Tolerance and humoral immune response to the yellow fever vaccine in sickle cell disease children treated with hydroxyurea: a multicentre prospective study

Berengere Koehl, Camille Aupiais, Nelly Schinckel, Pierre Mornand, Marie-Hélène Odièvre, Assa Niakate, Valentine Brousse, Ghislaine Ithier, Florence Missud, Laurent Holvoet, et al.

Tolerance and humoral immune response to the yellow fever vaccine in sickle cell disease children treated with hydroxyurea: a multicentre prospective study.

Berengere Koehl, MD, PhD [a,b,c], Camille Aupiais, MD, PhD [d,e], Nelly Schinckel, MD [f], Pierre Mornand, MD [g], Marie-Hélène Odièvre MD, PhD [g,c], Assa Niakate, MD [g], Valentine Brousse MD, PhD [h,c], Ghislaine Ithier, MD [a], Florence Missud, MD [a], Laurent Holvoet, MD [a], Malika Benkerrou, MD [a,d], Frederic Sorge, MD [a], Albert Faye, MD, PhD [b,d,f]

[a:] Department of Haematology, Reference Centre of Sickle Cell Disease, Hôpital Robert Debré, APHP, Paris, France

[b]:Université de Paris, France

[c]:INSERM UMRS 1134

[d]:INSERM UMRS 1123

[e:] Department of Paediatrics Emergency, Jean Verdier Hospital, APHP, Bondy, France

[f]: Department of General Paediatrics and Infectious Diseases, Robert Debré Hospital, APHP, Paris, France

[g:] Department of General Paediatrics, Centre for Sickle Cell Disease, Trousseau Hospital, APHP, Sorbonne Université, Paris, France

[h:] Department of General Paediatrics, Necker Enfants Malades Hospital, APHP, Paris, France

Running Title: Yellow fever vaccine in sickle cell disease children

Key words: haemoglobinopathy, immunization, hydroxycarbamide, travel, side effects, paediatric, Africa

Corresponding author

Dr. Berengere KOEHL

Centre de Référence de la Drépanocytose, Hôpital Robert Debré

48, Boulevard Sérurier, 75019 PARIS, FRANCE

Tél.: +33 (0)1 40 03 24 22– Fax: +33 (0)1 40 03 24 23 - E-mail: berengere.koehl@aphp.fr;

Abstract

Background: Sickle Cell Disease (SCD) children are frequent travellers to countries where Yellow Fever (YF) is endemic, but there are no data regarding the safety and immunogenicity of the vaccine in such children treated with hydroxyurea (HU). The main objective of this study was to compare the tolerance and immune response to YF vaccination in SCD children treated or not with HU.

Method: SCD Children < 18 years attending the international travel clinics of three large paediatric centres and requiring a first YF vaccination were included in a prospective study. Adverse events were collected 2 weeks after vaccination. YF vaccine antibody titres were measured approximately 6 months after vaccination.

Results: Among the 52 SCD children vaccinated against YF, 17 (33%) were treated with HU. Only mild adverse events, mainly fever and local reaction, were observed in the HU group with a similar frequency in the non-HU group (57% and 35%, respectively, *p=0.30).* YF antibody titres were measured in 15/17 patients in the HU group and 23/35 patients in the non-HU group after a median of 6.0 months (3.5-8.5) following vaccination. The geometric mean of YF antibody titre was similar in both groups. A protective antibody level was observed in 85% of the children in the HU group versus 100% in the non-HU group (*p=0.14*), suggesting a lower effectiveness of the vaccine in patients on HU similarly to what has been described in patients on immune suppressive therapy for other vaccines.

Conclusion: YF vaccination seems to be safe and efficient in SCD children treated with HU. Considering the potential risk of severe complications in cases of YF while travelling in Africa for those patients, the benefit-to-risk ratio argues for YF vaccination in all SCD children. Control of a protective antibody titre may also be useful to ascertain an adequate response in those treated with HU.

Background

Yellow fever (YF) is a mosquito-borne disease caused by an arbovirus of the Flavivirus genus; it has a broad spectrum of clinical manifestations, and 10–15% of patients are estimated to develop severe infection, which can lead to rapid multi-organ failure and is associated with a high mortality rate[1]. YF remains a major public health issue, particularly in sub-Saharan Africa, with an estimated burden of 84,000–170,000 severe cases and 29,000–60,000 related deaths annually.[2] All travellers to areas where YF is circulating should be vaccinated, and travel medicine providers need to be up to date on the epidemiological situation of YF globally[3].

Sickle cell disease (SCD) is currently one of the most frequent genetic diseases with approximately 300,000 births annually worldwide.[4] As many patients affected by SCD originate from sub-Saharan Africa or from other YF endemic areas where they are living or might travel, YF fever vaccination is a concern for these patients.

The YF 17D vaccine, which is based on a live attenuated viral strain, is highly effective with a seroconversion rate close to 100% after 3 months in healthy children.[5] According to WHO recommendations and travel regulation health authorities, all individuals aged 9 months or older who live or travel to endemic countries should receive the YF vaccine.[6] Hydroxyurea (HU) is the first approved drug for SCD given its many disease-modifying effects[7–9], and its indications have dramatically increased in recent years. In many countries, HU is recommended for adults and children over 2 years old with SCD who have a history of frequent and/or severe vaso-occlusive events. In the US, treatment is recommended in all infants aged over 9 months, regardless of clinical severity, to prevent or delay the occurrence of complications.[10]

HU is, however, a ribonucleotide reductase inhibitor with myelosuppressive effects. As a chemotherapy, HU is considered an immunosuppressive treatment, leading to a contraindication of the YF vaccine in patients under treatment.[11,12] In the context of immunodepression, YF vaccination may be associated with a theoretical risk of severe side effects[13,14] but also with a less effective immunological response and hence impaired protection[15]. There are no data on the severity of YF in children with SCD. Nevertheless, other flavivirus infections in SCD patients, such as dengue fever[16] or Zika virus infection, [17] are associated with a more severe disease. [18,19]

Considering the risk and severity of YF, some vaccination centres perform YF vaccination in SCD children before they travel to endemic areas whether they are treated with HU or not. However, there are no data concerning the safety and immune response to YF vaccines in children treated with HU.

In this prospective study, our main objective was to assess the tolerance and immune response of the YF vaccine in SCD children and to compare this response in SCD children treated or not with HU.

Patients and Methods

Study and population

Patients < 18 years of age with SCD (haemoglobin SS, SC or $S\beta^0$) attending the travel clinic of Robert Debré, Necker-Enfants Malades and Armand Trousseau Hospitals in Paris and travelling in an endemic area of YF requiring a first YF vaccination were included in a prospective multicentre study between March 2016 and July 2017. The clinician ensured that the patient had never been vaccinated by checking the immunization record. All patients included in the study were born in Europe where YF vaccination is not recommended, except for travel to endemic areas. All included patients were in preparation for their first trip to YF endemic areas. The guidelines were homogeneous among the 3 centres, and the management practices were identical.

Patients were included if their destination warranted YF vaccination according to international recommendations and if they had no contraindication to YF vaccination (i.e., patients with primary immunodeficiencies, malignant neoplasms, thymus disorder, organ transplants, HIV infection with severe immunodeficiency, or hypersensitivity to any of the vaccine's components and infants younger than 9 months of age), except for treatment with HU.

The immune response to YF vaccine was assessed through a test of seroneutralisation. The serology results are expressed in international units (IUs). A titre level higher than 5 IU/L was considered protective against YF disease and corresponds to the result of a plaque reduction neutralisation test (PRNT) ≥ 10 IU reported in other studies.[20] Positive sera after a dilution of $1/80^{th}$ (corresponding to the serological response of 80 IU/L) were not diluted further.

Serology was performed at the first medical visit of the patient requiring a blood test after vaccination. For ethical reasons, patients who did not require a blood test as part of their medical follow-up were not tested.

Ethical consideration

The study was approved by the Ethical Evaluation Committee for Biomedical Research Projects (CEERB) of Robert Debré Hospital, France (N° 2014/155). The collection of clinical and biological data was registered at the French National Commission for Information

Technology and Civil Liberties (CNIL). The parents or legal guardians of the minor patients were informed and gave their consent for the study.

Data collection

The data were collected in a standardized form that included the following baseline data: sex, age at the day of vaccination, treatment (or no treatment) with HU, and ongoing chronic transfusion program. Ten to 15 days after vaccination, the occurrence of side effects was collected during a phone interview based on a standardized form (Supplementary data). We considered all symptoms that did not require medical consultation or specific treatment as mild effects.

Statistical data

To highlight a difference in frequent side effects (i.e., affect up to 1 person out of 10) of approximately 30% between the 2 groups, we calculated a theoretical size of 23 patients in each group according to Arcsin's approximation (with a power (1-β) of 0.8 and α risk of 0.05).

Categorical variables were described as percentages and numbers. Continuous variables were described by medians and interquartile ranges (IQRs). We calculated GMTs and corresponding 95% CIs on the basis of the standard normal distribution of the log-transformed antibody titre. To compare the two groups (treated/untreated) and children with or without side effects, the $\chi 2$ or Fisher's exact test was used for categorical variables, and Mann-Whitney-Wilcoxon test was used for continuous variables. The Mann-Whitney-Wilcoxon test was used to compare the log-transformed antibody titres. The association between the log-transformed antibody titre and the age of the patients was analysed using Pearson's correlation coefficient. A p value of <0.05 was considered significant (two-sided). All statistical analyses were performed using R version 4.0.2.

Results

During the inclusion period, 52 SCD patients received the YF vaccination, and all were included in the study. Among them, 17 patients were treated with HU, and 35 patients were not treated with HU. No patient had other chronic treatments, except daily treatment with folic acid as recommended. The patients' characteristics are summarized in Table 1. Patients treated with HU were older than the nontreated patients (median age of 9.6 vs. 6.9 years old, p-value = 0.001), and the mean lymphocyte count was lower in the HU group than in the nontreated

group (3670 vs. 4710 $x10^9$/µL, p-value = 0.01) (Table 1). None of the patients had iron overload at the time of sampling with comparable median ferritinaemia in each group (p-value = 0.449) as follows: 259 µg/L in the HU group (min=48 µg/L and max=836 µg/L) and 182 µg/L in the non-HU group (min=30 and max=932 µg/L).

Side effects

In the group of patients treated with HU, 14/17 had a phone interview 2 weeks after the vaccination, while 3 patients had already left for Africa and could not be reached. Mild side effects were reported in 8/14 patients (57%) (Figure 1), and these side effects were characterized by pain at the injection site in 7/14 patients (50%) and fever in 1/14 patients (7%). One patient reported backaches within the week following vaccination. One patient who had not reported any vaccination-related adverse events died 9 weeks after vaccination upon his return from Africa from a pulmonary embolism following a severe vaso-occlusive event (acute chest syndrome). This dramatic event was not considered related to the vaccination given the time lapse since immunization and the cause of death clearly related to a SCD complication. YF antibody titres were not measured.

In the group of patients not receiving HU, 31/35 had a phone interview 2 weeks after the vaccination, while 4 patients were already travelling in Africa and could not be reached. Mild side effects were reported by 11/35 patients (35%) (Figure 1), and these side effects were characterized by pain at the injection site in 4/35 patients (13%), fever in 6/35 patients (19%) or digestive symptoms, including vomiting, nausea and diarrhoea in 4/35 patients (13%).

The comparison between children with and without side effects showed no difference in age (7.8 vs. 8.0 years old, p-value = 0.83) or total lymphocyte count (3.7 vs. 4.2 G/L, p-value = 0.18) between the two groups. When specifically analysing each side effect separately, a higher frequency of local pain was found in the group of children treated by HU (12.9% vs. 50%, p-value = 0.02).

Immune response to the YF vaccine

Among patients treated with HU, the YF immune response was assessed in 14/17 patients after a median of 5.1 months following vaccination (IQR 3.2-9.0, range 2.2 to 9.05). The remaining 3 patients were not seen within 9 months of vaccination, and/or a blood sample was not taken at the time of the consultation. The geometric mean of the YF antibody titre was 29.7 IU/L (CI 14.8; 59.7) (Figure 2B). Of note, 2 patients in this group had a nonprotective titre at 2.5 and 3.4 months after vaccination, and their YF antibody titres were measured a second time at 6.8 and

6.3 months after vaccination and were still negative for one and weakly positive for the second (5 IU/L, at the lower limit of positivity).

In the nontreated group, the immune response to the YF vaccine was assessed after a median delay of 6.3 months following vaccination (IQR 3.6-8.5, range 2.1 to 9.6) for 23/35 patients (Figure 2B). The geometric mean of the YF antibody titre was 42.5 IU/L (CI 33.5; 53.9). All patients in the nontreated group had protective titres after vaccination (Figure 2C).

Overall, the immune response after vaccination was not different between the two groups (ANCOVA p-value = 0.74), nor was the frequency of protective titres after vaccination (100% vs. 86%, p-value = 0.14; Figure 2A). As the median age was different within the two groups, we analysed the correlation between the log-transformed antibody titre and the age of the patients, and the serology title was not correlated with the age of the patients (Pearson correlation p-value = 0.08, p-value = 0.6269).

Discussion

Ensuring effective vaccination for SCD children travelling in endemic areas of Africa is paramount, and this issue has already been raised in studies involving other immunocompromised travellers. [21] Specific studies have had to be conducted to clarify the relevance of vaccine contraindications and the real risk of vaccinating immunocompromised patients.[22] Most of these studies have been reassuring due to evidence of efficacy and harmlessness after YF immunization.[23] Our objective in this study was of the same order.[24]

As the YF immunization guidelines do not mention the issue of vaccination in SCD patients treated with HU, the practices might vary among different centres, ranging from systematic YF vaccination to contraindication. In this study, we found that the YF vaccine seems to be safe in children treated with HU. However, HU treatment was associated with a slightly but not significantly lower frequency of protective titre of YF antibodies when compared to nontreated patients (86 vs. 100%) and a higher frequency of local pain (12.9% vs. 50%, p-value = 0.02). The patient sample was too small to draw any definitive conclusions. However, this result was slightly surprising as it could be expected that immunosuppression might be associated with a lower inflammatory local reaction.

The more frequent adverse events described after vaccination against YF are headaches, mild asthenia, pain or discomfort at the injection site, muscle pain, fever, vomiting and arthralgia (up to 1 person out of 10). Adverse events following immunization (AEFI) are rare but serious,

including severe allergic reactions, YF vaccine-associated neurologic disease (YEL-AND) and YF vaccine-associated viscerotropic disease (YEL-AVD). The rates of these AEFIs regarding the liver, kidney or nervous system are between 0 and 0.21 cases per 10,000 doses in regions where YF is endemic and from 0.09 to 0.4 cases per 10,000 doses in populations unexposed to the virus.[2] The risk of AEFI is higher in people over 60 years of age and in cases of severe immunodeficiency (e.g., symptomatic HIV/AIDS). These potentially severe adverse events have justified so far the recommendation not to immunize patients treated with HU given the myelosuppressive effects of HU. However, HU treatment is not associated with severe immunodepression.[25] Given the small size of our sample, it was expected that there would be only a few side effects observed, and most of which were nonsevere, preventing us from observing severe side effects. Nevertheless, despite the small sample size, we showed that the safety profile is comparable to that of larger studies. .

We assessed the humoral immune response in children treated with HU compared to nontreated children. A protective titre was found in all nontreated children, while 2/13 patients treated with HU had nonprotective titres. In a systematic review of the literature, Gotuzzo *et al.* found a seroconversion rate between 82% and 98% after vaccination in healthy children.[26] Belmusto-Worn and others also reported seroconversion rates of 90.6–94.9% among 1107 healthy children.[27] In our study, we found a seroconversion rate of 100% in the untreated group and 85% in the group treated with HU.

Recent publications have reported no alteration of the immune system in SCD patients treated with HU,[25] but this treatment could theoretically decrease and delay the maturation of T lymphocytes from naive to memory form and subsequently alter the immunological and vaccinal response.[28] Moreover, in a murine model of SCD, dysregulation of the postvaccination immune response has been described with lower IgG and IgM responses in SCD mice than in control mice.[29]

Although the difference in seroconversion between the 2 groups is noteworthy, the small size of our study does not allow further conclusions. Because the children were older in the HU group than in the untreated group and because splenic function alters with age, the HU group may be more "immunocompromised" than the non-HU group. In contrast, it has been shown that treatment with HU has the effect of preserving organ functions in the long run, especially splenic function.[24] Overall, it is difficult to know whether the HU group in our study had a different immune function than the non-HU group. Overall, systematic control of the serological response after vaccination in patients treated with HU may be suggested before travel if time limits allow it or before the next trip to ensure the persistence or occurrence of

protective antibodies. In 2013, the WHO Strategic Advisory Group of Experts on immunization (SAGE) concluded that a single dose of vaccination is sufficient to confer life-long immunity against YF disease. This proposal has been implemented in France since 2016 for all children over 2 years of age. Thus, this control of the serological response after vaccination is all the more justified.

The main weaknesses of the present study were the observational design with a nonstandardized control group and the small sample size in each group of patients, which limited the power of the statistical conclusions and did not allow a multivariate analysis.

In addition, multivaccination is often practiced during travel consultations, but the possible effect of combined vaccinations was not investigated in this study.

In conclusion, YF vaccination seems to be safe and efficient in SCD children treated with HU. Considering the potential risk of severe complications in cases of YF while travelling in Africa for those patients, the benefit to risk balance is in favour of YF vaccination for all SCD children. A control of the serological response between 3 and 6 months after immunization or if possible before travelling to the YF endemic zone may also be useful to control for a protective vaccine response in children treated with HU. Larger observational studies are needed to assess the safety of this vaccine in this context.

Author contribution

BK, CA, NS, MB and AF designed the project; BK, PM, MHO, AN, VB, GH, FM, LH and FS contributed to essential material and collected clinical history; BK and CA analysed data; BK, CA and AF discussed the results and wrote the manuscript.

Conflict of Interest/Disclosure

The authors have declared no conflicts of interest.

References

1. Ho Y-L, Joelsons D, Leite GFC, *et al.* Severe yellow fever in Brazil: clinical characteristics and management. *J Travel Med* 2019; **26**. DOI:10.1093/jtm/taz040.

2. Garske T, Van Kerkhove MD, Yactayo S, *et al.* Yellow Fever in Africa: estimating the burden of disease and impact of mass vaccination from outbreak and serological data. *PLoS Med* 2014; **11**: e1001638.

3. Gubler DJ. Pandemic yellow fever: a potential threat to global health via travelers. *J Travel Med* 2018; **25**. DOI:10.1093/jtm/tay097.

4. Piel FB, Patil AP, Howes RE, *et al.* Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. *Lancet Lond Engl* 2013; **381**: 142–51.

5. Breugelmans JG, Lewis RF, Agbenu E, *et al.* Adverse events following yellow fever preventive vaccination campaigns in eight African countries from 2007 to 2010. *Vaccine* 2013; **31**: 1819–29.

6. Detection and investigation of serious adverse events following yellow fever vaccination, Geneva, World Health Organization (WHO); 2008. https://www.who.int/ith/vaccines/yf/en. .

7. Charache S, Terrin ML, Moore RD, *et al.* Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *N Engl J Med* 1995; **332**: 1317–22.

8. Ferster A, Vermylen C, Cornu G, *et al.* Hydroxyurea for treatment of severe sickle cell anemia: a pediatric clinical trial. *Blood* 1996; **88**: 1960–4.

9. Strouse JJ, Lanzkron S, Beach MC, *et al.* Hydroxyurea for sickle cell disease: a systematic review for efficacy and toxicity in children. *Pediatrics* 2008; **122**: 1332–42.

10. awn BP, John-Sowah J. Management of Sickle Cell Disease: Recommendations from the 2014 Expert Panel Report. *Am Fam Physician* 2015; **92**: 1069–76.

11. https://www.bms.com/assets/bms/ca/documents/productmonograph/HYDREA_EN_PM.pdf

12. https://pdf.hres.ca/dpd_pm/00042485.pdf

13. Aung AK, Trubiano JA, Spelman DW. Travel risk assessment, advice and vaccinations in immunocompromised travellers (HIV, solid organ transplant and haematopoeitic stem cell transplant recipients): A review. *Travel Med Infect Dis* 2015; **13**: 31–47.

14. Monath TP. Review of the risks and benefits of yellow fever vaccination including some new analyses. *Expert Rev Vaccines* 2012; **11**: 427–48.

15. Colin de Verdiere N, Durier C, Samri A, *et al.* Immunogenicity and safety of yellow fever vaccine in HIV-1-infected patients. *AIDS Lond Engl* 2018; **32**: 2291–9.

16. Rankine-Mullings A, Reid ME, Moo Sang M, Richards-Dawson M-A, Knight-Madden JM. A Retrospective Analysis of the Significance of Haemoglobin SS and SC in Disease Outcome in Patients With Sickle Cell Disease and Dengue Fever. *EBioMedicine* 2015; **2**: 937–41.

17. Arzuza-Ortega L, Polo A, Pérez-Tatis G, *et al.* Fatal Sickle Cell Disease and Zika Virus Infection in Girl from Colombia. *Emerg Infect Dis* 2016; **22**: 925–7.

18. Elenga N, Celicourt D, Muanza B, *et al.* Dengue in hospitalized children with sickle cell disease: A retrospective cohort study in the French departments of America. *J Infect Public Health* 2020; **13**: 186–92.

19. Wilder-Smith A, Leong WY. Risk of severe dengue is higher in patients with sickle cell disease: a scoping review. *J Travel Med* 2019; **26**. DOI:10.1093/jtm/tay136.

20. Hepburn MJ, Kortepeter MG, Pittman PR, *et al.* Neutralizing antibody response to booster vaccination with the 17d yellow fever vaccine. *Vaccine* 2006; **24**: 2843–9.

21. de Jong W, de Man RA, Dalm VASH, Reusken CBEM, Goeijenbier M, van Gorp ECM. Yellow fever vaccination for immunocompromised travellers: unjustified vaccination hesitancy? *J Travel Med* 2019; **26**. DOI:10.1093/jtm/taz015.

22. Chang L, Lim BCW, Flaherty GT, Torresi J. Travel vaccination recommendations and infection risk in HIV-positive travellers. *J Travel Med* 2019; **26**. DOI:10.1093/jtm/taz034.

23. Hall V, Johnson D, Torresi J. Travel and biologic therapy: travel-related infection risk, vaccine response and recommendations. *J Travel Med* 2018; **25**. DOI:10.1093/jtm/tay018.

24. Hankins JS, Ware RE, Rogers ZR, *et al.* Long-term hydroxyurea therapy for infants with sickle cell anemia: the HUSOFT extension study. *Blood* 2005; **106**: 2269–75.

25. Lederman HM, Connolly MA, Kalpatthi R, *et al.* Immunologic effects of hydroxyurea in sickle cell anemia. *Pediatrics* 2014; **134**: 686–95.

26; Gotuzzo E, Yactayo S, Córdova E. Efficacy and duration of immunity after yellow fever vaccination: systematic review on the need for a booster every 10 years. *Am J Trop Med Hyg* 2013; **89**: 434–44.

27. Belmusto-Worn VE, Sanchez JL, McCarthy K, *et al.* Randomized, double-blind, phase III, pivotal field trial of the comparative immunogenicity, safety, and tolerability of two yellow fever 17D vaccines (Arilvax and YF-VAX) in healthy infants and children in Peru. *Am J Trop Med Hyg* 2005; **72**: 189–97.

28. Donehower RC. An overview of the clinical experience with hydroxyurea. *Semin Oncol* 1992; **19**: 11–9.

29. Szczepanek SM, Secor ER, Bracken SJ, *et al.* Transgenic sickle cell disease mice have high mortality and dysregulated immune responses after vaccination. *Pediatr Res* 2013; **74**: 141–7.

Table and Figure legends

Figure 1

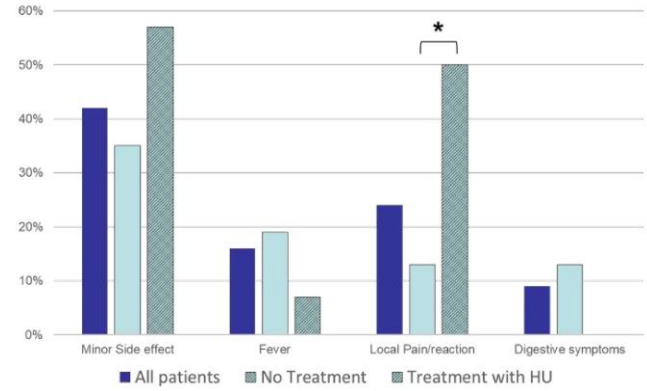

Figure 1: Occurrence of side effects after YF vaccination. Mann-Whitney test was used to compare the different group of patients; *: $p < 0.05$

Figure 1: Occurrence of side effects after YF vaccination. Mann-Whitney test was used to compare the different group of patients; *: $p < 0.05$

Figure 2

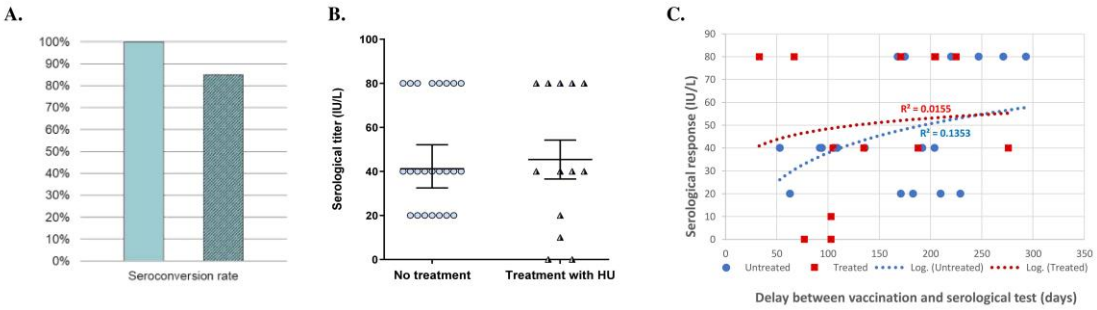

Figure 2: Serological response after vaccination. A: seroconversion rate on 37 SCD patients (23 without treatment (light blue), 14 treated with Hydroxyurea (hatched blue). **B:** Serological titer in 37 SCD patients collected after a median delay of 6.0 months [IQR 3.5 ; 8.5] after YF vaccination. **C**: Evolution of the serological response with the delay after vaccination.

Figure 2: Serological response after vaccination. A: seroconversion rate on 37 SCD patients (23 without treatment (light blue), 14 treated with Hydroxyurea (hatched blue). B: Serological titer in 37 SCD patients collected after a median delay of 6.0 months [IQR 3.5 ; 8.5] after YF vaccination. C: Evolution of the serological response with the delay after vaccination.

Table 1: Patient's characteristics. Comparison between SCD patients treated or not with Hydroxyurea: [1] :Chi2 or fisher test, [2] :Mann-Whitney-Wilcoxon test

	Total n = 52	No HU treatment n = 35	Treatment with HU n = 17	p-value	Missing value
Male, n (%)	32 (61.5)	22 (62.9)	10 (58.8)	0.99 [1]	
Age (years), median (IQR)	7.8 (2.9 ; 9.8)	6.9 (1.8 ; 9.0)	9.6 (8.0 ; 14.0)	**0.001** [2]	
Chronic exchange transfusion, n (%)	3 (5.8)	1 (2.9)	2 (11.8)	0.25 [1]	
Total leucocyte count (G/L), median (IQR)	10.7 (8.6 ; 12.1)	10.7 (8.5 ; 12.1)	10.7 (9.2 ; 11.6)	0.92 [2]	n = 18
Total lymphocyte count (G/L), median (IQR)	3.9 (3.3 ; 5.1)	4.7 (3.6 ; 5.9)	3.7 (2.4 ; 3.9)	**0.01** [2]	n = 18