Received: 21 March 2019 | First decision: 30 April 2019 | Accepted: 27 August 2019

DOI: 10.1111/apt.15504

AP&T Alimentary Pharmacology & Therapeutics WILEY

Safety of first year vaccination in children born to mothers with inflammatory bowel disease and exposed *in utero* to anti-TNFα agents: a French nationwide population-based cohort

Maxime Luu[1,2] | Eric Benzenine[3] | Alan Barkun[4] | Muriel Doret[5] | Christophe Michiels[6] | Thibault Degand[6] | Catherine Quantin[3,7] | Marc Bardou[1,2]

[1]Clinical Investigation Center (INSERM 1432), Dijon - Bourgogne University Hospital, Dijon, France

[2]UFR Sciences Santé, Université Bourgogne Franche-Comté, Dijon, France

[3]Biostatistics and Bioinformatics Department, Dijon Bourgogne University Hospital, Dijon, France

[4]The McGill University Health Centre, Montreal General Hospital, McGill University, Montreal, Canada

[5]Hôpital Femme-Mère-Enfant Service de Gynécologie Obstétrique, Bron, France

[6]Division of Gastroenterology, Dijon Bourgogne University Hospital, Dijon, France

[7]Biostatistics, Biomathematics, Pharmacoepidemiology and Infectious Diseases (B2PHI), UVSQ, Institut Pasteur, Université Paris-Saclay, INSERM, Paris, France

Correspondence
Dr. Maxime Luu, CIC 1432 - CHU Dijon Bourgogne, 14, rue Gaffarel, BP 77908, 21079 Dijon Cedex, France.
Email: maxime.luu@chu-dijon.fr

Funding information
Agence Nationale de la Recherche, Grant/Award Number: ANR-15-CE36-0006-01; European Union - European Fund for Regional Development (FEDER) and the "Conseil Régional de Bourgogne Franche Comté", Grant/Award Number: LUU-AOI-2016

Summary

Background: Children born to mothers with IBD may be exposed to anti-TNFα agents antenatally. Current European guidelines recommend postponing live vaccines until after 6 months of life in this population. Data on the safety of live vaccines administration in the first year of life of these children are sparse with one reported fatality following bacillus Calmette-Guerin (BCG) administration.

Aims: To describe the use and safety of vaccines administered in children born to mothers with IBD and exposed antenatally to anti-TNFα agents

Methods: Data from children born to mothers with IBD between 2013 and 2014 were collected retrospectively from the French Health Insurance Database. Vaccines recommended before or at 1 year of age were considered.

Results: Among 4741 children, 670 (14.1%) were exposed to anti-TNFα agents antenatally, with concomitant thiopurines in 16.0% (n = 107) and steroids in 19.3% (n = 214). Among these 670 children, 315 (47%) were exposed up to delivery. Exposed children were less likely than non-exposed to receive BCG (88/670, 13.1% vs 780/4071, 19.2% respectively, $P < .05$) and received it later in life (months, mean ± SD, 4.3 ± 3.9 and 2.4 ± 2.9 respectively, $P < .001$). In exposed children, 64/88 (73%) received BCG vaccination before 6 months of age, but with no BCG-related severe adverse event observed during the first year. Uptake of other vaccines recommended before 6 months was above 85% in both groups.

Conclusion: In children exposed antenatally to anti-TNFα agents, vaccinations are often not postponed in keeping with the recommendations, but no BCG-related severe adverse events were reported in children vaccinated before 6 months of life.

The Handling Editor for this article was Professor Jonathan Rhodes, and it was accepted for publication after full peer-review.

1 | INTRODUCTION

Control of IBD activity at the beginning of, and throughout pregnancy is essential to avoid maternal and fetal complications.[1-4] Still, the benefit-to-treat with TNFα antagonists (anti-TNFα) for the mother needs to be weighed in light of safety considerations for the fetus. This is particularly important as infliximab and adalimumab are both very efficiently transported across the placental barrier starting in the second and third trimesters via a FcRN receptor-mediated mechanism.[5,6] Pregnancy itself modulates the pharmacokinetics and exposure of anti-TNFα therefore leading to significant levels in cord blood and in infants at birth. Several studies showed median levels of infliximab and adalimumab, in children at birth that are on average one-and-a-half times higher than in their mothers.[7-10]

Julsgaard et al reported that children born to mothers exposed to infliximab may need up to 12 months to clear the drug from their system.[9] Of marked interest, these authors also reported that the mean half-lifes of infliximab and adalimumab were respectively 3.7 and 2 times longer in infants than in non-pregnant adults.

The initial precautionary approach had been to avoid anti-TNFα agents during pregnancy, or at least to stop their use during the last trimester, but reassuring data from exposed pregnancies now support the use of these medications throughout pregnancy despite fetal exposure.[10,11]

According to the World Health Organization (WHO), avert an estimated 2-3 million deaths yearly. Even though timing of vaccination and target populations vary between national guidelines, the following vaccines are recommended by the WHO in the first year of life[12]: Bacillus Calmette-Guerin for tuberculosis (BCG), Diphtheria-Tetanus-Poliomyelitis (DTP), Pertussis, Haemophilus Influenzae B (HiB), Hepatitis B virus (HBV), Pneumococcus, Rotavirus, Meningococcus C and Measles-Mumps-Rubella (MMR). Vaccination is a current debate in France in a growing social distrust towards vaccines. In 2007, French authorities changed mandatory BCG vaccination for all children into a strong recommendation to vaccinate only children considered at high risk of tuberculosis. The first administration of MMR vaccine is at 1 year old. The Reference Center on Teratogenic Agents (Centre de Référence sur les Agents Tératogènes - CRAT) considers children exposed *in utero* to anti-TNFα as immunosuppressed during the 6 months following the last maternal administration of anti-TNFα. Consequently, when exposure to anti-TNFα is known, BCG vaccination is contra-indicated during this period of immunosuppression status.[13]

There exists controversy as to the safety of live vaccines administered in early childhood to the children of mothers exposed to anti-TNFα during pregnancy, but data are sparse. European and North American guidelines recommend postponing the use of live vaccines until 6 months post-delivery,[15,16] but given the estimated infliximab clearance, some have suggested that live vaccines should not be given to children under one year of age unless benefits of a quiescent IBD outweigh the possible increased risk of vaccination-induced infections.[9,17] Even though no serious complications were observed in 15 children who received the BCG vaccination within 1 week of birth, there is at least one reported fatality due to disseminated BCG infection in an infant who received a BCG vaccination at 3 months of age and whose mother had been taking infliximab for Crohn's disease during pregnancy.[18] In light of conflicting recommendations and sparse safety data, we aimed to (a) describe the outcomes in children exposed *in utero* to anti-TNFα who were vaccinated during their first year of life and (b) assess the appropriateness of physicians' vaccine practices during the first year of life in light of current recommendations.

2 | MATERIAL AND METHODS

2.1 | Study design and data source

The source of data and the extraction protocol have already been described previously.[11] In brief, we extracted data from an observational retrospective French cohort of 11 275 pregnant women with a diagnosis of IBD and their children during the first year of life from the French Health Insurance database (Système National des Données de Santé). SNDS is the French national information system, formerly called SNIIRAM (Système Inter Régimes d'Assurance Maladie), that contains individual, exhaustive and linkable but anonymous data on health expenditures for about 87% of the French population. Each hospital stay is prospectively implemented in the SNDS, and quality of the SNDS database is ensured through yearly monitoring, recent validation and epidemiological studies.[19-21] It aggregates data from: (a) the hospital discharge abstract database (Programme de Médicalisation des Systèmes d'Informations, PMSI), which collects principal and associated diagnoses (secondary events and current comorbidities), encoded using the International Classification of Diseases, 10th revision (ICD-10), and procedures performed during hospital stays using the common classification system for medical procedures (Classification commune des actes médicaux, CCAM); (b) the database containing all prescriptions for expensive drugs fully reimbursed by the national health insurance, Common Dispensing Units (UCD for Unités de Dispensation Communes,) such as anti-TNF, in order to ensure equal access to medical care, (c) the codes for long-duration diseases (ALD for Affection de Longue Durée) that give access to full coverage of health expenditures by the national health insurance scheme (d) the reimbursement data for out-of-hospital drug purchases with the Presentation Identifier Code (CIP for Code Identifiant de Présentation), such as vaccines as well as drugs such as steroids and thiopurines (azathioprine and 6-mercaptopurine). Our study spanned a 36-month period extending from January 1st, 2013 to December 31st, 2015. All children with available data on vaccine dispensation with at least 1 year of follow-up were included (ie born before January 1st, 2015). This study was conducted in accordance with the Declaration of Helsinki.

2.2 | Variables of interest

Vaccines were retrieved using the reimbursement data for out-of-hospital drug purchases with the delivery identification codes (Code

Identifiant de Présentation, CIP) detailed in Table S1. We considered all vaccines recommended during the first year of life, including (BCG DTP, pertussis, HiB, HBV, pneumococcus, meningococcus C and MMR). The French vaccination schedule for infants during their first year is given in Table S2. Time of injection was assumed to be the date of out-of-hospital dispensation in retail pharmacies. Severe complications related to live vaccines were screened in the SNDS using specific ICD-10 codes: Y58.0 (adverse events related to BCG vaccination), A15-A19 (tuberculosis), M49.0 (vertebral tuberculosis), and M90.0 (bone tuberculosis) for BCG complications, and B05 (measles), B06 (rubella) and B26 (mumps) for MMR vaccines. Community acquired infections and infections requiring hospitalization were identified using ICD-10 codes detailed in a previous article.[11] Third trimester of pregnancy was assumed to start at 26 weeks gestation (ie. 28 weeks of amenorrhea).

2.3 | Statistical analysis

Descriptive univariable comparisons were conducted for the characteristics of pregnancies of children exposed to anti-TNFα *in utero* vs unexposed infants. Qualitative variables were tested using χ^2 or Fisher's exact test, as appropriate. Continuous variables were described as means with standard deviations and compared using Student's tests or non-parametric Mann-Whitney tests after the assessment of respective distributions using the Shapiro-Wilk test. Subgroup descriptive analyses were performed in the subgroup of children vaccinated for BCG, and children exposed solely to thiopurines. A sensitivity analysis including all children exposed to anti-TNFα *in utero*, regardless of their vaccine data, was then performed to search for any BCG related complication.Analyses were performed with the use of SAS v9.4 software (SAS Institute, Cary, NC, USA), and a *P*-value under .05 was considered significant for all tests.

3 | RESULTS

Characteristics of the pregnancies are described in Table 1. A proportion of 14.1% (670/4,741) children with available data on vaccination (Figure 1) were exposed to anti-TNFα *in utero*, mostly to infliximab (51.9%) or adalimumab (46.1%). Nearly two-thirds (412/670, 61.5%) of the children exposed to anti-TNFα were exposed up to the third trimester (≥26 weeks gestation); and 315/670 (47.0%) were throughout the pregnancy. Anti-TNFα-treated mothers were younger (29.5 ± 4.4 years vs 31.0 ± 4.8 years; $P < .001$) and more likely to have Crohn's disease (90.0% vs 61.5%; $P < .001$) than mothers not receiving anti-TNFα. Anti-TNFα-treated and untreated mothers reported similar levels of thiopurine use during pregnancy, whereas steroid use was more frequent in anti-TNFα-treated mothers. (Table 1) Infection rates were similar between children exposed and not exposed to anti-TNFα *in utero* for infections requiring hospitalizations (9.1% vs 9.4% respectively, $P = .83$) or community acquired infections (50.8% vs 53.2% respectively, $P = .24$). (Table 2).

TABLE 1 Comparison of the characteristics of the pregnancies exposed and not exposed to anti-TNFα agents (n=4741)

	Exposed to anti-TNFα during pregnancy (N = 670)	Not exposed to anti-TNFα during pregnancy (N = 4071)	*P*-value[a]
Mother's characteristics			
Age at pregnancy (y)	29.5 (4.4)	31.0 (4.8)	<.001
Crohn's disease	603 (90.0)	2571 (63.2)	<.001
Pregnancy characteristics			
Gestational age at birth (wk)			.019
<2	1 (0.2)	0 (0.0)	
26-36	118 (17.6)	634 (15.6)	
>37	551 (82.2)	3437 (84.4)	
Pregnancy rank			.55
1	514 (76.7)	2965 (72.8)	
2	141 (21.0)	995 (24.4)	
3+	15 (2.3)	111 (2.8)	
Treatments during pregnancy			
Anti-TNFα agents			
Infliximab	356 (51.9)		
Adalimumab	317 (46.1)		
Certolizumab pegol	5 (0.8)		
Golimumab	1 (0.2)		
Time of last exposure to Anti-TNFα (wk)			
<12	84 (12.5)	-	
≥12 and <26	174 (26.0)	-	
≥26	412 (61.5)	-	
Whole pregnancy[b]	315 (47.0)	-	
Thiopurines	107 (16.0)	639 (15.7)	.86
Steroids	214 (19.3)	456 (12.6)	<.001

Results are expressed as mean (SD) or number (%).
Abbreviation: WD, weeks of development.
[a]Calculated with chi-square test.
[b]Last dose within the last 4 wk of pregnancy. Total sums may not attain 100% due to rounding.

3.1 | Administration of live vaccines

Figure 2 displays the age at which children received their initial injection of recommended vaccines, and Table 3 shows vaccination coverage. Anti-TNFα exposed children were significantly less likely to be vaccinated against tuberculosis than unexposed children (13.1% vs 19.2% respectively, $P < .001$), and received BCG later in life (mean ± SD, 4.3 ± 3.9 months and 2.4 ± 2.9 months in exposed vs unexposed, respectively; $P < .001$) In both anti-TNFα-exposed and unexposed infants, BCG vaccination was mostly administered before 6 months of age (64/88, 73%, and 728/780, 93% respectively). Among the 88 exposed infants who received BCG, 38 (43.2%) had

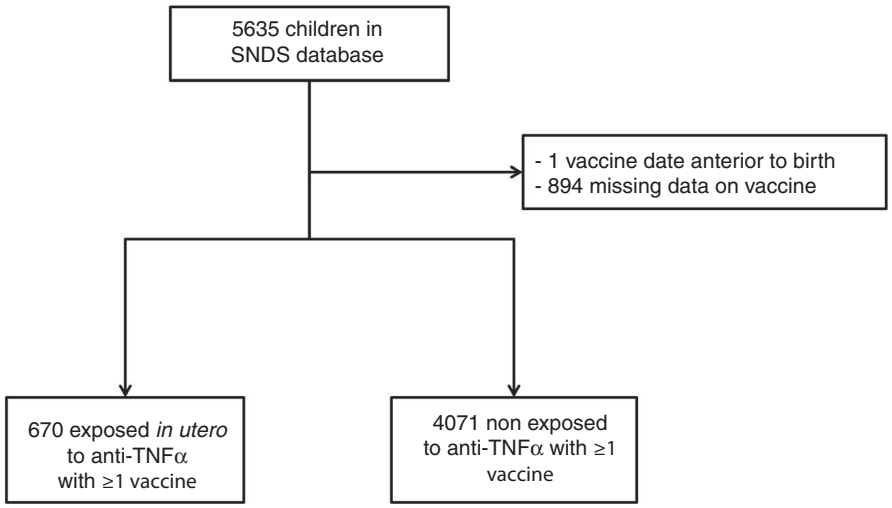

FIGURE 1 Flow chart

TABLE 2 Infectious outcomes in children vaccinated (N = 4741) during the first year of life

	Exposed to anti-TNFα during pregnancy (N = 670)	Not exposed to anti-TNFα during pregnancy (N = 4071)	*P*-value[a]
Infections requiring hospitalization	61 (9.1)	384 (9.4)	.83
General	25 (3.7)	131 (3.2)	.48
Digestive and hepatic	18 (2.7)	84 (2.1)	.31
Neurologic	—	11 (0.3)	.38
Skin	2 (0.3)	20 (0.5)	.76
Respiratory tract	36 (5.4)	188 (4.6)	.37
Ear-Nose-Throat	2 (<0.1)	22 (0.5)	.19
Perinatal	20 (3.0)	138 (3.4)	.64
Genito-urinary	8 (1.2)	52 (1.3)	1.00
Parasitic	—	2 (0.1)	1.00
Community infections	340 (50.8)	2165 (53.2)	.24

Results are expressed as number (%).
[a]Calculated with chi-square test or Fisher exact test.

been exposed throughout pregnancy (Table 4). The anti-TNFα was infliximab and adalimumab in 39 and 47 pregnant women respectively, the remaining 2 pregnant women received infliximab followed by adalimumab.

No case of disseminated BCG infection was reported during the first year amongst the 88 anti-TNFα-exposed children who received this live vaccine; the community acquired infection rate was similar when compared to non-exposed children vaccinated against BCG (60.2% vs 49.7%, *P* = .07). The time of initial BCG vaccine administration was similar for children exposed to anti-TNFα agents throughout pregnancy and those whose mothers stopped anti-TNFα before 26 weeks gestation (mean ± SD 4.6 ± 4.2 months vs 3.7 ± 3.4 months, respectively; *P* = .299). The same proportion of anti-TNFα exposed and non-exposed children received MMR vaccination (77.9% vs 79.1%, respectively; *P* > .05). The first injection of the MMR vaccine was generally administered according to recommendations in both groups, around 1 year of age (mean ± SD 13.4 ± 3.3 months in exposed vs 13.2 ± 2.7 months for unexposed infants, *P* = .467). Twelve exposed children were vaccinated against MMR before 9 months and three before 6 months (at 1, 2 and 4 months). No severe MMR infections were reported in any of these children.

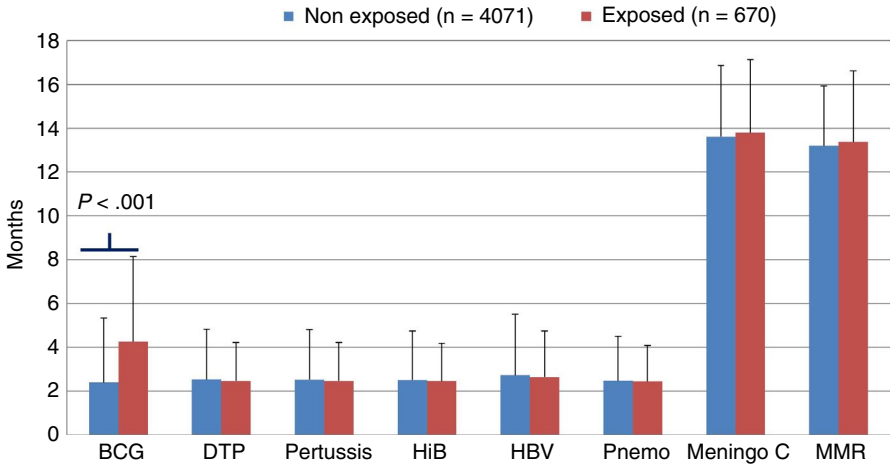

FIGURE 2 Time of first injection (mean ± SD) for recommended vaccines. BCG, Bacillus Calmette-Guerin (tuberculosis); DTP, diphtheria-tetanus-poliomyelitis; HiB, Haemophilus Influenzae B; HBV, Hepatitis B virus; pneumo, pneumococcus; meningo C, meningococcus C; MMR, measles-mumps-rubella

TABLE 3 Vaccine coverage in children during their first year of life (n = 4741)

	Exposed to anti-TNFα during pregnancy (N=670)	Non exposed to anti-TNFα during pregnancy (N=4071)	*P*-value[a]
Vaccinations			
BCG	88 (13.1)	780 (19.2)	<.001
HBV	603 (90.0)	3613 (88.8)	NS
HiB	645 (96.3)	3922 (96.3)	NS
MMR	522 (77.9)	3221 (79.1)	NS
Meningo C	420 (62.3)	2490 (61.2)	NS
DTP	649 (96.9)	3954 (97.1)	NS
Pertussis	649 (96.9)	3949 (97.0)	NS
Pneumococcus	648 (96.7)	3893 (96.7)	NS

Results are expressed as number (%).
BCG, Bacillus Calmette-Guerin (tuberculosis); DTP, diphtheria-tetanus-poliomyelitis; HiB, Haemophilus Influenzae B; HBV, hepatitis B virus; pneumo, pneumococcus; meningo C, meningococcus C; MMR, measles-mumps-rubella; NS, non-significant.
[a]Calculated with chi-square test.

3.2 | Administration of inert vaccines

Vaccine coverage for recommended inert vaccines during the first 6 months of life (DTP, pertussis, HiB, pneumococcus) was similar and above 95% in each group (Table 3). HBV vaccine coverage was almost equal and up to 90% in both groups (90% in anti-TNFα exposed vs 88.8% in unexposed infants, *P* = .379). Time of first injection for all those vaccines did not differ between anti-TNFα exposed and unexposed infants.

Meningococcus C vaccine was administered in the same proportion of anti-TNFα exposed and unexposed children (62.3% vs 61.2%, respectively; *P* > .05). It was administered around the recommended age of one year in all children (mean ± SD, 13.8 ± 3.3 months vs 13.6 ± 3.2 months in exposed and unexposed).

4 | DISCUSSION

The current cohort of 670 children born to mothers with IBD exposed to anti-TNFα during pregnancy is, to our knowledge, the largest reported to date. The cohort includes 88 (13.1%) infants vaccinated against tuberculosis and 522 (10.9%) against MMR, among which 38 (43.2%) and 241 (46.2%) respectively were exposed to anti-TNF agents *in utero* up to birth. After one year of follow up no cases of severe adverse events associated with any of the live vaccines had been identified.

Because infliximab clearance requires up to 12 months in children born to exposed mothers, Julsgaard et al[9] recommended that live vaccines be avoided during the first year of life, unless drug clearance has been confirmed with blood tests. A correspondence by Seow supported Julsgaard et al's findings,[17] even if the accompanying editorial nuanced the clinical significance of a level of 0.03 mg/

TABLE 4 Time of last exposure (number of weeks before delivery) to anti-TNFα *in utero* in children vaccinated against BCG (n = 88)

	Exposed children vaccinated against BCG (n = 88)	Exposed children vaccinated against BCG before 6 mo of age (n = 64)
>12 wk before delivery	44 (50.0)	35 (54.7)
Between 3 and 2 mo before delivery	3 (3.4)	2 (3.1)
12th to11th week	3 (3.4)	2 (3.1)
11th to 10th week	—	—
10th to9th week	—	—
9th to 8th week	—	—
Between 2 and last month before delivery	1 (1.1)	1 (1.6)
8th to 7th week	—	—
7th to 6th week	—	—
6th to 5th week	1 (1.1)	1 (1.6)
5th to 4th week	—	—
within last month before delivery	40 (45.5)	26 (40.6)
4th to 3rd week	—	—
3rd to 2nd week	1 (1.1)	1 (1.6)
2nd to last week	1 (1.1)	—
within last week	—	—
exposed at delivery	38 (43.2)	25 (39.1)

Note: Results are expressed as number (%).

mL observed in 1 infant at 12 months of age.[22] El-Matary argued against postponing live vaccines until after the first year of life as it may have major repercussions, especially in countries where the vaccines for measles alone or measles, mumps, and rubella are recommended between 9 and 15 months of age.[23] Another point going against postponing vaccination is the pathophysiology of paediatric tuberculosis. The earlier the primary infection is, the higher the risk of tuberculosis disease is. Half of children infected during their first year evolve to a tuberculosis disease, with a proportion of 4 pulmonary presentations for 1 disseminated disease. This risk falls down to 25% within the second year of life.[24] Overall, children under 5 years old account for 80% of paediatric tuberculosis mortality.[25]

Moreover, in countries with access to biotherapies and a high tuberculosis incidence in children, such as India or China,[26] delaying BCG vaccination may induce avoidable tuberculosis infections, although difficult to quantify, since data are mostly published aggregated in age classes to harmonize with the risk classes in the WHO tuberculosis action plan. In high burden countries, estimation is challenging but mathematical models predict that around 175 000 children under 5 years old are infected each year in India for example.[27] In France, a mean of 130 children aged 0-4 years old have been infected by tuberculosis each year over the last decade, representing roughly 3% of total reported cases, like in the US, all non-fatal. However, annual reports show a worrying increase of cases with 180 new cases reported in France in 2017, unprecedented since at least 2002.[28] In the US, an incidence rate of 2.8 per 100 000 population in children < 1 year old was estimated in 2017, far below India's one (42 per 100 000 population in the children ≤2 years old).[15,29,30] The level of risk between countries, and between socio-economic groups within countries, will have to be more precisely considered when issuing futures recommendations.

Relying on plasma levels of anti-TNFα sounds like a safe alternative, but does not reflect clinical practice nor necessarily correlate with clinical event as complex factors determine the relationship between exposure to this drug and response.[31] It seems thus all the more relevant to issue recommendations based on clinical outcomes more than detectable levels of drugs.

TNF-alpha is crucial for granuloma formation and anti-tuberculous immunity, and the majority of cases of disseminated BCG have been reported in immunocompromised hosts. Nevertheless, in the case series reported by Rezai et al,[32] 6 out of 15 cases (40%) of disseminated BCG infections after vaccination occurred in immunocompetent children. Therefore, even though the case of disseminated BCG reported by Cheent et al[18] deserves our attention, a single case report does not support causality or justify adoption of binding recommendation of such a magnitude, especially in light of the aforementioned benefits and risks. Our report on 88 children vaccinated with BCG after *in utero* exposure to anti-TNFα, and more importantly, with 38 children exposed up to birth, suggest this vaccination is reasonably safe, as did the much smaller cohort published by Bortlik et al[33] We have no data here to suggest a different safety profile for live vaccines according to the use of a non-pegylated (infliximab) or pegylated (adalimumab) anti-TNFα, but clinicians may have a better perception of safety to vaccine children born to mothers treated with the pegylated form as adalimumab clearance is significantly higher than for infliximab.[9]

We have shown that even though the first BCG vaccine injection was given later in children born to anti-TNFα exposed than unexposed mothers (mean: 4.3 months and 2.4 months, respectively), 73% of injections did not respect the current guidelines of delaying live vaccinations until the age of 6 months for anti-TNFα exposed children. It is not surprising, as healthy children are usually followed by their pediatrician or general physician rather than their mother's IBD specialist. Information on *in utero* exposure to anti-TNFα may have been not timely transmitted. It is of crucial to ensure the sharing of medical data between IBD specialists and other healthcare professionals, and individualized maternal counselling regarding risks and benefits of live vaccination, as tuberculosis incidence surged by 10% in France between 2015 and 2017, with a maximum of 24.3% increase in Paris area, partly explained by imported cases from migrants coming from endemic countries. The perceived low vaccination rate in our cohort reflects in fact that in France, BCG vaccination is no longer mandatory for children but is strongly recommended at birth in selected groups of children at increased risk of tuberculosis infection, such as those living in the Paris area and in some French overseas departments. We were not able to determine the location of children born to mothers exposed to anti-TNFα agents and vaccinated before 6 months of age. Our data nevertheless suggest that when exposure is known, physicians may take into account the interaction between anti-TNFα exposure and live vaccine safety during the first months of life, but that they do not refer to guidelines when planning the vaccination schedule of these children.

Completeness and accuracy in detecting the events of interest are major validation criteria for studies based on medico-administrative data. We used the date of vaccine purchase as a proxy for the vaccination date. This approach was validated, with the SNDS database, in previously published large vaccine safety assessment studies.[19,34,35] Assessing the risk of out-of-hospital events such as minor infections is a challenge, as their adjudication can be only performed using reimbursement information of anti-infectious drug dispensation. Consequently, we here focused on severe BCG complications, including both disseminated tuberculosis and specific locations, such as bony or ganglionic sites, because the codes used in our search strategy correspond to a specific or single diagnosis, with exhaustive information as their presence modify the patient journey's cost, thus hospital funding. General symptoms (fever, pain, fatigue), which are frequent reasons of consultation, can't be rigorously linked to the vaccines through codes, and are far less well provided as they are not “cost-modifiers”.

Vaccination data were unavailable for nearly 16% (n = 932) of children in the SNDS database. Among them, 131 (14%) of children were exposed *in utero* to anti-TNFα, with 82 (62%) treated during the last trimester. This might correspond to children vaccinated in mother-and-child care centers (Protection Maternelle et Infantile, PMI), which are public medical institutions for pre-natal and pediatric care up to 6 years of age.[36] As medical consultation and vaccinations are

free of charge, and treatment provisions are part of a global budget for the PMI centers, no data on vaccines are collected in the health insurance database. It is thus likely that the number of children born to mothers exposed to anti-TNFα during pregnancy and vaccinated with BCG is higher than the 88 reported here. Nevertheless, as BCG complications are managed in hospital facilities and as tuberculosis is a disease whose declaration to the health authorities is mandatory in France, any BCG-related severe event would have been recorded in our database. A dedicated post-hoc search to explore this possibility yielded no diagnostic codes for BCG or MMR complications in any of these children for which data on vaccination were missing, strengthening the validity of our results. Our findings are similar to preliminary results from a recent French multicentric retrospective study that reported no adverse events following BCG vaccination in 33 children born to mothers exposed to anti-TNFα during pregnancy. Around half of these children (19/33, 57%) were vaccinated against BCG before 6 months of age.[37] Arguments in favor of the benefits of anti-TNFα throughout pregnancy are accumulating, making it likely that the proportion of children exposed to anti-TNFα *in utero* will continue to increase. This probability makes it all the more urgent to conduct large, prospective cohort studies to gather long term safety data on live vaccines in this population.

5 | CONCLUSION

This study, to our knowledge, presents safety data on the largest cohort of children born to IBD mothers exposed to anti-TNFα during pregnancy published to date. In children receiving BCG vaccination before 6 months of life after *in utero* exposure, no safety signal was observed, especially disseminated BCG infection. Nevertheless, physicians do not follow the current guidelines for postponing the administration of live vaccines. Our results add valuable safety data for the debate, and suggest a need to improve dissemination of guidelines to increase adherence of the clinicians. These guidelines will have to consider the disquieting epidemiological context that may be observed in several European countries, such as France, at least partly because of the increase in migration from high prevalence countries.

ACKNOWLEDGEMENTS

Declaration of personal interests: CM received lecture fees from MSD and Abbvie, invitations to congresses from MSD, Abbvie and Ferring. TD received lecture fees from AbbVie, invitations to congresses from Janssens, MB is an expert, and chairman of the committee for initial assessment on the risks and benefits of health products, at the French Medicines Agency (Agence Nationale de la Securité du Médicament et des Produits de Santé, ASNM). The remaining authors disclose no conflicts.

AUTHORSHIP

Guarantor of the article: ML.

Author contributions: ML designed the study, performed analyses, drafted manuscript. EB extracted, performed analyses, and critically revised the manuscript. MD critically revised the manuscript. CM critically revised the manuscript. AB critically revised the manuscript. TD critically revised the manuscript. CQ supervised data collection, and critically revised the manuscript. MB was the project initiator, designed the study, critically and extensively revised the manuscript. ML is the guarantor of the article. Patient consent: All data used in this study only contained anonymous patient records.

FUNDING INFORMATION

This study was supported by a grant from the French Ministry of Health (ANR-15-CE36-0006-01) and by the European Union - European Fund for Regional Development (FEDER) and the "Conseil Régional de Bourgogne Franche Comté" (LUU-AOI-2016).

ORCID

Maxime Luu https://orcid.org/0000-0002-9024-293X
Alan Barkun https://orcid.org/0000-0002-1798-5526

REFERENCES

1. Stephansson O, Larsson H, Pedersen L, et al. Crohn's disease is a risk factor for preterm birth. *Clin Gastroenterol Hepatol*. 2010;8:509-515.
2. Boyd HA, Basit S, Harpsoe MC, Wohlfahrt J, Jess T. Inflammatory bowel disease and risk of adverse pregnancy outcomes. *PLoS ONE*. 2015;10:e0129567.
3. Shand AW, Chen JS, Selby W, Solomon M, Roberts CL. Inflammatory bowel disease in pregnancy: a population-based study of prevalence and pregnancy outcomes. *BJOG*. 2016;123:1862-1870.
4. Kammerlander H, Nielsen J, Kjeldsen J, Knudsen T, Friedman S, Norgard B. The effect of disease activity on birth outcomes in a nationwide cohort of women with moderate to severe inflammatory bowel disease. *Inflamm Bowel Dis*. 2017;23:1011-1018.
5. Malek A, Sager R, Kuhn P, Nicolaides KH, Schneider H. Evolution of maternofetal transport of immunoglobulins during human pregnancy. *Am J Reprod Immunol*. 1996;36:248-255.
6. Palmeira P, Quinello C, Silveira-Lessa AL, Zago CA, Carneiro-Sampaio M. IgG placental transfer in healthy and pathological pregnancies. *Clin Dev Immunol*. 2012;2012:985646.
7. Seow CH, Leung Y, Vande Casteele N, et al. The effects of pregnancy on the pharmacokinetics of infliximab and adalimumab in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2017;45:1329-1338.
8. Mahadevan U, Wolf DC, Dubinsky M, et al. Placental transfer of anti-tumor necrosis factor agents in pregnant patients with inflammatory bowel disease. *Clin Gastroenterol Hepatol*. 2013;11:286–292.
9. Julsgaard M, Christensen LA, Gibson PR, et al. Concentrations of adalimumab and infliximab in mothers and newborns, and effects on infection. *Gastroenterology*. 2016;151:110-119.
10. de Lima A, Zelinkova Z, van der Ent C, Steegers EA, van der Woude CJ. Tailored anti-TNF therapy during pregnancy in patients with IBD: maternal and fetal safety. *Gut*. 2016;65:1261-1268.
11. Luu M, Benzenine E, Doret M, et al. Continuous anti-tnfalpha use throughout pregnancy: possible complications for the mother but not for the Fetus. A retrospective cohort on the French National Health Insurance Database (EVASION). *Am J Gastroenterol*. 2018;113:1669-1677.

12. World Health Organization. Recommendations for routine immunization for children. http://www.who.int/immunization/policy/immunization_tables/en/
13. Centre de Référence sur les Agents Tératogènes (CRAT). Exposition maternelle aux antiTNF-alpha. https://lecrat.fr/spip.php?page=article&id_article=429
14. Ministère des solidarités et de la santé. Calendrier vaccinal. 2019. https://solidarites-sante.gouv.fr/IMG/pdf/calendrier_vaccinal_mars_2019.pdf
15. van der Woude CJ, Ardizzone S, Bengtson MB, et al. The second European evidenced-based consensus on reproduction and pregnancy in inflammatory bowel disease. *J Crohns Colitis*. 2015;9:107-124.
16. Nguyen GC, Seow CH, Maxwell C, et al. The toronto consensus statements for the management of inflammatory bowel disease in pregnancy. *Gastroenterology*. 2016;150:734–757.e1.
17. Seow CH, Nguyen GC. "Just in Time": when is it safe to administer live vaccines to infants exposed to anti-tumor necrosis factor agents in utero? *Gastroenterology*. 2016;151:1249-1250.
18. Cheent K, Nolan J, Shariq S, Kiho L, Pal A, Arnold J. Case report: fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's disease. *J Crohns Colitis*. 2010;4:603-605.
19. Hanf M, Quantin C, Farrington P, et al. Validation of the French national health insurance information system as a tool in vaccine safety assessment: application to febrile convulsions after pediatric measles/mumps/rubella immunization. *Vaccine*. 2013;31:5856-5862.
20. Kirchgesner J, Beaugerie L, Carrat F, et al. Increased risk of acute arterial events in young patients and severely active IBD: a nationwide French cohort study. *Gut*. 2018;67:1261-1268.
21. Basson M, Mezzarobba M, Weill A, et al. Severe intestinal malabsorption associated with olmesartan: a French nationwide observational cohort study. *Gut*. 2016;65:1664-1669.
22. Kathpalia P, Kane S, Mahadevan U. Detectable drug levels in infants exposed to biologics: so what? *Gastroenterology*. 2016;151:25-26.
23. El-Matary W. Risk of attenuated live vaccines-induced infections in infants of mothers receiving anti-tumor necrosis factor agents for inflammatory bowel disease. *Gastroenterology*. 2016;151:1250.
24. Newton SM, Brent AJ, Anderson S, Whittaker E, Kampmann B. Paediatric tuberculosis. *Lancet Infect Dis*. 2008;8:498-510.
25. Dodd PJ, Yuen CM, Sismanidis C, Seddon JA, Jenkins HE. The global burden of tuberculosis mortality in children: a mathematical modelling study. *Lancet Glob Health*. 2017;5:e898-e906.
26. World Health Organization. Global tuberculosis report. 2017. http://apps.who.int/iris/handle/10665/259366
27. Dodd PJ, Gardiner E, Coghlan R, Seddon JA. Burden of childhood tuberculosis in 22 high-burden countries: a mathematical modelling study. *Lancet Glob Health*. 2014;2:e453-e459.
28. Santé Publique France. Epidemiology of tuberculosis in France. 2017. https://www.santepubliquefrance.fr/maladies-et-traumatismes/maladies-et-infections-respiratoires/tuberculose/donnees/#tabs
29. Centers for Disease Control and Prevention. Tuberculosis – United States. 2018.
30. World Health Organization. Global Health Observatory data - Tuberculosis. 2017.
31. Adedokun OJ, Sandborn WJ, Feagan BG, et al. Association between serum concentration of infliximab and efficacy in adult patients with ulcerative colitis. *Gastroenterology*. 2014;147:1296-307.e5.
32. Rezai MS, Khotaei G, Mamishi S, Kheirkhah M, Parvaneh N. Disseminated bacillus calmette-guerin infection after BCG vaccination. *J Trop Pediatr*. 2008;54:413-416.
33. Bortlik M, Duricova D, Machkova N, et al. Impact of anti-tumor necrosis factor alpha antibodies administered to pregnant women with inflammatory bowel disease on long-term outcome of exposed children. *Inflamm Bowel Dis*. 2014;20:495-501.
34. Miranda S, Chaignot C, Collin C, Dray-Spira R, Weill A, Zureik M. Human papillomavirus vaccination and risk of autoimmune diseases: a large cohort study of over 2million young girls in France. *Vaccine*. 2017;35:4761-4768.
35. Hequet D, Pouget N, Estevez JP, Robain M, Rouzier R. Age impact on human papillomavirus vaccination in France in 2014: a study from the National Health Insurance Database. *Bull Cancer*. 2015;102:892-897.
36. Guthmann J-P, Desplanques L, Lévy-Bruhl D. Couverture vaccinale BCG chez les enfants nés après la suspension de l'obligation vaccinale et suivis dans les PMI de France. *Arch Pédiatrie*. 2010;17:1281–1287.
37. Bendaoud S, Gornet J, Pariente B, et al. Allaitement et vaccination par vaccins vivants chez des nouveau-nés exposés in-utero aux anti-TNFα: étude nationale multicentrique. JFHOD 2018 - CO113 [Internet]. https://www.jfhod.com/sites/www.jfhod.com/files/medias/jfhod_2018/documents/livreresume-jfhod2018_bd_vf.pdf

SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section at the end of the article.

How to cite this article: Luu M, Benzenine E, Barkun A, et al. Safety of first year vaccination in children born to mothers with inflammatory bowel disease and exposed *in utero* to anti-TNFα agents: a French nationwide population-based cohort. *Aliment Pharmacol Ther*. 2019;00:1–8. https://doi.org/10.1111/apt.15504