Ethical and Scientific Reflections on Studying Alternative Vaccination Schedules

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February 9, 2012
Disclaimer

• The opinions expressed herein are those of the presenter, and do not necessarily reflect the policies of the Food and Drug Administration or the Department of Health and Human Services.

• I have no conflicts of interest.
The Task

- The National Vaccine Advisory Committee (NVAC) recommended that “an external expert committee, such as the Institute of Medicine, with broad methodological, design, and ethical expertise to consider strengths and weaknesses, ethical issues and feasibility including timelines and cost of various study designs to examine outcomes in unvaccinated, vaccine delayed and vaccinated children and report back to the NVAC.”
Randomized Clinical Trial?

• In setting this task, “the NVAC believes that the strongest study design, a randomized clinical trial that includes a study arm receiving no vaccine or vaccine not given in accord with the current recommended schedule, is *not ethical*, would not pass Institutional Review Board (IRB) review, and *cannot be done*.”

NVAC, June 2, 2009 (emphasis added)
A clinical trial that included an alternate (or delayed) vaccination schedule would be unethical, as it is already known that under-immunized children would be placed at risk for vaccine-preventable disease. (See, for example, Glanz JM et al. 2009).

Whether the risks of a vaccine-preventable disease are worth taking to avoid the risks of vaccine-related adverse events depends upon the overall “herd immunity” of the population (along with other factors that may impact on the risk of disease exposure, such as travel and immigration).

Although I agree with the NVAC assessment, I thought it would be useful to examine some of the scientific and ethical issues a prospective randomized controlled clinical trial would raise.
Study Groups

- Vaccinated - ACIP Schedule
- Vaccinated - Alternate Schedule(s)
  - *Problem of heterogeneity*: How does one deal with the fact that there are more than one alternate schedule? This group may not be homogenous. How should we include children who have missed one or more vaccine (either intentionally or unintentionally) and were administered vaccines using a “catch-up” schedule? Would these children be considered on an “alternate schedule”? (Could an RCT impose uniformity?)
  - Estimates of parents who have elected an alternate vaccination schedule range from 13 to nearly 22 percent. (See Dempsey 2011 and Smith 2010.)
- Unvaccinated
  - Dempsey (2011) found that only 2% of parents surveyed refused all vaccinations (i.e., 17% of those who adopted an alternate vaccination schedule).
Herd Immunity

• The level of herd immunity in the general population is an important variable impacting on the risk of vaccine-preventable disease in the study population.

• Existing herd immunity in the United States would make it extremely unlikely to observe an increase in vaccine-preventable disease during an RCT of any feasible design.

• The level of herd immunity in the general population may have an impact on all three study groups, including those infants and children who are being vaccinated using the ACIP recommended vaccination schedule.

• How do we account for this important variable?
Failure of “Cocooning”

- "Compared with older children and adults, infants aged <12 months have substantially higher rates of pertussis and the largest burden of pertussis-related deaths. Since 2004, a mean of 3,055 infant pertussis cases with more than 19 deaths has been reported each year through the National Notifiable Diseases Surveillance System (CDC, unpublished data, 2011). The majority of pertussis cases, hospitalizations, and deaths occur in infants aged ≤2 months, who are too young to be vaccinated; therefore, other strategies are required for prevention of pertussis in this age group."

MMWR 60(41) October 21, 2011 (emphasis added)
Efficacy as an Outcome

• When administered according to the recommended dosing regimen, vaccines are known to be safe and effective in preventing the diseases for which they have been approved and licensed.
• The ethical concern is that the use of an alternate vaccination schedule would result in an increase in vaccine-preventable diseases.
• The risk of disease depends broadly on two factors - the individual child's degree of immunity and that child's exposure to the vaccine-preventable disease (e.g., travel, child care, school, herd immunity).
• Presumably the hypothesis of the proposed study would be that an alternate vaccination schedule offers a safety advantage (i.e., a reduction in vaccine-associated severe adverse events) while not resulting in an unacceptable increase in vaccine-preventable disease.
• Thus, the study endpoints must include the occurrence of vaccine-preventable diseases in addition to any vaccine-related adverse events.
Known to be Effective

• “During 2001–2008, a median of 56 (range: 37–140) measles cases were reported to CDC annually (2); during the first 19 weeks of 2011, 118 cases of measles were reported, the highest number reported for this period since 1996. Of the 118 cases, 105 (89%) were associated with importation from other countries, including 46 importations (34 among U.S. residents traveling abroad and 12 among foreign visitors). Among those 46 cases, 40 (87%) were importations from the World Health Organization (WHO) European and South-East Asia regions. Of the 118, 105 (89%) patients were unvaccinated. Forty-seven (40%) patients were hospitalized and nine had pneumonia.”
Safety as an Outcome

- *The safety and efficacy of new vaccines are established against the backbone of the recommended vaccination schedule.* In other words, infants and children who are enrolled in clinical trials of new vaccines have received the other routine vaccinations that are recommended for that age group. In effect, studies of new vaccines should be considered “add on” trials of the new vaccine along with the recommended vaccination schedule in use at the time of the trial. Thus, the safety of the new vaccine is, in effect, a measure of the overall safety of the recommended vaccination schedule.

- *The perception that the overall safety of the vaccination schedule has not been tested is, strictly speaking, not accurate.*

- That being said, there are limits to the power of prospective controlled clinical trials to detect exceedingly rare vaccine-related adverse events.
Randomization

• Children of parents who elect an alternate vaccination schedule may be systematically different than children whose parents elect the ACIP recommended schedule.

• The purpose of randomization is to avoid systematic bias between treatment groups due to subject characteristics that may impact on outcome.

• How do we ensure that any differences in the incidence of vaccine-preventable diseases are caused solely by the different vaccination schedules? The usual approach is randomization. Can we randomize children to one of the three study groups independent of parental preference?
Randomization

• The ethical justification of randomization includes:
  1. genuine scientific uncertainty about the relative merits of the interventions, and
  2. limitation of the risk exposure for any child randomized to the “control” group (i.e., alternative schedules, unvaccinated) to no more than a minor increase over minimal risk.
Two Ethical Principles in Pediatrics

1) Absent a prospect of direct therapeutic benefit to the children enrolled in a clinical trial, the risks to which those children would be exposed must be “low” (i.e., knowledge does not justify more than “low” risk).

2) Children should not be placed at a disadvantage after being enrolled in a clinical trial, either through exposure to excessive risks or by failing to get necessary health care.
Additional Protections for Children
21 CFR 50 subpart D

- An intervention or procedure involving children either
  - must be restricted to "minimal" or a "minor increase over minimal" risk absent a potential for direct benefit to the child, or
    - must present risks that are justified by anticipated direct benefits to the child; the balance of which is at least as favorable as any available alternatives.

- 21 CFR 50.51/53
- 21 CFR 50.52
Choice of Control Group

• ICH E-10 Choice of Control Group and the 2008 Declaration of Helsinki appear to have the same standard for the upper limit of allowable risk exposure from withholding effective or proven treatment (for adults).
  – ICH E-10: “effective treatment” may be withheld as long as this would not result in “serious harm, such as death or irreversible morbidity.”
  – Declaration of Helsinki (2008) permits a placebo control if it is scientifically “necessary to determine the efficacy or safety of an intervention and the patients who receive placebo or no treatment will not be subject to any risk of serious or irreversible harm.”
• In pediatrics, the risk of withholding known effective treatment must be no more than a minor increase over minimal risk. As such, the inclusion of such a control group must be approvable under 21 CFR 50.53.
Limiting Risks of Under-Vaccination?

• The incidence of vaccine-preventable diseases in under-vaccinated children depends on the level of herd immunity in the population (and the related risk of exposure).

• Limiting the risks of under-vaccination requires prior knowledge about the level of herd immunity (and other variables) in the population to which any enrolled child will be exposed.

• Setting the level of herd immunity to a high enough level to mitigate the risks of under-vaccination to no more than a minor increase over minimal risk undermines the scientific rationale (and feasibility) of the clinical trial.
More Problems with Randomization

- How would we set the randomization proportions? Do we randomize 1:1:1, effectively setting herd immunity in the study population to between 33 and 66% (depending on the details of the alternate vaccination schedule and the timing of the assessment of immunity)? How do we factor in the level of herd immunity in the non-study population? Since the outcome of vaccine-preventable diseases depends on the level of herd immunity, must we conduct more than one trial in disparate locations using a different level of herd immunity?
Conclusion on Randomization

• Randomization independent of parental preference would not be ethical nor feasible.
  – Unless the level of herd immunity is high enough to effectively mitigate the risks of under-vaccination, there is not scientific uncertainty about the comparative efficacy of an alternate vaccination schedule to prevent vaccine-preventable diseases when compared to the ACIP recommended vaccination schedules.
    In other words, the efficacy of the alternate vaccination schedules assumes a sufficient level of herd immunity to reduce the exposure risk for children who are under-immunized. The risks to an under-immunized child are greater than a minor increase over minimal risk unless one again assumes a sufficient level of herd immunity to effectively mitigate those risks.
Masking Group Assignment?

• The purpose of blinding is to reduce bias, for example, in the reporting of adverse events as related to the intervention.
  – Absent randomization, blinding the parent is not an option.

• Absent randomization and blinding, prospective observational studies are subject to confounding and bias (as are retrospective epidemiological studies).
Ethical Assumptions (1)

• Credible alternatives?
  – Does the fact that the federal government is proposing to study the health outcomes of alternate vaccination schedules, including no vaccinations at all, lend credibility to those who propose such schedules?
  – If the risks of vaccine-preventable disease are considered along with avoiding any risks of vaccine administration, the truth of the hypothesis that alternative vaccination schedules have an acceptable safety profile depends to a large extent on the assumption that the majority of parents would not elect to follow that same alternative schedule.
Ethical Assumptions (2)

• (Un)informed Parental Choice?
  – The parental decision to adopt an alternate vaccination schedule or to not vaccinate a child at all in order to avoid the risks of vaccination likely assumes a low risk of disease exposure.
  – This assumption may or may not be true depending on the level of “herd immunity” for many vaccine-preventable diseases.
NVAC on Observational Trials

• “The type of study that is being suggested would be an observational study of populations looking at *natural variation in vaccination schedules* including some children where vaccination is declined through parental intent. All children in the study should be recommended to receive the standard immunization schedule. Importantly, it may be *difficult to control for confounders* in a study of health outcomes of vaccinated and unvaccinated populations; the baseline health and social characteristics of these populations may be different, and meaningful results may be difficult to obtain.”

NVAC, June 2, 2009 (emphasis added)
Outcomes of Interest

• “Outcomes to assess include biomarkers of immunity and metabolic dysfunction, and outcomes including but not limited to neurodevelopmental outcomes, allergies, asthma, immune-mediated diseases, and other developmental disabilities such as epilepsy, intellectual disability and learning disabilities.”

• “The inclusion of autism as an outcome is desired. This review should also consider what impact the inclusion of Autism Spectrum Disorders (ASD) as an outcome would have on study designs and feasibility.”

NVAC citing Working Group, June 2, 2009.
Retrospective Study?

- Can one perform an epidemiological study based on health records, such as the Vaccine Safety Datalink, using de-identified data from participating managed care organizations (more than 8.8 million people annually, representing nearly 3% of the United States population)?

- Concern: Under-immunization is geographically variable (i.e., not uniform) and may be clustered such that some data sets (e.g., based on HMO participation) may not be representative of parents who elect alternate vaccination schedules and thus may under-estimate the risks to local populations. (See, for example, Omer SB et al 2008.)
Prospective Observational Study?

- The list of possible outcomes to evaluate may require standardized assessment protocols (rather than relying on clinically generated data alone). This approach would require a pre-specification of those outcomes of particular interest.

- The observational study may need to over-sample children whose parents have decided to either forgo vaccination or to follow a delayed (or reduced) vaccination schedule. The overall sample size would need to be large enough to detect exceedingly rare adverse events.

- As health outcomes should also include vaccine-preventable diseases, an observational study will be confounded by issues such as disease exposure and the level of herd immunity in the population to which any given child is exposed.
Good Ethics starts with Good Science!

- The interventions and procedures that likely would be included in a prospective observational study (e.g., blood tests, neurodevelopmental assessments) would be considered minimal risk or, at most, a minor increase over minimal risk.
- The ethical justification of such an observational study depends on the quality of the science.
References


2. (2011). "Updated recommendations for use of tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine (Tdap) in pregnant women and persons who have or anticipate having close contact with an infant aged <12 months --- Advisory Committee on Immunization Practices (ACIP), 2011." MMWR Morb Mortal Wkly Rep 60(41): 1424-1426.


Thank you.