Measles Virus Infection, a Systemic Rash Illness Commonly Acquired in Infancy and Early Childhood, is One of the Most Contagious Infectious Diseases in Humans

Measles virus infection, a systemic rash illness commonly acquired in infancy and early childhood, is one of the most contagious infectious diseases in humans [1]. Measles is also an important cause of global morbidity and mortality, primarily among infants and children living in resource-limited settings [2]. Since the development of measles vaccines in the 1960s, intensive vaccination efforts, especially in the 21st century, have led to substantial reductions in measles-related deaths on a global scale, resulting in a reduction in mortality from almost 750,000 childhood deaths worldwide in 2000 to 164,000 in 2008 [3]. Eradication of measles infection on a global scale can, in theory, be accomplished because measles virus has no nonhuman reservoirs, and vaccination strategies to prevent transmission are available and feasible [4]. However, because of the highly contagious nature of measles virus, at least 95% vaccination coverage with at least 1 dose (and preferably 2 doses) of measles vaccine must be achieved to suppress and eventually eradicate continued global measles transmission [5].

One important characteristic of measles infection is that it produces more serious illness and increased mortality among immunocompromised individuals, primarily those with defects in T-cell immunity [6]. Because >90% of human immunodeficiency virus (HIV)-infected children live in regions where measles is still endemic [7, 8], achieving high rates of measles vaccine coverage is especially important among these populations to suppress excess measles-associated morbidity and mortality. However, live virus vaccines may also result in disease and, in general, are not recommended for administration to severely immunocompromised individuals. Measles vaccines are also known to induce short-term immunosuppressive effects and, therefore, the risk of further adverse events among HIV-infected infants and children is of concern. Moreover, it is well known that the immunogenicity of live virus vaccines, including measles vaccines, among HIV-infected children is limited and primarily related to degree of immunocompromise [9]. Knowledge gaps in understanding measles immunogenicity among HIV-infected children arise because the preponderance of studies regarding measles vaccine immunogenicity are derived from domestic settings, and generally from healthy infants and children. In contrast, data from resource-limited settings rarely include populations of HIV-infected children, and may also be confounded by other factors, such as malnutrition and other environmental factors that may affect information about safety and immunogenicity of measles vaccines. In addition, the impact of HIV-related immunocompromise and subsequent effects of antiretroviral therapy (ART) on immune reconstitution and, ultimately, on vaccine immunogenicity are unclear.

In this issue of the Journal, Abzug and colleagues describe the safety and immunogenicity of 1 or 2 measles vaccine booster doses administered to HIV-infected children, living in the United States, who had received at least 1 prior measles-mumps-rubella (MMR) vaccine, and after stable administration of ART [10]. They investigated the baseline and long-term humoral immunity to measles, as measured by measles plaque reduction neutralizing antibodies, among 193 HIV-infected children aged 2–18 years before and after 1 booster dose of measles vaccine administered at least 6 months after initiation of ART for HIV infection. Not surprisingly, the investigators found that baseline measles seroprotection was only 52%, as defined by measles neutralizing antibody levels ≥120 mIU/mL. However, after 1 booster dose of measles vaccine, seroprotective measles antibody titers increased to 89% eight weeks later, and were sustained in 80% of children 80 weeks after the booster. Among a subset of 65 children
who received a second measles vaccine booster 4–5 years later and who had available serologic samples, 75% of children continued to demonstrate baseline evidence of seroprotective measles neutralizing antibodies, increasing to 95% after the second booster. Moreover, humoral immune responses and immunologic memory were strongly linked to HIV load, with seroresponders and those with persistent measles neutralizing antibodies more likely to have suppressed HIV load levels ≤400 copies/mL. The study demonstrated not only that HIV-infected children on prolonged ART were capable of robust development of humoral measles immunity after revaccination, but that they were also able to maintain persistent measles neutralizing antibodies through 4–5 years.

One limitation of the Abzug et al study is that information was not available for study subjects regarding the immune and ART status at the time of their primary measles immunization. However, data from 2 recently published studies demonstrate the relationship between early measles immunization, immune status, and humoral response in the absence of ART [11, 12]. Chandwani et al [11] randomized HIV-infected and uninfected US infants to receive either monovalent measles vaccine at 6 months, followed by the MMR vaccine administered at 12 months, compared with receipt of only MMR at 12 months. Among the 15 HIV-infected subjects, all 1 developed seroprotective measles neutralizing antibody responses by 6 weeks after the 12-month MMR dose, and at approximately 3 years of age, seroprotective neutralizing antibody titers were sustained in 4 of 5 (80%) of the 2-dose recipients and 4 of 6 (67%) of the 1-dose recipients. It is important to note that none of the HIV-infected subjects had received ART during the study period, suggesting that HIV-infected infants without severe immunocompromise were able to sustain a seroprotective measles immune response after early immunization. Fowlkes et al [12] conducted a similar study in Malawi among healthy and HIV-infected infants who had not received ART, and who were administered measles vaccine at 6 and 9 months of age. Among HIV-infected infants, only 44% of 23 children were able sustain measles neutralizing antibodies 20 months after immunization. Other studies of measles vaccine immunogenicity after primary or booster measles immunization among HIV-infected children on ART have been reported among study subjects from the United States, Europe, Thailand, Kenya, and Brazil [13–19]. These have demonstrated persistence of measles antibody titers up to 3 years after revaccination in HIV-infected children receiving stable ART and without severe immunosuppression, but have also demonstrated a lack of sustained humoral immunity in the presence of moderate to severe immunocompromise. In addition, a recent meta-analysis found that no serious adverse events were identified in published studies of measles vaccine administration among HIV-infected infants and children, regardless of degree of immunocompromise [20]. Taken as a whole, these studies are encouraging and provide evidence for the immunogenicity of primary and booster measles vaccine administration among HIV-infected infants who are not severely immune deficient, at least through 3–5 years after vaccination, especially when these infants and children are on stable ART. However, the persistence of humoral immunity beyond this period is unknown and remains an important knowledge gap.

Although the study reported by Abzug and colleagues provides promising information for guiding measles vaccine use among HIV-infected children, a number of obstacles still remain to reduction of global measles infection, especially among the larger population of HIV-infected infants and children living in resource-limited settings. First, prevention and identification of HIV infection among infants and children living in resource-limited settings is suboptimal. In 2009, approximately 370,000 children acquired HIV infection, primarily from perinatal transmission, and it is estimated that only 53% of pregnant women worldwide have the appropriate services available to prevent perinatal HIV infection [21]. Second, availability of ART for HIV-infected individuals living in resource-poor settings is limited, with only 35% of HIV-infected individuals worldwide receiving routine ART [22]. Early identification and anti-retroviral treatment of HIV-infected infants and children are critical to maximizing measles vaccine immunogenicity and providing protection against other HIV-related complications. Finally, despite global measles vaccination efforts, which have been intensified in the last decade, 2-dose measles vaccine uptake among infants in resource-limited settings remains poor overall [23]. Strategies to improve measles vaccine uptake among healthy and immunocompromised infants and children have been a major focus of global public health efforts.

Only 1 human infectious disease, smallpox, has been globally eradicated, and the campaign to eradicate poliomyelitis is very close to achieving its goal. Following these intensive efforts, there is good evidence that measles infection could also be targeted for global eradication [23]. A recent expert panel convened by the Centers for Disease Control and Prevention reviewed the current status of measles in the United States and concluded that endemic measles virus circulation has been eliminated from the United States for at least the last decade; however, the global status of measles vaccination is not as robust and renders measles elimination a fragile but sustainable goal [24]. The Abzug et al study provides further evidence to support recommendations for measles booster vaccination of HIV-infected children on stable ART with suppressed HIV loads, but this observation can only be successful in preventing
measles morbidity and mortality if it is coupled globally with aggressive identification and antiretroviral treatment of children with HIV infection.

**Note**

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**References**