

The Rotavirus Vaccine Story: When are Double Standards Justified?

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10/90 Divide*

- Less than 10% of medical research funds are spent on the diseases that account for 90% of the global burden of disease.
- Selgelid charges that bioethics apparently suffers from a misdistribution of research resources analogous to the 10/90 divide.
 - Although infectious diseases should be recognized as a topic of primary importance for bioethics, it has received little attention. Three themes:
 - 1) Significant impact of infectious diseases on health historically (Black Death and small pox) and currently (SARS and AIDS) is unrivalled in medicine.
 - 2) Public Health versus individual autonomy
 - 3) Justice: Burden is most heavily shouldered by the poor (in developing countries).

*MJ Selgelid, Ethics and Infectious Disease Bioethics; 2005: 19(3): 272-89.

Rotavirus (RV)

- Rotaviruses are the single most important cause of severe diarrhea in infants and young children in both developed and developing countries.
 - (Often with severe vomiting as well making oral rehydration difficult.)
 - Rotaviruses are responsible for 35-50% of severe diarrhea diseases in infants and young children < 2 years.
- In the U.S., they are responsible for >500,000 visits to physicians, 50,000 hospitalizations and 20 deaths.
- In developing countries, approximately 111 million episodes of diarrhea; 25 million clinic visits; 2 million hospitalizations, and 400,000-500,000 deaths in children < 5 years of age.

Development of an RV Vaccine

- Attempt #1:
- RIT 4237 was administered to Finnish infants derived from the bovine Nebraska calf diarrhea strain which resulted in substantial protection against RV diarrhea that lasted > 24 hours (Vesikari 1997)
 - Vaccine faltered when the high level of protection repeatedly shown in Finnish infants could not be reproduced among children enrolled in trials in several developing countries (including Peru, Rwanda and Gambia)

Development of an RV Vaccine

- Attempt #2 : Kapilian et al. developed a live attenuated agent from a non-human host as the immunogen.
 - MMU18006 which belongs to serotype VP7:3 (=G3).
 - (VP7 is an antigen located on the outer capsid. Antibodies to VP7 [and VP4] confer immunity in various animal models.)
 - Administered orally to >1500 children between 1 and 20 months in the US and overseas.
 - Efficacy 0-85% against moderate-to-severe diarrhea.
 - It appeared from these studies that serotype specific immunity was important.

Development of an RV Vaccine

- Attempt #3: Quadrivalent rotavirus vaccine that incorporates the VP7 specificity of each of the four epidemiologically important serotypes as well as the attenuation phenotype of RRV [rhesus-based rotavirus vaccine] in order to achieve protection against each of these 4 human rotavirus serotypes
 - Vaccine was known as RRV-TV (rhesus based rotavirus, tetravalent).

Protective Efficacy of RRV-TV on the occurrence of RV diarrhea of varying severity in infants and young children

Trial	# of individuals		Protective efficacy vs.		
	Vaccine	Placebo	All RV diarrhea	Severe RV diarrhea	Dehydration
US multi-center (1996)	398	385	49%	80%	100%
Finland (1997)	1128	1145	68%	91-100%	75%
Venezuela (1997)	112	1095	48%	88%	75%
US Native American (1997)	347	348	50%	69%	--*

RRV-TV Time-Line

- 2/11/1998 and 6/25/1998: U.S. Advisory Committee on Immunization Practices (ACIP) recommended routine immunization with three oral doses at 2,4, and 6 months of age.
- 8/31/1998: U.S. Food and Drug Administration (FDA) grants a license to Wyeth Labs for manufacture and distribution of RotaShield

Post-Marketing Surveillance

- Between 9/1/1998 and 7/7/1999, 15 cases of intussusception post-vaccination with RotaShield were reported to the Vaccine Adverse Event Reporting System (VAERS).
 - At the time, it was estimated that 1.5 million doses had been given.
 - Although the number of cases reported was within the expected value, it was of concern that 11 of the 15 cases had occurred within 1 week of administration of the first dose of vaccine.
- CDC recommended suspending further vaccination until further data obtained.

Review of the Pre-licensure Data

- N.B.: Five of 10,054 infants who received rotavirus vaccine and one of 4633 never-vaccinated infants developed intussusception pre-licensure.
 - None after the first dose.
- N.B. pre-licensure studies failed to demonstrate an etiological association between the rotavirus vaccine and intussusception.
 - Baseline data from New York 51 cases per 100,000 or 1 per 1961 infants.
 - But this was described in the package insert of RotaShield.

Policy Decisions re: RotaShield

- 10/22/1999: CDC-ACIP meeting.
 - 102 confirmed or presumptive cases of intussusception had been reported to VAERS.
 - 57 within 7 days of vaccine; 46 of the 57 after the first dose.
 - Intussusception occurs with significantly increased frequency in the first one-to-two weeks following vaccination with RRV-TV particularly following the first dose.
- ACIP withdrew its recommendation for RRV-TV and no longer recommended its use in the US.

International Policy Decisions

- 2/9-11/2000: World Health Organization (WHO) meeting on future directions for RV vaccine in developing countries.
 - 1) Could a vaccine withdrawn from the U.S. market be used in developing countries?
 - 2) Should testing a vaccine with known adverse risks that can be fatal be supported?
 - 3) What safeguards would be necessary?
 - 4) Is it ethical not to use a vaccine that could prevent a large burden of fatal disease?
 - 5) How should new candidate vaccines be tested: simultaneously in developed and developing countries or in sequence?

Could a vaccine withdrawn from the U.S. market be used in developing countries?

- CON

- Justice as Equality: Geographical location and economic status should not be a basis for determining what justice requires.
- Children in the developing countries are on equal footing to their counterparts in the US. If it is not safe enough for children in the US, it is not safe for children of the world.

- PRO

- Justice as Equity: Justice requires that like be treated like. This does not require treating everyone, everywhere the SAME. Must take into account the economic and social context. Since the severity of disease is different in the two communities, different standards are permissible.

Yes, Double (or at least Different) Standards are Appropriate

- There is one universal ethical standard for research ethics.
 - Consider the 3 principles enumerated in the Belmont Report
 - Respect for Persons; Beneficence; and Justice
- We can accept a single universal standard and yet argue that it permits different trials for different countries recognizing that the principle applies differently when local circumstances vary.

The Trials to Reduce the Vertical Transmission of HIV in Africa as a case study of whether double (or different) standards are ethical

U.S. Perinatal HIV Research, 1994 AIDS Clinical Trial Group (ACTG) Protocol 076

- Enrollment Criteria
 - HIV+ women,
 - 14-34 weeks of gestation
 - no medical indications for antiretroviral therapy during the current pregnancy

ACTG Protocol 076

- Protocol

- Oral AZT 100 mg 5x daily, initiated at enrollment.
- During labor, 2 mg/kg AZT in a one-hour bolus followed by 1 mg/kg/hr until delivery.
- Oral administration of AZT to the newborn: 2mg/kg q6 hours for the first 6 weeks post-natally, beginning 8-12 hours after birth.

RESULTS of ACTG 076

- The vertical transmission rate was 8.3% (CI 3.9 to 12.8%) among the women who received AZT compared to a vertical transmission rate of 25.5% (CI 18.4 to 32.5%) in the placebo group. (Connor et al., *NEJM* 1994; 331: 173-80.)

Response to ACTG 076

- Following the ACTG 076 study, AZT is recommended for pregnant women in the U.S.
 - Expected to prevent 600-1,200 cases of HIV-infected newborns yearly.
 - Cost per woman estimated at \$800.
 - HIV+ women are also discouraged from breastfeeding.
- Cost of AZT (~\$800) is prohibitive in all developing countries and not implemented.

**Universal Consensus:
need shorter, cheaper
protocol to decrease vertical
transmission of HIV**

Controversy regarding study design:
How to determine ethically a safe,
effective and cheaper protocol.

STUDY DESIGN OPTIONS

- Option #1: Compare AZT course as developed in ACTG 076 against a short course of AZT
- Option #2: Compare a short course of AZT against Placebo
- The short course involves 4 weeks of oral AZT and a large oral dose in labor.
- Option #1 is much more expensive. May not help those in developing countries.
- Option #2 tells whether a short course of AZT is better than current practice in developing world.

Ethical Questions

- Is it ethical to use placebo-trials to determine whether a short course of AZT decreases vertical transmission of HIV in developing countries?
- Is it ethically relevant that such a study would be unethical in the U.S. where the standard of care is based on ACTG 076?
- Is informed consent possible when the subjects are not being offered the best possible care? Is it adequate if they are told this?

The 2 study designs answer very different questions

- AZT as developed in ACTG 076 versus a short course of AZT:
 - Can we design a short course of AZT that has similar efficacy to ACTG 076?
- A short course of AZT versus placebo:
 - Is a short course of AZT better than nothing?

Were the studies ethical?

- Placebo controlled trials are ethical if they are being used not just because it is cheaper to do the research in this manner, but because placebos are needed for scientific rigor.
 - Vertical transmission may differ in these study populations. Women in developing countries are at an increased risk for anemia, malnutrition, and various infectious diseases. These conditions may affect the transmission rate.

Were the studies ethical?

- Placebo controlled trials are ethical (even if they could not be done in the host country) if the goal is to improve health in the country where the research is being done.
- Research was done as placebo-controlled trial.
- Vertical transmission rate without treatment is lower than in the US (surprising result)
- Short-course is effective (although not as effective as long course).

Were the studies ethical?

- The results were useful in the US for women who presented late in pregnancy because there was now data to suggest that treatment during labor and delivery could change the risk of vertical transmission.
 - This is ethical as a secondary gain, but the primary gain should be the benefit to those in the developing countries.
- Very few countries implemented the short course of AZT as standard of care because \$80 was still too expensive.
- Suggests that the study designers had not done their homework: To justify a study of a short course of AZT vs. placebo, one needed to ensure that the results could be implemented.

Yes, Double Standards are Appropriate

- At the February 2000 WHO meeting, Charles Weijer (ethicist) argued in favor of Double Standards:
- Failure to proceed with further trials of RRV-TV would further any existing inequities in health between developed and developing countries;
- Data developed for RRV-TV far exceed the data available on other rotavirus vaccines;
- Inaction, waiting for comparable data on other vaccines is NOT morally neutral, since the disease burden cannot be ignored in the interim;
- It would be immoral not to proceed with RRV-TV in developing countries.
- BUT, further study of the vaccine in developing countries should only proceed with assurances that the vaccine would be available for general use should the results of the trial prove to be positive.

Double Standards? Divergence of Recommendations for Infant Vaccines

Vaccine or vaccine presentation	DEVELOPING COUNTRIES	INDUSTRIALIZED COUNTRIES
DPT	Whole cell pertussis component; not presented in combo w/other vaccines	Acellular pertussis component; presented in combo w/other vaccines.
Hep B	Uncommon	Common
Measles	monovalent measles	trivalent MMR
Polio	Live polio vaccine	Inactivated polio vaccine
BCG vaccine	Common	Uncommon
Varicella	Uncommon	Common
Hib conjugate	Uncommon	Common
Product presentation	Stored as multidose with thiomerosal preservative	Stored as single dose with no thiomerosal preservative

Double Standard and Double Practice

- Double standard due mainly to expense
 - Little incentive to create vaccines for diseases only in the developing world; (e.g. TB, malaria, cholera)
 - Little incentive to create vaccines that will be used only for developing world (RotaShield)
- Double practice: When DPT → DTaP in the industrialized world, supply becomes more tenuous as a vaccine producers tailor their portfolios to the developed world.
- Double practice: Unfortunately while Expanded Program on Immunizations (EPI) achieved ~80% coverage in 1990, down to 50% by 2000 due to political events in the area.

Outcome of WHO Conference

- WHO recommended that research continue in the developing countries.
- Despite the WHO recommendations, representatives from developing countries had no desire to evaluate RRV-TV because of the ACIP recommendation for its withdrawal.
 - 3 options
 - 1) Change the recommendation back to “routine use”; highly unlikely.
 - 2) A “permissive recommendation” would remove the barrier. Unlikely but possible given the revised attributable risk data.
 - This would validate the concept that children in the developing countries are on equal footing to their counterparts in the USA.
 - 3) Statement indicating that risk of intussusception following vaccination is considerable less than original projections. This by itself would be ineffective in removing the barrier.

The Changing Risk of RRV-TV

- 10/22/99: CDC presented data indicating that the overall risk of intussusception was increased 60-80% such that there would be 1200-1600 excess cases of intussusception (40 per 100,000 or 1 per 2500 vaccinees).
- 1/1/2000: CDC revised attributable risk to be 1 case of intussusception per 4500 vaccinees.
- 4/11/2000: CDC again revised risk to be 1 case of intussusception 12,274 (almost fivefold reduction from figure presented to the ACIP in October 1999 when vaccine was withdrawn).

Denouement: The Demise of RotaShield

- ACIP did not change recommendation.
- Wyeth stopped manufacturing RRV-TV making further trials impossible.
- Of note, RotaShield cost \$38 per dose in the US which would be prohibitively expensive in developing countries.
 - Innovative strategies to address this disparity were being developed.
 - E.g. WHO's GAVI (Global Alliance for Vaccines and Immunizations (a public-private partnership initiative)
 - E.g. Fostering the development and production of RV vaccines by manufacturers in these countries.
- The withdrawal of RotaShield led to a reassessment of the future of live oral rotavirus vaccines.
 - At least 7 different live oral candidate vaccines were in development at the time.

Status of Rotavirus Vaccines in Development, December 2004

Vaccine	Manufacturer (location)	Rotavirus strains (genotypes)	Status of vaccine	Efficacy
RotaTeq	Merck (US)	Pentavalent human-bovine reassortants	Phase III trial, > 60,000 children	Pending
Rotarix	GlaxoSmithKline (Belgium)	Monovalent, attenuated human strain	Phase 3 trial > 60,000 children	90% in Venezuela, Brazil, and Mexico
LLR	Lanzhou Institute of Biological Products (China)	LLR strain	Licensed in China in 2000	Not evaluated in a RCT
RV3	Univ. of Melbourne (Australia) and Bio Farma (Indonesia)	Monovalent neonatal human strain	Phase II trial	Not determined
UK reassortant vaccine	NIH (US)	Tetravalent human-bovine reassortant	Phase II trial	Pending
Indian neonatal vaccines	Bharat Biotech (India)	Neonatal strains	Phase I trial	Not determined
Rhesus tetravalent	BIOVIRx (US)	Tetravalent human-rhesus reassortants	US FDA approval; currently not manufactured	>90% in US and Finland and 70% in Venezuela

Unanswered Questions: Challenges Regarding the Next Generation of RV Vaccines*

1. Will live oral RV vaccines work well for children in the developing world.
 - RIT 4237 worked well in Finnish children; not in developing world.
 - It has become increasingly common to find that vaccines perform less well in developing world country populations than in populations residing in the industrialized world.
 - These disparities mean that trials of vaccines needed before introduced in these settings.
 - But not a priority to vaccine producers; often deferred for years after vaccine licensure.
 - Need incentives to do studies simultaneously.

Unanswered Questions: Challenges Regarding the Next Generation of RV Vaccines

2) Will they be safe?

- Even studies of 60,000 children (30,000 vaccine recipients; 30,000 placebo) will not prove that they are safer than RotaShield. Only will know with post-licensure surveillance.

3) What will they cost and how can we pay for them?

- Vaccine Fund and GAVI have committed to purchase vaccines for the 74 poorest countries of the world.
 - This can be an incentive to do the research in developing countries (despite the costs) at the same time doing research in industrialized communities.
 - This can also be an incentive to do research on diseases that are most relevant in developing countries.
 - (Big advances since the AZT-HIV issues of the mid-1990s)

Unanswered Questions: Challenges Regarding the Next Generation of RV Vaccines

- 4) Who will provide the bulk of the vaccine supply?
 - Although the multinational vaccine manufacturers are best recognized for their new and innovative vaccines, most of the vaccines currently purchased by the United Nations Children's Fund come from emerging manufacturers.
 - India, China and Indonesia depend almost exclusively on domestic manufacturers for their vaccines.

Unanswered Questions: Challenges Regarding the Next Generation of RV Vaccines

- 5) Will countries be interested in a new RV vaccine?
- Despite global estimates of the enormous burden of RV diarrhea, few policy makers have adequate data to assess burden of RV in their own countries.
 - Surveillance networks set up in different regions to develop a global database. Confirmed the importance of RV as a major cause of mortality.
 - In fact, showed that the true burden of RV disease is greater than previously believed.
 - Diseases of the Most Impoverished (DOMI): Program funded by Bill & Melinda Gates Foundation to provide this sort of evidence for new generation vaccines.

Unanswered Questions: Challenges Regarding the Next Generation of RV Vaccines

- 6) Will parents accept a vaccine for only 1 cause of childhood diarrhea?
- HiB and pneumococcal vaccines only provide protection against a subset of pathogens and this has not been a problem.
 - The issue is not that an RV vaccine will prevent children from having viral gastroenteritis, but that an RV vaccine will prevent them from having a viral gastroenteritis that requires hospitalization or death.

The Future of an RV Vaccine, December 2004

- GAVI has identified the development and introduction of RV vaccine as one of the 3 key priorities
- Rotavirus Vaccine Program, a 30 million dollar effort funded for three years to achieve these goals.
 - Program will accelerate the introduction of vaccines nearing licensure; specifically addressing whether these vaccines are safe and efficacious for children in the poorest countries where support for the purchase may be facilitated through the Vaccine Fund.
- Additional efforts needed to encourage work on vaccines in earlier stages of development, including those being prepared by emerging manufacturers in the developing world.
- Currently, 4 organizations funded by the Bill and Melinda Gates Foundations working with an Indian manufacturer to develop the Indian neonatal vaccine as a first vaccine for India.

2 New RV Vaccines, January 2006

- Rotarix from GlaxoSmithKline
 - Monovalent vaccine.
 - 2 oral doses, one to two months apart.
 - 85% efficacy against severe RV disease
 - Trials mainly done in poor and middle income families in Latin America (and Finland)
- RotaTeq from Merck
 - Pentavalent vaccine based on a bovine strain that contains five human-bovine reassortant viruses.
 - 3 oral doses, each at least one month apart
 - 98% efficacy against severe RV disease.
 - Trials done mainly in US and Finland.

2 New RV Vaccines

- Both being given before 3 months of age.
 - To-date, pathogenic mechanisms involved in intussusception after vaccination are currently unknown, but risk seems to be associated with older age of the child.
- Neither of these large studies found evidence for increased risk of intussusception.
 - Unknown if the vaccines could cause intussusception if administered to older infants or to a larger number of infants.
- Whether it will be effective in other populations (with other RV antigens) is unknown.

Development of a Matrix of evidence in the DOMI program to help evaluate at the country level whether to introduce Typhoid Vi vaccine

	Bangla- desh	China	India	Indo- nesia	Paki- stan	Thai- land	Viet- nam
Prospective disease burden studies	X	X	X		X		X
Meta-analysis of disease burden	X	X	X	X	X	X	X
Assessment of Vi vaccine feasibility, acceptability and impact		X	X	X	X		X
Cost-of-illness studies		X	X	X	X		X
Cost of Vi vaccine delivery studies		X	X	X	X		X
Cost-effectiveness analysis		X	X	X	X		X
Assessment of demand/ willingness to pay for Vi vaccine		X	X	X	X		X
Policy analysis	X	X	X	X	X	X	X

Financing of new RV vaccines

- Expensive
 - RotaTeq (Merck) is \$63/dose or \$189 per child
 - Rotarix (GSK) commands a similar price in private markets in Latin America and other countries.
- Both companies have stated their commitment to tiered pricing, a strategy to lower the cost of vaccine substantially in the public sector markets in developing countries.
 - In Brazil, a tiered pricing arrangement has already allowed introduction of the GSK vaccine at \$7 per dose or \$14 per child.
- Private philanthropy will also defray costs.

The Rotavirus Saga: Success Story or Failure?

- Unanticipated setback to the RotaShield vaccine after two decades of research.
 - Within 7 years, two new vaccines (and others on the horizon).
 - Whether these vaccines are truly safer than RotaShield will only be known after post-licensure follow-up.
 - Clearly what we have learned about the relationship of age and risk of intussusception will help to reduce the number of cases of intussusception.
- However, in the intervening 7 years over 3 million children died in the developing world.
 - How long before these vaccines will be adequately studied and have adequate financing and infrastructure (for distribution of vaccine and mass vaccination programs) will influence how many additional children will suffer.
- I am optimistic in the infrastructure and funding available from GAVI, DOMI, EPI and other public-private partnerships.
- I regret the 7 lost years.

Concluding Thoughts: Lessons Learned

- Although there is only one ethical standard for research ethics, it applies differently depending on the socioeconomic circumstances.
 - The suspension of RotaShield in the US was morally appropriate
 - The decision by the governments of developing countries NOT to continue testing may have appeared to be the moral high ground, but they did so on the back of their most vulnerable citizens (children < 5 years).
- And yet, the saga has taught us important lessons.
 - The need for parallel testing of vaccines in industrialized and developing countries.
 - The need for multiple sources of innovation.
 - Age of immunization may be critical.
- These lessons, if learned, may partly compensate for the > 3 million unnecessary deaths if it prevents other delays in vaccine development and distribution in the communities that need them the most.