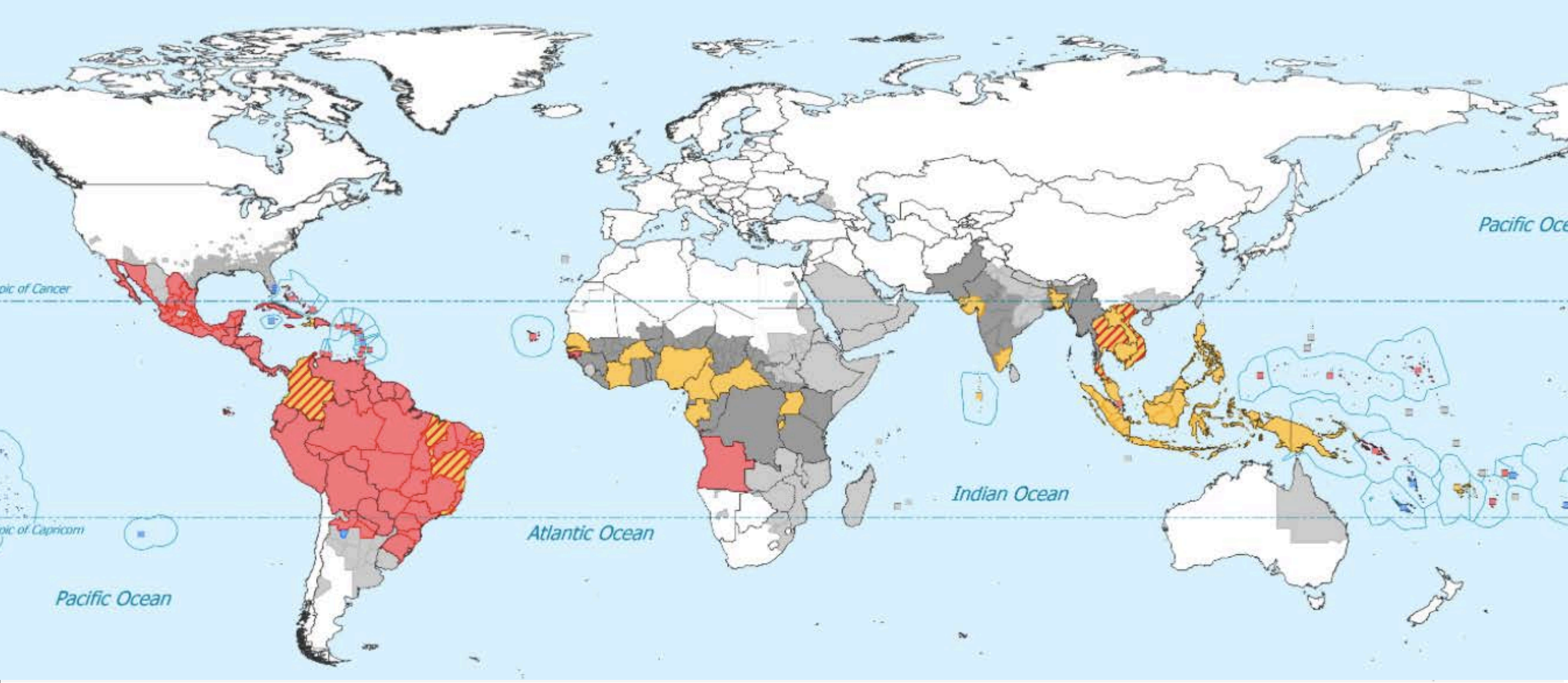
Disease burden in pregnancy

Nearly 4 million women give birth in the US each year

Many face medical conditions:

- Hypertension (approximately 5%; ~200,000)
- Diabetes (approximately 4%; ~160,000)
- Psychiatric illness (approximately 15%; ~600,000)
- Lupus, cancer, et cetera

Globally, pregnant women face HIV, malaria, TB, and more



Country classification category (Cat.) for Zika virus transmission

- Areas with virus transmission following virus new/re introduction (WHO Cat. 1)
- Areas with virus transmission following previous virus circulation (WHO Cat. 2)
- WHO Cat. 2 areas with new documented intense transmission
- Areas with interrupted transmission (WHO Cat. 3)
- Areas bordering a WHO Cat. 2 area (sub-category of WHO Cat. 4)
- Areas with potential for transmission (sub-category of WHO Cat. 4)
- Maritime Exclusive Economic Zones for non-visible areas

ecdc

ECDC. Map produced on 29 Aug 2017.
Map your data at: https://emma.ecdc.europa.eu

N Doce / Reuters 2016

J Decavele / Reuters 2016

“Pregnant women as drug orphans”

- Scaffidi, Mol, Keelan (2017)

1. 98% of drug treatments approved by the U.S. FDA since 2000 have insufficient data to determine teratogenic risk
2. 75% of drugs approved since 2000 do not have human pregnancy data
3. <98% of pharmacokinetic studies done provide any pregnancy-specific data

- McCormick, Best (2014)

Research “strategy” is to rely on data obtained in the clinical setting post-licensure

Post-licensure research “strategy”

1. Poor quality data
2. Long delays in safety determination
   - Mean time to assign risk level to drugs for pregnancy is 27 years

- Adam, Polifka, Friedman (2011)

Causes of reticence

1. Historical categorization of pregnant women as “vulnerable”
2. Misunderstandings about the regulations
3. Concerns about how to conduct research with pregnant women in an ethical way
4. Liability (duh)
5. Risk distortions

Four moral reasons for pursuing research with pregnant women

1. Achieving effective dosing
2. Reducing fetal risk
3. Combating reticence
4. Ensuring just access to trials involving prospect of benefit

Endorsement for responsible research with pregnant women

- WHO
- ACOG
- CIOMS
- 21st Century Cures Act

One Hundred Fourteenth Congress
of the
United States of America

"…The Secretary of Health and Human Services shall establish a task force to be known as the "**Task Force on Research Specific to Pregnant Women and Lactating Women.**"

– 21st Century Cures Act, Section 2041, 2016

Framework for regulatory ethics of research with pregnant women

- Code of Federal Regulations of the U.S. Department of Health and Human Services ("Subpart B")

Pregnant women: no longer vulnerable

- Common rule update, effective January 2018

Regulatory disjunct: Subpart B

No prospect of direct benefit

No more than minimal risk to the fetus

Prospect of direct benefit

Reasonable ratio of risk to benefit

No prospect of direct benefit

No prospect of direct benefit

No more than minimal risk to the fetus

"The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests"

- Subpart B

Prospect of direct benefit

- More complicated
- Whose risk? Whose benefit?

Prospect of direct benefit

Reasonable ratio of risk to benefit

Evidence needed for enrollment of pregnant women

- Must have data on risks

- Types include:
  - Preclinical, including reprotoxicity in relevant animal models (determined by the specific theoretical or biologically plausible risks), and studies with human placental tissue or organoid models
  - Observational or opportunistic clinical experience of the study intervention in pregnant women

Preliminary evidence

- Hypothesis generating, not conclusion generating
- If it's suggestive of something catastrophic, go precautionary principle
- If it's suggestive of something minor but the potential benefit is good, investigate

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