Revised BCG vaccination guidelines for children with HIV infection

Background

Following a careful review of relevant data, the Global Advisory Committee on Vaccine Safety (GACVS) at the Geneva meeting 29-30 November 2006, revised its previous recommendations concerning bacille Calmette-Guérin (BCG) vaccination of children with HIV infection.

WHO had previously recommended that in countries with a high burden of tuberculosis, a single dose of BCG vaccine be given to all healthy infants as soon as possible after birth, unless the child presented with symptomatic human immunodeficiency virus (HIV). However, recent evidence shows that children who were HIV-infected already when vaccinated with BCG at birth, and who later developed AIDS, were at increased risk of developing disseminated BCG disease. Among these children the benefits of potentially preventing severe tuberculosis are outweighed by the risks associated with the use of live BCG-vaccine. GACVS therefore altered its recommendation such that children who are known to be HIV-infected, even if asymptomatic, should no longer be immunized with BCG vaccine.

This brief document provides guidance on the implementation of these revised recommendations.

Key Issues

For infants who are already HIV-infected when vaccinated with BCG vaccine, the benefits of potentially preventing severe tuberculosis are outweighed by the risks associated with the use of live BCG-vaccine. Yet populations with high prevalence of HIV also have the greatest burden of tuberculosis, and in such populations, uninfected children will benefit from the use of BCG vaccine. Furthermore, with the increasing range and coverage of interventions to prevent vertical transmission [including early diagnosis of maternal HIV infection, management of sexually transmitted infections (STI), safe delivery, maternal and infant preventive antiretroviral drugs (ARV) or maternal antiretroviral treatment (ART) and safe infant feeding] the majority of infants born to HIV-infected mothers are themselves not infected, and these infants would also be expected to benefit from BCG vaccination.

Unfortunately, accurate diagnosis of HIV infection in the first year of life relies upon direct demonstration of the HIV virus, as maternal HIV antibody is passively transferred to the infant in utero. Currently available assays and diagnostic platforms that can be used for diagnosis of HIV in the first year of life include appropriately ongoing externally validated commercially and non-commercially available tests for HIV DNA (PCR) or HIV RNA and p24 antigen; these tests remain expensive and technically demanding for many countries with generalized HIV epidemics.

Signs and symptoms of HIV are not typically present in the first week of life when BCG is usually offered. Not all women are offered HIV testing during pregnancy and so children born to HIV-infected mothers are not always recognized at or around the time of birth. Even where maternal HIV infection is recognized in pregnancy, not all HIV-exposed children receive ARVs to prevent mother-to-child transmission.

Furthermore, clinical signs and symptoms of HIV in infants are non-specific, and no single clinical diagnostic algorithm has proved highly sensitive or specific for the diagnosis of HIV infection. Clinical algorithms are rarely more than 70% sensitive for the accurate diagnosis of infection and they vary considerably with age, and in particular are less reliable among infants. WHO has recently outlined clinical criteria for diagnosing presumptively severe HIV disease in children less than 18 months of age, in order to allow appropriate management of potentially HIV-infected children. Presumptive clinical diagnosis of severe HIV-related disease warrants the appropriate management of the presenting problem and management of presumed HIV infection; this may include consideration of revising BCG vaccination.

**Application of revised BCG recommendations**

Ideally HIV counselling and testing should be offered to all pregnant women, accompanied by provision of interventions to prevent mother-to-child transmission in those who test HIV antibody positive. However, it is recognized that counselling and testing facilities are often not available to all pregnant women in countries hardest hit by the HIV epidemic. Additionally, follow-up of the HIV exposed infant may not be undertaken by service providers who are aware of the HIV status of the mother and or infant (i.e., HIV exposed, and/or HIV virological testing undertaken) at the time of usual BCG vaccination.

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National and local decision-making on the revision and application of BCG immunization will ultimately be based on a range of locally determined factors. As part of that assessment, the following guidance should be noted:

**Risks outweigh benefits for BCG vaccination among:**
Infants who are known to be HIV infected, even if they show no symptoms of HIV infection. These infants should not be immunized.

**Benefits outweigh risks for BCG vaccination among:**
Infants born to women of unknown HIV status who demonstrate no signs or symptoms suggestive of HIV infection. These infants should be immunized.

**Benefits usually outweigh risks** for BCG vaccination among:
- Infants born to HIV infected women where the mother-baby pair received a complete course of ARV prophylaxis or the mother is well controlled on ART and the infant is well.
- Infants born to HIV infected mothers where early HIV diagnostic testing can be performed; BCG can be deferred until diagnostic testing results are available.
- HIV exposed infants found to have no virological evidence of HIV at early diagnostic testing but still at risk of HIV transmission through breastfeeding.

**Risks usually outweigh benefits** of BCG vaccination among:
- Infants born to HIV exposed mothers who are well but have early virological testing that suggests HIV infection.

A range of additional factors will also inform national and local decision-making on the adoption and implementation of revised guidelines for BCG immunization. Among them, in no order of priority:

- Prevalence of tuberculosis
- Potential for infant exposure to tuberculosis
- Prevalence of HIV
- Coverage of interventions that prevent mother-to-child transmission of HIV
- Rates of exclusive and mixed breastfeeding
- Capacity to conduct follow-up of immunized children
- Capacity to perform early virological infant diagnosis (in the first 0-9 months of life)
In summary, BCG vaccination should be offered under the following conditions:

<table>
<thead>
<tr>
<th>Maternal Status</th>
<th>Infant HIV Infection Status</th>
<th>Early virological testing *</th>
<th>BCG Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>If unknown or negative</td>
<td>None</td>
<td>Not available**</td>
<td>Give BCG</td>
</tr>
<tr>
<td>If known HIV positive</td>
<td>None</td>
<td>Not available</td>
<td>Give BCG but follow-up closely for complications</td>
</tr>
<tr>
<td>If known HIV positive</td>
<td>None</td>
<td>Available but not yet done</td>
<td>Defer BCG</td>
</tr>
<tr>
<td>If known HIV positive</td>
<td>Yes</td>
<td>Not available</td>
<td>Do NOT give BCG</td>
</tr>
<tr>
<td>If known HIV positive</td>
<td>None</td>
<td>Available and positive</td>
<td>Do NOT give BCG</td>
</tr>
</tbody>
</table>

* 'Early' refers to testing that is performed in the first 0-9 months of life

** The term 'available' refers to whether access to such lab testing is feasible, affordable and the results attainable