

CLINICAL TRIALS OF CHILDHOOD VACCINES

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THE NEED FOR CLINICAL TRIALS OF NEW CHILDHOOD VACCINES

- ◆ Direct need

- Virtually everyone will be exposed to vaccines
- Essential to ensure that they are both effective and safe
- Strongest possible evidence comes from randomized clinical trials

- ◆ Indirect need

- Vaccination is a critical component of public health protection
- Public concerns about vaccine safety may lead to reduced coverage and ensuing re-emergence of vaccine-preventable diseases

EFFICACY VS SAFETY

- ◆ Efficacy is the easy part
 - Most new vaccines are expected to be highly effective
 - Large numbers not typically necessary to evaluate efficacy unless outcome being prevented is rare
- ◆ Studying safety is very challenging
 - common events can be studied in relatively small trials
 - Less common events can be studied in large trials
 - Impractical to rely on randomized trials to identify rare outcomes (e.g., rate of $< 1/10,000$)

DESIGNING A VACCINE TRIAL

- ◆ Typically, there is some understanding about minimum level of protection that will be acceptable
 - Unlike the case for drugs, it is not enough to show that a vaccine is more effective than placebo—must be MUCH more effective
- ◆ Trial is designed to be large enough to show with great confidence that level of protection achieves or exceeds that threshold
- ◆ If there is a pre-existing safety concern, that will also figure into the sample size determination

ASSESSING LEVEL OF PROTECTION

- ◆ A big issue in trial design: determining the primary endpoint
- ◆ For new vaccines to protect against a currently non-preventable disease, clinical disease will typically be the primary endpoint
 - 1995: varicella
 - 1998: rotavirus
 - 2002: invasive pneumococcal disease
 - 2006: sequelae of human papillomavirus infection

ASSESSING LEVEL OF PROTECTION

- ◆ For new vaccines intended to replace or compete with an existing vaccine, clinical disease is not a feasible endpoint
 - If population is currently receiving an effective vaccine, clinical disease will be very rare
- ◆ Typical approach: determine whether immune response elicited by new vaccine is equivalent to that elicited by available vaccines
 - New version of existing vaccine (e.g, 13-valent pneumococcal conjugate vaccine)
 - New combination of existing vaccines

IMPLICATIONS OF ENDPOINT CHOICE

- ◆ Trials with clinical endpoints
 - Size of trial will depend on disease incidence
 - For common diseases, efficacy can be assessed in small trials
 - When disease is rare, large sample sizes will be required
 - Locations for trial implementation will depend on where disease incidence is high
- ◆ Trials with immune response endpoints
 - Sample sizes can be much smaller
 - Duration of follow-up will need to be long enough to assess durability of response
 - Geography less of a consideration

DO SAFETY CONSIDERATIONS AFFECT TRIAL DESIGN?

- ◆ When a safety issue has arisen, trial will need to be designed to address that issue
- ◆ Primary examples: second generation rotavirus vaccines
 - Initial vaccine, Rotashield, was approved on the basis of 3 small randomized placebo-controlled trials—sufficient to document clinical efficacy
 - Rotashield was withdrawn from market due to excess rate of intussusception (IS), an uncommon event
 - Newer rotavirus vaccines were still placebo-controlled but studied in trials large enough to rule out certain level of excess cases of IS

SAMPLE SIZES IN RECENT VACCINE PROGRAMS: CLINICAL ENDPOINTS

Vaccine	Size of Controlled Studies	Total Vaccinees Pre-Licensure	Post-Licensure Commitment*
Varicella	956	11,102	90,000
Rotavirus (1)	2258 (3)	11,463	20,000
Pneumococcal	38,000**	19,000	60,000
Rotavirus (2)	68,000	72,324	44,000
Meningococcal	6677 (3)**	7672	20,000
HPV (1)	19,953 (4)	11,792	44,000

*Single Arm Studies

** Active Control

VACCINE SCHEDULES WORLDWIDE

- ◆ Vaccine schedules vary from country to country—but not by much
- ◆ Common schedules for infant vaccinations requiring 3 doses
 - 2, 4, 6 months
 - 2, 3, 4 months
 - 3, 4, 5 months
 - 6, 10, 14 weeks
- ◆ Some vaccines given at birth in some countries
 - BCG
 - Hep B

CONSIDERATIONS FOR VACCINE SCHEDULE

- ◆ Infants will retain some (passive) immunity from mother for some period of time after birth
- ◆ Immune system must reach certain level of maturity to mount adequate response to some vaccines
- ◆ Younger infants are at greater risk of serious consequences of some vaccine-preventable diseases
- ◆ The more visits necessary to administer all recommended vaccines, the more likely some visits will be missed, reducing child's protection

WHAT IS THE OPTIMAL VACCINE SCHEDULE?

- ◆ Questions that have been raised
 - ◆ Are children immunized too early, and with too many different vaccines?
 - ◆ Should vaccination schedule be spread out over a longer period of time?
 - ◆ Are all the vaccines really necessary?

“ALTERNATIVE” SCHEDULES

- ◆ Some parents are choosing schedules that exclude and/or delay many vaccines as compared to the CDC-recommended schedule
- ◆ These parents believe these schedules reduce risk that their children will experience an adverse effect of a vaccine
- ◆ Public health experts are concerned that
 - Such children may not be adequately protected
 - The more parents choose such schedules, the more “herd immunity” may be threatened
- ◆ No real evidence regarding “schedule effect” on clinical outcomes

COULD ALTERNATIVE SCHEDULES BE STUDIED IN A CLINICAL TRIAL?

- ◆ Would need to evaluate both safety and efficacy
 - Safety is primary concern of parents, but must also look at potential loss of protection
 - Increased susceptibility to disease among a subset of children could weaken herd immunity
- ◆ Efficacy would have to be assessed by clinical outcome
 - Issue of major concern would be whether delay in some immunizations would lead to higher risk of disease in young infants and/or resurgence of disease in areas where trial was conducted (i.e., loss of herd immunity)

COULD ALTERNATIVE SCHEDULES BE STUDIED IN A CLINICAL TRIAL?

- ◆ Existing herd immunity would complicate efficacy assessment
 - Children with delayed vaccination would be protected by others in community vaccinated on standard schedule
 - Would need to have a substantial proportion of children in a community participating in the trial to see disease emergence with alternative schedule
 - In such cases, if delay of some vaccines did result in reduced efficacy, it would take some time before herd immunity conveyed by current high coverage was sufficiently diluted to observe effect

COULD ALTERNATIVE SCHEDULES BE STUDIED IN A CLINICAL TRIAL?

- ◆ Would require extremely large sample sizes and long duration of follow-up
 - Vaccine-preventable diseases now occur rarely due to high vaccine coverage
 - Safety outcomes of concern are uncommon
 - Some safety outcomes of interest may not be acutely evident—may need to follow subjects for 1-2 years or more following completion of vaccination series

HUGE ETHICAL ISSUE

- ◆ Recommended schedule is developed by public health experts to confer protection against disease at the earliest time that adequate immune response can be elicited
- ◆ Assigning some children to a schedule that delays or even skips some vaccines would increase risk of diseases (and their serious sequelae) if these children were exposed to pathogen
- ◆ Possible safety advantage of alternative schedules is not supported by any reliable data
 - Difficult to say that potential risk of disease is balanced by potential reduction in risk of adverse outcome

HOW BIG WOULD SUCH A TRIAL HAVE TO BE?

- ◆ Depends on
 - size of difference important to know about
 - frequency of the event being assessed
 - variability of the measures
 - How sure you want to be of your conclusion

POWER TO DETECT EVENT RATE DIFFERENCE BY FACTOR OF 2

<u>Sample size</u>	<u>5%-10%</u>	<u>1%-2%</u>	<u>0.1%-0.2%</u>
1000	0.82	0.17	0.05
5000	0.99+	0.80	0.07
10,000	0.99+	0.98+	0.17
50,000	0.99+	0.99+	0.79

NEED TO DEFINE PRIMARY OUTCOME

- ◆ Suppose our main purpose in doing the trial is to see whether there are more serious adverse outcomes with one schedule than another
- ◆ We could end up many such outcomes, since many serious illnesses and conditions first manifest during infancy
- ◆ When looking at many different outcomes, likelihood of finding a difference by chance is high; significance tests not meaningful when looking at multiple outcomes (or have to be adjusted for multiple testing)

ROLE OF CHANCE

- ◆ If we look at 10 outcomes for which there is no treatment effect, the probability that we will fail to find statistical significance for ANY of them is
 $1 - (0.95)^{10} = 1 - 0.599$ or 40%
- ◆ If we look at 20 outcomes the chance is 64%!

COULD WE EVALUATE ALTERNATIVE SCHEDULES IN OTHER WAYS?

- ◆ Observational study
- ◆ Let people choose what schedule they like
- ◆ Collect data on outcomes
- ◆ Test for differences
- ◆ Much easier than doing a randomized trial
- ◆ Can collect data retrospectively from large health care databases; could get longer-term follow-up quickly

ISSUES WITH OBSERVATIONAL APPROACH

- ◆ Substantial majority of children are vaccinated according to recommended schedule
- ◆ Herd immunity conferred by these children will protect children who skip or delay vaccination
- ◆ Impossible to see whether clinical disease would increase if most children were vaccinated on alternative schedules, unless a large proportion of families adopted alternative schedules

ISSUES WITH OBSERVATIONAL APPROACH

- ◆ When treatment is random, any differences in outcome can be assumed related to treatment
- ◆ When treatment is selected according to patient or physician preference, any differences in outcome could also be due to systematic differences in populations selecting different treatments
- ◆ We can try and control for such differences but can never be sure we know about or have measured all the important ones
 - All experience indicates that we usually don't or haven't
- ◆ Problem of looking at multiple outcomes is same for observational studies

SUMMARY

- ◆ Randomized clinical trials are the most reliable way to evaluate treatment effects
- ◆ In theory, alternative vaccine schedules could be studied in randomized trials, but would require large sample sizes and extended follow-up, and would raise difficult ethical questions
- ◆ Observational data could be evaluated but would not likely settle the question
 - Herd immunity conferred by majority of children on recommended schedule would protect children with skipped or delayed vaccinations
 - Any differences that would be observed would be confounded with differences between populations who chose each schedule

