THE ‘WHYs’ AND ‘WAYs’ OF ENCOURAGING MORE STUDIES RELATED TO VACCINATION IN PREGNANCY

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My starting assumptions

• Physicians should practice evidence-based medicine

• Pregnant women are capable of autonomous informed decision-making (trial participation and treatment)

• Pregnant women should have access to sound information and advice on the basis of which to make decisions for themselves and their fetuses

• Pregnant women care about fetal well-being
‘THE WHYS’
Reasons to include pregnant women in research

• Develop effective treatment for women during pregnancy

• Promote fetal safety

• Reduce harm from the reticence to prescribe potentially beneficial medication (under-treatment)

• Allow access to benefits of research participation

Reasons to include pregnant women in vaccine research

• Develop safe and effective immunization for women during pregnancy

• Develop safe and effective immunization for newborns and infants (0-6 months)

• Prevent diseases and complications of pregnancy

• Allow access to benefits of research participation
Potential and hypothetical benefits of vaccination in pregnancy

- Reducing or eliminating diseases women are susceptible to because of pregnancy (*poliomyelitis, hepatitis*)
- Congenital embryo and placental infection (*herpes simplex, varicella, HIV*).
- Neonatal infections (*group B streptococcus*).

- Reducing intrauterine infections that contribute to premature birth (*clostridium*).
- Decreasing nursery epidemics (*Klebsiella pneumoniae*).

Potential and hypothetical risks of vaccination in pregnancy

- Risks to fetal health are overstated
- Risks of research must be weighted against the risks of doing nothing
- Studies can be designed to manage the risks to fetal health
  - Wait till safety and efficacy established in non-pregnant population
  - Wait till third trimester
  - Ensure no prior indication that vaccine causes fetal harm (data from inadvertent vaccination of pregnant women; data from analogous vaccines)

‘THE WAYs’
Ending the knowledge gap

• Pursue innovative study designs
• Develop more nuanced research regulations
• Alter labelling to more effectively communicate evidence-based guidance to medical use in pregnancy
• Establish an Institute of Medicine working group to issue a report on the under-representation of pregnant women in research
• Create incentives for inclusion of pregnant women in biomedical research

http://secondwaveinitiative.org/Case_Statement.html
Ending the knowledge gap

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Barriers to inclusion

- Manufacturers (Pharma)
- Regulators (Health Canada, FDA)
- Research sponsors (CIHR, NIH, MRC)
- Oversight organizations (PRE; OHRP)
- REBs (RECs, IRBs)
- Researchers
- Research participants
Incentives for inclusion

- **Manufacturers:** Provide data exclusivity. Prohibit off-label prescribing.

- **Regulators:** For research involving additional risks to the fetus, index levels of risk to the severity of need.

- **Research sponsors:** Make research in pregnancy a funding priority – expand funding for cohort registries, case-control surveillance studies.
Incentives for inclusion

- **Oversight organizations:** Presume inclusion and provide clear criteria for managing risk; clear criteria for exclusion.

- **REBs:** No boiler-plates.

- **Researchers:** Justify exclusion.

- **Research participants:** Increase public awareness.
Fear of liability

- Concern about injury *in utero* to the fetus
  - Fetal malformations, miscarriage, stillbirth, premature labour

- Best to avoid lawsuits by excluding pregnant women from research (and advising against the use of product during pregnancy)
WHO Guidelines on clinical evaluation of vaccines: regulatory expectations

• Special attention should be given to the ethical considerations underlying testing of vaccines in healthy infants, children, pregnant women and the elderly. The use and nature of a placebo should be carefully considered as should the use of human challenge studies. Human challenge studies are appropriate only for selected diseases that have no serious complications or long-term sequelae and for which successful treatment is available. …

• Subjects participating in vaccine trials should not be exposed to unreasonable or serious risks of illness or injury and measures should be in place to ensure that all subjects receive the full benefits of scientific innovations. It is important to ensure that economically and socially deprived communities, which are often those at the greatest risk of disease, are not exploited in conducting research that will be of no benefit to them. Detailed information is available in the ethical guidance documents issued by WHO, Council for International Organizations of Medical Sciences (CIOMS), UNAIDS and other bodies and these should be consulted as appropriate.
Research ethics guidelines

- **WHO** *Operational Guidelines for Ethics Committees That Review Biomedical Research* (2000)


- **UNAIDS/WHO** *Ethical Considerations in Biomedical HIV Prevention Trials* (2007, updated 2012)

- **WMA** *Declaration of Helsinki* (2000)
CIOMS: Guideline 17

• “Pregnant women should be presumed to be eligible for participation in biomedical research. Investigators and ethical review committees should ensure that prospective subjects who are pregnant are adequately informed about the risks and benefits to themselves, their pregnancies, the fetus and their subsequent offspring, and to their fertility.”
UNAIDS/WHO Guidance document: Guidance Point 9

• “Researchers and trial sponsors should include women in clinical trials in order to verify safety and efficacy from their standpoint, including immunogenicity in the case of vaccine trials, since women throughout the life span, including those who are sexually active and may become pregnant, be pregnant, or be breast-feeding, should be recipients of future safe and effective biomedical HIV prevention interventions.”
UNAIDS/WHO Guidance document: Guidance Point 9

• During such research, women should receive adequate information to make informed choices about risks to themselves, as well as to their foetus or breastfed infant, where applicable.

• …women should be viewed as autonomous decision-makers, capable of making an informed choice for themselves and for their foetus or child.
Human Subjects Research
(45 CFR 46) Subpart A

• §46.204 Research involving pregnant women or fetuses.

  ...

• (e) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions of subpart A of this part, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest.
Innovative study designs

• “…the natural population to recruit for research is pregnant women already needing to take a drug. But we need to first know a drug is safe in the general population and that it works before heading in that direction.”

Maria Palmisan, director of clinical pharmacology-experimental medicine at Bristol-Myers Squibb Co. May-June 2001 FDA Consumer.
Two options

• Stand-alone Phase I trials concurrent with Phase III trials

• Phase I trials embedded into late Phase II or Phase III trials

Phase I concurrent with Phase III

- Greater clarity in the design and increased ease in the review and monitoring of the clinical trial because only pregnant women are included in the trial
- Use of safety end points that are specific for pregnant women and that build on the knowledge gained from previous trials in non-pregnant adults
Phase I concurrent with Phase III

- Phased enrollment so that pregnant women in the later stages of pregnancy can be enrolled in research before women in the first trimester of their pregnancy are enrolled
- Increased probability that there will be planning for long-term follow-up of newborns
Phase I embedded in late Phase II or in Phase III

- Integration of pregnant women into the clinical research and regulatory approval processes (clearly signals the importance of normalizing the inclusion of pregnant women in research)

- Involvement of investigators who are familiar with the protocol as they will have participated in earlier research phases with nonpregnant adults
Phase I embedded in late Phase II or in Phase III

- Reduced start-up costs and monitoring requirements
- Ability to provide pregnancy-specific data sooner than would be possible with stand-alone trials because the subgroup analysis could be given priority
Responsible inclusion of pregnant women in research

- Promote the inclusion of pregnant women in vaccine research
  - Presumed eligible for research participation
  - Presumed autonomous (able to make informed decisions)
- Address liability issues
- Develop more nuanced research regulations/guidelines
- Pursue innovative study designs
- Increase funding for maternal (and neonatal) vaccine research/strategies
Pregnant women deserve better

Clinical trials routinely exclude expectant mothers. This is unethical and unscientific, and regulators must mandate change, says Françoise Baylis, in the second of three related pieces on gender bias in biomedicine.

International ethical guidelines drawn up by the Council for International Organizations of Medical Sciences' clearly stipulate that pregnant women are eligible to participate in biomedical research. Yet they are routinely excluded from the vast majority of clinical trials of drugs, vaccines, nutraceuticals, natural health products and medical devices because of the harm the intervention might do to the developing fetus.

This is ethically and medically unacceptable for two reasons: pregnant women get sick, and sick women get pregnant. Patients who happen to be pregnant are as entitled as anyone else to safe and effective treatments, yet they are denied this and will be for as long as pregnant women are excluded from clinical studies. New drugs and devices are typically not approved for use in pregnant women as the many physiological changes that women experience during pregnancy — such as increased plasma volume, body weight, body fat, metabolism and hormone levels — make it impossible to calculate dose and safety information by extrapolating from data on men and non-pregnant women.

This means that when a pregnant woman has a health condition that requires treatment, her physician often has insufficient information to make an evidence-based recommendation. For example, some of the adjuvants in a recent H1N1 vaccine were tested extensively in clinical trials with different vaccines that excluded pregnant women.

There is an obvious alternative: small, well-designed trials for pregnant women, starting with phase I safety trials that would begin at the same time as phase III efficacy trials in the general population. With this staggered approach, pregnant women and fetuses would not be exposed to any compounds that failed in phase I and II trials. Another option would be to allow pregnant women to join phase III trials once a drug had passed safely through phases I and II. This would need to include enhanced safety monitoring for pregnant women, similar to that done in a stand-alone phase I trial. As researchers and sponsors are unlikely to make such changes of their own volition, regulators will need to make the inclusion of pregnant women in such trials mandatory, and oblige drug companies to conduct follow-up studies to identify any short- or long-term effects of the drugs.

Persuading pregnant women to take part in research can be difficult because of the perception that trials are riskier than taking prescribed medication. Trial organizers should take pains to demonstrate that this is often a false belief, and that it is generally safer for pregnant women to use drugs in a trial under controlled circumstances.