

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