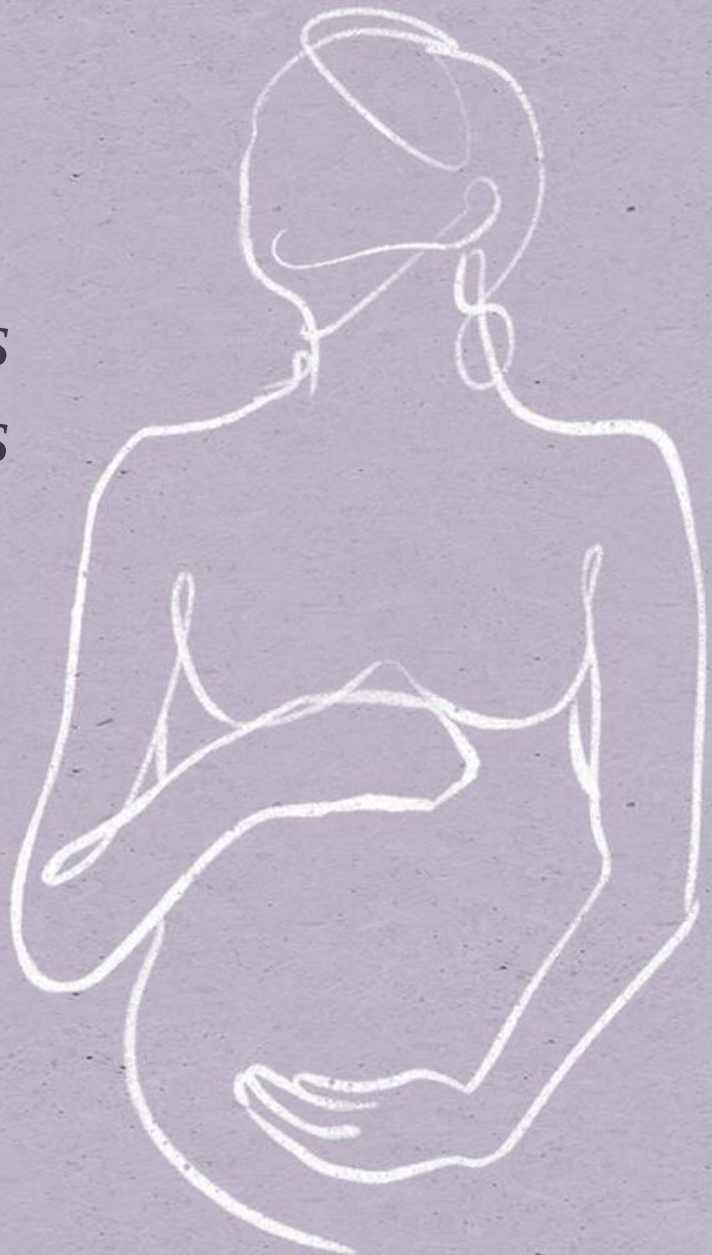
*Impacte **immunmològic** en **nounats** fills de mares amb **malalties inflamatòries** exposats a fàrmacs **biologics** durant l'**embaràs**: **calendari vacunal**?*

IV Diada Reumatològica - Societat Catalana de Reumatologia



Presenter	**Yiyi Luo, PhD**	**Email**	**yiyi.luo@sjd.es**
Affiliation	**H. Sant Joan de Déu**	**Date**	**April 4th, 2025**

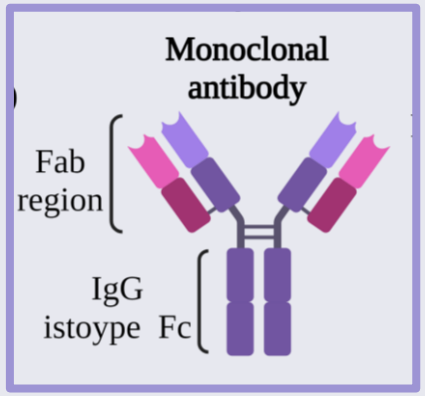
INTRODUCTION

To define the **safety** of Tumor necrosis factor inhibitor **(TNFi)** during **pregnancy:** from the **newborn's perspective**.

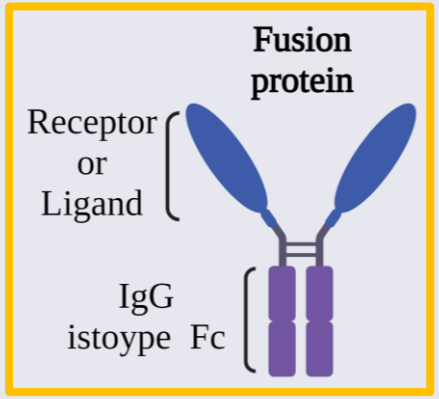
¿WHY?

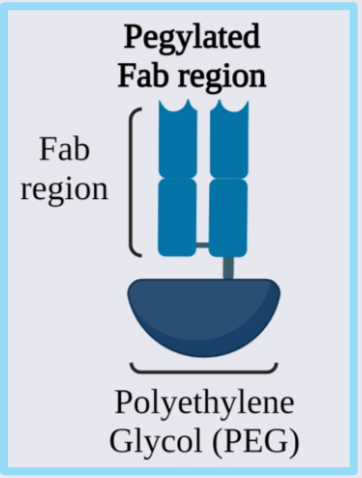
Generic name	Brand name	Structure
Adalimumab	Humira	IgG1 mAb
Infliximab	Remicade	IgG1 mAb
Golimumab	Simponi	IgG1 mAb
Etanercept	Enbrel	Fusion protein: IgG1 Fc + TNF receptor
Certolizumab Pegol	Cimzia	Pegylated protein

IgG1 isotype mAb



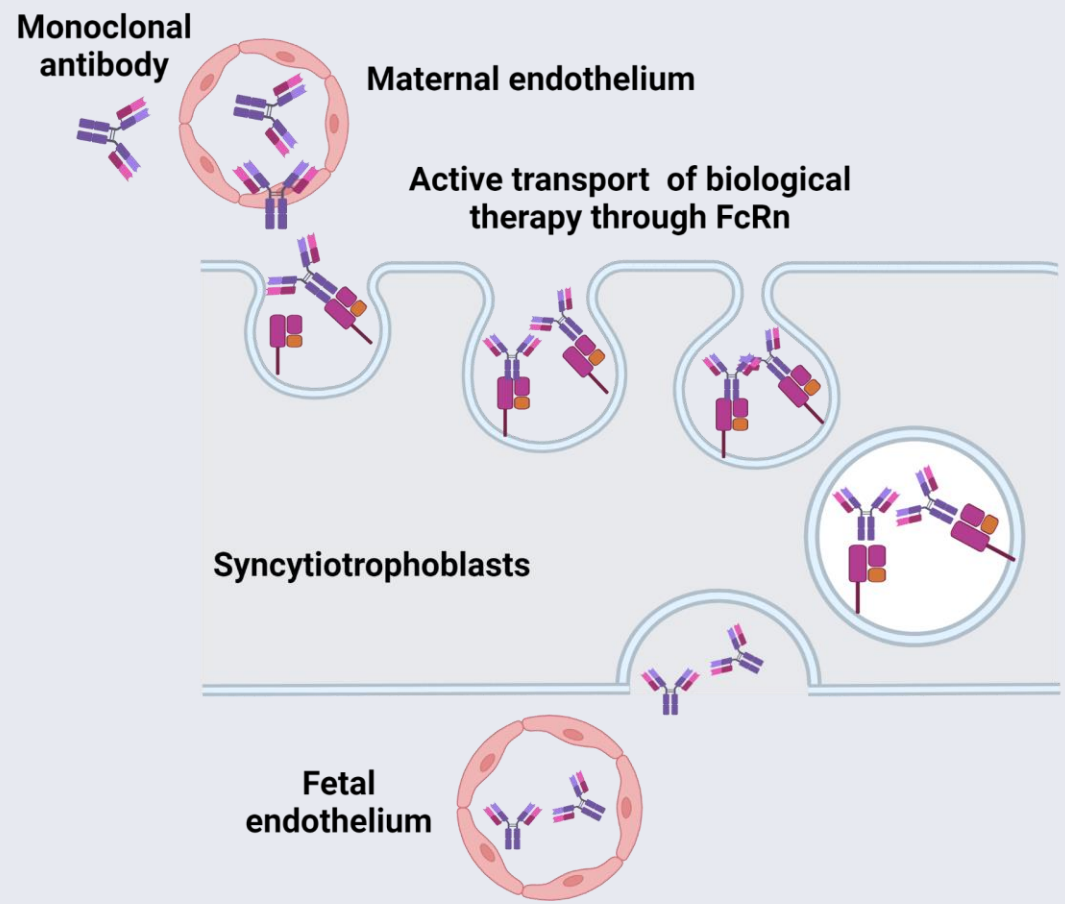
IgG1 isotype Fc





Chung et al. Korean J Intern Med. 2023; PMID: 35581954. *Lungaro et al. J Pers Med. 2023; PMID: 36836400.*

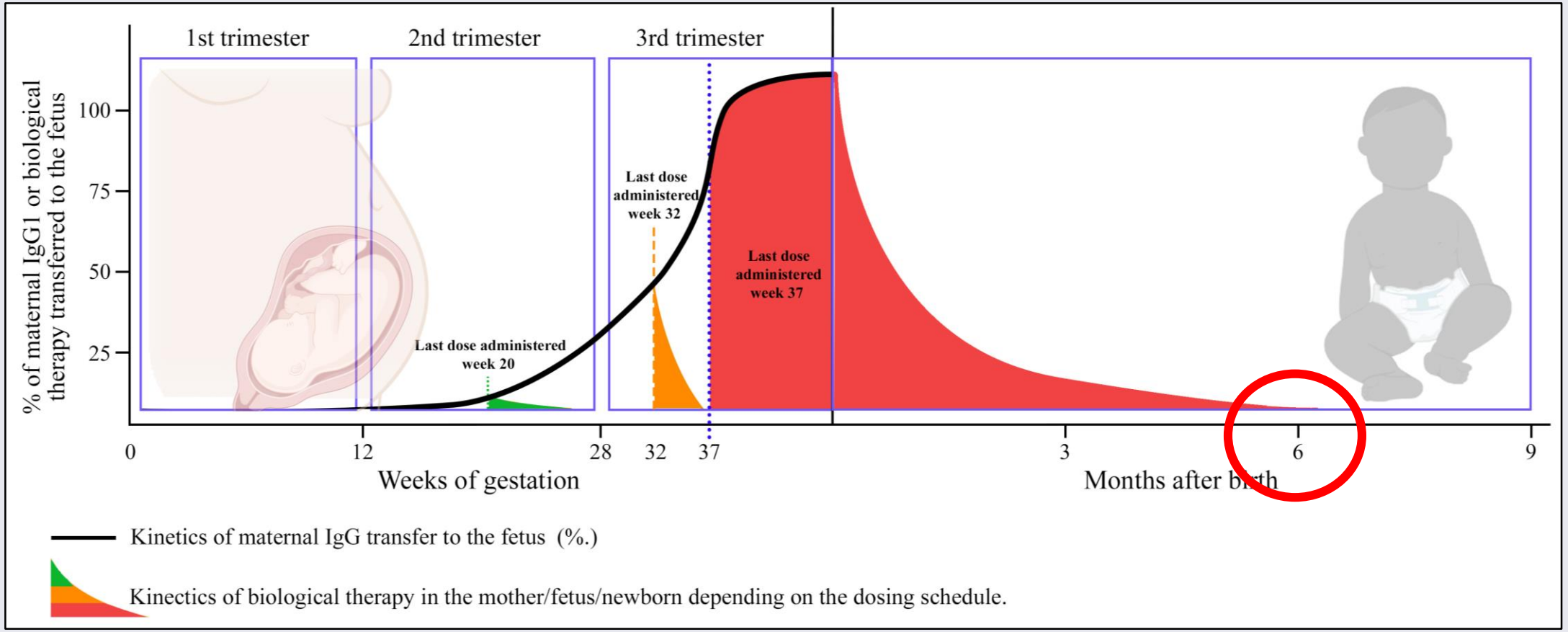
INTRODUCTION



This figure is original and created by Y. Luo in Biorender.com; PMID: 36825745

in Biorender.com; PMID: 36825745

INTRODUCTION



This figure is original and created by Y. Luo in Photoshop; PMID: 36825745

Esteve-Solé et al. Front Immunol. 2017; PMID: 28983301. *Julsgaard et al. Gastroenterology. 2016; PMID: 27063728.*

GUIDLINE RECOMMENDATIONS for in utero use of biological drugs:

Guidelines

British Society for Rheumatology guideline on prescribing drugs in pregnancy and breastfeeding: immunomodulatory anti-rheumatic drugs and corticosteroids

Mark D. Russell [1], Mrinalini Dey [2], Julia Flint [3], Philippa Davie [1], Alexander Allen [4], Amy Crossley [5], Margreta Frishman [6], Mary Gayed [7], Kenneth Hodson [8], Munther Khamashta [9], Louise Moore [10], Sonia Panchal [11], Madeleine Piper [12], Clare Reid [5], Katherine Saxby [13], Karen Schreiber [14,15,16], Naz Senvar [17], Sofia Tosounidou [18], Maud van de Venne [19], Louise Warburton [20], David Williams [21], Chee-Seng Yee [22], Caroline Gordon [23], Ian Giles [24,*]; for the BSR Standards, Audit and Guidelines Working Group [†]

Rheumatology 2023; PMID: 36318966.

The Toronto Consensus Statements for the Management of Inflammatory Bowel Disease in Pregnancy

Geoffrey C Nguyen [1], Cynthia H Seow [2], Cynthia Maxwell [3], Vivian Huang [4], Yvette Leung [5], Jennifer Jones [6], Grigorios I Leontiadis [7], Frances Tse [7], Uma Mahadevan [8], C Janneke van der Woude [9]; IBD in Pregnancy Consensus Group; Canadian Association of Gastroenterology

Nguyen et al. Gastroenterology. 2016; PMID: 26688268.

Recommendation

The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation FREE

Carina Götestam Skorpen [1, 2, 3], Maria Hoeltzenbein [4], Angela Tincani [5], Rebecca Fischer-Betz [6], Elisabeth Elefant [7], Christina Chambers [8], José da Silva [9], Catherine Nelson-Piercy [10], Irene Cetin [11], Nathalie Costedoat-Chalumeau [12, 13], Radboud Dolhain [14], Frauke Förger [15], Munther Khamashta [16], Guillermo Ruiz-Irastorza [17], Angela Zink [18], Jiri Vencovsky [19], Maurizio Cutolo [20], Nele Caeyers [21], Claudia Zumbühl [22], Monika Østensen [1, 2]

Annals of the Rheumatic Diseases. 2016; PMID: 26888948.

1. To ensure maternal **disease remission** during pregnancy.

2. The need to ensure the newborn to have the **minimal level** of drug as possible at **birth**.

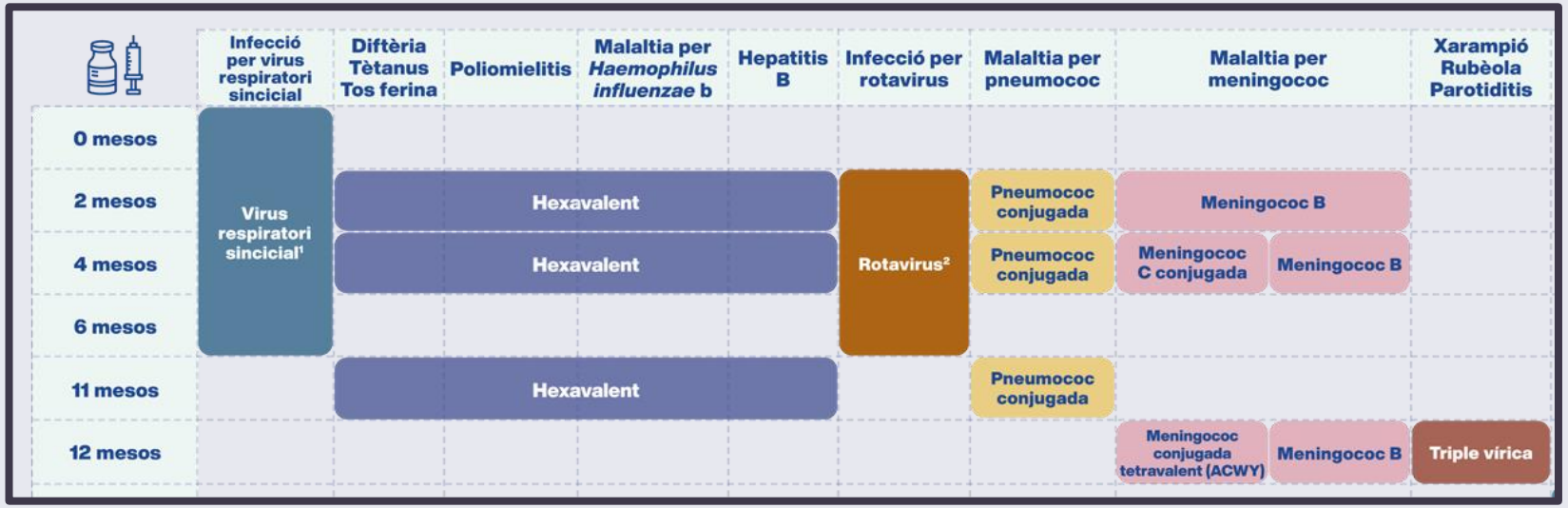
*3. To avoid the drug after **third trimester** of pregnancy.*

Specific recommendations are on the next page

4. Drug discontinuation is subject to ensuring remission of maternal disease activity.

GUIDLINE RECOMMENDATIONS – VACCINE SCHEDULE

Resum de l'exposició materna a biològics de la British Society for Rheumatology: PMID: 36318966	
Fàrmac	**Aturar**
CZP	Compatible **tot** l'**embaràs.**
IFX ADA GOL ETN	• IFX: **20** SG • ADA i GOL: **28** SG • ETA: **32** SG

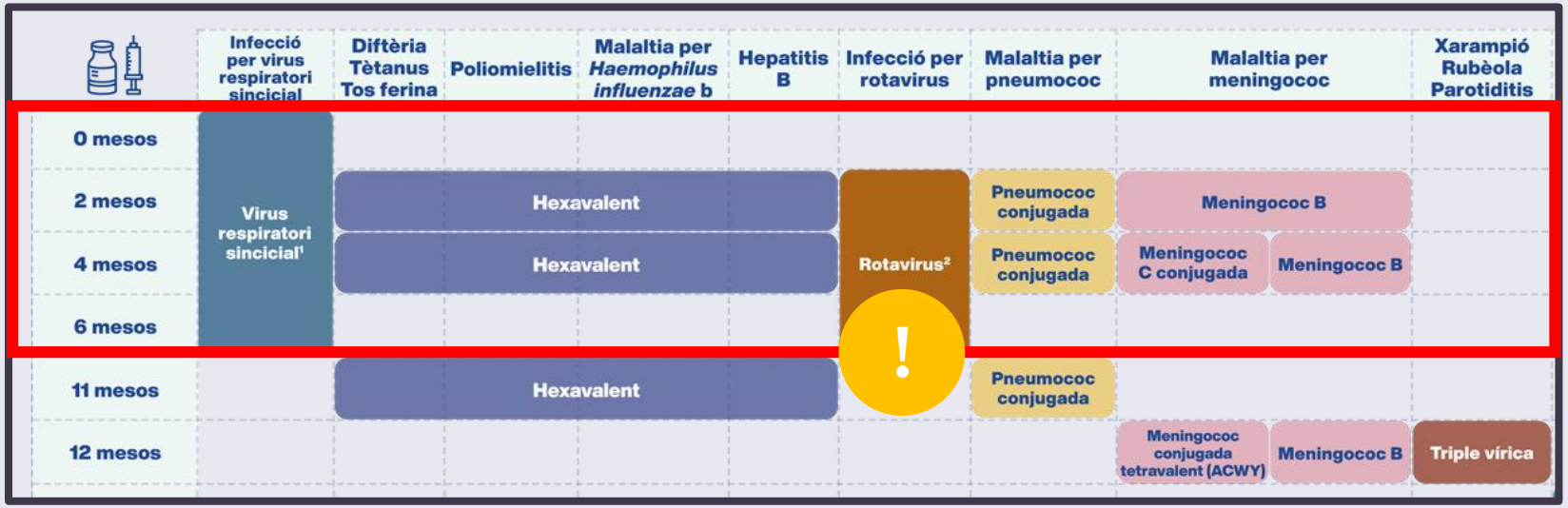


2025 - Calendaris de vacunacions i immunitzacions sistemàtiques from *canalsalut.gencat.cat*
Generalitat de Catalunya.

GUIDLINE RECOMMENDATIONS – VACCINE SCHEDULE

Resum de l'exposició materna a biològics de la British Society for Rheumatology: PMID: 36318966

Fàrmac	**Aturar**
IFX, ADA, GOL, ETN. *IL-1, ABA, BEL, IL-17, IL-12/23, RTX, IL-6.*	Exposició durant **3r trimestre.**

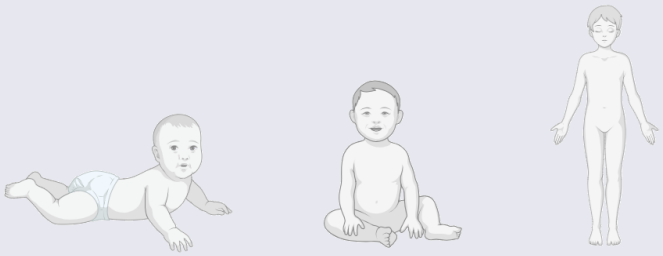


2025 - Calendaris de vacunacions i immunitzacions sistemàtiques from canalsalut.gencat.cat

CONCERNS

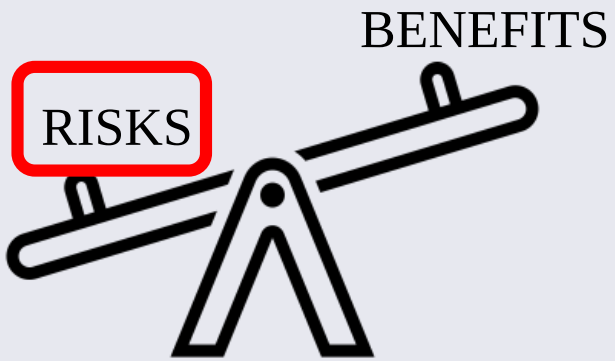
TNFi is an **immunomodulator** that **blocks** the action of the **cytokine TNF** → immune changes.

Long target-side effect: biological drugs with placental transfer capacity are not only **immunomodulating** the maternal immunity, but also the **fetal/neonatal immune system**.



Perinatal immunity is still **maturing**, any alterations during this critical period could have **long-term consequences** on **immune integrity** and **function** later in life.

Secondary immunodeficiency due to drug exposure ????

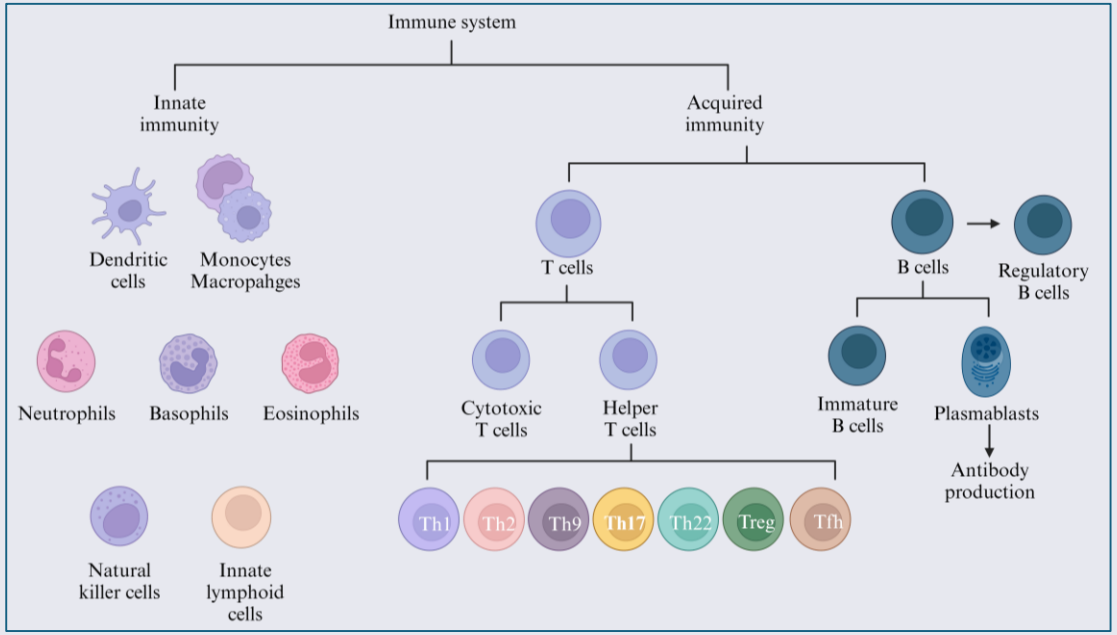


CONCERNS: lymphoid organogenesis

¿What elements are we concerned about?

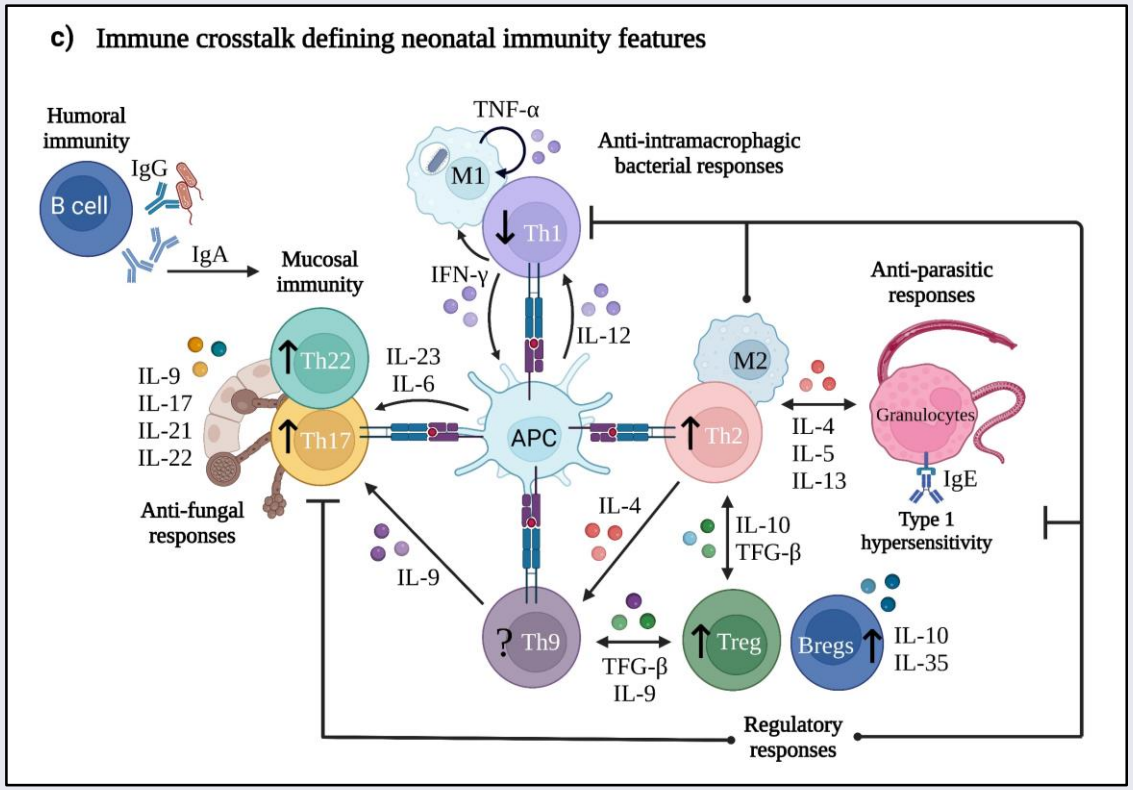
Lymphoid profile

TNF is a key cytokine for **lymphoid organogenesis** during early life.



This figure is original and created by Y. Luo in Biorender.com; PMID: 36825745

TNFi may affect the **immune responses balance**.



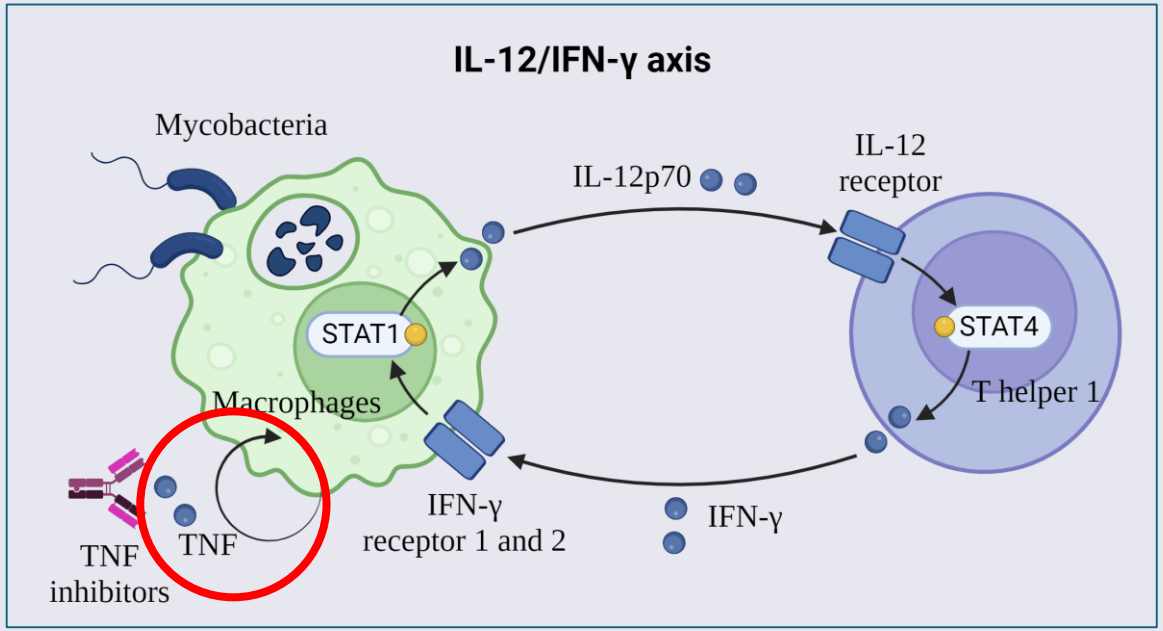
This figure is original and created by Y. Luo in Biorender.com; PMID: 36825745

CONCERNS: mycobacterial challenge

¿What elements are we concerned about?

Responses to Mycobacterial challenge

TNF plays a key role in the **IL-12/IFN-Ɣ** axis.
Mycobacterial elimination.



This figure is original and created by Y. Luo in Biorender.com; PMID: 36825745

SHORT REPORT

Case Report: Fatal case of disseminated BCG infection in an infant born to a mother taking infliximab for Crohn's Disease

Kuldeep Cheent [a], Jonathan Nolan [a], Sohail Shariq [a], Liina Kiho [b], Arabinda Pal [a], Jayantha Arnold [a,*]

Cheent et al. Journal of Crohn's and Colitis. 2010; PMID: 21122568.

If the newborn needs the BCG vaccine, consult a pediatrician-immunologist

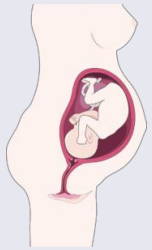
OUR PROJECT– STUDY DESIGN

FIS PI18/00223

MULTICENTER AND **MULTIDISCIPLINARY** STUDY (2014-2024)

SJD (IP); HCB; HVH

Rheumatologists
Gastroenterologists
Obstetricians
Paediatricians



Pregnant patients treated with TNFi:

- Rheumatic diseases (RMD)
- Inflammatory bowel diseases (IBD)

AFTER DELIVERY…

Immune follow-up

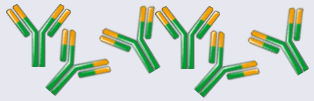
- Umbilical cord blood (at birth)
- Peripheral blood (at 3, 6 and 12 months)

Clinical follow-up

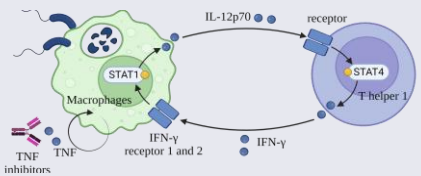
At 3, 6 12 months with paediatricians.

- Drug **clearance** in the newborn

- **T and B cell** maturation course



- **Humoral** immunity (levels of Ig)



- Integrity of **IL-12/IFN-γ axis** in response to mycobacterial challenge.

OUR PROJECT– COHORT

Table 1. Summary of the study cohort.

Maternal disease		Disease subgroups		In utero exposure to TNFi			Concomitant drug	
				Type of TNFi	N	TNFi during 3rd trimester of pregnancy		
RMD	23	RA	10	untreated	7	-	prednisolone	6
		JIA	6	CZP	11	Yes	hydroxychloroquine	2
		SpA	6				paracetamol (PRN)	1
		SAPHO	1	ETN	5	Yes	NSAID (PRN)	1
IBD	27	CD	19	ADA	16	Yes	prednisolone	2
		UC	8	IFX	11	Yes	azathioprine	5
							Oral mesalzine	1

***RA**: Rheumatoid arthritis*
***SpA**: Spondyloarthritis*
***JIA**: Juvenile idiopathic arthritis*
***SAPHO**:Synovitis-acne pustulosishyperostosis-osteitis*
***CD**: Chron diseases*
***UC**: Ulcerative colitis*

Study cohort: N = 50 pairs of mother-child.
Healthy control group: N = 30

We observed **no** case of **fetal death**.

The TNFi-exposed newborns did **not** present **congenital abnormalities** and had **normal pondostatural** and **neurological** development.

OUR PROJECT– DRUG LEVELS

At **birth**, all newborns exposed to **ADA/IFX** presented positive levels of drug.

The TNFi **drug** levels in the newborns **exceeded** those of the mother.

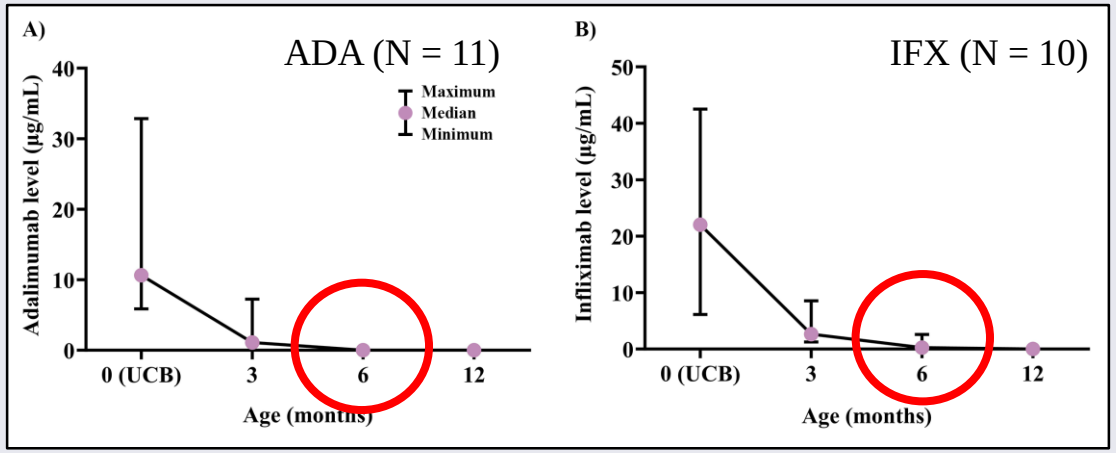
- Ratio ADA: UCB/maternal level = 1.05
- Ratio IFX: UCB/maternal level = 2.23

Drug **clearance** (mean half-life) in neonatal peripheral blood was **slower** than in the mother.

Mothers: 28 days **Newborns: 30.67 days**

Drug levels were detectable in infants until **6 months** of age.

Figure 1. ADA and IFX drug clearance in neonatal bloodstream.



Statistical significance < 0.05; Spearman correlation (r): low association 0.1-0.3; moderate positive association between 0.3-0.5; and strong positive association 0.5-1

OUR PROJECT– MAIN RESULTS.

TNFi with higher

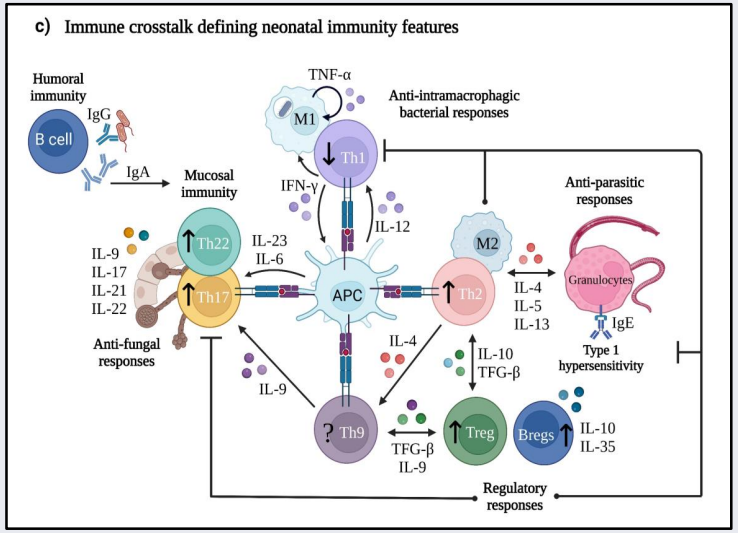
ADA/IFX-exposed s Untreated, ETN, CZP. Almost norm

B cell compartme l newborns and Untreated gr

Humoral immunity

- TNFi exposed
- Normal vaccin
- 6 newborns received **rotavirus** vaccine without adverse effects.

Immature T cell profile:
¿Immune cellular responses?

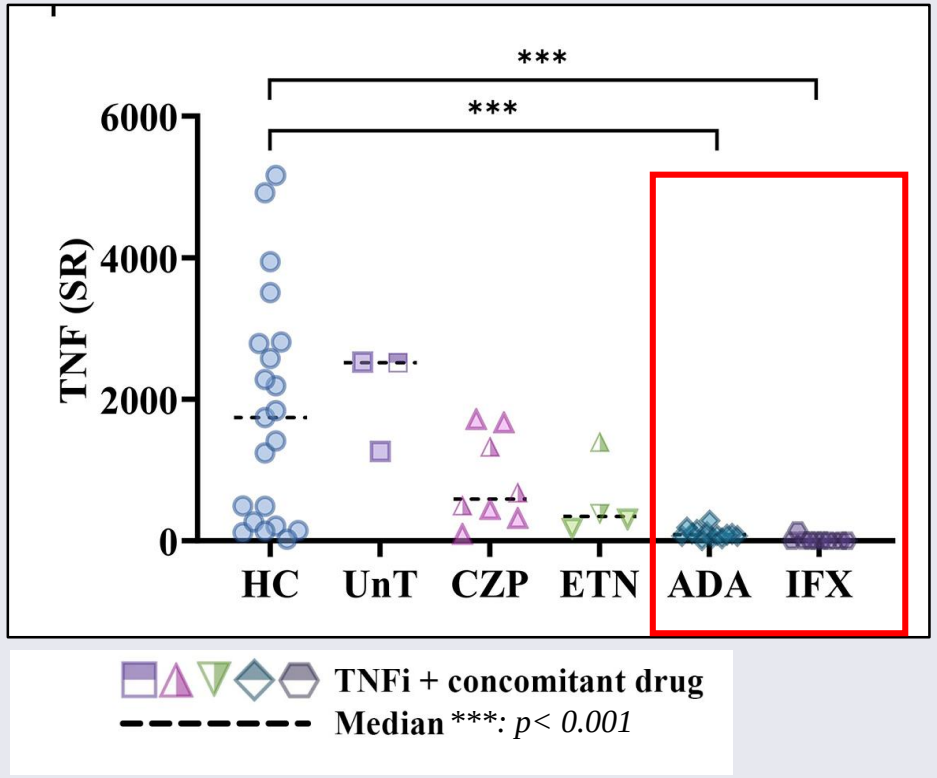


¿Immune balance?
¿Long-term consequences?

OUR PROJECT– MAIN RESULTS.

TNFi with higher placental transfer activity (IFX/ADA) had more impact on IL-12/IFN- γ axis.

At birth, IL-12/IFN-γ axis activity was **reduced** in <u>ADA /IFX</u> exposed newborns. TNF levels normalized along with drug clearance.



Risks to intracellular pathogen infections?
i.e., tuberculosis, leishmania.

BCG is included in the vaccine annual schedule.

OUR PROJECT– TO RAISE AWARENESS

FIS PI24/00467

REVIEW ARTICLE

WILEY

Expected impact of immunomodulatory agents during pregnancy: A newborn's perspective

Yiyi Luo[1,2,3] | Daniel Acevedo[1,2,3] | Núria Baños[4] | Andrea Pluma[5] | Raúl Castellanos-Moreira[6] | Estefania Moreno[5] | Sebastian Rodríguez-García[6] | Angela Deyà-Martínez[1,2,3] | Ana García-García[1,2,3] | Estefania Quesada-Masachs[5] | Mireia Torres[5] | Manel Casellas[7] | Dolors Grados[8] | Celia Martí-Castellote[1,3] | Jordi Antón[3,9,10] | Alexandru Vlagea[11] | Manel Juan[2,10,11,12] | Ana Esteve-Solé[1,2,3] | Laia Alsina[1,2,3,10]

Luo et al., Pediatric Allergy Immunol. 2023; PMID: 36825745.

Must reed article along with an Editorial Comment.

EDITORIAL

WILEY

Editorial comment on "Expected impact of immunomodulatory agents during pregnancy: A newborn's perspective"

Yiyi Luo

Treating maternal conditions during pregnancy requires balancing the desired beneficial effect and maternal and fetal toxicity. Over the last decades, several drugs and toxins have been associated with substantial organ damage in the fetus, resulting in altered organogenesis or functional derangements.[1] However, improving disease control might indirectly favor reproductive plans in women of childbearing potential. Recently developed biological therapies and small molecule protein kinase inhibitor drugs employed for treating autoimmune diseases have a powerful biological effect and may result in specific and possibly complete suppression of the targeted pathway.[2] The physiological consequence can be reversible upon discontinuing the drug or could result in a long-term influence on the immune system, according to the half-life and mechanism of action of the drug. For example, targeting B cells may induce long-term effects on antibody production after treatment discontinuation, and anti-CD20 monoclonal antibody administration may even result in B-cell aplasia, which can be irreversible in specific clinical situations.[3]

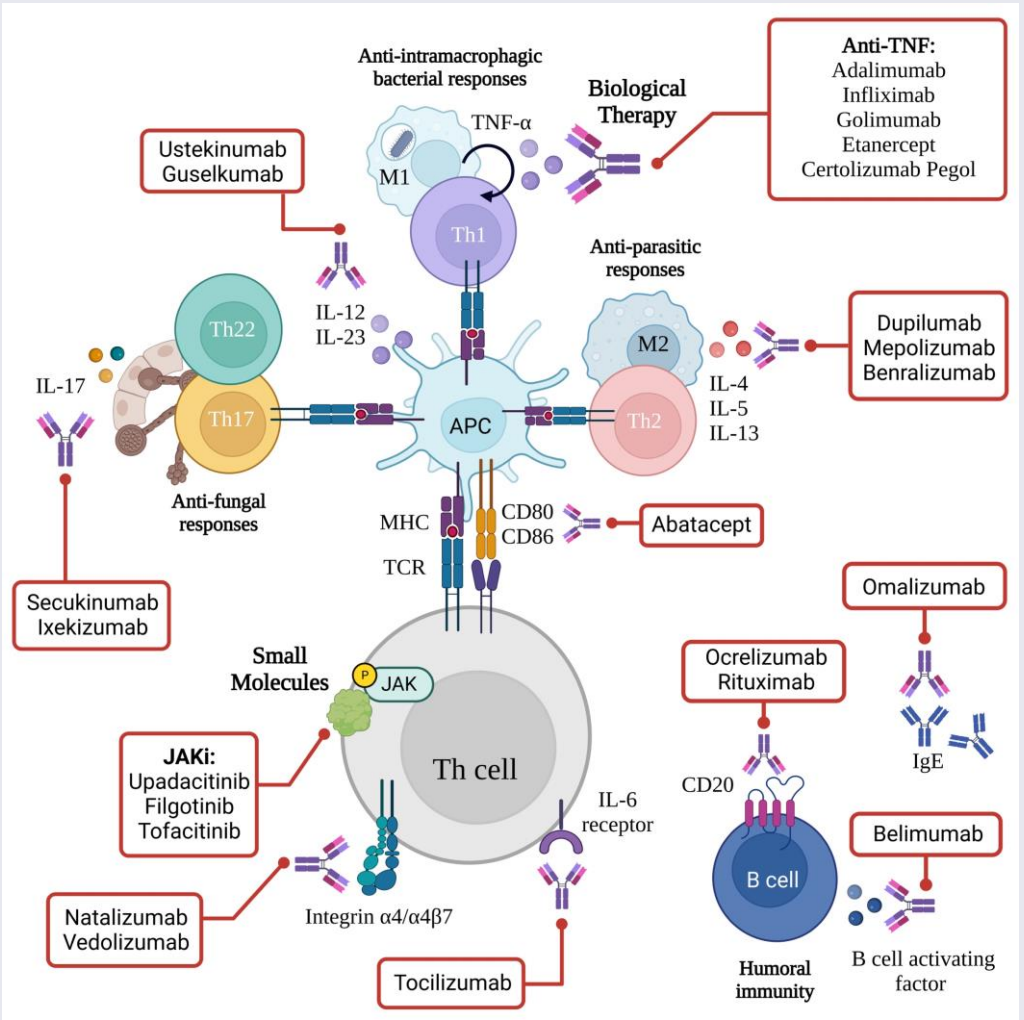
During the fetal period and early life, the immune system undergoes major changes to adapt to the varying

with

only

t also

Graphical abstract



Luo et al., Pediatric Allergy Immunol. 2023; PMID: 36825745.

TAKE HOME MESSAGES

1. Most **biological** drugs **cross** the **placenta** and may exert **immunomodulatory** effects on both the mother and the newborn.
2. Each biologic **targets** a specific **immune component**, which can impact the **newborn's immune** development.
3. Expert-driven **recommendations** are needed to guide the use of **immunomodulators** during **pregnancy** and support safe treatment decisions.
4. Adjusting maternal treatment schedules may ensure optimal disease control while minimizing unnecessary fetal exposure.
5. This project has strong potential to improve maternal-fetal care by addressing **key gaps** in the management of in utero exposure to immunomodulatory drugs.
6. Close **follow-up** of biologic-exposed **newborns** is essential, due to possible effects on lymphoid ontogeny and risk to infections.

OUR TEAM

Estudio de enfermedades por disfunción inmune en pediatría (GEMDIP)

Dra. Laia Alsina, MD, PhD (PI)
Jefa del Servicio de Alergia e Inmunología Clínica
Hospital Sant Joan de Déu
Email: **laia.alsina@sjd.es**

Acknowledgment

Pediatric Allergy and Clinical Immunology Department/
Study of Immune Deficiency Diseases in Paediatrics (GEMDIP)
Hospital Sant Joan de Déu (HSJD):

- **Laia Alsina**
- **Ana Esteve-Solé** --> FSJD
- **Yiyi Luo** → FSJD
- **Dani Acevedo** → FSJD
- A. Garcia-Garcia
- Celia Martínez
- Gilda Yanez
- Ángela Deyà

Servei Immunologia HCP:

- **Manel Juan**
- Mireia Anton
- Noemi de Moner
- **Jordi Yagüe**
- **Alexandru Vlagea**
- Sara Peiró Carmona
- Francesc Sibina
- Mar Díaz Pavón
- Joan.J Barceló
- Víctor Bolaños
- Mariona Pascal

• Servei Microbiologia HCB (BCG):
• Julia González

Samples exposed newborns
Casa Maternitat HCB:
• Irene Teixido/**Núria Baños**/Lorena Fernández

Servicio de Reumatologia HCP:
• Victoria Hernández
• Raúl Castellanos
• Sebastián C. Rodríguez-García

Secció de Reumatologia HVH
• **Andrea Pluma**
• Estefanía Moreno
• Sara Marçal

• Obstetrícia HVH: M. Casellas

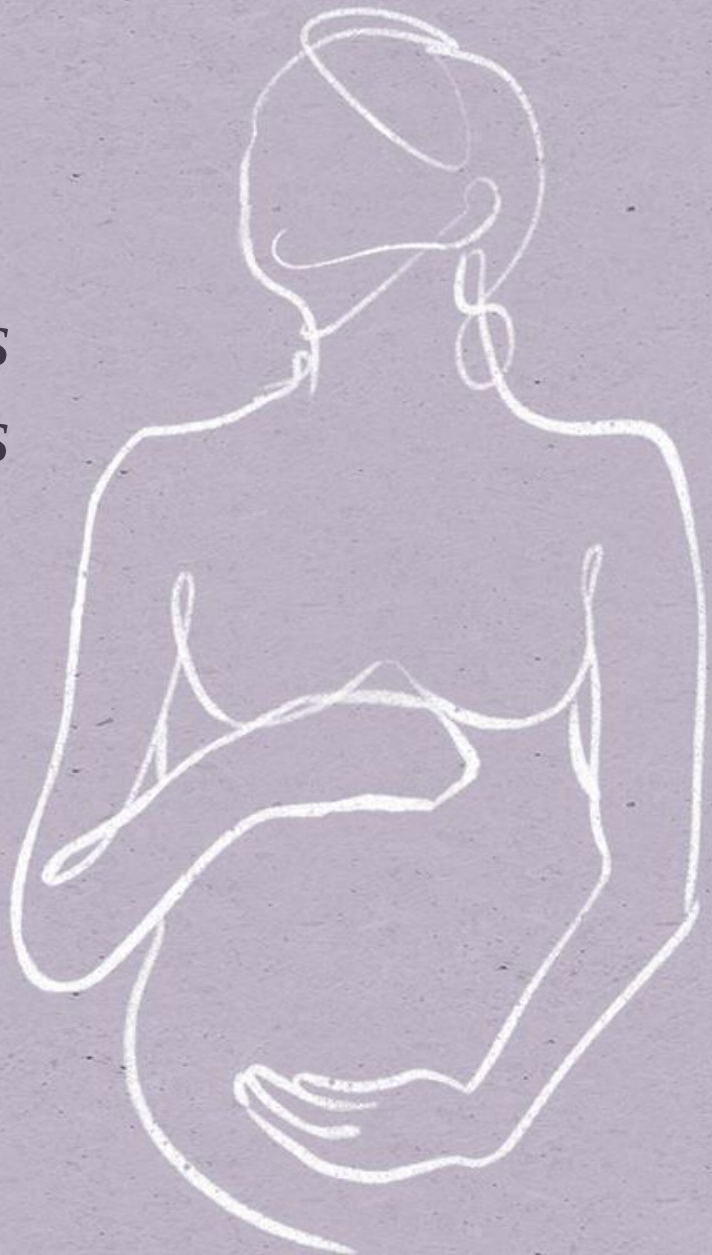
• Pediatria/Neonatologia HVH: Mireia Torres

Pediatric healthy controls
Biobanc HSJD:
• Cristina Jou
• **Anna Codina**
• Jesús Márquez

Patients Family

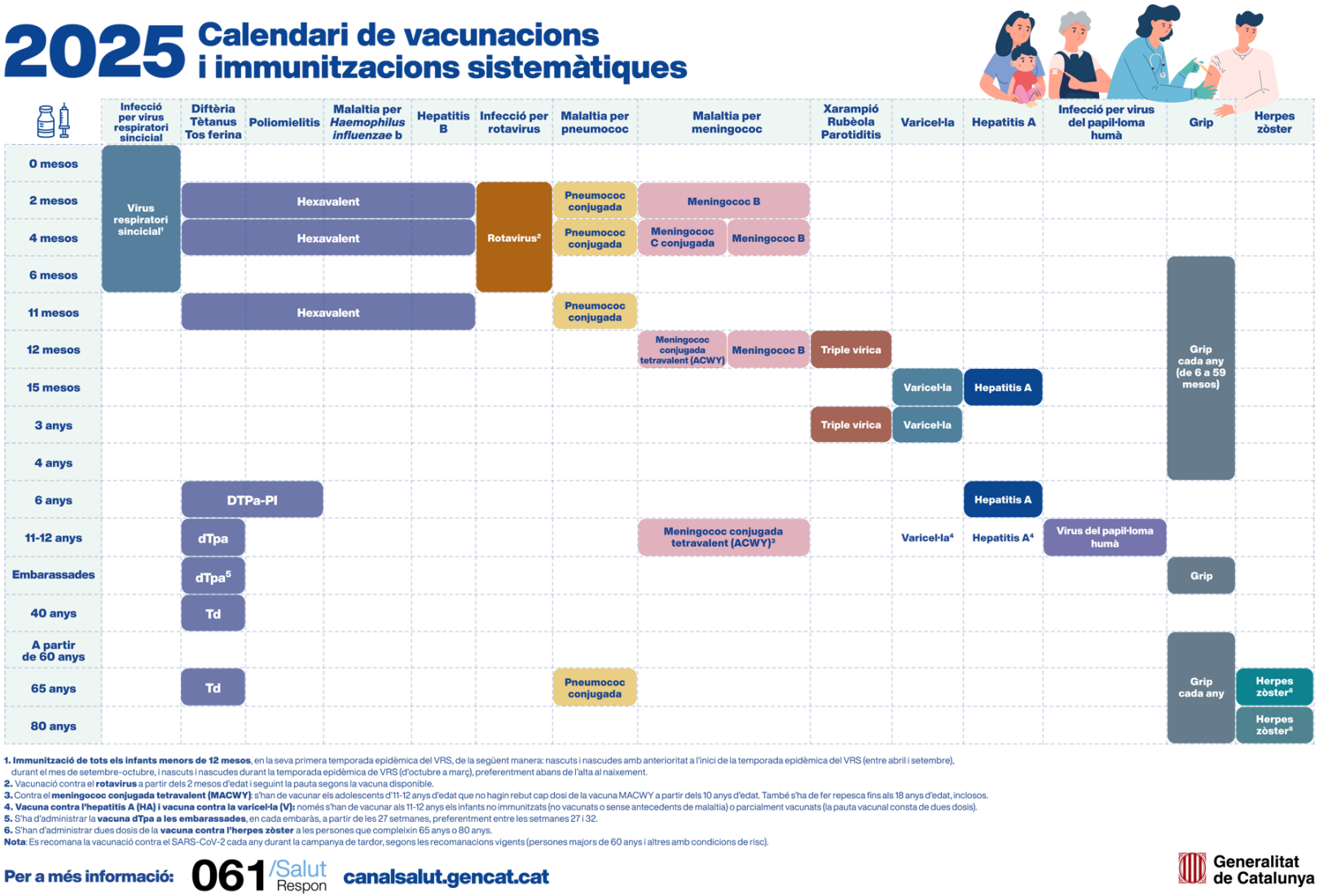
*Impacte **immunmològic** en **nounats** fills de mares amb **malalties inflamatòries** exposats a fàrmacs **biologics** durant l'**embaràs**: **calendari vacunal**?*

IV Diada Reumatològica - Societat Catalana de Reumatologia



Presenter	**Yiyi Luo, PhD**	**Email**	**yiyi.luo@sjd.es**
Affiliation	**H. Sant Joan de Déu**	**Date**	**April 4th, 2025**

Consideracions en el calendari vacunal si exposició materna a FAME biològics durant la gestació



Resum de l'exposició materna a FAME biològics de la British Society for Rheumatology

Fàrmac	Recomanació
CZP	• Compatible amb els tres trimestres de l'embaràs • No requereix **cap alteració en el calendari de vacunació infantil**
INF ADA GOL ETA	Seguir **calendari de vacunació normal** si: • **INF aturat** a les **20 SG** • **ADA** i **GOL** aturat a les **28 SG** • **ETA** aturat a les **32 SG**
INF, ADA, GOL, ETA, IL-1, ABA, BEL, IL-17, IL-12/23, RTX, IL-6	Si utilitzats en el **tercer trimestre**: • **Evitar** totes les **vacunes vives** en el calendari de vacunació infantil **fins als 6 mesos d'edat** • 5 mesos després de l'última dosi d'ADA • 16 setmanes després de l'última dosi d'ETA

SG: setmana de gestació, FAME: fàrmac modificador de la malaltia, CZP: Certolizumab, INF: Infliximab, ADA: Adalimumab, GOL: Golimumab, ETA: Etanercept, ABA: Abatacept, BEL: Belimumab, RTX: Rituximab, IL-1: Inhibidors interleuquina 1, IL-6: Inhibidors interleuquina 6, IL-17: Inhibidors interleuquina 17, IL-12/23: Inhibidors interleuquina 12/23.