SAFETY CANNOT BE CONSIDERED SEPARATELY FROM EFFICACY

- An ineffective product is by definition unsafe
- A product with nonzero risk of serious side effect may be preferable to a product without that side effect but with substantially lower efficacy against a serious disease
- Risks and benefits must be considered together
SAFETY ISSUES: NAÏVE POPULATIONS

- Rare risks (e.g., myocarditis, TTS) now believed associated with deployed vaccines
- Most data suggest mRNA vaccines are more effective than other deployed vaccines
- Other vaccine candidates in development; not clear whether the same or new risks will be identified
- Could lower dose levels of mRNA vaccines be evaluated in naïve adult populations?
- Should age and/or sex be considered in selecting vaccine for primary series?
SAFETY ISSUES: BOOSTERS

- Safer to boost with a vaccine that had different rare side effects than for primary series?
  - Myocarditis more common after second dose of mRNA vaccine; better to avoid a third dose?
  - Only in young men, or everyone?
- What is the optimal dose level for booster?
- Does timing of booster have safety implications?
LARGE RCTs COULD ANSWER IMPORTANT QUESTIONS

- **Naïve populations**
  - Can a smaller dose than currently given in the primary series be equally effective and perhaps safer?
    - May need clinical outcomes, since thresholds for immune responses as correlates of protection not yet established
  - What are the relative risks and benefits of currently deployed vaccines as well as new candidates?

- **Vaccinated populations**
  - Is the benefit-to-risk ratio more favorable with heterologous than homologous boosters?
  - Does it depend on what vaccine is given as primary series and what as booster?
EVALUATION OF NEW VACCINES

- Ongoing studies of new vaccine candidates could incorporate booster questions
  - Where vaccines not yet widely deployed, could even randomize to primary series as well as booster strategy
    - Heterologous vs homologous
    - Timing of booster
    - Dose level of booster
  - An already deployed vaccines would be a control arm
  - WHO is probably the only possible sponsor of such a study