Scientific justification for the participation of children and adolescents in HIV-1 vaccine trials in South Africa

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UNAIDS estimates that there were 4.9 million new HIV infections in the year 2004, and that 640 000 of these infections occurred in children less than 15 years old.[1] The first national population-based survey conducted in South Africa in 2002[2] showed that 9.3% of persons between the ages of 15 and 24 years of age were HIV-positive and that female youth were more likely to be HIV-infected than male youth (Table I). In South Africa sexual debut is at an early age,[3] with 50% of adolescents sexually active by the age of 15. Transgenerational sex, transactional sex and non-consensual sex put adolescent girls at high risk for acquiring HIV infection.[4]

National antenatal data show that the prevalence of HIV in women < 20 years old rose from 15.8% in 2003 to 19.5% in 2004, indicating that the epidemic is being fuelled by incident infection during adolescent years.[5] Approximately 1 million women give birth each year in South Africa, with more than 250 000 of these infants being born to HIV-infected mothers. Although there are programmes in place to prevent mother-to-child transmission (MTCT), most of the interventions currently available only impact on intrapartum and early postpartum transmission, and have minimal impact on prevention of postnatal transmission through breast-feeding.[6] Whatever the route of infection, it is clear that both infant children and adolescents are at the highest risk of HIV infection. This epidemiological fact makes it imperative that an HIV vaccine target this group to have any hope of successful epidemic control. We should not withhold the availability of a vaccine to this population because of lack of data through delays in clinical trial work.

There are many promising HIV vaccine candidates in or about to enter human clinical trials. The road to the licensing of a successful candidate is long, since phase I - III trials usually take at least 10 years. No preventive HIV vaccine trials

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Table I. HIV prevalence by age group from the HSRC National Survey, South Africa, 2002[2]

Age	N	Percentage HIV-positive	95% CI
Children (2 - 14 years)	2 348	5.6	3.7 - 7.4
Youth (15 - 24 years)	2 099	9.3 (12% females, 6% males)	7.3 - 11.2
Adults (> 25 years)	3 981	15.5	13.5 - 17.5
Total	8 428	11.4	10.0 - 12.7

have included adolescents, and only 2 completed trials have targeted neonates.[7-9] In South Africa, in order to license a vaccine for use in children and adolescents, data must exist on the safety, immunogenicity and efficacy of the vaccine in children and adolescents, although exact criteria for approval have not yet been defined. In the past, vaccine trials in young children and infants have been accelerated because of the existence of correlates of immunity to the disease; however, since the immune marker necessary for protection against HIV is not yet defined, the task of approving a vaccine for infants, children and adolescents is arduous and may take longer than usual.

As there are physiological differences between children and adults, one cannot necessarily extrapolate adult data to children. Surface area, body mass and metabolic differences affect the dosage and safety profile of drugs and vaccines. The bioavailability and safety of vaccines is affected by physiological differences such as increased liver size, immature liver enzymes, decreased renal clearance, and increased blood-brain-barrier permeability, among others. In addition, the immune response to vaccines is different in infants, and probably in adolescents. Here we review the differences between the immune systems and response to vaccination in children (both infants and adolescents) versus adults.

The immune system, an overview

Generally, the immune response has two arms; humoral and cellular.[10] The adaptive cellular immune response is mediated by B- and T-lymphocytes. B-lymphocytes mature into plasma cells and produce antibody. T-cells either express CD4 or CD8 on their surface, and are known as CD4+ helper T-cells (Th) and cytotoxic T-lymphocytes (CTLs) respectively. Th cells primarily exert their helper functions through secretion of soluble proteins called cytokines. CTLs are thought to be very important in the initial control of HIV infection and kill infected cells by lysis and/or apoptosis.

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Paediatric immunity

The immaturity of the infant immune system is demonstrated by the increased susceptibility of children to infections by both viral and bacterial pathogens. The humoral arm of the immune system is underdeveloped and differs greatly from that of adults. Infants only develop the ability to make a significant amount of immunoglobulins at around 6 - 12 months of life. Maternal immunoglobulin G (IgG) is actively transported across the placenta predominantly during the third trimester, and is present at high levels. Maternal immuno-globin A (IgA) is secreted in breast-milk.[10] These passively acquired antibodies can alter the antibody-dependent response to immunogens in as long as 18 months in infants of infected or immunised mothers, but other cellular immunity seems less affected by maternal antibody.

There are less obvious impairments in the T-cell repertoire of the infant immune system. Antigen-specific T-cell precursors are lower in neonates than in adults.[11] Differences in cytokine profiles exist and may be responsible for much of the poor capabilities of the developing immune system and an impaired induction of cytotoxic CD8 T-cells.[12,13]

Puberty is characterised by an increase in gonadotropic hormones which promote the secretion of androgens and oestrogens in both boys and girls. There is direct evidence that immunology and sex steroids are linked both at the physiological and cellular level. Post-pubertal females are at increased risk for autoimmunity, which strongly suggests that sex steroids affect immune function. Most cells of the immune system express both intra and extracellular receptors for sex steroids.[14] In addition to the effects of pubertal hormones on immunity, there are quantitative differences in the cells of the immune system between infants, children, adolescents and adults.

Since there are vast differences in all arms of the immune system between different age groups, it is difficult to predict responses to vaccinations without actual clinical trials.

Paediatric responses to vaccination

HIV vaccinology has required innovative approaches to vaccine design.[15,16] Briefly, the live-attenuated vaccine approach is considered too risky for use in a human HIV vaccine, killed virus is poorly immunogenic, subunit vaccines are unlikely to elicit neutralising antibodies and are poor T-cell stimulants, and some promising DNA vaccines and vector-based vaccines are in phase I and II trials at the moment.

At birth, the ability to respond to antigens is greatest for protein antigens and less for glycoproteins and polysaccha-rides.[17] The decreased response to some vaccinations is thought to be due partly to the effects of maternal antibody. However, the degree of passive antibody influence varies according to vaccine. In general, passively acquired antibodies may suppress humoral response to active immunisation in the first few months of life dependent on the maternal antibody/vaccine antigen ratio, but do not affect the response to boosting.[18] Maternal antibody seems to have less of an effect on T-cell responses.[18] T-cell response to vaccination can also differ in early life. Neonatal Th1 responses are not easily elicited with conventional vaccines capable of eliciting Th1 responses in adults.[19]

There are multiple viral and bacterial vector-based HIV vaccines in human trials and in the pipeline (www.iavi.org; www.hvtn.org). Pre-existing titres to the vector delivery system can affect the response to the immunogen and therefore can be affected by age. For example, schoolchildren may have higher adenoviral titres, although age-related adenoviral titres are yet to be determined in South Africa.

In addition to theoretical differences in the immune response that children may have to vaccines, there are many examples *in vivo* of how children and adolescents behave differently to specific vaccines (Table II). There are limited human data on age-related responses to HIV vaccine candidates; however, the first preventive trial in neonates born to HIV-1 infected mothers used recombinant gp120. About one-third of the infants were able to mount lymphoproliferative and antibody responses.[20,21] An important finding was that the antibody response in the accelerated schedule subjects was not affected by the higher levels of maternal antibody found at earlier age. Current HIV envelope vaccine candidates elicit high gp120 antibody titres, but neutralising antibody is difficult to elicit.[16]

There are not a lot of data on vector vaccine approaches, other than data for gene therapy. There have been HIV vaccine trials involving poxvirus vectors in HIV-exposed neonates. PACTG 326 part I evaluated the safety and immunogenicity of ALVAC vCP205 (high dose versus low dose) in neonates born to HIV-infected mothers. This canarypox vector contains HIV-1 subtype B envelope genes, plus gag and pol genes. Lympho-proliferative and CTL responses were present in about one-third of vaccine recipients. CTL responses were detected as early as 6 weeks of age.[9] Another arm of PACTG 326, a phase I/II study of ALVAC-HIV vCP1452, a modified recombinant canarypox expressing multiple HIV-1 genes alone or with Envelope (AIDSVAX B/B), also showed lymphoproliferative and CTL responses in a few subjects at preliminary analysis.[22]

Discussion

The development of a vaccine for paediatric and adolescent use is an urgent global priority. There is a complex interplay between age and immune function, which will make responses to vaccination difficult to predict. Additionally, adolescence, a time of rapid physiological change, also poses potential immunological challenges. Almost every vaccine category has an example of an age-dependent response. We cannot just expect that a vaccine that shows promise in adults is going to be safe, immunogenic and efficacious in children. To enrol

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Table II. Age-related responses to vaccines for pathogens other than HIV according to vaccine type

Vaccine type	Pathogen	Age-related response
Live attenuated	Mumps	Seroconversion rates for mumps-susceptible Swedish toddlers were 95%, versus only 80% in adolescents.[23] Seroconversion rates to mumps vaccination are generally slightly lower in adults than in children
	BCG	In the pubertal period androgen levels have an effect on BCG immune response. Responses to BCG vaccination via tuberculin test were affected by pubertal stage, and testicular volume[24]
	Varicella	Administered to children < 13 years of age, induces protective antibodies in > 95% of recipients after a single dose. For susceptible persons > 13 years of age, 2 doses separated by 4 - 8 weeks are recommended[25]
Killed	Hepatitis A	The dosage of both forms of inactivated hepatitis A vaccines licensed in the USA are half of the adult dose in those 2 - 18 years of age
Protein subunit	Hepatitis B	Adolescents may require only 2 doses[26]
	RTS,S/AS02A	A 3-dose phase IIb in 1 - 4-year-olds showed efficacy for the first clinical episodes of 29.9%. Efficacy for severe malaria was 57.7%. Immunogenicity was greater in the < 24-month age group. There was no evidence of waning efficacy against clinical disease and limited waning efficacy against infection. This sustained protection was not found in trials in malaria-naïve volunteers or Gambian adults[27-29]

only adults in HIV vaccine research will result in even greater delay for the benefits of a vaccine to reach children and adolescents, owing to the requirement for safety, immunogenicity and efficacy data in the age groups for which the vaccine will be licensed. The window of opportunity exists to ensure that this information is gathered now, and delay for whatever reason can be seen as a failure to safeguard our most vulnerable population.

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