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Short communication

High rate of rubella seronegativity in perinatally-infected HIV women of childbearing age: A case-control study

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ABSTRACT

Rubella infection is a vaccine preventable disease. Maternal infection during pregnancy may lead to congenital infection and severe foetal malformations. Thanks to antiretroviral therapy, perinatally HIV-infected women have better prognosis and are now experiencing pregnancy. We evaluated the rate of rubella seronegativity in a cohort of HIV perinatally-infected women of childbearing age. A high rate of seronegativity was found in this group as compared to age-matched non-perinatally infected HIV-infected women (34.5% vs 6.90%, $p < 0.01$). MMR administration before rubella testing was identified in 75.8% of perinatally-infected women (22/29) with a mean of 2 doses (range: 1–3 doses). HIV perinatally-infected women of childbearing age should be screened repeatedly for rubella immunity.

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1. Introduction

Rubella infection is caused by an RNA virus of the *Togaviridae* family and usually presents as a mild or asymptomatic infection. Maternal infection during pregnancy, especially during the first trimester, may lead to serious complications such as miscarriage, foetal death and congenital abnormalities, including the congenital rubella syndrome (CRS), consisting of various birth defects [1]. Rubella is a vaccine preventable disease and mass immunization has been associated with a dramatic decrease of CRS incidence [1]. The World Health Organization (WHO) recommends a vaccination coverage of ≥95% with a rubella containing vaccine (RCV) to prevent CRS, with the aim to achieve rubella elimination before 2020 in Europe [2].

Immune response to vaccination in HIV-infected children has been shown to be suboptimal [3,4]. This has been more extensively studied for measles than for rubella, reporting a lower conversion rate following measles-mumps-rubella (MMR) vaccination and decreased persistence of antibody response [5,6].

Thanks to the success of antiretroviral therapy (ART), perinatally HIV-infected children are now living longer and the number of adolescents living with HIV is increasing worldwide [7]. Perinatally HIV-infected women (PHIV) are now experiencing pregnancy and recent reports from developed countries indicate that the first pregnancy occurs early, between 16 and 20 years [7,8].

In the present study, we assessed rubella seroprevalence among PHIV women of childbearing age and compared it to age-matched non-perinatally HIV-infected (nPHIV) women.

2. Materiel and methods

All the PHIV women of childbearing age (15–39 years) in follow-up at the infectious diseases' department of CHU Saint-Pierre hospital, Brussels (Belgium) who had their rubella serostatus assessed between 2006 and 2018 were retrospectively identified and age-matched 1:2 to nPHIV controls. Each PHIV patient was matched to two nPHIV women with the closest age. Both PHIV and nPHIV were identified in the hospital's HIV database. Rubella testing was part of routine testing. Data on mode of HIV transmission were based on available medical records as provided by

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treating infectious disease specialists and paediatricians. Rubella serology testing was interpreted as protective (≥10 IU/mL) or not protective (<10 IU/mL) according to WHO recommendations [1]. Three different assay were used during the study period: Liaison (Diasorin) between 2006 and August 2009, Architect (Abbott) between September 2009–2015 and Cobas (Roche) since January 2016. Vaccination history was retrieved from the available hospital files in the PHIV group and only data on documented administration were included (written notes in medical files and vaccination cards). The majority of PHIV subjects had active follow up in the paediatric clinic since early childhood and had frequent documented vaccination history. Immunization status could not be retrieved in the nPHIV women as the majority had immigrated recently in Belgium with no available vaccination documentation.

Conditional logistic regression was used for statistical analysis between the PHIV and nPHIV subjects. All statistical analyses were performed using SAS (version 9.4; SAS Institute, Cary, NC, USA).

3. Results

Twenty-nine PHIV (cases) and fifty-eight nPHIV (controls) were identified. Characteristics of the 2 groups are depicted in Table 1. PHIV patients were slightly but significantly younger than nPHIV patients. In both groups the maximum age was 34.8 years. Median age at diagnosis, as determined by HIV serological assay in Belgium, was 4.4 years in PHIV and 22.9 years in nPHIV group (p value <0.01).

There was no significant difference between cases and controls considering country of birth (Belgium vs. outside Belgium), proportion of Sub-Saharan African origin, on ART at time of rubella testing, rubella serological assay used, HIV viral load <50 copies/mL at time of testing, CD4+ T cell count >350 cells/μL at time of testing and CD4+ T cell count nadir >200 cells/μL. Median duration of living in Belgium was significantly different in the two groups: 15.9 years vs. 2 years for the nPHIV group (p value <0.01). Although the proportion of Sub-Saharan African origin was similar in both groups, their country of birth for those of Sub-Saharan African origin were different (the majority of PHIV were from the Democratic Republic of the Congo (DRC), Rwanda and Burundi and the majority of nPHIV were from the Republic of Guinea, the DRC and Cameroun).

Time since HIV diagnosis was longer in the PHIV group and there was a trend for higher proportion of AIDS-defining events before rubella testing in the PHIV group. Among PHIV, seronegativity rate was 34.5% (10/29) while seronegativity was 6.90% (4/58) in the nPHIV group (Odds ratio 8.6, 95% confidence interval 1.8–81.7). MMR administration before rubella testing was identified in 75.8% of PHIV women (22/29) with a mean of 2 doses (range: 1–3 doses). Notably, in the PHIV women with documented immunization, the seronegativity rate was 31.8% (7/22).

Table 1
Characteristics of PHIV and nPHIV patients included in the study and results of rubella serological testing.

Characteristics	Perinatally HIV-infected subjects 29 patients n/total (%)	Non perinatally HIV-infected subjects 58 patients n/total (%)	P-value
Rubella IgG titers			<0.01
≥10 IU/mL	19/29 (65.5)	54/58 (93.1)	
<10 IU/mL	10/29 (34.5)	4/58 (6.9)	
Median age at time of testing, years (IQR)	22.7 (19–25.6)	24.7 (21.8–26.2)	<0.01
Time since HIV diagnosis			<0.01
<10 years	2/26 (7.7)	56/57 (98.3)	
≥10 years	24/26 (92.3)	1/57 (1.7)	
Median age at time of HIV Diagnosis, years (IQR)	4.4 (0.4–9.3)	22.9 (19.9–24.9)	<0.01
Country of birth			0.75
Belgium	2/29 (6.9)	3/58 (5.2)	
outside Belgium	27/29 (93.1)	55/58 (94.8)	
Median duration of stay in	15.9 (10.8–22.3)	2.0 (1.1–5.6)	<0.01
Belgium, years (IQR)			
Sub-Saharan African origin			0.83
no	5/29 (17.2)	9/58 (15.5)	
yes	24/29 (82.8)	49/58 (84.5)	
On ART at time of testing			0.12
yes	20/29 (69.0)	30/58 (51.7)	
no	9/29 (31.0)	28/58 (48.3)	
Rubella serological assay			0.47
Liaison, Diasorin	5/29 (17.2)	17/58 (29.3)	
Architect, Abbott	15/29 (51.7)	27/58 (46.6)	
Cobas, Roche	9/29 (31.0)	14/58 (24.1)	
Viral load <50 copies/mL at time of testing			0.32
≤50	15/27 (55.6)	27/56 (48.2)	
>50	12/27 (44,4)	29/56 (51.8)	
CD4+ count at time of testing			0.36
≥350 cells/μL	20/29 (69.0)	45/57 (79.0)	
<350 cells/μL	9/29 (31.0)	12/57 (21.0)	
CD4+ nadir			1
>200 cells/μL	25/29 (86.2)	44/51 (86.3)	
≤200 cells/μL	4/29 (13.8)	7/51 (13.7)	
AIDS defining events before testing			0.08
no	23/29 (79.3)	54/58 (93.1)	
yes	6/29 (20.7)	4/58 (6.9)	

4. Discussion

In the present study, we identified a very high rubella susceptibility rate of 34.5% in PHIV women of childbearing age compared to nPHIV women. Recent studies performed in Europe that have assessed rubella seronegativity in HIV-infected subjects did not specifically assess the impact of perinatal infection [9,10]. We and another group from Ireland have recently identified that vertical HIV transmission was a risk factor for measles seronegativity in young HIV-positive adults [11,12].

The majority of the PHIV and nPHIV women included in the study originated from Sub-Saharan Africa. The PHIV women emigrated in early life, grew up in Belgium and have benefited from the Belgian childhood vaccination program. In Belgium, MMR first dose is recommended at one year of age. MMR status is checked by medical school services giving a window of opportunity for catch-up at 5–6 years and the second dose is recommended at 11–12 years. The high seronegativity rate reported here for the PHIV is thus not likely to be the consequence of lack of immunization, with most of the PHIV subjects having regular follow up in paediatric care. Moreover, a high rate of seronegativity was found in the large subgroup of PHIV subjects with documented immunization status. The high seronegativity rate of the PHIV group reflects the defective vaccine-induced immune responses previously reported in this group [4].

In the HIV-uninfected population, rubella-specific antibodies have been shown to persist in more than 95% of subjects immunized for at least 15 years after one dose of vaccine and 20 years after 2 doses of vaccines [1]. In a study performed in HIV-infected children receiving ART and with documented immune recovery, 79% had protective levels of rubella-specific antibody three years after revaccination [13]. A recent study performed in almost 200 PHIV children, rubella seropositivity was 72.9% as compared to 98% in HIV-exposed uninfected infants following immunization in childhood [3].

The mechanisms underlying such deficiency in the ability to mount long term humoral responses are probably multifactorial in PHIV subjects. A SIV animal model of perinatal infection has shown that the infection has a profound impact on the developing germinal centres [14]. The preservation of CD4+ T cells, T follicular helper T cells and memory B cells in PHIV children requires sustained viral control [15]. PHIV are more likely to have frequent structured or unstructured treatment interruptions [16].

In contrast, a substantial proportion of the nPHIV subjects included in this study are presumed to have grown-up in Sub-Saharan Africa, this group having a median stay in Belgium of 2 years. Rubella virus is circulating in Sub-Saharan Africa where infection usually takes place in childhood [17]. Rubella vaccine was introduced in a limited number of countries in Sub-Saharan Africa only since 2012 [18]. Seropositivity rates in the nPHIV group thus likely reflects infection-induced immunity.

According to a 2017 meta-analysis, the pooled estimate for rubella seronegativity prevalence in pregnant and childbearing-age women of the WHO African region was 10.7% (95%CI: 8.6–12.9) [18]. This is slightly higher than the 6.7% reported for the nPHIV women here suggesting that HIV infection in nPHIV women has no impact on rubella seropositivity. This is in sharp contrast with the PHIV group were a seronegativity rate of 34.5% was found, indicating that perinatal HIV infection has a significant impact on the vaccine-induced rubella immunity in this group.

The present study has some limitations. Firstly, vaccine status could not be assessed in the nPHIV group. However, seronegativity rate in this group was close to estimates previously reported in the Sub-Saharan Africa region [17,18] and probably reflects infection-induced immunity. Secondly, the number of subjects in the PHIV group is limited and the findings should be confirmed in a larger cohort. Nevertheless, the high seronegativity rate found in this group of PHIV with high MMR vaccine coverage, reflecting defective vaccine-induced immunity, is of particular concern for the ongoing rubella eradication strategy.

5. Conclusion

Current guidelines for the vaccination of HIV-infected children living in Europe [19] recommend 3–5 yearly testing for both measles & rubella IgG. The British HIV association guidelines on the use of vaccines in HIV-infected adults recommend rubella serological testing in women of childbearing age only in case of unknown status [20]. We recommend that PHIV women of childbearing age should be regularly tested for rubella immunity, even in the case of past positive rubella IgG test.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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