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How infectious diseases interplay with autoimmune diseases?: from epidemiological evidence to pathophysiological hypotheses

Arthur Mageau

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Arthur Mageau. How infectious diseases interplay with autoimmune diseases?: from epidemiological evidence to pathophysiological hypotheses. Genetics. Université Paris Cité, 2023. English. NNT : 2023UNIP5084 . tel-04918652

HAL Id: tel-04918652

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UNIVERSITÉ PARIS CITÉ

ÉCOLE DOCTORALE PIERRE LOUIS DE SANTÉ PUBLIQUE :
ÉPIDÉMIOLOGIE ET SCIENCES DE L'INFORMATION BIOMÉDICALE (ED n° 393)

Unité de recherche : Infection, Anti-microbiens, Modélisation, Évolution (UMR-S 1137)
Équipe : DeSCID

How infectious diseases interplay with autoimmune diseases?

From epidemiological evidence to pathophysiological hypotheses

par **Arthur MAGEAU**

Thèse de doctorat d'épidémiologie clinique

Dirigée par Jean-François TIMSIT
et co-dirigée par Karim SACRÉ

Soutenue publiquement le 03 octobre 2023

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*'Där hänger på boklådsfönstret
En tunnklädd liten bok.
Det är ett urtaget hjärta
Som dinglar där på sin krok.'*

Ringraziamenti / Ευχαριστίες / Remerciements / Acknowledgements

Au Professeur Jean-François Timsit pour m'avoir encadré pendant ce travail. Merci à vous pour votre accompagnement, pour vos précieux conseils ainsi que pour m'avoir fait profiter de votre passion pour la recherche et les biostatistiques pendant ces 3 années.

Au Professeur Karim Sacré pour m'avoir également encadré pendant ce travail. Merci de m'avoir transmis ton intérêt pour la recherche clinique et pour ton accompagnement avant, pendant et après cette thèse.

Au Docteur Nicolas Charles pour avoir été mon "baby-sitter" au laboratoire et pour avoir accepté de participer à ce jury de thèse. Merci à toi de m'avoir accompagné avec tant de patience et de m'avoir transmis ton exigence scientifique au cours de mon passage dans l'équipe.

To the Doctor Elizabeth V. Arkema for agreeing to be part of this jury. Thank you for responding to an email from a French stranger and welcoming me into your team. I am sincerely grateful for your guidance and teaching during this wonderful year in Sweden.

I miei più calorosi ringraziamenti vanno alla Professoressa Marta Mosca. La ringrazio sinceramente di fare parte della giuria del mio dottorato. La difesa di questa tesi di dottorato mi dà l'opportunità unica di poter beneficiare dei commenti e delle revisioni di un'esperta rinomata internazionalmente: Le sono veramente grato per questo.

Επίσης, θα ήθελα να ευχαριστήσω θερμά την καθηγήτρια Τεκτονίδου που με τίμησε με την συμμετοχή της στην επιτροπή της διδακτορικής μου διατριβής, διαθέτοντας μέρος από τον πολύτιμο της χρόνο. Η εμπειρογνωμοσύνη σας πάνω στην ερευνητική μου εργασία θα είναι ουσιαστικής σημασίας για την υπεράσπιση αυτού του διδακτορικού!

Au Professeur Laurent Arnaud pour avoir accepté de participer à ce jury de thèse. J'ai la chance d'avoir pu bénéficier de la qualité de ton enseignement depuis l'époque des conférences d'internat jusqu'à aujourd'hui, et je t'en suis très reconnaissant.

À la Professeure Raphaèle Seror pour avoir également accepté de participer à ce jury de thèse. Merci à vous d'avoir pris le temps d'évaluer ce travail et de me faire bénéficier de vos connaissances, de votre expérience et de votre expertise du sujet.

Mes plus sincères remerciements s'adressent également:

À Noémie, pour sa patience, ses encouragements et son soutien sans faille pendant toutes ces années.

À mes parents, pour m'avoir offert toutes les chances de réussir.

À la Fondation pour la Recherche Médicale pour avoir soutenu financièrement mon travail.

À John, pour son aide, pour ses conseils et pour la vie au labo.

À Descid, Sylvie, Diane, Houda, Niccolo, Stéphane, Mathieu. Merci pour votre soutien.

À Bipid, Alexandra & Selma. Merci pour vos conseils et pour l'ambiance.

À Valentine, pour son implication, son expertise et son soutien dans les différents projets.

À Tiphaine, pour son apport apprécié et indispensable à l'organisation et la conduite des différents projets.

À Pascale, pour son investissement, sa réactivité et la qualité de ses conseils.

À Chrystelle & Nicole, pour leur aide précieuse et pour leur disponibilité.

À Aloïs, pour sa confiance et pour son travail.

À Adriana, pour sa relecture experte du manuscrit.

À Christel, pour son aide dans l'apprentissage du maniement de l'EDS et de Python.

À La Suède et aux Suédois, pour leur accueil. Tack så mycket!

Aux patients ayant accepté de participer à COVALUS, et à ceux ayant accepté que leurs données soient utilisées dans nos autres projets de recherche.

À Cosette, pour sa présence.

Au Professeur Bruno Falissard pour avoir transformé ma vision des statistiques et de la recherche médicale.

My warmest thanks also go to:

To Ngoc and Marina, thank you so much for making me feel so welcome in the team, and for the singing!

To Anton, Arda, Renata, Peter & Karin, thank you for making the life in KEP so nice and interesting.

To the whole KEP team for their warm welcome and for the quality of our discussions.

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Scientific output of the thesis

Publications:

1. **Mageau A**, Aldebert G, Van Gysel D, Papo T, Timsit JF, Sacre K. SARS-CoV-2 infection among inpatients with systemic lupus erythematosus in France: a nationwide epidemiological study. *Ann Rheum Dis.* août 2021;80(8):1101-2.
2. **Mageau A**, Nicaise Roland P, Goulenok T, Farkh C, Charles N, Sacre K. Systemic lupus erythematosus flare following SARS-CoV2 infection: the implication of IFN α and anti-IFN α autoantibodies. *Clinical and Experimental Rheumatology* juill 2022;40(7):1450.
3. **Mageau A**, Papo T, Ruckly S, Strukov A, van Gysel D, Sacre K, et al. Survival after COVID-19-associated organ failure among inpatients with systemic lupus erythematosus in France: a nationwide study. *Ann Rheum Dis.* 10 déc 2021;annrheumdis-2021-221599.
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Oral presentations in scientific meetings:

SLE Swedish scientific network (Marstrand, Sweden), 24th-25th May, 2023:

- Anti-SARS-CoV-2 mRNA vaccination among patients living with SLE in Sweden: Coverage progression and clinical effectiveness

SLE euro meeting (Stockholm, Sweden) 5th-8th October 2022:

- Efficacy and Safety of The Anti-Sars-Cov-2 BNT162b2 Vaccine Among SLE Patients

- Risk of Covid-19 Induced Systemic Lupus Erythematosus Flare : Analysis of the AP-HP Clinical Data Warehouse

Société Nationale Française de Médecine Interne (Marseille, France) 7th-9th December, 2022:

- Impact du vaccin BNT162b2 sur la production d'interféron alpha et l'auto-immunité cellulaire au cours du lupus érythémateux systémique. Le projet COVALUS.

- Risque de poussée de lupus érythémateux systémique après un épisode sévère de COVID -19
Analyse de l'Entrepôt de Données de Santé (EDS) de l'AP-HP

Société Nationale Française de Médecine Interne (Paris, France) 16th December, 2022:

- Survie hospitalière après un épisode de COVID-19 sévère chez les patients lupiques : une étude cas-contrôle à l'échelle nationale

List of abbreviations

AMI: Acute myocardial infarction	Th2: T helper 2
ANCA: antineutrophil cytoplasmic antibodies	TMEV: Theiler's murine encephalomyelitis virus
AI: Autoimmunity	TNF: Tumor necrosis factor
Aid: Autoimmune disease	WHO: World health organization
ANR: Agence nationale pour la recherche	
AP-HP: Assistance publique – hôpitaux de Paris	
COVID-19 AOF: COVID-19 associated organ failure	
APC: Antigen presenting cell	
BCG: Bacille Calmette et Guérin	
BILAG: British Isles lupus assessment group	
COVID-19: Coronavirus disease 2019	
dsDNA: Double-stranded DNA	
EAE: experimental autoimmune encephalomyelitis	
EBV: Epstein-Barr virus	
EHR: Electronic health record	
ELISA: Enzyme-linked immunosorbent assay	
EULAR: European alliance of associations for rheumatology	
ES: Epitope spreading	
GBS: Guillain-Barre syndrome	
GPA: Granulomatosis with polyangiitis	
HBV: Hepatitis B virus	
HLA: Human leukocyte antigen	
HR: Hazard ratio	
HV: Healthy volunteer	
ICU: Intensive care unit	
iDC2s: type 2 inflammatory dendritic cells	
IFN α : Interferon α	
IgG: Immunoglobulin G	
IMID: Immune-mediated inflammatory disease	
INF-I: Type 1 interferon	
IR: Incidence ratio	
IS: Immune system	
MHC-I: Major histocompatibility complex, type 1	
MMR: Measles, mumps and Rubella	
mRNA: Messenger-ribonucleic acid	
MS: Multiple sclerosis	
NOD: Non-obese diabetic	
PCP: pneumocystis	
pDC: Plasmacytoid dendritic cell	
PMSI: Programme de médicalisation des systèmes d'information	
RA: Rheumatoid arthritis	
ReA: Reactive arthritis	
RNP: Ribonucleoprotein	
SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2	
SLE: Systemic lupus erythematosus	
SLE-DAS: SLE disease activity score	
Sm: Smith	
T1D: Type 1 diabetes	

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Abstract (in English)

Title: How infectious diseases interplay with autoimmune diseases? From epidemiological evidence to pathophysiological hypotheses

Background: The interplay between autoimmunity and infectious diseases is complex and only partially understood. The emergence of the COVID-19 pandemic in early 2020 and the anti-SARS-CoV-2 vaccination campaign in 2021 provided a unique opportunity to study how immune-mediated inflammatory diseases (IMIDs) such as systemic lupus erythematosus (SLE) interact with infections and infectious stimuli.

Objective: We sought to better understand the relationships between infections and autoimmunity, using SLE and SARS-CoV-2 as a model in a translational approach, both epidemiological and immunological.

Methods: For the epidemiological analyses, we used three different large databases: the French national medico-administrative hospital database (Programme de médicalisation des systèmes d'information, PMSI), the Assistance Publique-Hôpitaux de Paris (AP-HP) data warehouse and the Swedish National Registers. From these databases, we created matched cohorts and used different statistical methods (descriptive statistics, survival analyses, and competing risk analyses) to answer our several research questions. For the immunological analyses, we established a prospective observational cohort of SLE patients and healthy volunteers at the time of their first anti-SARS-CoV-2 mRNA vaccine dose. Enrolled subjects had follow-up visits at one month, three months, and six months after their first vaccine dose. We evaluated the immunogenicity of the vaccine as well as its effect on the innate and adaptive immune system, focusing on plasmacytoid dendritic cells (pDCs) and autoreactive T cells.

Results: **i)** With PMSI data, we showed that lupus patients were frequently hospitalized, especially if they had comorbidities and that they had a late-onset poor prognosis compared with general population after COVID-19-associated organ failure. **ii)** In the prospective COVALUS study we observed that vaccine protection was significantly diminished in lupus patients, compared with healthy volunteers. Vaccination led to an activation of pDCs and to an increased production of IFN- α by these cells. However, the vaccine was well tolerated from a clinical perspective, and we observed that the number of autoreactive T cells decreased over the follow-up. **iii)** In the Swedish data, we found that the clinical effectiveness of the vaccine was lower in SLE compared to general population. The vaccine uptake pace was very similar between SLE patients and matched comparators from the general

population **iv)** Using the AP-HP data warehouse, we observed that SLE patients have an increased risk of lupus flare and an increased lupus biological activity after a hospitalization for COVID-19. **v)** In PMSI, we found a high incidence of IMIDs after sepsis. This incidence of IMIDs was higher after sepsis than the one observed in hospital controls after acute myocardial infarction.

Conclusion: Taken together, our results confirm that infections can trigger or worsen IMIDs such as SLE, and that patients with IMIDs are more susceptible to infections. On the other hand, we found that vaccination is safe and effective in SLE, although vaccine-induced protection is reduced, particularly in those on immunosuppressants.

Key words: Immune-mediated inflammatory disease, autoimmunity, systemic lupus erythematosus, COVID-19, infections, infectious pathogens, SARS-Cov-2, vaccination.

Résumé court (en français)

Titre : Comment les maladies infectieuses interagissent-elles avec les maladies auto-immunes ? Des données épidémiologiques aux hypothèses physiopathologiques.

Contexte : Les liens complexes entre l'auto-immunité et les maladies infectieuses ne sont que partiellement compris. L'émergence de la pandémie de COVID-19 début 2020 et la campagne de vaccination anti-SARS-CoV-2 en 2021 furent une occasion unique d'étudier comment les maladies inflammatoires médiées par l'immunité (MII) telles que le lupus érythémateux systémique (LES) interagissent avec les infections et les stimuli infectieux.

Objectif : Notre objectif était de mieux comprendre les relations entre les pathologies infectieuses et l'auto-immunité, en utilisant le LES et le SARS-CoV-2 comme modèles, dans une approche translationnelle à la fois épidémiologique et immunologique.

Méthodes : Nous avons utilisé pour les analyses épidémiologique trois grandes bases de données : le Programme de médicalisation des systèmes d'information (PMSI), l'entrepôt de données de santé de l'Assistance publique-Hôpitaux de Paris (AP-HP) et les registres nationaux suédois. À partir de ces différents éléments, nous avons créé des cohortes appariées et utilisé différentes méthodes statistiques (statistiques descriptives, analyses de survie et analyses de risques compétitifs) pour répondre à nos questions de recherche. Pour les analyses immunologiques, nous avons constitué une cohorte prospective observationnelle de patients atteints de LES et de volontaires sains inclus au moment de leur première dose de vaccin ARNm anti-SARS-CoV-2. Les sujets étaient suivis à un mois, trois mois et six mois après leur première dose de vaccin. Nous avons évalué l'immunogénicité du vaccin ainsi que son effet sur le système immunitaire inné et adaptatif, en nous concentrant sur les cellules dendritiques plasmacytoïdes (CDps) et les cellules T auto-réactives.

Résultats : **i)** A partir des données PMSI, nous avons montré que les patients atteints de lupus étaient fréquemment hospitalisés, en particulier s'ils présentaient des comorbidités, mais aussi qu'ils avaient un mauvais pronostic tardif comparé à la population générale après une défaillance d'organe associée au COVID-19. **ii)** Dans l'étude prospective COVALUS, nous avons observé que la protection vaccinale était significativement diminuée chez les patients atteints de lupus par rapport aux volontaires sains. La vaccination a conduit à une activation des CDps et à une production accrue d'IFN- α par ces cellules. Néanmoins, le vaccin était bien toléré d'un point de vue clinique et nous avons observé que le nombre de cellules T auto-réactives diminuait au cours du suivi. **iii)** Dans les données suédoises, nous avons constaté que l'efficacité clinique du vaccin était plus faible chez les patients atteints de lupus comparé

à la population générale. En revanche, la progression de la couverture vaccinale était similaire entre patients lupiques et population générale. **iv)** En utilisant l'entrepôt de données de santé de l'AP-HP, nous avons observé que les patients atteints de lupus ont un risque accru de poussée de lupus et une activité biologique lupique augmentée après une hospitalisation pour COVID-19. **v)** Dans le PMSI, nous avons constaté une incidence élevée de MII après un sepsis. Cette incidence de MII était plus élevée après un sepsis que celle observée chez les témoins hospitalisés après un infarctus aigu du myocarde.

Conclusion : Dans l'ensemble, nos résultats confirment que les infections peuvent déclencher ou aggraver des MII telles que le LES, et que les patients atteints de MII sont plus sensibles aux infections. D'autre part, nous avons constaté que la vaccination est sûre et efficace dans le cas du LES, bien que la protection induite par le vaccin soit réduite chez les lupiques, en particulier chez ceux sous immunosuppresseurs.

Mots-clés : Maladie inflammatoire médiée par l'immunité, auto-immunité, lupus érythémateux systémique, COVID-19, infections, pathogènes infectieux, SARS-Cov-2, vaccination.

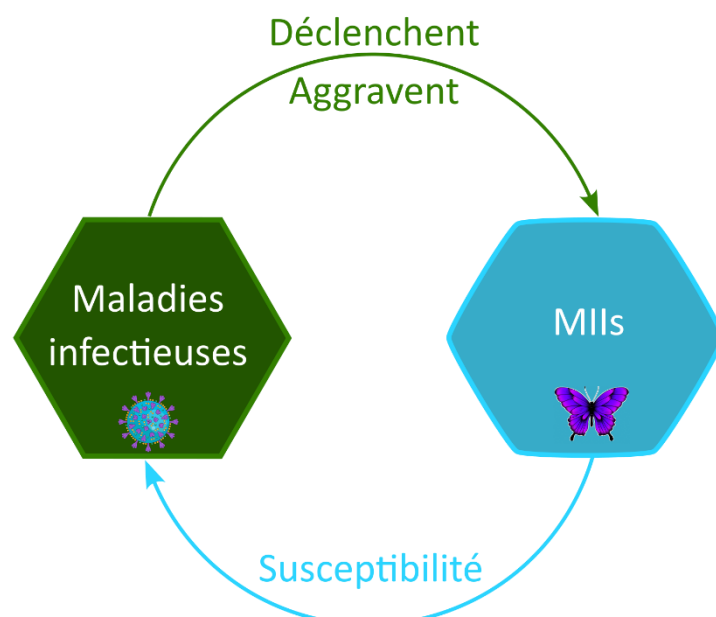
Résumé long (en français)

Introduction

La fonction principale du système immunitaire (SI) est de protéger l'organisme contre les éléments du non-soi potentiellement dangereux. Pour fonctionner correctement et sans risquer d'être nocif pour l'organisme, le SI doit être capable de reconnaître des millions d'antigènes différents appartenant au non-soi, tout en ne réagissant pas aux antigènes du soi. Cette capacité du SI à ne pas réagir vis-à-vis des antigènes du soi est appelé "tolérance immunitaire" (1,2). Une rupture de cette tolérance immunitaire conduit à l'auto-immunité (AI) qui peut être définie comme une auto-réactivité du SI vis-à-vis de l'organisme. Le lupus érythémateux systémique (LES) apparait comme un exemple pertinent et un bon prototype d'AI : il touche différents organes et présente des caractéristiques auto-immunes marquées telles que des auto-anticorps pathogènes que l'on peut trouver à la fois dans le sang et dans les tissus des patients (4). Aujourd'hui, le concept de maladie auto-immune a été élargi à celui de maladie inflammatoire à médiation immunitaire (MII) pour inclure toutes les maladies caractérisées par un dérèglement immunitaire conduisant à une inflammation (5).

Les agents infectieux sont suspectés d'altérer la tolérance immunitaire et de provoquer ou de déclencher l'AI depuis plusieurs décennies (8,9). Dans certaines situations spécifiques, la relation de cause à effet entre les maladies infectieuses et les MIIs est bien documentée. Par exemple, une étude récente a fourni des éléments solides prouvant le rôle causal du virus d'Epstein-Barr (VEB) dans l'apparition de la sclérose en plaques (SEP) (10).

Par conséquent, les relations entre maladies infectieuses et les MIIs est communément décrite ainsi :



La vaccination apparaît alors comme un moyen idéal pour prévenir les effets délétères des maladies infectieuses. En prévenant les infections, et en renforçant le système immunitaire, les vaccins devraient permettre de rompre le cercle vicieux décrit précédemment. Dans ce contexte, la vaccination est devenue la pierre angulaire de la prophylaxie anti-infectieuse chez les patients atteints de maladies auto-immunes (18). Par ailleurs, le bénéfice des vaccins pourrait même porter sur l'auto-immunité car une étude italo-américaine a montré que le vaccin polysaccharidique antipneumococcique est également capable de réduire l'auto-immunité de souris MRL/Lpr couramment utilisées comme modèle murin de LES (19). Cependant, la vaccination a malheureusement été remise en question par la croyance commune selon laquelle la vaccination pourrait induire de l'auto-immunité (20). En outre, l'efficacité des vaccins est souvent réduite chez les patients atteints de MII et de nombreux microorganismes ne sont pas couverts par les vaccins actuellement disponibles.

Ainsi, dans le contexte de la pandémie et des liens denses et complexes reliant les maladies infectieuses à l'auto-immunité, de nombreuses questions restent en suspens :

- 1- Les patients atteints de MII telle que le LES ont-ils un risque particulier face au COVID-19 ?
- 2- Quelle est la protection conférée par les vaccins à ARNm chez les patients atteints de MII telle que le LES ?
- 3- Quel est l'effet d'une vaccination par ARNm au cours d'une MII telle que le LES ?
- 4- Quel est l'impact d'une infection virale comme le COVID-19 sur l'activité des MIIs systémiques ?
- 5- D'une manière plus générale, l'infection sévère est-elle un facteur déclenchant de MII ?

Par une approche translationnelle, épidémiologique et immunologique, nous avons cherché à mieux comprendre les relations entre infection et auto-immunité et plus particulièrement les liens entre LES, COVID-19 et vaccination anti-SARS-CoV-2.

Etat de l'art

A - Mécanismes physiopathologiques reliant les maladies inflammatoires à médiation immune aux maladies infectieuses.

1) Des relations directes entre certaines MII et certains microorganismes.

Certaines MII sont étroitement liées à des pathogènes infectieux particuliers. On peut, par exemple, mentionner l'association entre la bactérie *Campylobacter jejuni* et le syndrome de Guillain-Barré. *Campylobacter* est suspecté de déclencher une lésion des nerfs périphériques en utilisant un processus immunologique connu sous le nom de mimétisme moléculaire. *Campylobacter* ayant des épitopes proches de ceux des gangliosides, l'immunisation contre cette bactérie entraîne la production d'auto-anticorps qui attaqueront les cellules nerveuses périphériques. (22). Ce phénomène conduit à une rupture de la tolérance vis-à-vis des auto-antigènes, et donc à une réaction auto-immune (23,24). Cependant, le mimétisme moléculaire n'explique pas toutes les MII induites par des agents infectieux. L'arthrite réactionnelle (ReA) est une autre MII bien connue qui peut être déclenchée par une infection (25). Ici, c'est la présence microbienne persistante au sein des tissus qui est responsable du processus inflammatoire. Ainsi, il a été démontré que les composants bactériens persistants de *Chlamydia trachomatis* provoquent une inflammation chronique et contribuent au développement de la ReA (26). Dans ce contexte, un stimulus infectieux persistant stimule le système immunitaire qui y répond en provoquant une inflammation pouvant se chroniciser. Ces maladies ne peuvent donc pas être considérées comme des maladies auto-immunes primitives, mais font partie du spectre des MII.

2) Mécanismes physiopathologiques plus généraux reliant infections et MII.

Parmi les mécanismes pouvant engendrer de l'auto-immunité post infectieuse, nous citerons l'activation de proximité et la diversification épitopique. L'activation de proximité implique l'activation, par un environnement pro-inflammatoire, de cellules immunitaires auto-réactives non infectées (30,31). Au cours d'une infection, de nombreuses cellules présentatrices d'antigènes (CPA), telles que les cellules dendritiques, sont activées. Ces CPA activées peuvent à leur tour activer des cellules T auto-réactives pré-amorcées, conduisant à l'auto-immunité. En 1998, Horwitz et al. (32) ont montré que le diabète de type 1 survenant après une infection par le virus *Coxsackie* était plus certainement lié à l'activation de proximité plutôt qu'au mimétisme moléculaire.

La diversification épitopique (DE) est un autre mécanisme proposé pour expliquer l'apparition ou l'aggravation de maladies auto-immunes après une infection. La DE se caractérise par un élargissement du spectre ou une diversification de la réponse immunitaire déclenchée par antigène peptidique (33). Si, au cours de ce processus, les réponses des cellules T et/ou B deviennent réactives vis-à-vis d'un auto-antigène, une réaction auto-immune peut être déclenchée. La DE peut être consécutive à la libération d'auto-antigènes par un tissu endommagé au cours du processus infectieux. Un tel phénomène a été mis en évidence dans la pathogenèse de l'encéphalomyélite auto-immune expérimentale (EAE), qui est un modèle murin de la sclérose en plaques. Même en dehors de tout contexte infectieux, il a été démontré que la DE était impliquée dans la pathogenèse de différentes MII telles que le LES. Des études de la réactivité antigénique du sérum de patients lupiques ont mis en évidence une évolution au cours du temps avec l'apparition progressive de nouveaux autoanticorps (par exemple, propagation intermoléculaire de l'antigène Sm à la réactivité RNP) ainsi que dans la réactivité à différents épitopes au sein du même antigène (35,36).

3) COVID-19 et auto-immunité, un mécanisme particulier ?

Depuis le début de la pandémie en 2019, l'hypothèse selon laquelle le COVID-19 puisse induire de l'auto-immunité suscite une inquiétude particulière (37). L'implication de l'IFN de type 1 (IFN-I) et des auto-anticorps anti-IFN-I à la fois dans la réponse immunitaire antivirale, dans les formes sévères de COVID-19 et dans la physiopathologie des MII permet de formuler des hypothèses physiopathologiques étayant cette inquiétude. Il a été montré que des auto-anticorps neutralisant les IFN de type I sont présents chez 20 % des patients qui meurent du COVID-19 (38,39). Par ailleurs, ces auto-anticorps anti-IFN-I ont été identifiés depuis les années 1980 chez des patients atteints de LES (40), chez des patients atteints de thymome et/ou de myasthénie grave (41) et chez presque tous les patients atteints de polyendocrinopathie auto-immune de type 1 (42). En bloquant les voies de signalisation de l'IFN-I, ces auto-anticorps auraient un effet protecteur contre l'inflammation aberrante observée dans le LES, alors qu'ils seraient délétères dans la réponse antivirale. Wang et al. (43) ont pu identifier des auto-anticorps ciblant 2 770 protéines extracellulaires, telles que des cytokines et des chimiokines, dans le plasma de patients atteints de COVID-19. Il est intéressant de noter que certains de ces auto-anticorps ont été induits par l'infection par le SARS-CoV-2, ce qui indique que le COVID-19 pourrait bel et bien entraîner une perte de tolérance (44).

B- Les données épidémiologiques documentant l'existence d'une immunité post-infectieuse.

1) Les associations entre maladies infectieuses et immunité.

Plusieurs études ont confirmé le rôle des infections dans la pathogenèse de certaines maladies auto-immunes. Par exemple, Bjornevik et al. (10) ont récemment démontré qu'une infection par le VEB est un élément absolument nécessaire mais non suffisant dans la pathogenèse de la sclérose en plaques. Ces données épidémiologiques sont venues confirmer un élément physiopathologique suspecté depuis des décennies. Un autre exemple célèbre est l'étude de Cao-Lormeau et al. (47) qui ont étudié l'épidémie de virus Zika de 2013-2014 en Polynésie française et ont apporté la preuve que l'infection par le virus Zika peut provoquer le syndrome de Guillain-Barré. Ces études épidémiologiques sont délicates à mener car, dans la mesure où les patients atteints de MII sont plus sensibles aux infections, le risque de causalité inversée doit être évalué avec précaution (48). L'épidémiologie permet également de quantifier le poids de l'auto-immunité associée à l'infection. Nielsen et al. (49) a ainsi pu mesurer la force d'association entre un antécédent d'hospitalisation pour infection et l'incidence de 29 maladies auto-immunes dans les données des registres danois.

2) Les MIIs déclenchées ou aggravées par le COVID-19.

La pandémie a remis l'auto-immunité post-infectieuse sur le devant de la scène (57). Au-delà de la maladie aiguë, les patients peuvent présenter après un épisode de COVID-19, des symptômes chroniques -appelés "COVID long" - qui peuvent impliquer des manifestations pulmonaires mais aussi systémiques (58). Même si la nature auto-immune de l'entité "COVID long" est encore débattue (59), plusieurs études ont observé un risque d'apparition de MII après l'infection par COVID-19. Chang et al. (60) ont utilisé le réseau collaboratif américain TriNetX pour comparer des patients avec et sans COVID documenté par PCR. Parmi les 3 814 479 participants appariés, la cohorte COVID-19 présentait des risques significativement plus élevés d'apparition de 14 MII différentes.

3) Les infections comme facteur de protection contre les MII : l'hypothèse hygiéniste.

Paradoxalement, il a également été montré que dans certaines situations, les infections peuvent également protéger ou diminuer l'activité des MII. Pour certains auteurs, comme J-F Bach (64), le facteur principal de l'augmentation de la prévalence des maladies allergiques et auto-immunes dans les pays industrialisés est la réduction de l'incidence des maladies infectieuses dans ces pays. Cette hypothèse, souvent appelée "hypothèse hygiéniste", n'est pas nouvelle puisqu'elle a été décrite dès les années 1960 par Leibowitz et al. (65), qui ont observé que le risque de développer une SEP pouvait être plus élevé chez les personnes ayant un niveau élevé d'hygiène dans leur foyer d'enfance. La preuve la plus convaincante à l'appui de cette hypothèse est la réduction de l'atopie et des maladies

allergiques chez les personnes infectées par des helminthes tels que *Schistosoma haematobium*, qui a été démontrée par plusieurs études immuno-épidémiologiques et interventionnelles (66,67). En dehors des maladies allergiques, des résultats contradictoires ont été observés dans les MII.

C- Le risque infectieux des patients atteints de MII.

1) Les patients atteints de MII ont un risque infectieux important.

La plupart des patients atteints de MII sont considérés comme étant immunodéprimés, et donc particulièrement susceptibles aux infections, soit en raison de leur traitement immunosuppresseur, soit en raison de leurs comorbidités et parfois même en raison de la MII elle-même. Les maladies infectieuses sont à la fois fréquentes et graves dans cette population, constituant la première raison d'admission en unité de soins intensifs selon une étude française menée dans 10 hôpitaux universitaires (71). Le poids de l'infection a été bien étudié dans la polyarthrite rhumatoïde (PR) depuis les années 1950, avec des études d'observation évaluant la mortalité globale de ces patients. Mehta et al. (73) ont rapporté que le taux d'incidence des infections nécessitant une hospitalisation chez les patients atteints de PR était de 1,5 (IC à 95 % : 1,2 à 1,5) en utilisant comme référence les patients atteints de maladies rhumatismales non inflammatoires. Outre l'âge et les comorbidités, les traitements de fond, souvent immunosuppresseurs, des MII sont responsables d'au moins une partie du risque infectieux observés chez ces malades. Le nombre sans cesse croissant d'options thérapeutiques rend ce sujet complexe à étudier. Dans une étude très récente, Frisell et al (74) ont étudié l'incidence relative des infections graves chez les patients atteints de PR en Suède au sein de différents sous-groupes définis par l'utilisation de différents traitements. Ils ont observé que les patients traités par infliximab et par rituximab présentaient un risque plus élevé que les patients traités par etanercept, utilisé comme référence.

2) Les patients lupiques ont un risque infectieux particulier.

Les infections sont reconnues comme l'une des principales causes de mortalité prématurée chez les patients atteints de LES (13). Dans leur célèbre étude sur la mortalité bimodale au cours du LES, Urowitz et al. (81) ont observé que sur 6 patients décédés au cours de l'année suivant le diagnostic, 4 (67%) sont morts d'un épisode septique majeur. En utilisant les données du Nationwide Inpatient Sample (NIS) américain, Tektonidou et al. (82) ont démontré que les risques relatifs de pneumonie, d'infection urinaire, d'infection opportuniste, de septicémie ou d'infection cutanée étaient plus élevés pour les patients atteints de LES que pour la population générale, et qu'ils avaient augmentés entre 1996 et 2011. Par exemple, le risque relatif d'hospitalisation pour des infections opportunistes est passé de 8,8 en 1996 à 24,1 en 2011. Ces résultats ont été confirmés par une mise à jour de l'étude

(83), par une revue systématique et une méta-analyse bayésienne réalisées en 2017 (84) et par Simard et al. (85) qui ont étudié le risque d'infection chez les patients atteints de LES en Suède.

D- L'enjeu de la vaccination au cours des MII.

1-Protection vaccinale chez les patients atteints de MII.

Au cours de mon Master 2 (88), nous avons observé que 10 % des épisodes infectieux graves touchant la population lupique française étaient associés à des pathogènes accessibles à la vaccination. Au-delà du problème de couverture vaccinale, et même si les vaccins ont une place centrale dans la prophylaxie anti-infectieuse chez les patients atteints d'une maladie auto-immune (18), de nombreux problèmes subsistent en ce qui concerne leur immunogénicité et leur efficacité. Il existe très peu de données scientifiques sur l'efficacité clinique des vaccins chez les patients atteints de MII (90). La plupart du temps, la protection induite par le vaccin est étudiée à l'aide de marqueurs d'immunogénicité tels que la réponse humorale qui a notamment été étudiée pour les vaccins antigrippaux (94), antipneumococciques (95) et anti-SRAS-CoV-2 (96). Plusieurs études ont observé que, par rapport à la population générale, les vaccins induisent une réponse plus faible chez les patients atteints de MII, avec un effet important du traitement immunosuppresseur (90).

2- Les vaccins comme facteur déclenchant d'auto-immunité.

Malheureusement, la littérature sur la sécurité vaccinale a été polluée par la fraude scientifique historique d'Andrew Wakefield, qui a prétendu à tort qu'il existait des liens de causalité entre le vaccin ROR et l'autisme (117). Aujourd'hui, le seul vaccin qui a été clairement associé d'un point de vue scientifique à l'apparition d'une MII est le vaccin antigrippal. La première preuve de l'existence d'un risque de syndrome de Guillain-Barré (SGB) date de la campagne vaccinale contre la grippe porcine de 1976 aux États-Unis (118). Schoberger et al. ont observé un risque attribuable de SGB lié à la vaccination dans la population adulte légèrement inférieur à un cas pour 100 000 vaccinations, avec une période d'augmentation du risque se concentrant principalement sur les 5 semaines post-vaccination. Les autorités suédoises (122) et finlandaises (123) ont récemment établi une autre association inattendue entre le vaccin Pandemrix (grippe H1N1) et la narcolepsie infantile auto-immune. L'évaluation du risque de développer une SEP après une vaccination anti-VHB a donné lieu à un débat qui a largement dépassé la communauté médicale et scientifique. Toutefois, les analyses les plus récentes concluent qu'il n'y a pas de risque accru d'apparition de la SEP après une vaccination contre le VHB (128).

3- Les vaccins comme un remède contre l'auto-immunité.

La recherche sur les vaccins en tant que traitement possible de l'auto-immunité n'a pas reçu autant d'attention que leurs effets secondaires immunologiques. Cependant, plusieurs éléments indiquent que certains vaccins pourraient avoir un impact bénéfique sur l'évolution des MII. Par exemple, des résultats intéressants ont été rapportés à propos du vaccin contenant le bacille de Calmette et Guérin (BCG) (129) chez les souris diabétiques non-obèses (NOD) dans lesquelles une seule injection intraveineuse de BCG à l'âge d'environ 10 semaines a produit une réduction importante de l'inflammation pancréatique et du diabète (130). En ce qui concerne le LES, des résultats intéressants ont également été décrits chez les souris MRL-lpr, qui développent spontanément un syndrome de type lupus. Cantarelli et al. (19) ont rapporté que 3 mois après une vaccination antipneumococcique, les souris vaccinées présentaient une réduction importante des principaux marqueurs de la maladie lupique, comparées aux souris contrôles.

Partie 1 : Le risque associé au COVID-19 des patients atteints de LES (études 1 & 2).

Au début de la pandémie, en 2020, alors que la communauté médicale et scientifique n'avait à sa disposition que très peu d'information sur le SARS-CoV-2, la préoccupation principale des patients lupiques était leur risque de faire face à une forme grave de COVID-19. En effet, le LES était déjà connu pour être un facteur de risque d'infection grave, en particulier respiratoire. L'immunosuppression médicamenteuse était supposée être responsable de la majeure partie du risque infectieux. Cependant, les premières données concernant le COVID-19, provenant de la population générale ou de populations de patients atteints de MII, nous ont appris qu'en dehors de l'âge, les principaux facteurs de risque de COVID-19 grave étaient les comorbidités telles que le diabète, l'hypertension et l'insuffisance rénale chronique, que les patients atteints de LES présentent en plus grande proportion que la population générale (135). Plus tard, les inquiétudes concernant les patients lupiques ont été renforcées par les études immunologiques montrant que les auto-anticorps anti-IFN de type 1, précédemment décrits dans le LES, étaient impliqués dans la pathophysiologie du COVID-19 sévère. (39). Le LES étant une maladie relativement rare, les premières analyses évaluant le pronostic du COVID-19 au cours du LES étaient basées sur un petit nombre de patients. En outre, la prédominance féminine ainsi que le profil de comorbidité particulier de la population lupique rendaient difficile la comparaison avec les données publiées précédemment, car la plupart des patients COVID-19 issus de la population générale et inclus dans les études étaient des hommes relativement âgés.

Pour mieux évaluer le pronostic du COVID-19 chez les patients vivant avec un LES en France, nous avons exploité la base de données médico-administrative nationale française "Programme de médicalisation des systèmes d'information" (PMSI) dans le cadre de deux études. La première, que nous avons publiée sous forme de lettre de recherche dans *Annals of the Rheumatic Diseases*, avait pour objectif de décrire quelles caractéristiques des patients étaient associées i) à une hospitalisation liée à un épisode de COVID-19 et ii) une issue favorable ou défavorable de l'épisode de COVID-19. Dans la seconde étude, publiée sous forme d'article complet dans la même revue, nous voulions comparer la survie des patients atteints de LES avec celle de témoins appairés non-lupiques après une défaillance d'organe associée au COVID-19.

Partie 2 : Efficacité et tolérance du vaccin BNT162b2 dans une cohorte de patients lupiques : le projet COVALUS (études 3 & 4).

Le développement rapide des vaccins anti-SARS-CoV-2 a soulevé beaucoup d'espoir dans la communauté des patients et des médecins concernés par le LES. Les vaccins antipneumococciques ou antigrippaux, avaient précédemment démontré une innocuité globale au cours du LES, mais une immunogénicité souvent réduite, en particulier chez les patients sous immunosuppresseurs. Malheureusement, les patients atteints de maladie auto-immune n'ont pas été inclus dans les essais cliniques initiaux des vaccins anti-SARS-CoV-2, et très peu de données scientifiques étaient alors disponibles quant à l'efficacité et la tolérance de la technologie de l'ARN messager dans cette population. En outre, l'émergence de différentes souches du virus, telles que les variants alpha ou omicron, a suscité des inquiétudes supplémentaires quant à l'immunogénicité de ces vaccins vis-à-vis des différents variants d'intérêt.

Pour étudier l'immunogénicité et la tolérance du vaccin BNT162b2 dans le LES, nous avons mené une étude prospective, monocentrique et observationnelle incluant des patients lupiques et des volontaires sains au cours de la première séquence de vaccination par le BNT162. Les individus étaient vus juste avant la première dose (T0), juste avant la deuxième dose (M1), 3 mois après la première dose (M3), et 6 mois après la première dose (M6). L'immunogénicité et la tolérance des patients atteints de LES, étaient évaluées aux niveaux clinique et biologique en prenant des volontaires sains comme référence. Nous avons recruté 55 patients atteints de LES et 11 volontaires sains entre mars et mai 2021. Le projet COVALUS a été financé par l'Agence Nationale pour la Recherche (ANR). Dans le

premier article, publié sous forme de lettre de recherche dans *Annals of the Rheumatic Diseases*, nous avons détaillé la réponse humorale dirigée contre les différents variants d'intérêt du SARS-CoV-2. Dans le second article, publié dans le *Journal of Autoimmunity*, nous avons analysé les effets du vaccin BNT162b2 sur les cellules dendritiques plasmacytoïdes et les cellules T auto-réactives.

Partie 3 : Progression de la couverture vaccinale et efficacité clinique des vaccins anti-SARS-CoV-2 à ARNm au sein de la population lupique de Suède (étude 5).

L'immunogénicité du vaccin anti-SARS-CoV-2 chez les patients atteints de LES a été étudiée peu de temps après la mise à disposition de ces vaccins, dans des études au nombre de sujets relativement limité. La concentration d'anticorps anti-Spike induite par le vaccin n'est cependant qu'une facette de l'immunogénicité du vaccin, qui n'est elle-même qu'un marqueur de substitution de l'efficacité vaccinale, définie par l'OMS comme une mesure de l'efficacité du vaccin dans le monde réel, avec des résultats cliniques. De plus, la question préliminaire et fondamentale de la couverture vaccinale n'a malheureusement pas été étudiée à grande échelle et avec un suivi à long terme dans le cas du LES.

Nous avons utilisé les registres nationaux suédois pour décrire la progression de la couverture et évaluer l'efficacité de la vaccination anti-SARS-CoV-2 chez les patients atteints de LES. En Suède, le système de santé est financé par les contribuables et accessible à tous les résidents. Les données générées par l'interaction avec le système de santé sont consignées dans différents registres qui peuvent être reliées entre eux à l'aide du numéro fiscal d'un individu. Nous avons pu relier le registre national des patients au registre des vaccinations et à d'autres registres afin de créer une cohorte de patients atteints de LES et de témoins appariés sur l'âge et le sexe vivant en Suède au début de l'année 2021.

Dans l'étude suivante, qui vient d'être soumise à *Rheumatology*, nous avons cherché à déterminer si l'efficacité clinique de la vaccination anti-SARS-CoV2 par ARNm est affectée par le LES, et si oui, dans quelle mesure et chez quels patients. Plus précisément, nous avons cherché à répondre aux questions suivantes : i) La progression de la couverture vaccinale a-t-elle été similaire entre les patients atteints de LES et la population générale ? ii) Les patients lupiques vaccinés présentent-ils un risque accru d'hospitalisation pour COVID-19 par rapport aux personnes vaccinées non atteintes de LES issues de la population générale ? iii) Parmi les patients atteints de LES, le risque d'hospitalisation pour COVID-19 varie-t-il en fonction du traitement immunosuppresseur ?

Partie 4 : Risque de poussée lupique après admission pour COVID-19 dans la population lupique (étude 6).

Si la première préoccupation des patients atteints de LES au début de la pandémie a été le risque de COVID-19 sévère, celle du risque de poussée de lupus induite par le COVID-19 a également rapidement émergé. Dans le service de médecine interne de l'hôpital Bichat, nous avons été marqués par un cas de poussée de lupus induite par COVID-19 chez une femme de 20 ans. Ce cas, rapporté dans une lettre aux éditeurs de la revue *Clinical and Experimental Rheumatology*, nous a conduits à émettre l'hypothèse que le LES pourrait avoir une interaction particulière avec le SARS-CoV-2 en raison de l'importance de l'IFN de type 1 et de la présence d'auto-anticorps anti-IFN de type 1 dans la pathophysiologie des deux maladies. Le risque d'une poussée de LES induite par une infection est difficile à étudier avec les données des registres, car il est impératif d'évaluer parfaitement la séquence temporelle entre l'infection et la poussée afin d'éviter le piège de la causalité inversée.

Nous avons donc décidé d'utiliser l'Entrepôt de Données de Santé (EDS) de l'Assistance Publique - Hôpitaux de Paris (APHP), qui collecte et agrège quotidiennement toutes les données anonymes générées par les hospitalisations et les consultations dans un groupe de 39 hôpitaux publics situés dans l'agglomération parisienne. La base de données rassemble des informations médicales, biologiques et administratives structurées, collectées prospectivement auprès de 11 millions de patients. Les principales différences entre cette base de données, le PMSI et les registres nationaux suédois sont que dans l'EDS, nous avons eu accès aux mesures biologiques et aux dossiers médicaux électroniques (DME) rédigés en langage naturel par le personnel médical en charge du patient.

Dans cette étude, soumise à *Rheumatology* le 22 août 2023, nous avons inclus 4 533 patients ayant reçu un code CIM-10 de LES dans l'un des 39 hôpitaux universitaires de l'agglomération parisienne entre le 15 juillet 2017 et le 9 février 2022. J'ai personnellement examiné les dossiers médicaux des 128 patients qui ont également reçu un code de diagnostic COVID-19 au cours de l'une de leurs hospitalisations afin de vérifier la validité des diagnostics de LES et de SARS-CoV-2. Nous avons pu appairer 79/81 des cas vérifiés avec 79 témoins appariés dont les dossiers médicaux électroniques ont également été examinés. Dans cette population appariée, nous avons examiné le risque absolu et relatif de poussées au cours du suivi.

Partie 5 : Incidence des MII après un épisode de sepsis en France (étude 7).

Les études précédentes de cette thèse se sont concentrées sur l'interaction entre le SARS-CoV-2 (qu'il s'agisse d'une infection ou d'une vaccination) et le LES. Cependant, ces deux pathologies ne sont qu'un cas particulier de la relation plus générale qui lie les maladies infectieuses et les MII. Nous avons vu dans le projet COVALUS et dans l'étude sur le risque de poussée de LES induite par COVID-19 que l'un des moyens possibles de communication entre ces deux entités est l'utilisation de cytokines pro-inflammatoires. Nous avons donc émis l'hypothèse que les cytokines pro-inflammatoires produites par le système immunitaire lors d'une infection pourraient déclencher l'apparition de MII.

Pour tester notre hypothèse, nous avons décidé de retourner aux données de la base médico-administrative hospitalière nationale française (le PMSI) afin d'étudier le risque de survenue d'une MII après une infection sévère. Pour ce faire, nous avons étudié le taux d'apparition d'une MII systémique chez les survivants d'un sepsis par rapport aux survivants d'un infarctus aigu du myocarde (IAM), après avoir exclu les patients chez qui une MII avait déjà été diagnostiquée. Nous avons choisi le sepsis comme marqueur d'infection grave, parce qu'il implique la libération de cytokines pro-inflammatoires qui sont responsables de la plupart des symptômes systémiques observés au cours du sepsis.

Nous avons inclus 62 257 patients ayant présenté un sepsis en France en 2020 et le même nombre de patients ayant présenté un IAM, appariés sur l'âge ± 2 ans, le sexe et certaines comorbidités grâce à un algorithme d'appariement exact aléatoire sans remise. Chez ces patients, nous avons comparé le taux d'apparition des MII globalement et pour chaque MII à l'aide d'un modèle marginal de Cox. Nous avons observé une incidence remarquablement élevée de MII chez les survivants d'infections graves. J'ai mené cette étude avec Aloïs Héлары, qui réalisait sa thèse de Master 2 dans notre unité de recherche. Ce manuscrit est actuellement soumis depuis le 31 juillet 2023 auprès du *Journal of Internal Medicine*.

Synthèse

Un résumé des principaux résultats de cette thèse est présenté ci-dessous :

Questions de recherche	Résultats
Les patients atteints de MII telle que le LES ont-ils un risque particulier face au COVID-19 ?	<ul style="list-style-type: none">- Les patients lupiques sont plus susceptibles de développer une forme sévère de COVID-19, s'ils présentent des comorbidités déjà identifiées comme des facteurs dans la population générale, tels que l'âge avancé, le sexe masculin et l'hypertension.- La défaillance d'organes associée au COVID-19 est associée à un mauvais pronostic de révélation tardive chez les patients atteints de LES, par rapport aux patients non atteints de LES indépendamment des comorbidités.
Quelle est la protection induite par les vaccins à ARNm chez les patients atteints d'une MII, comme le LES ?	<ul style="list-style-type: none">- Deux doses du vaccin BNT162b2 ont entraîné une faible réponse immunitaire chez les patients atteints de LES. La réponse vaccinale était encore plus faible contre les variantes d'intérêt du SARS-CoV-2 autres que la souche historique "Wuhan".- L'efficacité vaccinale était moindre chez les patients atteints de LES, par rapport aux contrôles issus de la population générale, et plus faible chez ceux traités par immunosuppresseurs.
Quel est l'effet d'une vaccination par ARNm au cours d'une MII telle que le LES ?	<ul style="list-style-type: none">- Le vaccin BNT162b2 induit une activation transitoire in vivo des CDp qui contribue à la réponse immunitaire anti-SARS-CoV-2.-Le vaccin BNT162b2 réduit le nombre de cellules T auto-réactives circulantes, ce qui suggère que la vaccination pourrait avoir un impact bénéfique sur le LES
Quel est l'impact d'une infection virale comme le COVID-19 sur l'activité des MII systémiques telles que le SLE ?	<ul style="list-style-type: none">- Les patients atteints de LES présentent un risque accru de poussée de lupus à la suite d'épisodes symptomatiques de COVID-19 ayant nécessité une hospitalisation- Les infections virales pourraient déclencher une poussée auto-immune par le biais d'une interaction entre l'IFN de type 1 et les auto-anticorps anti-IFN de type 1.
L'infection sévère est-elle un facteur déclenchant de MII ?	<ul style="list-style-type: none">- Nous avons observé une incidence de MII après un sepsis. Cette incidence était supérieure à celle observée chez des témoins hospitalisés pour un infarctus aigu du myocarde.

L'objectif principal de cette thèse était de fournir des données scientifiques qui contribueraient à une meilleure compréhension de l'interaction entre les MII systémiques telles que le LES et les maladies infectieuses. Les années 2020, 2021, 2022 et 2023, au cours desquelles ce travail a eu lieu, ont également été les années d'émergence et de régression de la pandémie de COVID-19, pandémie qui a fait surgir de nouvelles préoccupations urgentes en rapport avec le même sujet. J'ai donc décidé d'adapter mes efforts de recherche en considérant l'interaction entre le LES et le COVID-19 comme un modèle de la relation entre les MII et les maladies infectieuses. Ce faisant, mon objectif était de fournir des informations pertinentes et actualisées aux patients atteints de LES et aux médecins pendant la crise aiguë du COVID-19, mais aussi d'aborder la plus large question de fond des liens entre les maladies infectieuses et les MIIs.

Les résultats de cette thèse pourraient être synthétisés en deux sections : le risque infectieux des patients atteints de SLE et la modulation de l'auto-immunité par les stimuli infectieux.

A- Le risque infectieux des patients atteints de SLE.

Au début de la pandémie, très peu de données étaient disponibles sur le risque spécifique des patients lupiques vis-à-vis du SARS-CoV-2. Cependant, on les savait plus sensibles à d'autres infections, notamment respiratoires, telles que la pneumonie à pneumocoque ou la grippe. D'un point de vue épidémiologique, on aurait pu émettre l'hypothèse que les comorbidités (qui sont fréquentes au cours du LES) sont le médiateur responsable du risque de COVID-19 sévère, et que le LES n'implique pas de risque particulier en soi. Dans la première étude de cette thèse, nous avons pu confirmer que le risque d'hospitalisation et d'évolution défavorable après COVID-19 était principalement associé à des comorbidités déjà identifiées comme facteurs de risque d'infection sévère dans la population générale, telles que l'âge avancé, le sexe masculin et l'hypertension. Nous avons observé qu'un antécédent de néphrite lupique était également associé à un risque d'hospitalisation et à une mauvaise évolution de la COVID-19. Par la suite, nous avons élargi notre champ d'étude pour inclure tous les patients hospitalisés pour un sepsis en France. Nous avons alors pu comparer le devenir des patients atteints ou non de LES après un sepsis COVID-19. Il est à noter que nous avons décidé d'utiliser le terme de défaillance d'organe associée au COVID-19 dans l'article plutôt que celui de sepsis COVID-19 à la demande des relecteurs, qui estimaient que le mot sepsis devait être limité aux infections bactériennes. Notre description des 196 patients atteints de LES avec un sepsis COVID-19 a confirmé que ces patients présentaient plus de comorbidités que les 113 371 contrôles non-lupiques atteints de sepsis COVID-19, même si les patients atteints de LES étaient plus jeunes et plus souvent des femmes.

Après appariement sur l'âge ± 2 ans, le sexe, l'insuffisance rénale chronique, l'hypertension artérielle, les antécédents cardiovasculaires, le diabète sucré, les maladies pulmonaires chroniques et l'obésité, nous avons mis en évidence un mauvais pronostic de révélation tardive chez les patients atteints de LES, qui pourrait être attribué au LES spécifiquement, indépendamment des comorbidités.

Ces travaux soutiennent l'idée qu'au sein d'un groupe d'âge, les patients souffrant d'une MII systémique, comme le LES, devraient être vaccinés en priorité.

Malheureusement, les MII interfèrent également avec la protection induite par le vaccin. Nos études sur l'immunogénicité et l'efficacité clinique du vaccin chez les patients atteints de LES ont montré que la protection conférée par le vaccin est moindre dans cette population. A l'aide d'un test ELISA multiplex original, nous avons évalué les réponses vaccinales humorales spécifiques contre les variantes B (ancestrales), alpha, delta et omicron chez des patients atteints de LES et chez des volontaires sains. Nous avons observé une réponse vaccinale considérablement réduite chez les patients atteints de lupus érythémateux disséminé. Les patients sous traitement immunosuppresseur lourd (azathioprine, mycophénolate mofétil ou anti-CD20) ont été exclus de cette analyse et la plupart des patients inclus n'avaient que de faibles doses de stéroïdes. Par conséquent, nos résultats suggèrent que la réponse au vaccin n'est pas entièrement déterminée par le traitement immunosuppresseur en cours et que la réponse humorale au vaccin devrait être surveillée chez les patients atteints de LES, même en l'absence de traitement immunosuppresseur. Ce suivi pourrait nous aider à identifier les patients pouvant bénéficier d'autres stratégies prophylactiques telles que les anticorps monoclonaux préexposition, qui sont efficaces dans cette population (136).

Ensuite, nous avons pu examiner plus en détail l'immunogénicité du vaccin en analysant les lymphocytes B et T spécifiques induits par le vaccin. Nous avons observé, grâce à la cytométrie en flux, que l'absence de production d'anticorps était associée à une absence d'induction de cellules B spécifiques chez les patients lupiques. Nous avons également observé une réponse T plus faible chez les patients atteints de LES, par rapport aux volontaires sains, même si cette différence n'était pas significative. Ces résultats confirment que les vaccins ARNm sont moins immunogènes chez les patients atteints de lupus érythémateux disséminé. Notre étude COVALUS, manquait malheureusement de puissance pour évaluer l'efficacité vaccinale, c'est-à-dire la protection clinique induite par le vaccin en « vraie vie ».

Pour pouvoir étudier l'efficacité clinique du vaccin, j'ai dû revenir aux données des registres nationaux qui offraient la puissance suffisante pour cette analyse. En France, il est impossible de fusionner les registres de vaccination aux registres médicaux. Ceci m'a conduit vers la division d'épidémiologie clinique de l'Institut Karolinska de Stockholm, où j'ai pu tirer parti de l'exhaustivité des registres nationaux suédois. En effet, la fusion entre le registre national médical et le registre recensant les vaccinations et à d'autres registres utiles est possible en Suède

Puisqu'il ne peut y avoir de protection vaccinale sans administration du vaccin, nous avons d'abord cherché à comparer l'évolution de la progression vaccinale chez les patients atteints de LES et chez les témoins de la population générale appariés selon l'âge et le sexe. Nous avons observé que presque tous ont reçu leur 1^{ère} dose de vaccin au printemps 2021 et que la progression de la couverture vaccinale fut similaire entre les patients lupiques et la population générale. En quelques mois, 90 % de la population était vaccinée. Bien que 90 % puisse passer pour un chiffre élevé, nous pourrions collectivement espérer encore mieux. En analysant les différences entre les patients lupiques vaccinés et non vaccinés, nous avons observé que les patients non vaccinés étaient plus jeunes et plus souvent nés hors de Suède. Les médecins devraient être conscients de ces résultats afin de mieux promouvoir la vaccination dans cette population.

En ce qui concerne l'efficacité vaccinale, nous avons observé une très faible incidence d'hospitalisations dues au COVID-19 après l'administration de deux doses de vaccin à ARNm, tant chez les personnes atteintes de lupus érythémateux systémique que chez les autres. Cela confirme que les vaccins SARS-CoV-2 à ARNm constituent une prophylaxie efficace contre les formes graves de COVID-19. Cependant, en comparant l'efficacité des vaccins entre les patients atteints de LES et les individus issus de la population générale, nous avons constaté que le rapport de risque [IC 95 %] associé à une hospitalisation pour COVID-19 était de 3,47 [1,63-7,39] pour les patients atteints de LES. Cela corrobore nos résultats précédents basés sur l'immunogénicité du vaccin et appelle à une surveillance étroite de la réponse vaccinale chez les patients atteints de LES et les patients atteints de MII en général, d'autant plus que ces patients pourraient se voir proposer une prophylaxie alternative efficace telle que les anticorps monoclonaux. Il est intéressant de noter que le risque d'hospitalisation du sous-groupe de patients non exposés aux immunosuppresseurs était très similaire à celui des comparateurs issus de la population générale.

B- Modulation de l'auto-immunité par des stimuli infectieux.

Comment l'auto-immunité peut être modulée par des stimuli d'origine infectieuse est une question difficile à étudier. Le choix du critère de jugement est crucial : les éléments biologiques caractérisant

l'auto-immunité, telles que la production d'auto-anticorps, constituent un marqueur de substitution pertinent et facile à étudier, mais ils ne correspondent pas totalement aux critères cliniques qui nous intéressent réellement, à savoir l'induction d'une activité auto-immune clinique ou l'apparition d'une MII de novo. L'exposition est également difficile à évaluer, car l'organisme est constamment exposé à des agents pathogènes infectieux. Et, comme nous l'avons déjà vu, les patients atteints de MII sont souvent immunodéprimés, donc plus susceptibles de s'infecter, ce qui signifie que le risque de causalité inversée doit être évalué avec prudence.

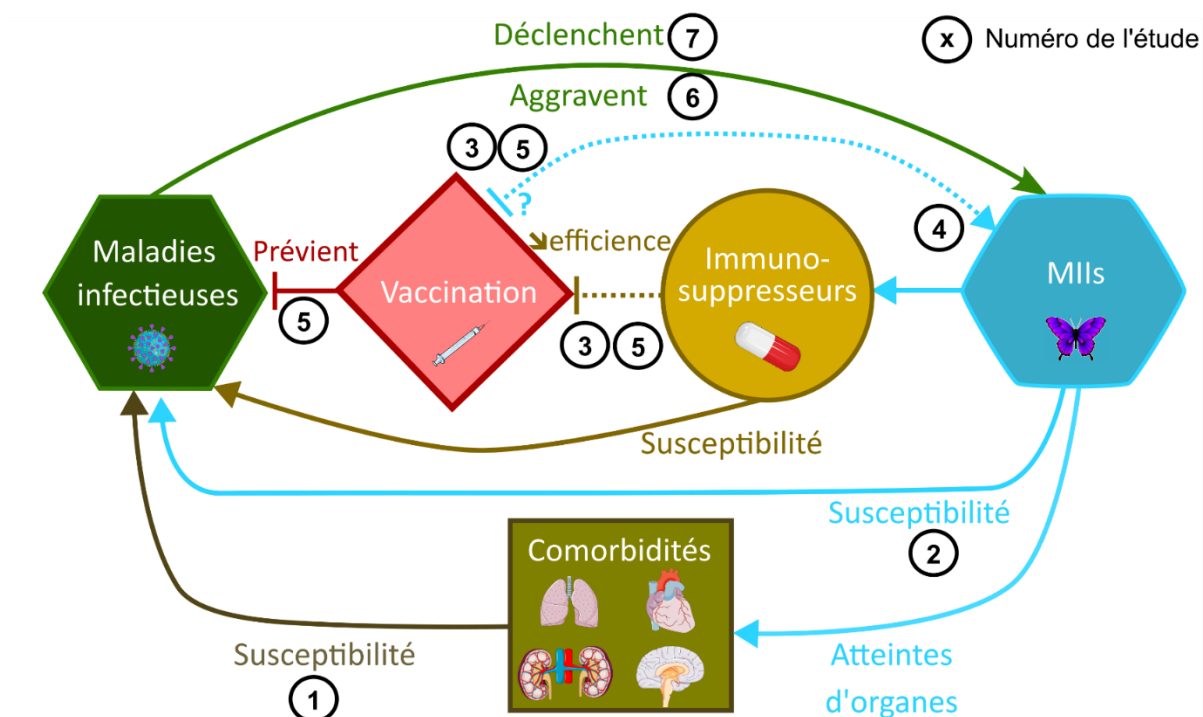
Au cours du projet COVALUS, nous avons pu suivre de près l'impact du vaccin sur plusieurs marqueurs d'auto-immunité. Nous avons observé qu'un mois après la première dose (M1), la production ex-vivo d'IFN-I par les CDp était accrue, tant chez les patients lupiques que chez les volontaires sains. Cependant, à M3, cette production est restée élevée uniquement chez les patients atteints de LES. Compte tenu de l'importance de l'IFN α dans la physiopathologie du LES et des preuves accumulées montrant que le niveau d'IFN α circulant est corrélé à l'activité de la maladie, ce résultat pourrait suggérer un effet délétère du vaccin chez les patients atteints de LES. D'autre part, nous avons également constaté que l'activation des CDp induite par le vaccin contribue à la réponse vaccinale puisque le niveau d'expression de CD86 et de HLA-DR à la surface des CDp est corrélé à l'immunogénicité du vaccin. Néanmoins, l'activation du système immunitaire inné est contrebalancée par une diminution de l'activité des lymphocytes T auto-réactifs chez les patients atteints de LES au cours du suivi post-vaccinal. Cette constatation, associée à l'absence de variation des niveaux des marqueurs biologiques d'activité lupique (niveaux d'IgG anti-ADN natif et de complément), nous a permis de conclure que l'effet global sur l'auto-immunité du vaccin BNT1362b2 n'était pas cliniquement significatif chez les patients atteints de lupus érythémateux systémiques.

Après avoir étudié les effets de la vaccination, nous avons étudié ceux de l'infection par le virus SARS-CoV-2 chez les patients atteints de LES. Au sein de l'Entrepôt de Données de Santé de l'AP-HP, nous avons appariés des patients atteints de LES avec et sans hospitalisation pour COVID-19 sur des variables démographiques (âge, sexe), des marqueurs d'activité du LES (complément, taux d'anti-ADN natif), et des marqueurs d'insuffisance d'organe attribuables au LES (maladie rénale chronique). Nous avons observé une incidence significativement accrue de poussées de lupus après COVID-19. Les poussées observées après COVID-19 étaient plus graves, avec davantage de poussées rénales, que celles observées dans le groupe de comparaison. Ces résultats confirment l'impression donnée par le cas précédemment rapporté, à savoir qu'une infection virale telle que COVID-19 pourrait être responsable d'une poussée auto-immune chez les IMID.

Après avoir étudié les interactions entre le LES et le SARS-CoV-2, nous avons élargi le spectre de notre analyse en étudiant le risque d'apparition de MII chez les survivants d'un épisode de sepsis. Grâce à la base de données nationale PMSI, nous avons pu comparer les patients ayant présenté un sepsis en 2020 en France à tous les patients hospitalisés pour un infarctus aigu du myocarde (IAM) au cours de la même période. Nous avons observé un risque accru de MII de l'ordre de 2,80 (HR ; 95%CI [2,22-3,54]) à partir du 16e jour après l'admission dans le groupe sepsis. Cette relation importante et significative est restée stable dans de multiples analyses de sensibilité, et le risque d'incidence de MII après un sepsis était superposable lorsque nous avons effectué la même analyse avec les sepsis de 2019, soit avant l'ère COVID-19. Le risque de MII après une infection grave différait selon la nature de la maladie auto-immune et était plus élevé pour la thrombopénie immunologique, l'anémie hémolytique auto-immune et la vascularite associée aux ANCA, qui étaient déjà connues comme pouvant potentiellement être déclenchées par un agent pathogène infectieux. Ces résultats ont confirmé notre hypothèse initiale selon laquelle une infection grave, telle qu'un sepsis, quel que soit l'agent pathogène en cause, est associée à un risque accru d'apparition d'une MII.

Conclusion

En utilisant une approche translationnelle, à la fois épidémiologique et immunologique, pour étudier les relations entre les infections et les MII, et en utilisant le LES et le SARS-CoV-2 comme modèle, nous avons pu répondre à nos questions de recherche et valider certaines de nos hypothèses. Notre travail a permis de mieux comprendre les intrications des infections et des MII, qui peuvent maintenant être décrites comme ceci :



Nous avons validé le cercle vicieux reliant les maladies infectieuses et les MII, mentionné dans l'introduction, en montrant que les patients atteints de MII telles que le LES, sont plus susceptibles de souffrir d'infections graves et que les maladies infectieuses peuvent déclencher ou exacerber les MII. Cependant, nous avons également identifié d'autres acteurs importants dans cette relation. Nous avons constaté que la vaccination peut prévenir efficacement les maladies infectieuses chez les patients atteints de LES, mais que l'immunogénicité et l'efficacité clinique du vaccin sont réduites par les traitements immunosuppresseurs. En ce qui concerne l'effet du LES, indépendamment du traitement immunosuppresseur, sur la protection induite par la vaccination, nous avons observé que les patients atteints de LES ont une immunogénicité réduite du vaccin, mais que l'efficacité clinique pourrait être préservée. Nous n'avons pas constaté d'impact cliniquement significatif de la vaccination sur l'évolution du LES, mais nous avons observé un impact significatif du vaccin sur le système immunitaire inné et adaptatif des patients lupiques.

Introduction

The main task of the immune system (IS) is to protect the human body from non-self-, threatening-entities. The various immune components act either as barriers, sensors, regulators, auxiliaries, memory, or effectors against microorganisms such as bacteria, viruses and parasites which are widespread in the environment and potentially dangerous. To perform well and safely, the IS must be able to recognize millions of different non-self-antigens while being non-responsive to self-antigens. In 1948, this ability for the IS to remain unresponsive when facing specific antigens such as self-antigens was named “immune tolerance” by the Australian immunologist Macfarlane Burnet (1,2). A breakdown of this immune tolerance can lead to autoimmunity (AI) which can be defined as a self-responsiveness of the IS toward the organism. AI is involved in the pathophysiology of nearly 100 different types of autoimmune diseases (AId), including some very common, organ-specific conditions like autoimmune thyroid disease, or type 1 diabetes (T1D), while others AId involve multiple organs and exhibit a variety of immunologic dysfunctions (3). Systemic lupus erythematosus (SLE) may be considered as a good example and a prototype of AI: it affects several organs and involves marked autoimmune features such as pathogenic autoantibodies that can be found both in the blood and in the damaged tissues of the patients (4). Nowadays, the concept of autoimmune disease has been broadened to the one of *immune-mediated inflammatory disease* (IMIDs) to include all the diseases characterized by an immune dysregulation leading to inflammation (5). IMIDs are a public health issue since they impact approximately 3-5% of the population (6,7).

Infectious agents continually challenge the IS. If microorganisms succeed in penetrating the first defense barriers, infection occurs. This infection will stimulate the immune system, which can respond in different ways, with varying intensity and efficacy, depending on the individual infected, the source of infection and the pathogen. Infectious stimuli has been suspected for decades to alter immune tolerance and to cause or to trigger AI in various ways (8,9). In some specific situations, the causal relationship between infectious diseases and IMIDs is well documented. For example, a recent study provided strong evidence for a causative role of Epstein-Barr Virus (EBV) in the onset of multiple sclerosis (MS)(10). Besides, among patients with already established IMIDs, infections have also been suspected to be responsible for a worsening of the disease (11).

On the other hand, patients with IMIDs are often immunocompromised, facing a high risk of severe infection (12), either by non-opportunistic or opportunistic pathogens. In Spain, it has been recently showed that severe infections are still the leading cause of death among patients living with SLE (13).

In most cases, immunosuppression is mainly driven by the specific treatment received for the IMID but an association between the activity of the IMID and the risk of severe infectious diseases, independent of the treatment has also been observed (14).

Therefore, the relationship between infectious and autoimmune diseases is commonly described as this (**Figure 1**):

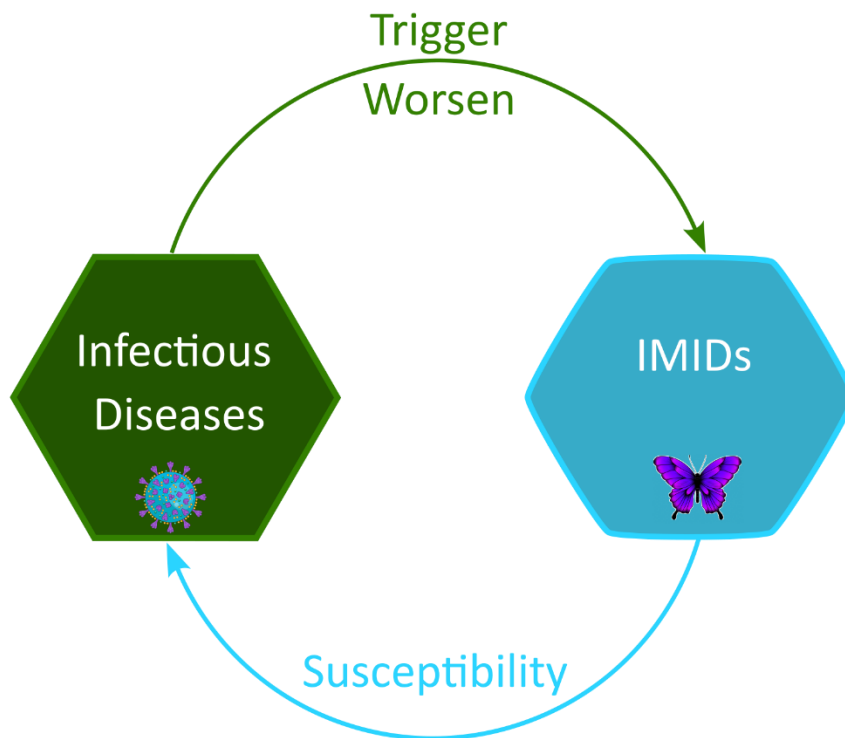


Figure 1: Usual representation of the relationship between infections and IMIDs.

It then appears that infectious diseases and autoimmune diseases interplay through complex relationships and that they even may share some common pathophysiological mechanisms. Primary immune deficiencies, such as common variable immunodeficiency, which increase the risk of both infection and autoimmunity (15) indicate they have such intertwined roots. However, this circle probably does not represent reality's complexity nor its complete picture. For example, in 1970, Greenwood and Voller observed that infecting lupus-prone New-Zealand mice, with the parasite *Plasmodium berghei* prevented the development of severe lupus nephritis (16). The mechanism underlying this phenomenon was recently further investigated by Amo et al. (17) who observed that parasite-induced protection was not due to a systemic effect of infection on autoimmunity, as previously thought, but rather to alterations in specific immune cells (bone marrow-derived type 2 inflammatory dendritic cells) that hindered their ability to infiltrate the kidneys.

To prevent the deleterious effects of infectious diseases, vaccination is a promising hope. By avoiding infections and reinforcing the immune system, vaccines could break this previously described vicious cycle. In this context, vaccines have become the cornerstone of infectious disease prophylaxis in patients living with autoimmune disease (18). Interestingly, one study showed that the pneumococcal polysaccharide vaccine is also able to decrease the autoimmune features of MRL/lpr mice which spontaneously develop autoimmunity and which are commonly used as a SLE murine model (19). However, vaccination coverage has unfortunately been challenged by the common belief that vaccination could induce flare of autoimmunity (20). Furthermore, vaccine effectiveness is often diminished among patients with IMIDs, and a lot of pathogens are not covered by the vaccines currently available.

The emergence of the SARS-CoV2-pandemic in 2020 followed in 2021 by the global anti-SARS-CoV2 vaccination campaign has brought this topic back to the forefront. According to the World Health Organization (WHO)(21), as of April 19th, 2023, there have been 763,740,140 confirmed cases of COVID-19, including 6,908,554 deaths. And, as of April 16th, 2023, a total of 13,337,787,446 vaccine doses have been administered. With 3-5 % of the population having an IMID, that means that millions of COVID-19 cases occurred in patients with IMIDs, and millions of vaccine doses were administered to IMID patients. Since the beginning of the pandemic, patients with IMIDs such as SLE raise a special concern. Their risk of facing a severe infection with this newly emerged virus and the impact of an infection on their autoimmune disease were unknown. Additionally, because patients with IMIDs were excluded at first from SARS-CoV-2 vaccine clinical development programs, data regarding the immunogenicity and the safety of these new vaccines in this population were scarce.

Thus, given the pandemic context and amidst the dense and complex links between infectious diseases and autoimmunity a lot of unresolved questions remains:

- 1- Do patients with systemic IMIDs such as SLE are at a special risk when facing COVID-19?
- 2- What is the protection conferred by mRNA vaccines in patients with SLE?
- 3- What is the impact of a mRNA vaccination in IMIDs such as SLE?
- 4- What is the impact of a severe viral infection such as COVID-19 in IMIDs such as SLE?
- 5- In a more general sense, is severe infection a risk factor for developing IMIDs?

Using a translational, i.e. epidemiological and immunological, approach we sought to better understand the relationship between infection and autoimmunity and more particularly the links between SLE, COVID-19 and anti-SARS-CoV-2 vaccination.

State of the art

A-Pathophysiological pathways leading from infection to immune-mediated inflammatory diseases.

Direct relationships between specific pathogens and IMID onset.

Some autoimmune diseases have been closely related to specific infections. One of the most famous examples is the association between the bacteria *Campylobacter jejuni* and acute inflammatory demyelinating polyradiculoneuropathy also called Guillain-Barré syndrome. It is believed that *Campylobacter* can trigger an immune-mediated damage to the peripheral nerves by employing a process known as molecular mimicry. Because *Campylobacter* has epitopes that resemble gangliosides, the immunization against it will lead to the production of autoantibodies that attack peripheral nerve targets. (22). During the molecular mimicry process, a susceptible host becomes infected with a microorganism that possesses antigens which are similar to the host's own antigens, but still distinct enough to provoke an immune response when they interact with T cells. This leads to a breakdown of tolerance towards autoantigens, causing the immune response to cross-react with the host's own structures, ultimately resulting in autoimmune reactions. (Figure 2) (23,24).

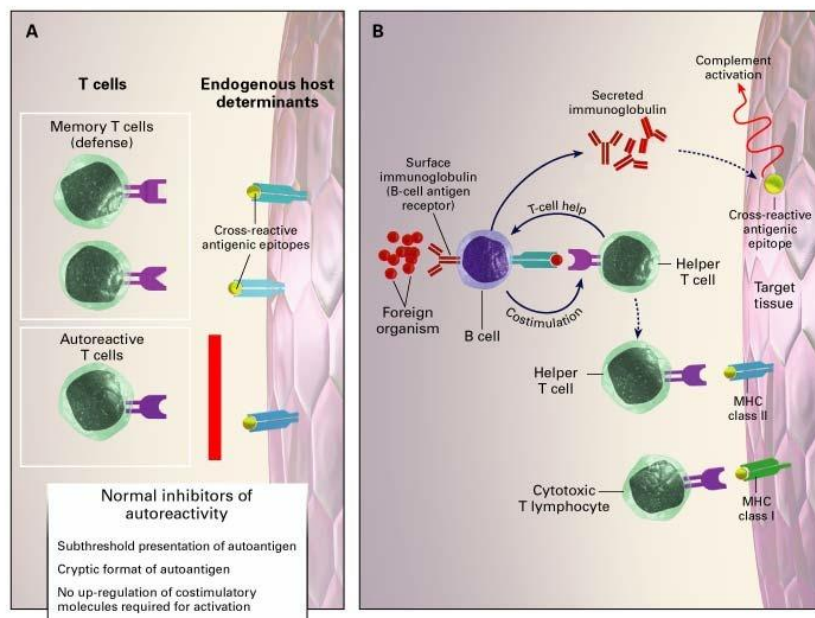


Figure 2: Molecular mimicry, from Albert et. Inman, NEJM 1999 (23)

However, not all infection-induced autoimmunity can be explained by molecular mimicry. Reactive arthritis (ReA) is another well-known IMID that can be triggered by an infection (25), but in this case through infection persistence. ReA encompasses a range of symptoms, including joint, skin, and eye problems, that can occur following a genito-urinary, respiratory, or enteric infection. Persistent bacterial components of *Chlamydia trachomatis*, the most common cause of ReA, have been shown to cause chronic inflammation and contribute to the development of ReA (26). Similarly, in other IMIDs triggered by specific pathogens, such as sub-acute sclerosing panencephalitis triggered by *Paramyxovirus* (27), *Chikungunya* arthritis (28), or polyarteritis nodosa triggered by hepatitis B virus (29), it is believed that it is the persistence of the pathogen that induces a chronic immune response leading to the IMID onset. In this setting, a chronic infectious stimulus challenges the immune system which respond to it by causing inflammation. Therefore, these diseases cannot be considered typical primary autoimmune diseases, but fall within the spectrum of IMIDs.

However, molecular mimicry and microbial persistence do not account for all the mechanisms linking infection to autoimmune diseases.

More general mechanisms linking infections and IMIDs.

A lot of broader pathophysiological mechanisms have been proposed to explain the connection between infectious diseases and immune-mediated inflammatory diseases (IMIDs). One such mechanism is known as bystander activation, which involves the activation of uninfected auto-reactive immune cells due to an inflammatory environment, co-signaling ligands, and interacting neighboring cells (30,31). During viral infection a lot of antigen-presenting cells (APCs) like dendritic cells are triggered. These activated APCs can potentially activate pre-primed autoreactive T cells, which may lead to autoimmunity. In addition to APCs, virus-specific T cells can also initiate bystander activation. CD8+ T cells can recognize infected cells and release cytotoxic granules, resulting in the death

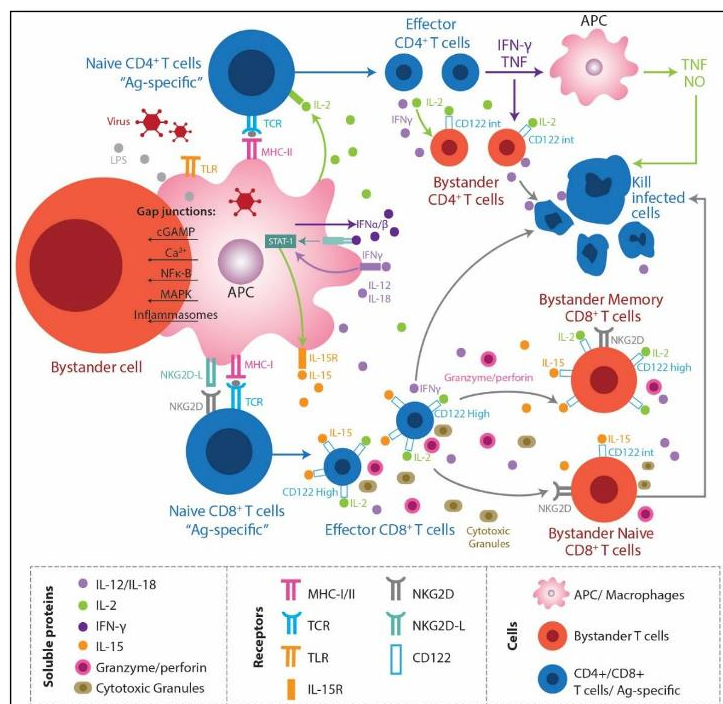


Figure 3: Bystander activation mechanisms, from (31)

of the infected cells. In this scenario, the dying cells, CD8+ T cells, and inflammatory cells (macrophages) within the inflammatory focus release cytokines that can lead to the killing of uninfected neighboring cells in a bystander manner. Bystander activation has been shown, with molecular mimicry, to be involved in the pathogenesis of type 1 diabetes (T1D) following infection by enteroviruses in mice. In 1998, Horwitz et al. (32) demonstrated that induction of T1D by coxsackievirus was more likely triggered by bystander activation than by molecular mimicry. Indeed, mice with a susceptible MHC-I capable of recognizing either autoantigens or the virus epitope did not develop disease after viral infection. In contrast, mice with quiescent autoreactive T cells (recognizing pancreatic islet antigens but not the virus) developed T1D after viral challenge. Authors concluded that T1D viral-induced onset was more the result of the stimulation by the proinflammatory milieu rather than through a molecular mimicry process.

Epitope spreading (ES) is another mechanism proposed in order to explain the onset or the worsening of autoimmune diseases after infection. ES is characterized by a broadening or a diversification of the initial immune response induced by immunization with a peptide antigen (33). If, during the process, T and/or B cell responses become reactive against an autoantigen, an autoimmune reaction may be triggered. ES can follow the release of endogenous self-antigens that can occur when an infection causes damage to a tissue. Such a phenomenon has been shown in the pathogenesis of experimental autoimmune encephalomyelitis (EAE) which is a murine model of multiple sclerosis. EAE can be triggered by the infection with Theiler's murine encephalomyelitis virus (TMEV), a natural mouse pathogen. In 1997, Miller et al observed that TMEV induces EAE because of de novo priming of self-reactive T cells to sequestered autoantigens released secondary to virus-specific T cell-mediated demyelination whereas they did not find any argument for cross-reactivity between TMEV and self-epitopes (34). Even without any infectious context, ES has been shown to be involved in the pathogenesis of different IMIDs such as SLE. Studies of the antigen reactivity of the sera of patients with lupus have demonstrated temporal shifts in both the recognition of another antigen (e.g., intermolecular spreading from Sm antigen to RNP reactivity) as well as in the reactivity to different epitopes within the same antigen (e.g., intramolecular spreading within a given antigen) (35,36).

COVID-19 and autoimmunity: the special case?

Since the beginning of the COVID-19 pandemic in 2019, a particular concern has arisen regarding the risk for COVID-19 to induce autoimmunity (37). One of the most intriguing, hypothesized framework between COVID-19 and AI is the involvement of type-1 IFN (IFN-I) and anti-IFN-I autoantibodies in the pathophysiology of normal antiviral immune response, of severe COVID-19 and in the one of IMIDs. It has been shown that autoantibodies neutralizing type I IFNs are present in 20 % of patients who died

from COVID-19 (38,39). Interestingly, these anti-IFN-I autoantibodies have been identified since the 1980s in patients with SLE (40), patients with thymoma and/or myasthenia gravis (41), and nearly all patients with autoimmune polyendocrinopathy syndrome type 1 (42). By blocking the IFN-I signaling pathways, these autoantibodies are thought to have a protective effect against IFN-I-driven inflammation, while they are deleterious in antiviral response. However, anti-IFN-I antibodies are not the only antibodies suspected to play a role in the putative raise of autoimmunity after COVID. Wang et al.(43) used a technique called rapid extracellular antigen profiling (REAP) to display a variety of human extracellular proteins on the surface of yeasts. Through this method, they were able to identify antibodies targeting 2,770 extracellular and secreted proteins, such as cytokines and chemokines, in the plasma of COVID-19 patients. They observed that patients with COVID-19 exhibit marked increases in autoantibody reactivities as compared to uninfected individuals. These autoantibodies were found to be functional and to increase disease severity in a mouse model of SARS-CoV-2 infection. Additionally, COVID-19 patients showed the presence of autoantibodies against tissue-associated antigens, which were positively correlated with disease severity. Interestingly, it was observed that some of these autoantibodies were induced by SARS-CoV-2 infection , indicating that COVID-19 could lead to loss of tolerance (44). Of note, the same authors observed that autoantibody dynamics were not affected by anti-SARS-CoV2 vaccination (45). Another research team observed that severe COVID-19 drives an extrafollicular pathway immune response in B cells characterized by a marked increase of type 2 double-negative B cells (CD19⁺ CD27⁻ IgD⁻ CD11c⁺ CD21⁻). Of note, this extrafollicular pathway activation had already been described in patients with active SLE (46). Besides, severe COVID-19 was also associated with a reduction of unswitched memory B cells, a feature consistently observed in SLE and other autoimmune diseases.

B- Epidemiological evidence linking infections to IMIDs.

The connection between infectious diseases and IMIDs.

Epidemiological science has provided several types of evidence regarding the relationship between infectious diseases and IMIDs. First, several epidemiologic studies have confirmed the role of infection in the pathogenesis of some autoimmune diseases. For example, very recently, Bjornevik et al. (10) demonstrated that a previous EBV infection is mandatory for the onset of MS. Here, epidemiologic data confirmed a pathophysiologic element that had been suspected for decades. Another famous example was the study of Cao-Lormeau et al. (47) who studied the 2013-2014 *Zika* virus outbreak in French Polynesia and provided evidence that Zika virus infection can cause Guillain-Barré syndrome. These epidemiological studies are challenging to conduct because reverse causation could bias the assessment of post-infection IMIDs (48). Epidemiology can also quantify the burden of autoimmunity

associated to infection. Nielsen et al. (49) found an association between hospital admission for an infection and 29 autoimmune diseases in the Danish register data. These associations were time and « dose » dependent with adjusted incidence rate ratios ranging from 1.24 to 2.58. The spectrum of the IMIDs that are more frequent after infection is so broad that the authors argue that infections should be considered as an environmental risk factor for IMIDs onset. Among patients already diagnosed with IMIDs, the impact of infections has also been studied during epidemiological studies. Buljevac et al (11) observed that patients with MS had a risk ratio of 2.1 (95% CI 1.4-3.0) of experiencing flares-up of the disease during a period of 2 weeks before and up to 5 weeks after the onset of a clinical infection, compared to the other periods.

The specific relationship between infections and lupus.

Among all the pathogens that have been suspected to play a role in SLE pathogenesis, EBV is probably the most studied one (50). Two meta-analyses by Li et al. (51) and Hanlon et al. (52) found an association between EBV and SLE, showing that the presence of anti-VCA and anti-EBNA IgG is more frequent in patients with SLE than in control individuals. This difference is even more marked in pediatric populations. In a US cohort of children or young adults only 70% of 125 controls were infected with EBV, whereas almost all (99%) of the 117 patients who developed pediatric lupus had already encountered the virus (53). The hypothesis that EBV could be, at least partly, responsible for SLE onset is supported by the fact that EBV has been described as an actor or a potential actor in many IMIDs (54). EBV is probably involved through several mechanisms in SLE pathophysiology (55): viral persistence, molecular mimicry, epitope spreading, and bystander activation. For example, it has been shown that antibodies directed against different regions of EBNA-1 protein cross-react with Sm antigen.

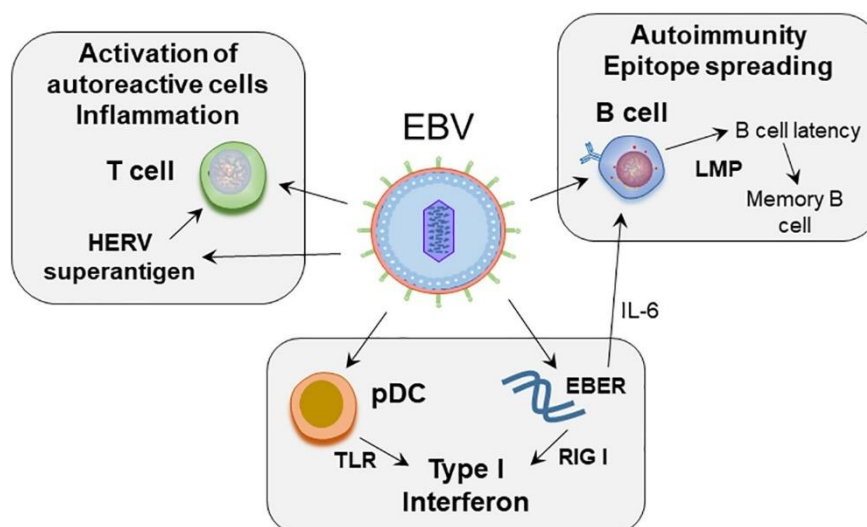


Figure 4: Proposed role of EBV in SLE pathogenesis, from (55)

However, EBV is not the only pathogen suspected of being involved in SLE pathogenesis. In addition to other herpes viruses such as CMV, Joo et al (56) used a self-controlled case series design to study the risk of hospitalization for autoimmune flare after an influenza infection. They observed an incidence ratio (IR) for lupus flares during the risk interval as compared with the control interval of 25.75 (95% CI 17.6–37.6).

IMIDs triggered or worsened by COVID-19.

The COVID-19 pandemic has put this topic back in the spotlight (57). Evidence suggests that, beyond the acute illness, patients who survive COVID-19 may experience post-acute sequelae - also referred as “long COVID” - which can involve pulmonary and broad extrapulmonary organs systemic manifestations (58). Even though the autoimmune nature of the “long COVID” entity is still debated (59) several studies observed a risk of IMIDs onset after COVID-19 infection. Chang et al. (60) used the TriNetX U.S. Collaborative Network to compare propensity score matched-patients with and without PCR-documented COVID. Among the 3,814,479 participants after matching, the COVID-19 cohort exhibited significantly higher risks of IMIDs onset (details in Figure 5).

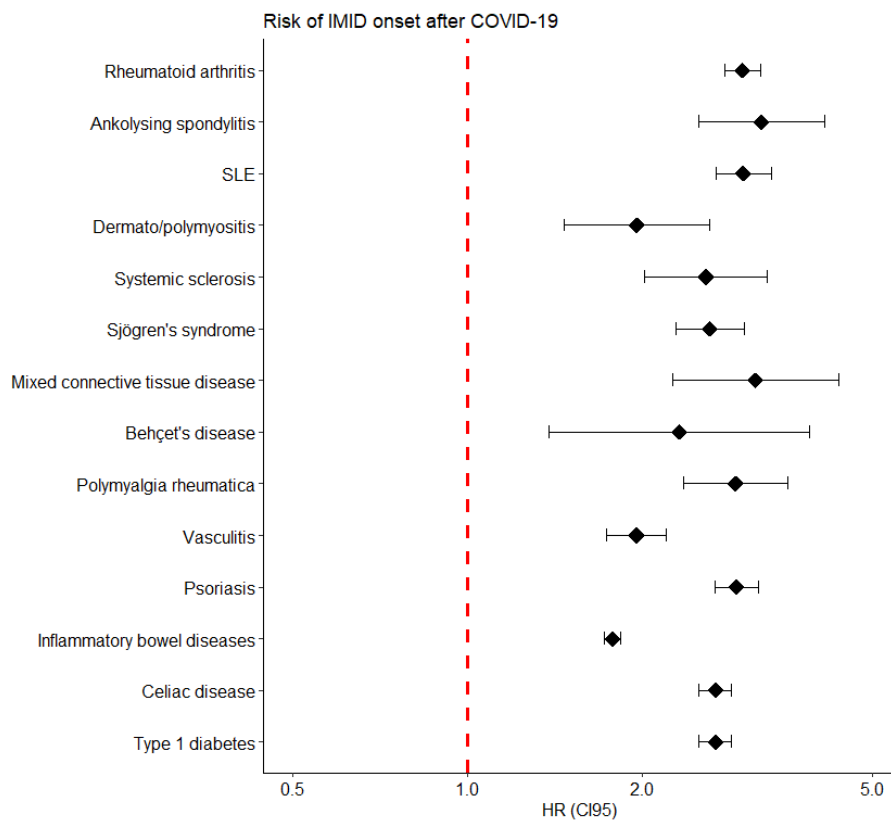


Figure 5: Risk of IMID onset after COVID-19, adapted from (60)

Similar findings were found in the German routine healthcare data (preprint not yet peer-reviewed) by Tesh et al. (61) who observed a 42.63% higher likelihood of developing autoimmunity for patients who had suffered from COVID-19 compared to matched control patients without COVID-19.

Evidence that COVID-19 can worsen already established IMIDs are scarcer. A very recent Dutch study (62) observed an increased disease activity after a first COVID-19 among patients with IMIDs. Beyond the immunologic effect of COVID-19, the more global impact of the pandemic on healthcare systems and its impact on the follow-up of patients with IMIDs should also be considered. Ciurea et al. (63) analysed the consequences of the transient reduction of activity in rheumatology services imposed by virus containment measures in the Swiss Clinical Quality Management cohort. They observed that a short interruption of in-person patient–rheumatologist interactions had no major detrimental impact on the disease course of spondylarthritis, rheumatoid arthritis and psoriatic arthritis as assessed by patient-reported outcomes.

Infections that protect against IMIDs: the hygiene hypothesis.

Interestingly, it has also been shown that in some situations, infections can also protect from or decrease the activity of IMIDs. For some authors, such as J-F Bach (64), the main factor in the increased prevalence of allergic and autoimmune diseases in industrialized countries is the reduction in the incidence of infectious diseases in those countries. This hypothesis, often referred as the “hygiene hypothesis” is not new as it was described already in the 1960’s by Leibowitz et al.(65) who observed that the risk of developing MS may be higher in individuals with a high level of sanitation in the childhood home. The most studied evidence supporting that hypothesis is the reduction of atopy and allergic diseases among individuals infected by helminths such as *Schistosoma haematobium*. This has been demonstrated by several immunoepidemiological and interventional studies (66,67). Apart from allergic diseases, contradictory results were observed in IMIDs. For example, a phase 2 trial (68) testing the efficacy and safety of a treatment by eggs of *Trichuris suis* for Crohn’s disease was very promising but the results of the phase 3, randomized control trial (69) were disappointing. Finally, the most compelling epidemiological evidence for a protective role of an infectious agent in IMID onset could be the study of Pedrini et al.(70) who performed a case-control study investigating the hypothesized role of *Helicobacter pylori* in the onset of MS. They observed that *Helicobacter pylori* seropositivity was found to be lower in the patients with MS than in the control group (16% vs 21%) with the decrease pertaining to females (14% vs 22%, $p=0.027$) but not males (19% vs 20%, $p=1.0$).

C- The burden of infection among patients with IMIDs.

Patients with IMIDs face an increased risk of severe infections.

Most of the patients living with IMIDs are considered as being more susceptible of experiencing infections, either because of their immunosuppressive treatment, of their comorbidities and sometimes even because of the IMID itself. In patients with IMIDS, severe infectious diseases are the primary reason for admission in intensive care unit according to a French study conducted in 10 university hospitals (71). The burden of infection has been well studied in rheumatoid arthritis since the 1950s, with observational studies evaluating the overall mortality of these patients. Cobb et al. (72) presented in the *New England Journal of Medicine* in 1970 data on rate of survival and cause of death of 475 patients with rheumatoid arthritis in which they observed that 25 % of deaths were related to infections which was the most common reported cause. More recently, Mehta et al. (73) reported that the incidence rate ratio of infections requiring hospitalization in patients with RA was 1.5 greater (95% CI 1.2 to 1.5) than in patients with non-inflammatory rheumatic disease. In addition to age and important comorbidities, disease modifying drugs which are often immunosuppressive could be considered responsible for at least a part of this burden. However, the ever-increasing number of therapeutic options makes this topic complex to study. In a very recent study, Frisell et al. (74) studied the relative incidence of serious infections in RA patients in Sweden within different subgroups defined by the use of different biological and targeted synthetic disease-modifying antirheumatic drugs. They observed that patients treated by infliximab and by rituximab were at higher risk compared to etanercept which was used as a reference.

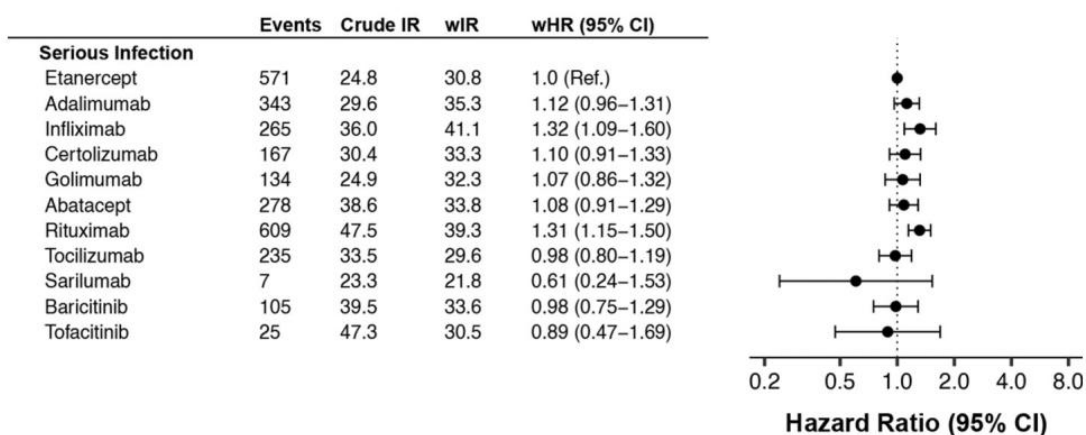


Figure 6: Relative risk of serious infections in RA according to the treatment received. Adapted from (74)

Corticosteroids (CS), which are used in the treatment of most IMIDs, are also known to increase the risk of infection, in a dose-dependent manner. Dixon et al (75) used data from Québec to assess the risk of infection associated to CS in RA patients and observed that current and recent doses of CS have a great impact on infection risk. They also noted that the cumulative impact of doses taken in the last 2–3 years also affects the risk.

Patients with IMIDs are susceptible to different pathogens.

Patients living with IMID can experience community-acquired non-opportunistic infections, but they also face the risk of being infected by opportunistic agents or to experience healthcare-associated infections because of their regular contact with the healthcare system. Certain opportunistic infections are more prevalent and associated with specific immunosuppressive treatments, like *Mycobacterium tuberculosis* in individuals undergoing anti-TNF biologic therapies (76) or progressive multifocal leukoencephalopathy in those exposed to natalizumab or rituximab (77). But other opportunistic infections, such as herpes zoster, affect a broader spectrum of patients (78). Pneumocystis (PCP) is a great concern in patients living with IMIDs. Of note, PCP in patients with autoimmune diseases often presents with a more severe and fulminant course with higher morbidity and mortality rates than in HIV patients (79). Interestingly, the frequency of PCP differs among the different IMIDs, granulomatosis with polyangiitis (GPA) being the one with the highest percentage (up to 6%) (80). The European Alliance of Associations for Rheumatology (EULAR) has recently provided recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with IMIDs (18). Regarding PCP, EULAR recommends now that prophylaxis should be considered in patients with IMIDs in whom high doses of glucocorticoids are used, especially in combination with immunosuppressants and depending on the risk–benefit ratio. Unfortunately, the minimum dose and duration of glucocorticoid treatment above which prophylaxis is recommended is not clearly defined but a threshold of >15–30 mg/day of prednisolone or equivalent for >2–4 weeks is proposed for all IMIDs.

SLE is special.

Infections are recognized as one of the leading cause of premature mortality in patients with SLE (13). In their famous study about the bimodal mortality pattern in SLE, Urowitz et al (81) observed that among 6 patients who died within the first year after diagnosis, 4 (67%) died from a major septic episode. Using data from the American Nationwide Inpatient Sample (NIS), Tektonidou et al. (82) demonstrated that the relative risk for SLE patients, compared with general population, to experience pneumonia, urinary tract infection, opportunistic infections, sepsis or skin infection was higher and that it increased between 1996 and 2011. For example, the relative risk of hospitalization for

opportunistic infections increased from 8.8 in 1996 to 24.1 in 2011. These results were confirmed by an update of the study (83), by a systematic review and Bayesian meta-analysis performed in 2017 (84) and by Simard et al. (85) who studied the risk of infection in SLE patients in Sweden. Risk factors for SLE patients to suffer from severe infections have been studied by several authors but remained not fully elucidated. Immunosuppressive treatment is a major component of the high risk for SLE patients. In their study, Simard et al observed that azathioprine was the DMARD the most associated with infections whereas a British study (86) performed in the British Isles Lupus Assessment Group Biologics Register (BILAG-BR) observed that in patients with moderate-to-severe SLE, rituximab, belimumab, and standard immunosuppressive therapy have similar serious infection risks. In this study, key risk factors for serious infections included multimorbidity, hypogammaglobulinemia, and increased glucocorticoid doses. Of note, patients with monogenic SLE belong to a special group for the risk of infection as it often involves an immune deficiency (87). During my master thesis (88), my supervisors and I looked for the factors associated with 1-year mortality after sepsis in patients with SLE. At 1-year after ICU admission, independently of the acute illness severity and comorbidities, an associated Sjögren's syndrome (HR: 1.39 [1.02–1.90]) was significantly associated with death. The only infectious characteristic associated with increased mortality was fungal infection.

D-Vaccination challenges in patients with IMIDs.

Vaccine efficacy, effectiveness, and protection in patients with IMIDs.

In our analysis of sepsis and septic shock in SLE patients (88), we observed that 10 % of the severe infectious episodes were associated with vaccine-preventable pathogens. Then, even if vaccines have become the cornerstone of infectious diseases prophylaxis in patients living with autoimmune disease (18), a lot of challenges remain regarding their vaccination. The first concern is that vaccines may not be as effective in this population. Of note, vaccine efficacy and effectiveness should not be confused. According to the WHO (89), *“vaccine’s efficacy is measured in a controlled clinical trial and is based on how many people who got vaccinated developed the ‘outcome of interest’ (usually disease) compared with how many people who got the placebo (dummy vaccine) developed the same outcome”*. Vaccine effectiveness is a measure of how well vaccines work in the real world. There is very little scientific data on vaccine efficacy and/or effectiveness in patients with IMIDs (90). Most of the time, vaccine-induced protection is studied through immunogenicity markers such as the humoral response measured by the serum concentration of vaccine-induced IgG. However, immunogenicity is only a surrogate marker of the protection induced by the vaccine. Even the relationship between IgG

concentration and the ability for the serum to neutralize a virus is not linear (91), especially with mutating viruses such as SAR-CoV-2 (92). Besides, humoral response is just one facet of a vaccines immunogenicity since they are also able to induce a cellular response. Bitoun et al (93) recently provided evidence showing that the T-cell response is not impaired in patients with IMIDs treated by an anti-CD20 therapy. Regarding immunogenicity, the most studied vaccines are influenza (94), pneumococcal (95) and SARS-CoV-2 vaccines (96). Several reports observed that, compared with the general population, vaccines induce lower response in patients with IMIDs, with a strong effect of the immunosuppressive treatment received by the patients (90). If we look at vaccine efficacy, as it is defined by the WHO, we can only cite the study by Izumi et al. (97) who randomized patients with RA to receive the 23-valent pneumococcal polysaccharide vaccine or a placebo. They observed the same rate of pneumonia in both groups during follow-up. For vaccine effectiveness, Saxena et al. (98) recently analysed the occurrence of breakthrough SARS-CoV-2 infections after vaccination in 163 patients with SLE. They reported that, after a mean follow-up time of 11.2 months from the initial vaccine dose, 44 patients (27.0%) had a COVID-19, and that the additional third dose was beneficial for these patients.

Vaccine safety among patients with IMIDs.

Vaccination coverage among patients with IMIDs is unsatisfactory (99,100), and one component of the identified barriers to vaccination is the fear that vaccination may induce an autoimmune flare of the disease (20). Before the COVID-19 era, the safety of vaccines, mostly influenza and pneumococcal, were studied in patients with IMIDs and all the accumulated evidence has been reassuring. In 2012, A French group reported the safety of seasonal and 2009 A/H1N1 influenza vaccines in a prospective study which included 199 patients with IMIDs (101). In addition to flu syndromes and local reaction, 6 mild autoimmune flares occurred during follow-up. However, the absence of control group makes this number difficult to interpret. Good safety results were also seen in MS (102,103), in RA (104) and in another study that included only SLE patients (105). Similarly reassuring safety results were observed in prospective (95,106) and retrospective studies (107,108) of pneumococcal vaccines in patients with IMIDs. The risk of multiple immunizations was studied by Battafarano et al. (109) who investigated 73 SLE patients that simultaneously received pneumococcal, tetanus toxoid, and *Haemophilus influenzae* type B vaccines. Six patients developed a mild increase in SLE disease activity, but an equal number of patients improved clinically after immunization. Overall, lupus disease activity was unaffected by immunization. Of note, reassuring results were also observed in SLE patients with HBV (110) and herpes zoster (111) vaccines. The quick development of anti-SARS-CoV-2 vaccines in 2020 acutely reopened the question of vaccine safety for patients with IMIDs. These patients were excluded at first

from SARS-CoV-2 vaccine clinical development programs and most of the accumulated data has come from retrospective and prospective cohort studies. The largest effort to assess the safety of SARS-CoV-2 vaccines in patients with IMIDs was conducted by the EULAR through the COVAX physician-reported registry (112) which included 5,121 patients from 30 countries. Authors described the safety profile of SARS-CoV-2 vaccines in patients with IMIDs as reassuring and comparable with the one of patients with non-inflammatory rheumatic diseases. The majority of patients tolerated their vaccination well with rare reports of autoimmune flare after an average of 66 days of follow-up. These results were confirmed by an observational multicentre study that included 686 patients with IMIDs and general populations controls in Israel (96). In addition, a sub study of the national Dutch study “Target-to-B” (113) that included 2,111 patients with IMIDs observed that self-reported increased disease activity after vaccination against SARS-CoV-2 was recorded in a minority of patients and was generally mild. Moreover, the authors observed that disease related factors, rather than vaccinations were the major determinants for increased disease activity in multivariable analyses. Several other studies assessed the safety of these new vaccines among different group of particular interest. The Vacolup study (114) included 696 SLE patients from 30 countries in a cross-sectional study based on a 43-question web-based survey. Among the 696 included patients, 21 (3%) reported a medically confirmed SLE flare after a median of 3 days after vaccination. Overall, these results were found to be reassuring. SARS-CoV-2 vaccination was also found to be not associated with the onset of flare in rheumatoid arthritis (115), even in patients under targeted therapies (116).

Vaccines as a trigger of autoimmunity ...

Vaccines have been suspected for a long time to be able to trigger autoimmunity. Unfortunately, vaccine safety literature has been polluted by the historical scientific fraud of Andrew Wakefield who falsely claimed non-existent, causative links between the MMR vaccine, colitis, and autism (117). By now, the only vaccine which have been clearly scientifically associated with IMID onset is the influenza vaccine. The first compelling evidence was demonstrated for the risk of Guillain-Barré syndrome (GBS) after the 1976 swine-influenza vaccine in the United States (118) by Schoberger et al. who used data from an active surveillance system established after the apparition of two GBS clusters that were reported to the Center for Disease Control. The estimated attributable risk of vaccine-related GBS in the adult population was just under one case per 100,000 vaccinations, and the period of increased risk was concentrated primarily within the 5-week period after vaccination. Thereafter, numerous studies have examined the potential link between seasonal inactivated influenza vaccines and GBS. The majority of these studies did not find a substantial connection between the seasonal influenza vaccine and GBS. Based on the results of two positive studies (119,120), the risk estimates of 1

additional GBS case per 1 million persons vaccinated has been communicated to the public and can be found in the Vaccine Information Statements for influenza vaccines (121). Another unexpected association was more recently found between Pandemrix (H1N1 influenza) vaccine and childhood narcolepsy by Swedish (122) and Finnish (123) authorities. Interestingly, the mechanism of this very serious but very uncommon adverse event was further elucidated. It appeared that autoimmunity to hypocretin was triggered by molecular mimicry among patients positive for positive for human leukocyte antigen (HLA)–DQB1*0602 (124). The assessment of the risk of developing MS after HBV vaccination ended up in a debate that went far beyond the medical and scientific community. In 2000, a French court awarded damages to three people with MS who had received HBV vaccine, in a decision that was later highly criticized (125). While the debate was considered as closed in 2002 (126), Hernàn et al reopened the question in 2004 with a nested case-control study within the British General Practice Research Database (127). They found a 3.1 (95% CI 1.5, 6.3) OR of MS for vaccination within 3 years before the index date compared to no vaccination. However, these results were not supported by any other studies and the most recent literature reviews concludes that there is no increased risk for MS onset after HBV vaccine (128).

... or as a treatment for autoimmunity?

Research about vaccines as a possible treatment for autoimmunity did not receive as much attention as their immunological side effects. However, several pieces of evidence indicate that some vaccines could have a beneficial impact on the course of IMIDs. For example, intriguing results were reported about the Bacille de Calmette et Guérin (BCG) vaccine (129) in non-obese diabetes-prone (NOD) mice in which a single intravenous injection of BCG at approximately 10 weeks of age produced a potent suppression of insulinitis and overt diabetes (130). In humans, a randomized controlled trial was conducted in patients with T1D and an elevation of C-peptide levels was observed in the treatment group, but not in the placebo arm (131). BCG was also studied as an immunomodulatory drug in a randomized controlled trial which involved patients who just suffered from a first demyelinating event. During the initial 6 months-follow-up, the cumulative number of new lesions was significantly lower in vaccinated people and, after 60 months, the cumulative probability of clinically definite multiple sclerosis was lower in the BCG arm (132). In SLE, interesting results were also described in MRL-*lpr* mice, that spontaneously develop a lupus-like syndrome. Cantarelli et al. (19) treated these mice by the pneumococcal vaccine Prevnar-13 or by a vehicle. After three months, vaccinated mice showed reduced albuminuria, renal histological lesions, and milder dermatitis compared to vehicle-treated controls (Figure 7).

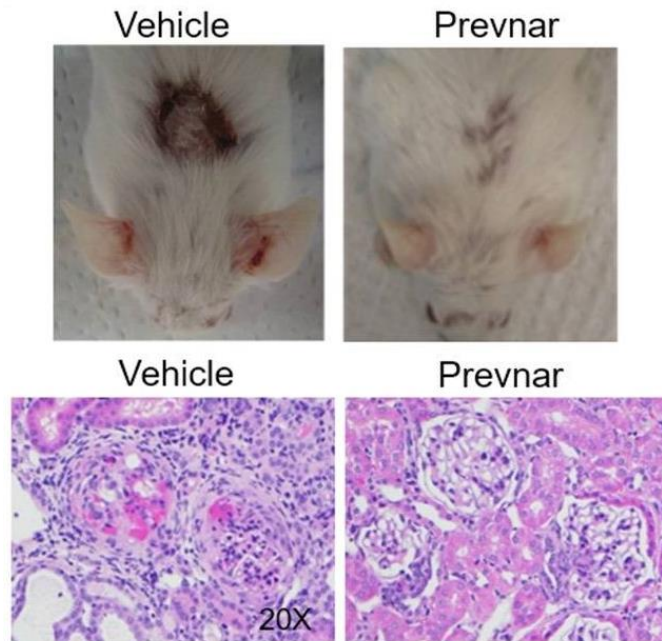


Figure 7: Skin and renal biopsies of MRL-lpr mice treated by a vehicle or by Prevnar, from (19)

Finally, in the 2000s, the idea of creating a peptide-based therapeutic vaccines for allergic and IMID was increasingly recognized as a promising hope to effectively prevent or cure IMIDs (133). The main idea was to modulate the immune response directed against the peptide targeted by the pathogenic autoantibody by potentiating CD4 T helper 2 (Th2) responses. Reductions in disease severity have been observed in animal models of experimental allergic encephalomyelitis, T1D, and various forms of antigen-induced arthritis, even when administered after symptoms have already started. However, in the case of experimental autoimmune encephalomyelitis (EAE) and T1D in NOD mice, the repeated administration of peptide fragments of target antigens in incomplete Freund's adjuvant has led to severe anaphylactic reactions. (134). Thereafter, no credible therapeutic vaccine for IMID emerged until now.

COVID-19 outcome in patients with SLE. Studies 1 & 2.

At the beginning of the pandemic, in 2020, when not much was known about SARS-CoV-2 infection, patients living with SLE were most concerned about their hypothetical risk of severe COVID-19. Indeed, SLE was already a known risk factor for severe infection, and especially respiratory viruses such as influenza. Immunosuppression was thought to account for most of the risk. However, the first data coming from general or from IMID populations reported that apart from age, the main risk factors for severe COVID-19 were comorbidities such as diabetes, hypertension and chronic kidney disease which SLE patients have in higher proportions than the general population (135). Later, concerns were heightened by immunological studies showing that anti-type 1 IFN autoantibodies, previously described in SLE, were involved in the pathophysiology of severe COVID-19. (39). As SLE is a relatively rare disease, early studies evaluating COVID-19 outcomes in SLE were based on a small number of patients. In addition, the marked gender imbalance as well as the special comorbidity profile of the SLE population made comparison with previously published evidence difficult, as most hospitalized patients from the general population were older males.

To better evaluate the outcome of COVID-19 in patients living with SLE in France we leveraged the power of the French nationwide medico administrative database “*programme de médicalisation des systèmes d’information*” (PMSI) in two studies. In the first one, published as a research letter in *Annals of the Rheumatic Diseases* our objective was to describe which patients’ characteristics were associated with i) a COVID-19 hospitalization and ii) a good or a poor outcome after COVID-19. In the second study, published as a full paper in the same journal, we wanted to compare the survival of SLE patients with the one of matched hospital controls after a COVID-19 associated organ failure.

Study 1

SARS-CoV-2 infection among inpatients with systemic lupus erythematosus in France: a nationwide epidemiological study

Since the global emergence of SARS-CoV-2 at the end of 2019, a special concern has raised regarding patients with rheumatic and inflammatory diseases, such as systemic lupus erythematosus (SLE).¹ Indeed, many treated patients with SLE are immunocompromised and often suffer from chronic kidney or cardiovascular diseases.² Recently, anti-interferon antibodies have been implicated in severe SARS-CoV-2 infection³ while it has been known for decades that patients with SLE may produce such autoantibodies.⁴ Although available data from short SLE series are reassuring,^{5,6} large-scale nationwide studies are still needed to assess the risk of developing severe SARS-CoV-2 infection in SLE.

We therefore used the French healthcare database system called 'Programme de Médicalisation des Systèmes d'Information'—which contains hospitalisation data of all inpatients in France—to analyse the population with SLE that had at least one stay in a French hospital between March and 30 October 2020 (online supplemental material). On this population, we compared inpatients with SLE with or without SARS-CoV-2 infection (SLE/COVID-19⁺, SLE/COVID-19⁻). Among SLE/COVID-19⁺ inpatients, we distinguished patients with poor outcome after SARS-CoV-2 infection and patients with good outcome after COVID-19. We defined poor outcome as admission to intensive care unit (ICU) or death. We also compared the in-hospital mortality associated with SARS-CoV-2 infection in SLE and in the total population in France.

Based on the 10th International Classification of Diseases 'M32' and 'L93' diagnosis code, we identified 11 055 patients with SLE who had at least one stay in a French hospital between 1 March and 31 October 2020 (online supplemental material S1). Among them, 1411 (12.8%) also had a COVID-19 diagnosis code. Characteristics of SLE/COVID-19⁺ and SLE/COVID-19⁻ patients are given in table 1. These 1411 SLE/COVID-19⁺ patients experienced 1721 inpatient hospital stays during the period of study.

Among these SLE/COVID-19⁺ inpatient hospital stays, 293 (17%) took place in ICU. The mean Simplified Acute Physiology Score II at admission was 35.4±16.8. In ICU, 78 (26.7%) and 71 (24.7%) SLE/COVID-19⁺ patients required invasive or non-invasive mechanical ventilation, respectively. Overall, 134 (9.5%) patients with SLE admitted for COVID-19 died. The in-hospital mortality rate was almost four times higher in SLE/COVID-19⁺ as compared with SLE/COVID-19⁻ inpatients admitted during the same period (9.5% vs 2.4%, p<0.001). Interestingly, while the overall mortality rate was lower in SLE/COVID-19⁺ inpatients as compared with the total population admitted for SARS-CoV-2 infection in France during the same period (9.5% vs 15.7%, p<0.0001), the mortality rate at a younger age tended to be higher in patients with SLE. The difference failed however to reach statistical significance (online supplemental material S2).

Our study based on a comprehensive nationwide database confirms that inpatients with SLE are more likely to develop severe SARS-CoV-2 infection when they have comorbidities already identified as risk factors of severe infection in the general population, such as older age, male gender and hypertension.¹ Poor outcome was associated with chronic kidney disease (CKD) status thus confirming that CKD increases the risk for severe infection in SLE and is a major predictor of mortality and morbidity in these patients.² Since we only included hospitalised patients, excluding asymptomatic or mild forms of COVID-19, our results cannot be applied to all patients with lupus.

Given the importance of male sex as a poor prognosis factor of COVID-19, the lower mortality rate observed among inpatient population with SLE may be explained by an unbalanced sex ratio (F/M 8.5:1.5). On the other hand, the mortality of SLE/COVID-19⁺ patients seemed higher in the youngest patients as compared with the general population with SARS-CoV-2 infection. Because lupus activity and the need for immunosuppressive drugs decline with age, the higher mortality rate observed in younger patients, as compared with the one observed in general population, suggests that SLE disease may impact COVID-19 outcome.

Table 1 Characteristics of inpatients with SLE in France with and without COVID-19 infection between March and October 2020

	SLE/COVID-19 ⁻ n=9644	SLE/COVID-19 ⁺		P value*
		Good outcome n=1070	Poor outcome n=341	
Age, years (mean±SD)	52.1±17.2	55.8±18.7	61.5±17.6	<0.0001
Male gender, n (%)	1 561 (16.2)	171 (16.0)	96 (28.2)	<0.0001
Chronic kidney disease, n (%)	1 312 (13.6)	184 (17.2)	108 (31.7)	<0.0001
Diabetes, n (%)	1 251 (13.0)	173 (16.2)	72 (21.1)	0.03
High blood pressure, n (%)	3 404 (35.3)	480 (44.9)	215 (63.0)	<0.0001
Obesity, n (%)	1 811 (18.8)	240 (22.4)	86 (25.2)	0.29
Chronic pulmonary disease, n (%)	1 275 (13.2)	240 (22.4)	102 (29.9)	0.005
Cardiovascular event history, n (%)	2 050 (21.3)	291 (27.2)	140 (41.0)	<0.0001
Lupus nephritis history, n (%)	1 271 (13.2)	158 (14.8)	77 (22.6)	0.0007
Sjögren syndrome, n (%)	1 088 (11.3)	124 (11.6)	38 (11.1)	0.8
Antiphospholipid syndrome, n (%)	803 (8.3)	107 (10.0)	44 (12.9)	0.13
Solid organ transplantation, n(%)†	212 (2.2)	22 (2.1)	14 (4.1)	0.04

*Level of significance for the difference between SLE/COVID-19⁺ with good outcome versus SLE/COVID-19⁺ with poor outcome. Student's t-test was performed for quantitative variables and χ^2 test was used for categorical variables.

†Solid organ transplantation during the last 10 years.

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Handling editor Josef S Smolen

Contributors AM designed and conducted the analysis and wrote the manuscript. GA, DvG and TP were involved in the project development and edited the manuscript. KS and J-FT directed the project and wrote the manuscript.

Funding PhD fellowship support for AM was provided by Agence Nationale pour la recherche (no: ANR-19-CE17-0029).

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement French hospital data for COVID19 are available at <https://www.data.gouv.fr/fr/datasets/donnees-hospitalieres-relatives-a-lepidemie-de-covid-19/>.

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► Additional material is published online only. To view please visit the journal online (<http://dx.doi.org/10.1136/annrheumdis-2021-220010>).



To cite Mageau A, Aldebert G, Van Gysel D, *et al.* *Ann Rheum Dis* Epub ahead of print: [please include Day Month Year]. doi:10.1136/annrheumdis-2021-220010

Received 27 January 2021

Revised 2 March 2021

Accepted 3 March 2021

Ann Rheum Dis 2021;**0**:1–2. doi:10.1136/annrheumdis-2021-220010

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SARS-COV2 INFECTION AMONG SYSTEMIC LUPUS ERYTHEMATOSUS INPATIENTS IN FRANCE - ELECTRONIC SUPPLEMENTARY MATERIALS

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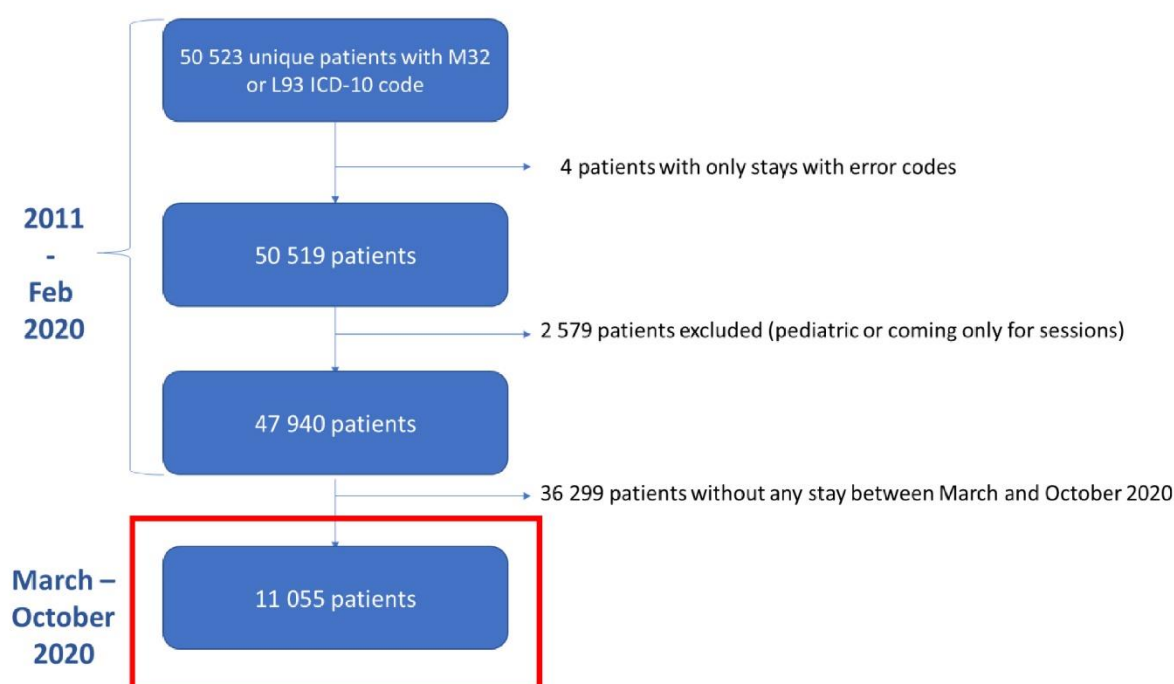
1- POPULATION SELECTION

The “Programme de Médicalisation des Systèmes d’Information” (PMSI) database compiles discharge abstracts related to all admissions in the public and private French healthcare facilities. Information in these abstracts covers both medical and administrative data. Each facility produces its own anonymous standardized data, which are then compiled at the national level. Even though these data are anonymous, we were able to follow all hospital stay for each patient. Routinely collected medical data includes main diagnosis, secondary diagnoses, and procedures performed. Administrative collected data includes age, gender, year, duration of the stay, and location of the hospital. In-hospital death is reported. Diagnoses identified during the hospital stay are coded according to the International Classification of Diseases, tenth revision (ICD-10). Procedures performed during the stay are coded according to the “Classification Commune des Actes Médicaux” (CCAM). Since 2004, each hospital’s budget has depended on the medical activity described in this specific program. Regular checks are made by the social insurance authority to ensure that data are correctly imputed. In Intensive Care Units (ICU), severity at admission is measured by the Simplified Acute and Physiology Score II (SAPS II) and all the procedures are systematically recorded. To select

the SLE population we first extracted from the PMSI database all the records of patients for whom at least one ICD-10 M32 or L93 diagnosis code was reported between 2011 and October 30th, 2020. We excluded patients less than 15 years old and patients who came to hospital only for sessions (chronic hemodialysis, radiotherapy, chemotherapy). We also excluded all the hospital stays identified with an error code.

At last, we excluded all the stays that took place before March 2020. Flow chart of the population selection is on Figure S1.

Figure S1: Flow chart of the selection from PMSI database



2- CODES USED

2-1 Diagnosis codes

List of the ICD 10 diagnosis codes used. ICD-10 is available at

<http://apps.who.int/classifications/icd10/browse/2010/en>

SLE	
SLE	M32x, L93x
SLE specific complications	
Lupus nephritis	N085, N164
Autoimmune hemolytic anemia	D591
Evans syndrome/Thrombocytopenic immunologic purpura	D693
Haemophagocytic lymphohistiocytosis	D761
Pericarditis	I328
Pleural effusions	J90,J91
Antiphospholipid syndrome	D686
Gougerot-Sjögren syndrome	M350

COVID-19	U07x
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Other comorbidities	
Chronic kidney disease	N183, N184 ,N185 , N189 , N180, N188
High blood pressure	I10x
Diabetes mellitus	E10, E100,E101,E109,E11, E110,E111,E119, E1108,E1110,E1118,E1190,E1198,E12,E120,E121,E129, E13,E130,E131,E139,E14,E140,E141,E149, O24,O240,O241,O242,O243,O244,O249,E136,E138,E139,E146,E148,E149, E120,E121,E129,E13,E130,E131,E139,E130,E131,E139,E14,E140,E141,E149, E140,E141,E149, O24,O240,O241, O242,O243,O244,O249,E1100,E100,E101,E106,E108,E109,E110,E111,E116,E118,E119
Chronic pulmonary disease	J40, I278, I279, J40, J41, J410, J411, J418, J42, J43, J430, J431, J432, J438, J439, J44, J440, J441, J448, J449, J450, J451, J458, J459, J46, J47, J60, J61, J620, J628, J630, J631, J632, J633, J634, J635, J638, J64, J65, J660, J661, J662, J668, J670, J671, J672, J673, J674, J675, J676, J677, J678, J679, J684, J701, J703, J96, J9610, J96100, J96101, J9611, J96110, J96111, J9619, J96190, J96191, J9690, J9691, J9699
Obesity	E66x excepted 'E6603','E6609','E6613','E6619','E6683','E66890,E669,E6699
Cardiovascular event	
Myocardial infarction	I21x, I22x
Ischemic stroke or transient ischemic attack	I63x, G45, G46, I64

Angina pectoris	I20x,
Sudden death	I461
Mesenteric ischemia	K550x
Arterial ischemia	I74x
Cardiovascular history	
Cardiovascular condition :	Z867, Z8660, F01, Z951, I25, I516, I461, I70, I65, I693

2-2 Procedure codes

CCAM list of procedures codes is available (in French) at:

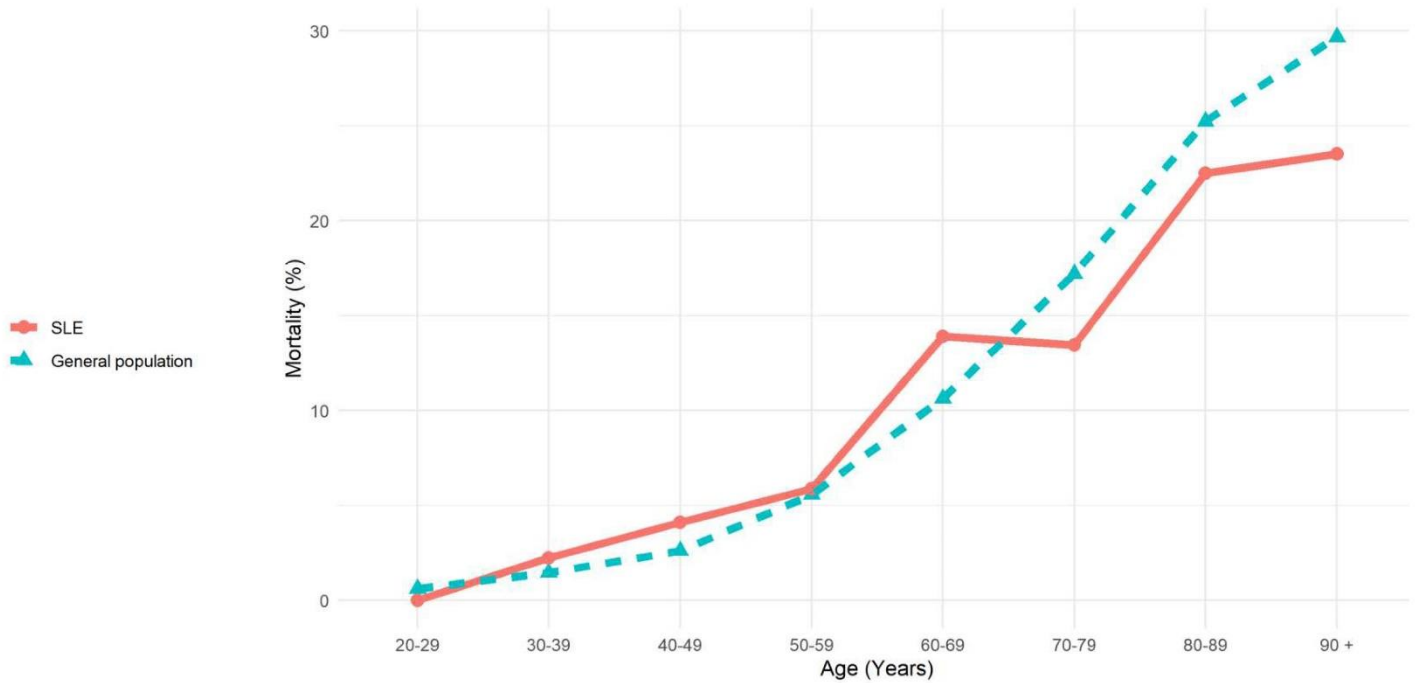
https://www.ameli.fr/fileadmin/user_upload/documents/CCAM_V52.pdf

Invasive mechanical ventilation	"GLLD0150", "GLLD0080", "GLLD0040", "GLLD0060", "GLLD0130", "GLLD0050", "ZZLB0040"
Noninvasive mechanical ventilation	"GLLD0030", "GLLD0020", "GLLD0120", "GLLP0030", "GLLD0190"
Transplantation	"JAEA0030", "DZEA002", "DZEA003", "DZEA001", "DZEA004", "DZFA004", "GFFA020", "GFEA005", "GFEA002", "GFEA007", "GFEA004", "GFEA001", "GFEA006", "HLEA002", "HLEA001"

3- COMPARISON OF COVID-19 MORTALITY BETWEEN SLE PATIENTS AND GENERAL POPULATION

We used data of all COVID-19 inpatients in France published by French authorities to compare in hospital mortality between SLE and general population. Data for French general population is available at <https://www.data.gouv.fr/fr/datasets/donnees-hospitalieres-relatives-a-lepidemie-de-covid-19/>. We excluded SLE patients from general population to perform the comparison. Mortality rate was calculated as number of people dead in the hospital divided by the number of people admitted from 1st March, 2020 to October 30th, 2020. We compared the mortality between SLE and general population by performing univariate logistic regression in each stratum of age taking general population as class of reference.

Figure S2 COVID-19-associated mortality in France among SLE patients compared to general population.



Number of hospitalisation	SLE	75	179	220	256	230	223	160	34
	General population	4622	7500	11158	18865	25822	31253	35998	18325
Number of death	SLE	0	4	9	15	32	30	36	8
	General population	28	109	290	1048	2747	5375	9087	5439
Odds ratio [IC 95]		-	1,55 [0,57-4,25]	1,59 [0,81-3,15]	1,06 [0,62-1,79]	1,36 [0,93-1,98]	0,75 [0,5-1,1]	0,86 [0,59-1,25]	0,73 [0,33-1,61]

Odds ratio are given for each group of age taking general population as reference.

4- SENSITIVITY ANALYSIS

Because the code “L93” could be ambiguous and refer to skin-limited lupus or other form of non-systemic lupus we performed a sensitivity analysis by excluding patients having only a “L93” diagnostic code and no “M32” code.

Using this definition, we found 7 992 SLE patients with at least one hospital stay between March and November 2020. Among these patients, 1 057 (13.2 %) had a COVID-19 diagnostic code. Based on the same definition as we used in the manuscript, we found 265 patients experiencing a poor outcome of their COVID infection with 98 deaths.

Description of this population is presented in Table S3

Table S3 Characteristics of M32-defined SLE inpatients in France with and without COVID-19 infection between March and October 2020.

	SLE/COVID-19 ⁻ n= 6935	SLE/COVID-19 ⁺		p*
		good outcome n= 741	poor outcome n= 265	
Age, years (mean +/-sd)	51.4+/-17.1	54.1+/-18.3	60.2+/-17.3	<0.0001
Male gender, n (%)	999 (14.4)	108 (14.6)	67 (25.3)	<0.0001
Chronic kidney disease, n (%)	1 123 (16.2)	159 (21.4)	97 (36.6)	<0.0001
Diabetes, n (%)	923 (13.3)	128 (17.3)	60 (22.6)	0.02
High blood pressure, n (%)	2 535 (36.6)	365 (49.2)	175 (66.0)	<0.0001
Obesity, n (%)	1 350(19.5)	187 (25.2)	73 (27.6)	0.22
Chronic pulmonary disease, n (%)	945 (13.6)	177 (23.9)	78 (29.4)	0.002
Cardiovascular event history, n (%)	1 517 (21.9)	218 (29.4)	108 (40.8)	<0.0001
Lupus nephritis history, n (%)	1 256 (18.1)	158 (21.3)	77 (29.1)	0.003
Sjögren syndrome, n (%)	853 (12.3)	105 (14.2)	33 (12.4)	0.8
Antiphospholipid syndrome, n (%)	730 (10.5)	103 (13.9)	38 (14.3)	0.6
Solid organ transplantation, n(%) **	203 (2.9)	21 (287)	13 (4.9)	0.1

* Level of significance for the difference between SLE/COVID-19⁺ with good outcome vs SLE/COVID-19⁺ with poor outcome. Student’s T test was performed for quantitative variables and chi-square test was used for categorical variables.

** Solid organ transplantation during the last 10 years.

Study 2

EPIDEMIOLOGICAL SCIENCE

Survival after COVID-19-associated organ failure among inpatients with systemic lupus erythematosus in France: a nationwide study

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Handling editor Josef S Smolen

► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/annrheumdis-2021-221599>).

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Received 30 September 2021
Accepted 25 November 2021
Published Online First
10 December 2021



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To cite: Mageau A, Papo T, Ruckly S, et al. *Ann Rheum Dis* 2022;**81**:569–574.

ABSTRACT

Objective We analysed the incidence of, the specific outcomes and factors associated with COVID-19-associated organ failure (AOF) in patients with systemic lupus erythematosus (SLE) in France.

Methods We performed a cohort study using the French national medical/administrative hospital database for the January 2011–November 2020 period. Each patient with SLE diagnosed in a French hospital with a COVID-19-AOF until November 2020 was randomly matched with five non-SLE patients with COVID-19-AOF. We performed an exact matching procedure taking age ± 2 years, gender and comorbidities as matching variables. COVID-19-AOF was defined as the combination of at least one code of COVID-19 diagnosis with one code referring to an organ failure diagnosis.

Results From March to November 2020, 127 380 hospital stays in France matched the definition of COVID-19-AOF, out of which 196 corresponded with patients diagnosed with SLE. Based on the presence of comorbidities, we matched 908 non-SLE patients with COVID-19-AOF with 190 SLE patients with COVID-19-AOF. On day 30, 43 in-hospital deaths (22.6%) occurred in SLE patients with COVID-19-AOF vs 198 (21.8%) in matched non-SLE patients with COVID-19-AOF: HR 0.98 (0.71–1.34). Seventy-five patients in the SLE COVID-19-AOF group and 299 in the matched control group were followed up from day 30 to day 90. During this period, 19 in-hospital deaths occurred in the SLE group (25.3%) vs 46 (15.4%) in the matched control group; the HR associated with death occurring after COVID-19-AOF among patients with SLE was 1.83 (1.05–3.20).

Conclusions COVID-19-AOF is associated with a poor late-onset prognosis among patients with SLE.

INTRODUCTION

The interplay between COVID-19 and systemic lupus erythematosus (SLE) has yet to be defined. Indeed, many patients with SLE are exposed to immunosuppressive drugs, are more susceptible to viral infections and often suffer from chronic kidney or cardiovascular diseases, which are additional risk factors for severe COVID-19.¹ On the other hand, glucocorticoids and hydroxychloroquine, the drugs most widely used in SLE treatment, have also been investigated to treat COVID-19.^{2,3} Moreover, type 1 interferon (IFN) such as IFN α and the antibodies anti-IFN α are involved both in SLE and severe COVID-19.^{4–7} Although currently available data regarding the impact of COVID-19

Key messages

What is already known about this subject?

- The interplay between COVID-19 and systemic lupus erythematosus (SLE) has yet to be defined.
- Currently available data regarding the impact of COVID-19 in SLE sound reassuring, but most studies are based on a small number of patients.

What does this study add?

- In this nationwide cohort study, we found that patients with SLE had a poor late-onset prognosis after COVID-19-associated organ failure compared with a matched control population.
- The HR associated with SLE for risk of death between day 30 and day 90 after the first day in the hospital for COVID-19-associated organ failure was 1.83 (1.05–3.20; $p=0.03$).

How might this impact on clinical practice or future developments?

- Anti-SARS-CoV-2 vaccination among the SLE population appears to be a priority.

in SLE sound reassuring,^{8–11} most studies are based on a small number of patients. Finally, comparison between SLE, which mainly affects women of child-bearing age, and the general population with regard to severe COVID-19 may be challenging.

We used a French nationwide medical and administrative database to analyse the incidence, the specific outcomes and the characteristics associated with COVID-19-associated organ failure (COVID-19-AOF) in patients with SLE.

METHODS

Study population and data source

Data of all patients admitted to French hospitals from January 2011 to November 2020 with at least one diagnosis of infection associated with an organ failure and/or SLE were collected from the national medical administrative database, the PMSI (Programme de Médicalisation des Systèmes d'Informations, Information System Medicalization Program). The PMSI database provides a summary with diagnosis and individual medical conditions at discharge of any public or private French healthcare

facilities. Information covers both medical and administrative data. Each facility produces its own anonymous standardised set of data, which are then compiled at the national level. Even though these data are anonymous, the system allows to follow all hospital stays for each individual patient. Routinely collected medical data include, among other data, main diagnosis, secondary diagnoses and the procedures performed. Administrative data include, among other data, age, gender, year, duration of hospital stay and location of the hospital. In-hospital death is also reported. Diagnoses identified during the hospital stay are coded according to the International Classification of Diseases, 10th Revision (ICD-10). Procedures performed during the hospital stay are coded according to the 'Classification Commune des Actes Médicaux' (French Common Classification of Medical Procedures). Since 2004, each hospital's budget depends on the medical activity described in this specific programme. Regular checks are made by the social insurance authority to ensure that data are correctly imputed. To select the SLE population, we first extracted from the PMSI database all records of patients for whom at least one ICD-10 M32 diagnosis was reported. We excluded patients younger than 15 years old and patients admitted to hospital only for scheduled sessions (chronic haemodialysis, radiotherapy, chemotherapy).

Definitions

We defined COVID-19-AOF as the combination of at least one of the diagnosis codes of COVID-19 (ICD-10 codes 'U071', 'U0710', 'U0711', 'U0712', 'U0714', 'U0715'), with one code referring to an organ failure diagnosis (listed in online supplemental materials). This definition, which matches the definition for sepsis, has been previously used and validated in medical administrative database studies.¹²⁻¹⁴ To be allocated in the SLE group, COVID-19-AOF had to follow or be concomitant with an SLE 'M32' code. For an exhaustive description of diagnosis and procedure codes used, see online supplemental materials. To determine patients' phenotype, we used all the specific diagnostic codes reported during or before the COVID-19-AOF stay.

Matching procedure

Each patient with SLE who experienced COVID-19-AOF during the period of study was randomly matched with five non-SLE control patients with COVID-19-AOF and one patient with SLE without evidence of COVID-19 infection. We used a random exact matching procedure (without replacement) using the following matching variables: age ± 2 years, gender, chronic kidney disease, arterial hypertension, cardiovascular history, diabetes mellitus, chronic pulmonary disease and obesity. We verified matching accuracy and efficacy by calculating the standardised differences for the matching variables between the various matched populations.

Survival analysis

Kaplan-Meier method was used to present 90-day survival, taking day 0 as the first hospital admission for COVID-19-AOF. For the control SLE non-COVID-19 population, we used the first day of a randomly selected stay before 2020 (2011-2020 period) as day 0.

In order to calculate the HR of death after COVID-19-AOF according to SLE status, and because we cannot assume the proportional hazard hypothesis for the whole period between day 0 (D0) and day 90 (D90), we split this period into two parts: D0-D30 and D30-D90. For the second time period, we considered only the subgroups of patients who survived after 30 days

of follow-up, taking D30 as the new day 0. We used standard univariable Cox proportional hazard model for the unmatched analysis and univariable marginal Cox proportional hazard model¹⁵ for the postmatching analysis.

Statistical statement

Categorical variables are presented as number (percentage). Quantitative variables are presented as median (first quartile-third quartile). HRs are presented with their 95% CI. We used Student's t-test and χ^2 test for univariable comparisons, as appropriate. All analyses were performed using SAS V.9.4 software. Kaplan-Meier curves were built with R V.4.0.3 software.

RESULTS

Characteristics of patients with SLE experiencing COVID-19-AOF

From March to November 2020, 127 380 hospital stays in France matched the definition of COVID-19-AOF. Among them, there were 196 unique patients with SLE and 113 567 unique patients without SLE. A flow chart of these selected populations is presented in online supplemental figure S1. A comparison of SLE patients with COVID-19-AOF versus non-SLE patients with COVID-19-AOF is presented in **table 1**. The characteristics of patients with SLE admitted to hospital within the study period but without any evidence of COVID-19 are also presented for information. Briefly, SLE patients with COVID-19-AOF were younger (65 (52-76) years vs 76 (64-86) years; $p < 0.0001$), less frequently male ($n = 50$ (25.5%) vs $n = 56 601$ (57.8%); $p < 0.0001$) and had more comorbidities than the general population with COVID-19-AOF. Patients with SLE were also more frequently admitted to the intensive care unit (ICU) ($n = 83$ (42.4%) vs $n = 40 304$ (35.6%); $p = 0.04$) and underwent more often renal replacement therapy for acute kidney injury (AKI; $n = 14$ (7.1%) vs $n = 3744$ (3.3%); $p = 0.003$).

Crude analysis of 30-day and 90-day survival of patients with SLE experiencing COVID-19-AOF

At D30, 43 (21.9%) in-hospital deaths occurred among SLE patients with COVID-19-AOF vs 31 274 (27.6 %) in the unmatched non-SLE patients with COVID-19-AOF. In the D0-D30 period, the HR of death associated with presence of SLE was 0.69 (0.51-0.93). At D90, there was no perceptible difference regarding in-hospital mortality between both groups: 59 deaths (30.1%) in the SLE group vs 35 130 (30.9%) in the control group. In the D30-D90 period, the HR of death associated with presence of SLE was 1.52 (0.93-2.47). A sensitivity analysis using Cox model adjusted for age and sex is presented in online supplemental figure S6.

The Kaplan-Meier curve of the 90-day survival of these populations is displayed in **figure 1**. The survival of an unmatched SLE population without any evidence of COVID-19 is also displayed for information.

Postmatching analysis of 30-day and 90-day survival of patients with SLE experiencing COVID-19-AOF

Based on the presence of comorbidities, we were able to match 908 non-SLE patients with COVID-19-AOF and 170 SLE patients without COVID-19 with 190 SLE patients with COVID-19-AOF.

The characteristics of these matched populations as well as the standardised differences for the matching variables are displayed in **table 2**. The rate of ICU admission was similar

Table 1 Characteristics of patients with and without SLE experiencing COVID-19-AOF from March to November 2020 in France

	COVID-19-AOF		P value*	SLE non-COVID-19
	SLE n=196	Non-SLE n=113 371		n=7139
Age, years, median (Q1–Q3)	65 (52–76)	76 (64–86)	<0.001	45 (33–59)
Male sex, n (%)	50 (25.5)	56 601 (57.8)	<0.0001	992 (13.9)
Arterial hypertension, n (%)	139 (70.9)	72 701 (64.1)	0.05	2384 (33.4)
Cardiovascular history, n (%)	85 (43.4)	41 675 (36.8)	0.05	1699 (23.8)
Chronic kidney disease, n (%)	81 (41.3)	21 750 (19.2)	<0.001	1100 (15.4)
History of solid organ transplantation, n (%)	8 (4.6)	579 (0.5)	<0.001	157 (2.2)
Obesity, n (%)	69 (35.2)	31 210 (27.5)	0.2	888 (12.4)
Chronic pulmonary disease, n (%)	55 (28.1)	22 182 (19.6)	0.003	831 (11.6)
ICU admission, n (%)	83 (42.4)	40 304 (35.6)	0.04	
SAPS II at ICU admission, median (Q1–Q3)†	35 (26–52)	36 (27–47)	0.41	
Invasive mechanical ventilation, n (%)	36 (18.4)	17 513 (15.5)	0.26	
Renal replacement therapy for AKI, n (%)	14 (7.1)	3774 (3.3)	0.0003	
Use of pressor amines, n (%)	31 (15.8)	14 683 (13.0)	0.23	

Characteristics of the SLE population admitted to French hospitals without any evidence of COVID-19 during the same period are also presented for information.

*P values are given for significance of the difference between the first two groups.

†SAPS II is only available for ICU-admitted patients.

AKI, acute kidney injury; AOF, associated organ failure; ICU, intensive care unit; Q1, first quartile; Q3, third quartile; SAPS II, Simplified Acute Physiology Score; SLE, systemic lupus erythematosus.

between patients with SLE and matched patients without SLE experiencing COVID-19-AOF: n=82 (43.2%) in the SLE group vs n=242 (43.3%) in the non-SLE matched control group.

The Kaplan-Meier curve of the 90-day survival of these matched populations is displayed in figure 2. More details about the type of discharge after hospital stay following COVID-19-AOF are provided in online supplemental figure S3.

At D30, 43 deaths (22.6%) were observed within SLE patients with COVID-19-AOF vs 198 (21.8%) within the matched non-SLE patients with COVID-19-AOF. The HR of death associated with presence of SLE for this period was 0.98 (0.71–1.34).

A follow-up from D30 to D90 was possible for 75 SLE patients with COVID-19-AOF and 299 non-SLE patients with COVID-19-AOF. A comparison of their baseline features as well as detailed data of their follow-up is available in online

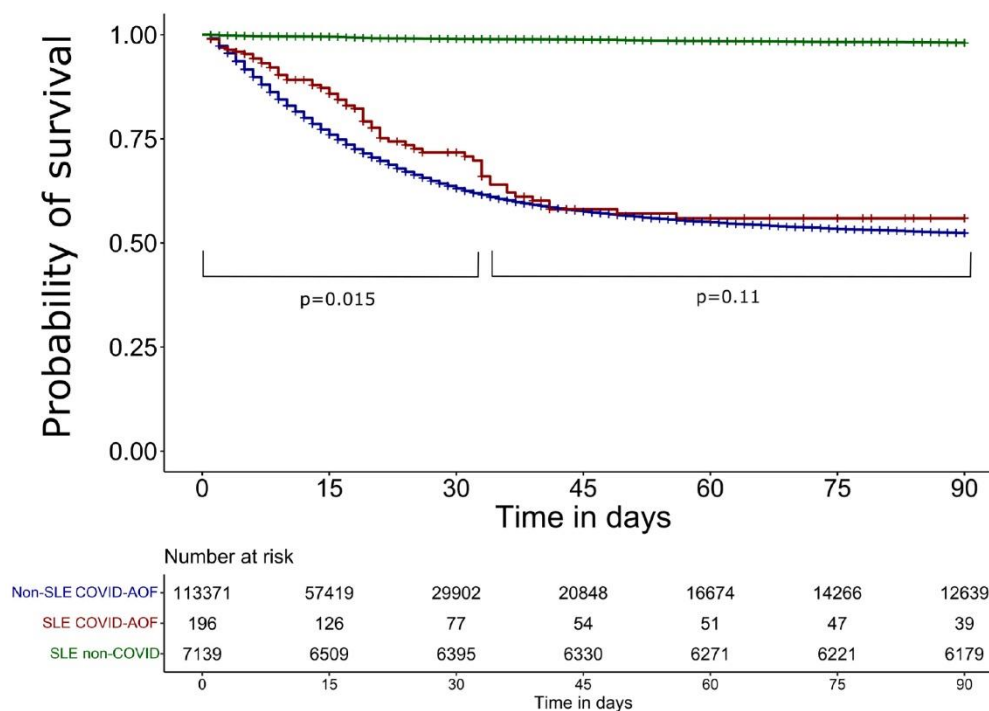


Figure 1 Survival at D90 of patients with SLE experiencing COVID-19-AOF in France (in red) from March 2020 to November 2020 compared with an unmatched control population without SLE (in blue) with COVID-19-AOF during the same period. For information, the survival of an unmatched SLE population admitted in France during the same period without any evidence of COVID-19 is shown in green. P value is given for the time periods D0–D30 and D30–D90 for comparison between SLE patients with COVID-19-AOF and non-SLE patients with COVID-19-AOF. AOF, associated organ failure; D, day; SLE, systemic lupus erythematosus.

Table 2 Characteristics of matched patients with and without SLE experiencing COVID-19-SLE from March to November 2020 in France

	COVID-19-AOF		SLE non-COVID-19	Standardised differences†
	SLE n=190	Non-SLE n=908	n=170	
Age, years, median (Q1–Q3)‡	65 (54–76)	66 (55–77)	63 (52–75)	–0.0630
Male sex, n (%)‡	48 (25.3)	235 (25.8)	37 (21.8)	0.0142
Arterial hypertension, n (%)‡	137 (72.1)	656 (72.3)	124 (72.9)	–0.0032
Cardiovascular history, n (%)‡	81 (42.6)	380 (41.9)	69 (40.6)	0.0158
Chronic kidney disease, n (%)‡	75 (39.5)	341 (37.6)	66 (38.8)	0.0394
Obesity, n (%)‡	68 (35.8)	318 (35.0)	56 (32.9)	0.0160
Chronic pulmonary disease, n (%)‡	53 (27.9)	253 (27.9)	40 (23.5)	0.0007
Diabetes mellitus, n (%)‡	51 (26.8)	254 (27.9)	42 (24.7)	–0.0254
ICU admission, n (%)	82 (43.2)	391 (43.1)		
SAPS II at ICU admission, median (Q1–Q3)*	36 (27–53)	37 (27–50)		0.0028
Invasive mechanical ventilation, n (%)	36 (18.9)	169 (18.6)		0.0086
Renal replacement therapy for AKI, n (%)	13 (6.8)	61 (6.7)		0.0049
Use of pressor amines, n (%)	31 (16.3)	147 (16.2)		0.0034

Characteristics of a matched SLE population admitted to French hospitals without any evidence of COVID-19 during the same period are also presented for information.

*SAPS II is only available for ICU-admitted patients.

†Standardised differences are given for significance of the difference between the first two groups.

‡Matching variables.

AKI, acute kidney injury; AOF, associated organ failure; ICU, intensive care unit; Q1, first quartile; Q3, third quartile; SAPS II, Simplified Acute Physiology Score; SLE, systemic lupus erythematosus.

supplemental figures S3–S4. The Kaplan-Meier curve of their D30–D90 survival is displayed in figure 3. During this period, we observed 19 deaths in the SLE group (25.3%) and 46 (15.4%) in the matched control group. The HR for death occurring from day 30 to day 90 after COVID-19-AOF among patients with SLE was 1.83 (1.05–3.20). A sensitivity analysis using a rematch procedure for patients still alive at D30 is presented in online supplemental figure S7–S8.

All HRs calculated for the crude and the matched analyses are summarised in table 3.

Healthcare use after COVID-19-AOF

Analysis of healthcare use post COVID-19-AOF for the matched population still alive at D30 is presented in online supplemental figure S5. We observed that patients with SLE had more reports of coinfection diagnoses than the matched control patients (mean (\pm SD): 9.09 (\pm 8.5) in the SLE group vs 7.6 (\pm 6.1) in the control group). Otherwise, we found no difference in the number of SLE-related outcomes such as renal biopsy or dialysis for AKI. Similarly, we found no difference

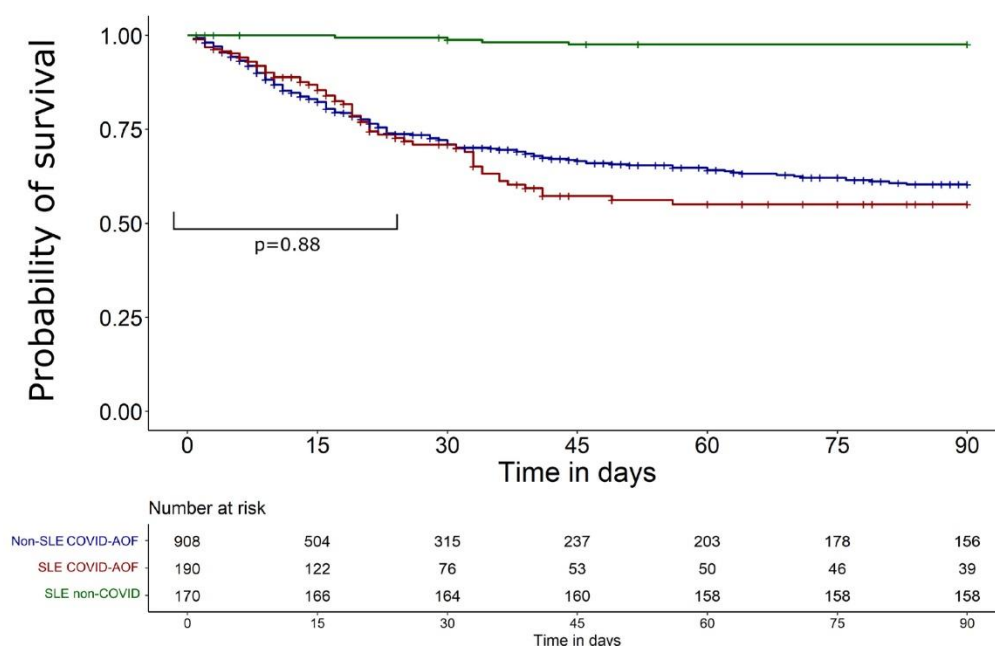


Figure 2 Survival at D90 of patients with SLE experiencing COVID-19-AOF in France (in red) from March 2020 to November 2020 compared with a matched control population (in blue) with COVID-19-AOF but without SLE admitted during the same period. For information, survival of a matched SLE population admitted in France during the same period without any evidence of COVID-19 is shown in green. P value is given for the time period D0–D30 for comparison between SLE patients with COVID-19-AOF and non-SLE patients with COVID-19-AOF. AOF, associated organ failure; D, day; SLE, systemic lupus erythematosus.

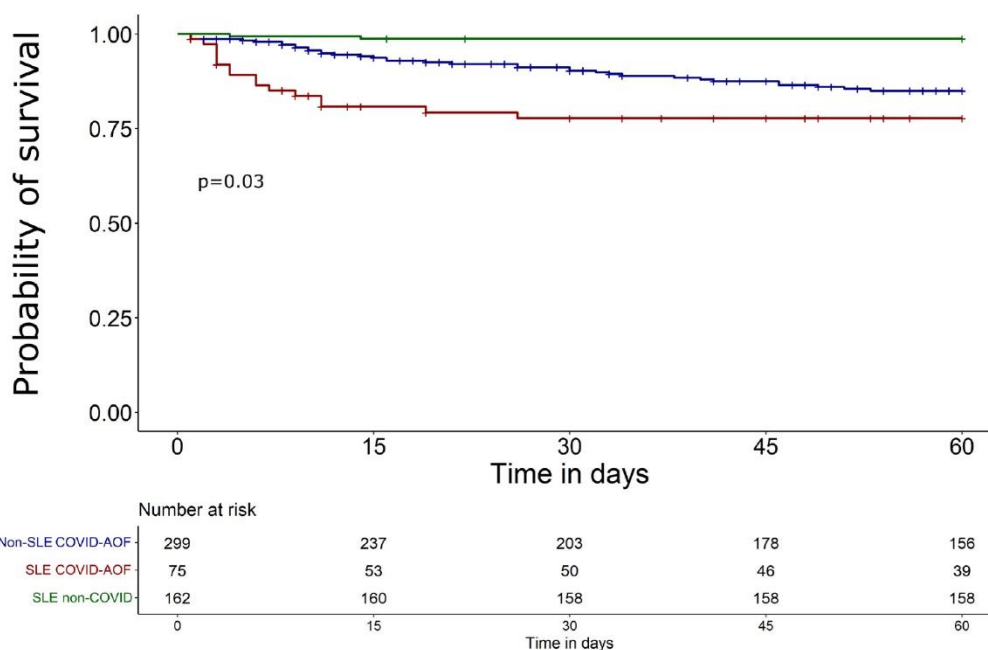


Figure 3 D30–D90 survival of patients still alive at D30. Patients with SLE experiencing COVID-19-AOF in France from March 2020 to November 2020 (in red) compared with a matched control population without SLE (in blue) with COVID-19-AOF during the same period. For information, survival of a matched SLE population admitted in France during the same period without any evidence of COVID-19 is shown in green. P value is given for comparison between SLE patients with COVID-19-AOF and non-SLE patients with COVID-19-AOF. AOF, associated organ failure; D, day; SLE, systemic lupus erythematosus.

in unspecific outcomes such as number of hospital stays, diagnosis of pulmonary embolism or coronary angiography for myocardial infarction.

DISCUSSION

Our analysis of the French national medical and administrative database showed that SLE is associated with a worsened prognosis during COVID-19-AOF requiring hospitalisation. Importantly, we observed an increased late-onset mortality, between D30 and D90, for hospitalised patients with SLE still alive 30 days after the first day of admission, independently of age, gender and various comorbidities such as chronic kidney disease.

Conversely, in our selected unmatched population, the crude analysis of the COVID-19-AOF outcome showed that hospitalised patients with SLE have an unchanged prognosis as compared with the general population. Such observation may be biased because patients with SLE are younger and more frequently female. On the other hand, patients with SLE have more comorbidities.¹⁶ Using a matching strategy that was devised to limit such biases, a specific delayed risk was unravelled in hospitalised SLE patients with COVID-19-AOF. Such increased risk might be related to the high coinfection rate during or after COVID-19

in these patients. Patients with SLE could be more susceptible to coinfection due to their treatment. They may also be at risk of COVID-19-induced immune paralysis. Of note, SLE flares or cardiovascular events rates did not seem to be increased after COVID-19-AOF. Since we did not have access to patients' detailed files and treatments, we were not able to confirm that SLE disease went uneventful.

Several studies have assessed the specific prognosis of patients with SLE during COVID-19 and displayed heterogeneous results.^{8,9,17–20} Most studies analysed a mixed subset with various rheumatic diseases and included a very limited number of patients with SLE. Moreover, no matching strategy was used to limit the bias related to age, sex and comorbidities among the SLE population.

We found a relatively low number of patients with SLE among the French population with COVID-19-AOF (196 of 113 371, 0.2%) between March and November 2020, whereas Cordtz *et al*²¹ recently reported an increased risk of hospitalisation for SLE patients with COVID-19 in Denmark compared with the general population. It might be due to a lack of precision in coding SLE procedures; however, our results fit well with the prevalence of SLE in France, estimated at 5 for 10 000.²² Moreover, the characteristics of our patients with SLE are consistent with previously published large epidemiological studies on patients with SLE conducted in France.²²

Because it is a hospital database, we only had access to in-hospital mortality. Since patients with SLE are more likely to be admitted to hospital, the proportion of in-hospital mortality for patients with SLE is expected to be higher than for the general population. However, we found that most of the patients discharged before D90 went home; therefore, we can assume that a very limited number of them died after discharge. Follow-up was limited to 90 days after COVID-19, with data gathered before November 2020; thus, the investigated population encountered almost exclusively the original 'Wuhan' SARS-CoV-2 strain.

Table 3 Summary of the main results of the study

Analysis	Period	HR of SLE	95% CI
Crude	D0–D30	0.69	0.51 to 0.93
	D30–D90	1.52	0.93 to 2.47
Matched	D0–D30	0.98	0.71 to 1.34
	D30–D90	1.83	1.05 to 3.20

HR is given for risk of death associated with SLE diagnosis after a COVID-19-AOF. For crude analysis HR was calculated using a standard univariable Cox proportional hazard model.

HR for the matched analysis was calculated using a univariable marginal Cox proportional hazard model.

AOF, associated organ failure; SLE, systemic lupus erythematosus.

Our work has several strengths. First, in accordance with the French Health Insurance System, PMSI gather exhaustive data of all French hospitals, meaning that our data included every patient with at least one diagnosis of SLE reported from 2011 to 2020. Thanks to linking between the successive hospitalisation episodes, we were able to examine all hospital records of each individual patient and to assess 30-day and 90-day outcomes. Our matched study allowed us to take into account several confounding factors that usually blur the comparison between patients with SLE and the general population. Although the severity of COVID-19-AOF was not included in the matching procedure, we observed a very similar rate of ICU admission, Simplified Acute Physiology Score II and healthcare use between patients with SLE and the matched control population, confirming the validity of the matching process.

COVID-19-AOF has a late-onset poor prognosis in patients with SLE. Further studies are warranted to delineate the clinical course of patients with SLE who survived severe COVID-19.

Acknowledgements The authors thank Celine Feger, MD (EMIBiotech) for her editorial support.

Contributors AM designed and conducted the analysis and wrote the manuscript. TP, SR, DvG, AS and KS were involved in the project development and edited the manuscript. J-FT directed the project and wrote the manuscript. AM is the guarantor of this study.

Funding PhD fellowship support for AM was provided by Agence Nationale pour la recherche (n°ANR-19-CE17-0029).

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval In accordance with the French regulatory system regarding personal and medical data and after agreement of the institutional review board (IRB), our institution was allowed to access the PMSI database. We only had access to patients diagnosed with infection-associated organ failure and/or SLE according to our definition. All data were anonymised. This study does not involve human participants.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

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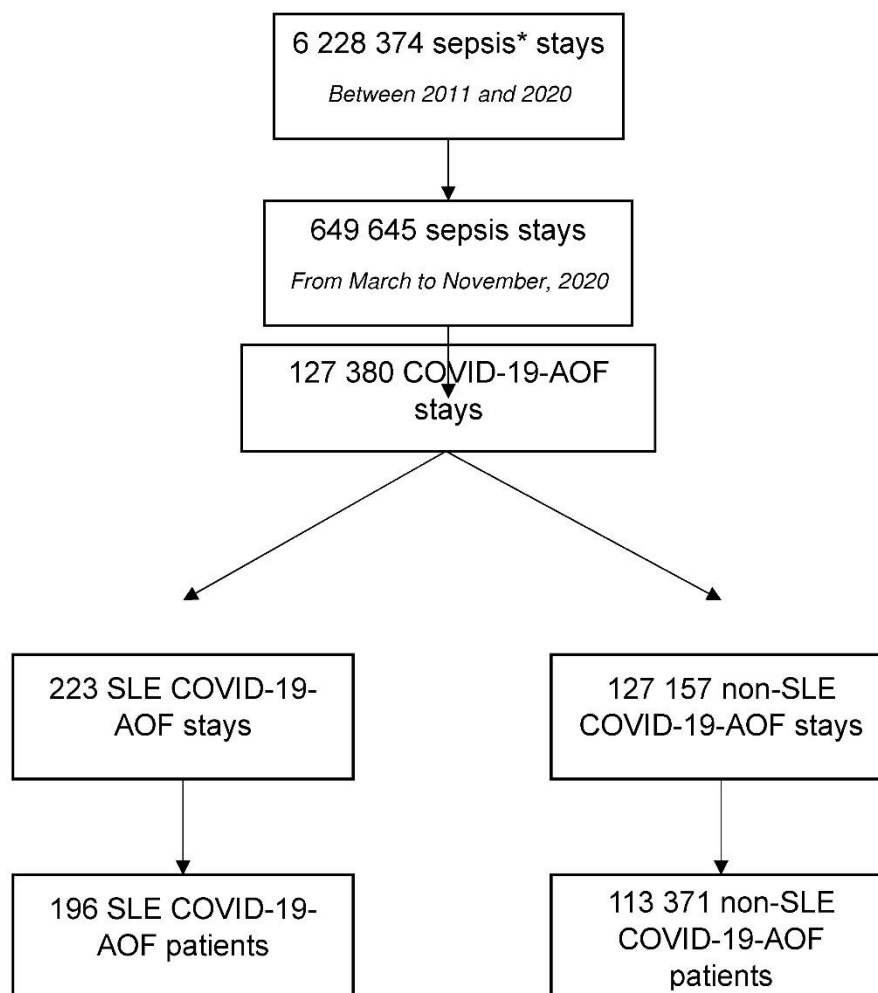
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COVID-19-associated organ failure among Systemic Lupus Erythematosus inpatients in France: a nationwide study.

ELECTRONIC SUPPLEMENTARY MATERIALS

Figure S1: Flow chart of the study



* sepsis= one diagnosis of infection + one diagnosis of organ failure during the same stay.
AOF: associated organ failure

Figure S2: Type of discharge for hospital stays following COVID-19-associated organ failure in the matched population for the D0-D90 period.

	SLE n=595	Non-SLE n= 2 713
Temporary transfer	0	6 (0.2%)
Mutation (same administrative facility)	8 (1,3%)	62 (2.3%)
Definitive transfer	82 (13,8%)	355 (13.1%)
Home	446 (74,9%)	2 056 (75.7%)
Death	59 (9.9%)	234 (8.6%)

Figure S3: Comparison of the matched patients still alive at D30

	SLE n= 75	Non-SLE- n=299	Standardized difference
Age, years [IQR]	64 [52-72]	62 [52-74]	-0.128
Male sex, n (%)	19 (25,3%)	84 (28.1)	0.0624
Arterial hypertension, n (%)	57 (76,0 %)	234 (78.3)	-0.0539
Cardiovascular history, n (%)	35 (46,7%)	138 (46.2)	0.0103
Chronic kidney disease	35 (46,7%)	138 (46.2)	0.0103
Obesity, n (%)	31 (41,3%)	106 (35.6)	0.1212
Chronic pulmonary disease, n (%)	20 (26,7%)	94 (31.4)	-0.1052
Diabetes mellitus, n(%)	53 (30,7%)	88 (29.4)	0.0269
Admission in ICU	36 (48,0%)	166 (55.5)	-0.1509

Figure S4: Follow-up details for the matched patients still alive at D30

	SLE n=75	Non-SLE n=299
Number of lost to follow-up D30-D60	9 (12,0 %)	73 (24.4)
Median follow-up time [IQR] D30-D60	30 [11-30]	30 [19-30]
Number of lost to follow-up D30-D90	20 (26.7%)	107 (35.8%)
Median follow-up time [IQR] D30-D90	60 [11-60]	60 [19-60]
Number of patients in ICU at D30	10 (13.3%)	36 (12.0%)
Number of patients with invasive mechanical ventilation at D30	9 (12.0%)	30 (10.0%)

Figure S5: Post-COVID19-associated organ failure healthcare use for the matched patients still alive at D30

	SLE n=75	Non-SLE n=299	p
Number of hospital stays, mean (+/-sd)	2.93(+/-2.0)	2.87 (+/- 1,97)	0,61
Number of days spent in hospital, mean (+/-sd)	15,8 (+/-20,8)	14,8 (+/- 23,7)	0.58
Number of infectious codes reported, mean (+/-sd)	9.09 (+/-8.5)	7.6 (+/-6,1)	0.022
Dialysis for AKI, n (%)	8 (10.7%)	46 (15.4%)	0.30
Onset of chronic dialysis, n (%)	0	0	
Renal biopsy, n (%)	3 (4.0%)	14 (4.7%)	0.80
Coronary angiography, n (%)	1 (1.3%)	3 (1.0%)	0.80
Pulmonary embolism, n (%)	2 (2.7%)	2 (0.7%)	0.13

SENSITIVITY ANALYSES

Figure S6: Crude analysis of the 30-day and 90-day survival of SLE patients experiencing COVID-19-associated organ failure.

Here are provided the results of the proportional hazard cox model performed on the unmatched populations, adjusted on age (taken as continuous variable) and sex. HR = hazard ratio; CI: confidence interval.

<i>Period</i>	<i>Variable</i>	<i>HR</i>	<i>95% CI</i>
<i>D0-D30</i>	SLE	1.12	0.83-1.52
	Age (years)	1.05	1.04-1.05
	Sex (Male)	1.31	1.28-1.34
<i>D30-D90</i>	SLE	2.11	1.29-3.45
	Age (years)	1.02	1.02-1.03
	Sex (Male)	1.32	1.23-1.41

Figure S7-S8: New matching procedure using D30 as a landmark.

Here are displayed the results of the matched analysis with a new random, exact, without replacement, matching procedure performed on the SLE COVID-19-AOF patients still alive at D30. Controls were selected among the population of non-SLE COVID-19-AOF patients still alive at D30. We used the same matching variables as in the main analysis plus two new ones: the presence in ICU at D30 and the use of invasive mechanical ventilation at D30.

With this new procedure, 67/75 cases were matched with 184 unique non-SLE controls. The standardized differences of these populations are displayed in figure S7. The Kaplan-Meier curves of their survival are displayed in figure S8.

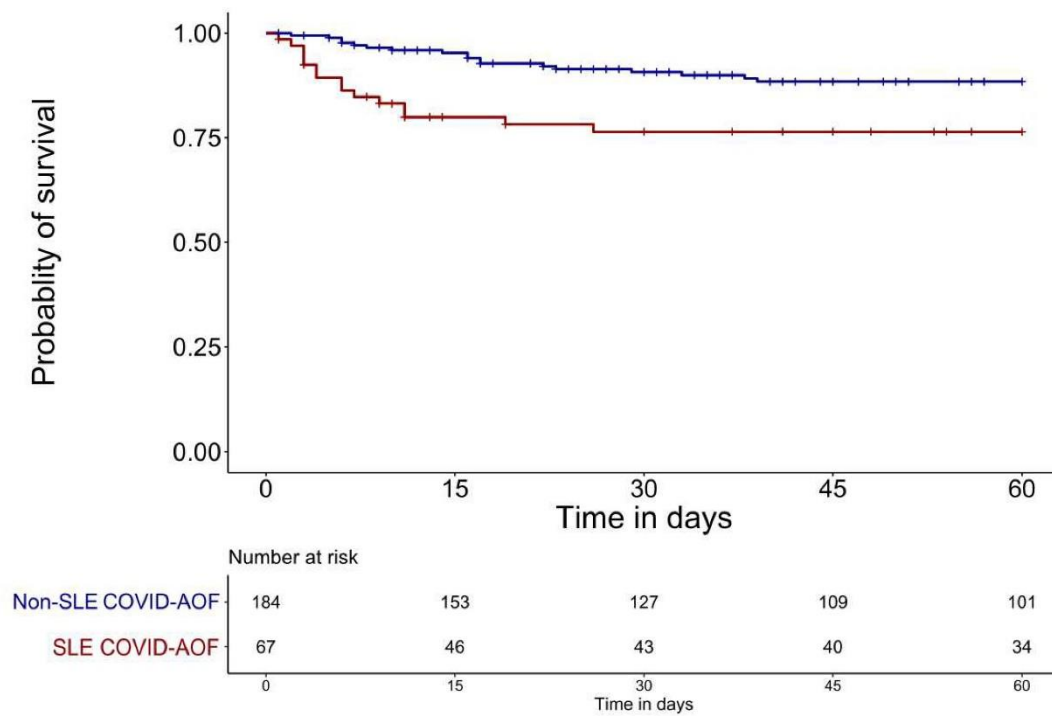
We observed 15 (22.4 %) deaths in the SLE group versus 18 (9.8%) in the control group. The HR for death associated with SLE was 2.48 [1.31-4.67] for the D30-D90 period with the marginal Cox model.

Figure S7: Comparison of the matched patients still alive at D30 after the new matching procedure.

	SLE n= 67	Non-SLE n=184	Standardized difference
Age, years [IQR]	65 [52-72]	64 [54-72]	-0.0141
Male sex, n (%)	17 (25,4%)	51 (27.7)	0.0531
Arterial hypertension, n (%)	52 (77.6%)	142 (77.2)	0.0105
Cardiovascular history, n (%)	31 (46.3)	84 (45.7)	0.0124
Chronic kidney disease	30 (44.8)	77 (41.9)	0.059
Obesity, n (%)	26 (38.8)	65 (35.3)	0.0721
Chronic pulmonary disease, n (%)	17 (25.4)	49 (26.6)	-0.0297
Diabetes mellitus, n (%)	20 (29.9)	60 (32.6)	-0.595
In ICU at D30	8 (11.9%)	20 (10.9%)	0.0337
Invasive mechanical ventilation at D30	6 (8.9%)	11 (5.6%)	0.1134

Figure S8: D30-D90 survival of patients still alive at D30. In red, SLE patients experiencing COVID-19-associated organ failure in France from March 2020 to November 2020 compared to a re-matched (at D30) control population without SLE (in blue) and with COVID-19-associated organ failure during the same period. P value is given for the comparison between SLE COVID-19-AOF patients and non-SLE COVID-19-AOF patients.

SLE: systemic lupus erythematosus; AOF: associated organ failure



CODES USED**1 Diagnosis codes**

List of the ICD 10 diagnosis codes used. ICD-10 is available at

<http://apps.who.int/classifications/icd10/browse/2010/en>

SLE	
SLE	M32x,

COVID-19	'U071','U0710','U0711','U0712','U0714','U0715'
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Other comorbidities	
Chronic kidney disease	"N183", "N184", "N185", "N189", "N180", "N188"
High blood pressure	I10x
Diabetes mellitus	E10, E100,E101,E109,E11, E110,E111,E119, E1108,E1110,E1118,E1190,E1198,E12,E120,E121,E129, E13,E130,E131,E139,E14,E140,E141,E149, O24,O240,O241,O242,O243,O244,O249,E136,E138,E139,E146,E148,E149, E120,E121,E129,E13,E130,E131,E139,E130,E131,E139,E14,E140,E141,E149, E140,E141,E149, O24,O240,O241, O242,O243,O244,O249,E1100,E100,E101,E106,E108,E109,E110,E111,E116,E118,E119
Chronic pulmonary disease	J40, I278, I279, J40, J41, J410, J411, J418, J42, J43, J430, J431, J432, J438, J439, J44, J440, J441, J448, J449, J450, J451, J458, J459, J46, J47, J60, J61, J620, J628, J630, J631, J632, J633, J634, J635, J638, J64, J65, J660, J661, J662, J668, J670, J671, J672, J673, J674, J675, J676, J677, J678, J679, J684, J701, J703, J96, J9610, J96100, J96101, J9611, J96110, J96111, J9619, J96190, J96191, J9690, J9691, J9699
Obesity	E66x excepted 'E6603','E6609','E6613','E6619','E6683','E66890,E669,E6699
Cardiovascular event	
Myocardial infarction	I21x, I22x
Ischemic stroke or transient ischemic attack	I63x, G45, G46, I64
Angina pectoris	I20x,
Sudden death	I461
Mesenteric ischemia	K550x
Arterial thrombosis or ischemia	I74x
Cardiovascular condition :	Z867, Z8660, F01, Z951, I25, I516, I461, I70, I65, I693

Organ failure	'I95','I951','I958','I959','I981','E86','E872','R55','R571','R65','R651','R659','R57','R570','R572','R578','R579','D65','D689','D695','D696','D762','K72','K720','K729','R17','F05','F050','F058','F059','F079','F09','G934','R40','R400','R401','R4018','R402','R4028','R410','R451','R392','R34','N17','N170','N171','N172','N178','N179','N19','J80','J951','J952','J96','J960','J9600','J9601','J9609','J969','J9690','J9691','J9699','R092','R230'
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2 Procedure codes

[CCAM list of procedures codes is available \(in French\) at:](#)

https://www.ameli.fr/fileadmin/user_upload/documents/CCAM_V52.pdf

Invasive mechanical ventilation	"GLLD0150", "GLLD0080", "GLLD0040", "GLLD0060", "GLLD0130", "GLLD0050", "ZZLB0040"
Noninvasive mechanical ventilation	"GLLD0030", "GLLD0020", "GLLD0120", "GLLP0030", "GLLD0190"
Transplantation	"JAEA0030", "DZEA002", "DZEA003", "DZEA001", "DZEA004", "DZFA004", "GFFA020", "GFEA005", "GFEA002", "GFEA007", "GFEA004", "GFEA001", "GFEA006", "HLEA002", "HLEA001"
Use of pressor amines	"EQLF0030", "EQLF0010"
Renal replacement therapy for AKI	"JVJF0030", "JVJF0020", "JVJF0060", "JVJF0050", "JVJF0070", "JVJB0020"
Therapeutic coronary angiography	"DDAF0010", "DDAF0060", "DDAF0040", "DDAF0030", "DDAF0100", "DDAF0080", "DDAF0070", "DDAF009"
Organ failure	"EQLF0030", "EQLF0020", "DKMD0010", "DKMD0020", "FELF0030", "GELD0040", "ABQP0010", "AAQP0030", "JVJF0020", "JVJF0050", "GLLD0030", "GLLD0040", "GLLD0080", "GLLD0120", "GLLD0150", "GLLD0190"

3- Definitions

Cardiovascular history: history of cardiovascular event (myocardial infarction, ischemic stroke transient ischaemic attack, sudden death, mesenteric ischaemia, arterial thrombosis, or ischaemia) or a code of cardiovascular condition, or a history of therapeutic coronary angiography.

Safety and immunogenicity of mRNA anti-SARS-CoV2 vaccines among patients living with SLE: the COVALUS project. Studies 3 & 4.

The rapid development of anti-SARS-CoV-2 vaccines has brought great hope to the SLE community. Data from other vaccines, such as pneumococcal or influenza vaccines, had previously shown that overall vaccine safety in SLE was reassuring, although vaccine immunogenicity was often reduced, particularly in patients on immunosuppressants. However, as this was the first time that mRNA vaccine technology had been used, and because patients with IMiDs were initially excluded from the original clinical trials, many questions, specific to the SLE population, were raised. In addition, the emergence of different strains of the virus, such as the alpha or omicron variants, raised further concerns about immunogenicity against the different variants.

To investigate the immunogenicity and tolerability of the BNT162b2 vaccine in SLE we conducted a prospective, monocentric, observational study including SLE patients and healthy volunteers during and after the initial phase of the vaccination with the BNT162 vaccine. Individuals had study visits just before the first dose (T0), just before the second dose (M1), 3 months after the first dose (M3), and 6 months after the first dose (M6). We evaluated both immunogenicity and safety in SLE patients, compared to healthy volunteers, at the clinical and biological levels. We enrolled 55 SLE patients and 11 healthy volunteers between March and May 2021. The COVALUS project was funded by the Agence Nationale pour la Recherche (ANR). In the first related paper, published as a research letter in *Annals of the Rheumatic Diseases*, we detailed the humoral response directed against the different SARS-CoV-2 variants of concern. In the second paper, published as a full paper in the *Journal of Autoimmunity*, we presented the effects of the BNT162b2 vaccine on plasmacytoid dendritic cells and autoreactive T cells.

Study 3

Severely impaired humoral response against SARS-CoV-2 variants of concern following two doses of BNT162b2 vaccine in patients with systemic lupus erythematosus (SLE)

Severe COVID-19 is associated with a poor prognosis among patients with systemic lupus erythematosus (SLE).¹ Accordingly, patients with SLE receiving immunosuppressive drugs have been prioritised for vaccination in France.² However, patients with autoimmune diseases—especially those receiving anti-CD20—are now known to mount a suboptimal humoral response following COVID-19 vaccination.³ Furthermore, vaccine-induced humoral protection against omicron, the current dominant variant of concern (VOC) worldwide, is not known in SLE.

Patients with SLE were prospectively enrolled in the vaccine task force set up between March and May 2021 in our national centre for autoimmune diseases.⁴ Humoral vaccine responses against B (ancestral), alpha, delta and omicron variants were assessed using a specific multiplex ELISA assay (CoViDiag kit, Innobiochips, Loos, France). Humoral response was defined by a specific SARS-CoV-2 anti-spike IgG (anti-S) level in serum >260 binding antibody units (BAU)/mL, according to French Health Authorities.⁵ Data were compared between groups using Fisher's exact test for dichotomous variables and Mann-Whitney test for continuous variables.

Fifty-five patients with SLE were enrolled in the vaccine task force. Among them, 10 had prior COVID-19 and 10 were under immunosuppressive drugs and received three-dose primary series of BNT162b2 vaccine following national recommendation.² Eventually, 35 COVID-19-naïve patients with SLE (43.4 (36.0, 48.6) years; 88.6% female; table 1) and 9 healthy volunteers (HV) (59.0 (56.0, 62.0) years; 88.8% female) who received two doses of BNT162b2 vaccine 4 weeks apart were screened for humoral vaccine responses at baseline, at second dose, and 2 and 5 months after second dose. The two-dose and three-dose primary series of BNT162b2 vaccine were performed following an interval of 4 weeks between doses as recommended.²

Patients with SLE and HV had no detectable anti-S and anti-nucleocapsid at baseline. Two months after the second-dose vaccine, 54.3% (n=19/35), 54.3%, 42.9% and 28.6% of patients with SLE had specific anti-S titres >260 BAU/ml against B, alpha, delta and omicron variants, respectively. At the same time point, the percentage of subjects able to mount humoral response against VOC were lower in SLE as compared with HV (100% of HV for B, p=0.016; 100% for alpha; p=0.016; 88.9% for delta; p=0.023; 55.6% for omicron, p=0.235). In patients with SLE, when the humoral responses against VOC was obtained 2 months after the second dose, it was maintained at 5 months in only 10.5% (n=2/19), 10.5% (2/19), 13.3% (2/15) and 10% (1/10) for B, alpha, delta and omicron variants, respectively. Overall, 5 months after the second-dose vaccine, the percent of patients with SLE with humoral response against B (n=2/35, 5.7% vs n=7/9, 88.9% p<0.001), alpha (5.7% vs 77.8%, p<0.001) and delta (5.7% vs 55.6%, p=0.002) variants were dramatically low as compared with HV. Almost all vaccinated subjects (n=34/35, 99% patients with SLE and n=7/9, 77.8% HV, p=0.101) failed to mount long-lasting humoral response against Omicron after two doses of BNT162b2 vaccine (figure 1). Of note, 50% (n=4/8), 50% (n=4/8), 37.5% (n=3/8) and 12.5% (n=1/8) of patients with SLE who were

Table 1 Characteristics of patients with SLE

	Two-dose primary, n=35	Three-dose primary, n=10	Prior COVID-19 n=10
Age, years (median (IQR))	43.4 (36.0, 48.6)	44.6 (38.5, 49.88)	50.1 (40.2, 59.6)
Female gender, n (%)	31 (88.6)	8 (80.0)	9 (90.0)
Delay since diagnosis, years (median (IQR))	7.8 (4.0, 12.9)	18.8 (12.9, 21.3)	8.9 (3.6, 27.5)
SLE involvement, n (%):			
Cutaneous	22 (62.8)	9 (90.0)	4 (40.0)
Joint	25 (71.4)	9 (90.0)	5 (50.0)
Renal	12 (34.3)	7 (70.0)	5 (50.0)
Serosal	10 (28.6)	6 (60.0)	4 (40.0)
Haematologic	11 (31.4)	4 (40.0)	4 (40.0)
Neuropsychiatric	4 (11.4)	2 (20.0)	2 (20.0)
Antiphospholipid syndrome	6 (17.1)	1 (10.0)	2 (20.0)
SLE treatment at BNT162b2 vaccine, n (%)			
Hydroxychloroquine (HCQ)<200 µg/L	30 (85.7)	10 (100.0)	9 (90.0)
(HCQ) 200–1500 µg/L	2 (6.6)	2 (20.0)	2 (20.0)
(HCQ)>1500 µg/L	24 (80.0)	7 (70.0)	6 (60.0)
Steroids	4 (13.3)	1 (10.0)	1 (10.0)
Daily dose, mg (median (IQR))	16 (45.7)	9 (90.0)	8 (80.0)
Belimumab	7(5,10)	7.5(7, 10)	6.5(5, 7)
Azathioprine	1 (2.9)	0 (0)	0 (0)
Methotrexate	0 (0)	2 (20.0)	0 (0)
Mycophenolate mofetil	0 (0)	0 (0)	0 (0)
Cyclophosphamide	0 (0)	7 (70.0)	1 (10.0)
Anti-CD20	0 (0)	0 (0)	0 (0)
Anti-CD20	0 (0)	3 (30.0)	0 (0)
Lymphocyte count, ×10 ⁹ /L (median (IQR))	0 (0)	3 (30.0)	0 (0)
Gammaglobulins, g/L (median (IQR))	1.52 (1.28, 2.00)	1.10 (0.97, 1.91)	1.44 (1.20, 2.60)
SLEDAI, median (IQR)	11.9 (9.6, 15.6)	12.2 (10.3, 14.9)	14.0 (11.2, 15.5)
SLEDAI, median (IQR)	0 (0, 2)	2 (0, 2)	1 (0, 2)

HCQ:level measured in whole blood.

HCQ, hydroxychloroquine; SLE, systemic lupus erythematosus; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

under immunosuppressive drugs (azathioprine, mycophenolate mofetil or anti-CD20) and received three-dose primary series of BNT162b2 had a preserved humoral response for B, alpha, delta and omicron variants, respectively, 5 months after the third dose. Moreover, all but one (83.4%, n=5/6) patients with SLE who had COVID-19 6.2 (3.9–11.6) months before the first BNT162b2 dose had a sustained humoral response 5 months after the second dose against all VOC including omicron (online supplemental figures S2 and S3; online supplemental table S2).

In this 6-month prospective monocentric study, we show that more than 90% of COVID-19-naïve patients with SLE failed to reach vaccine-induced humoral response after two doses of BNT162b2. To our knowledge, this is the first evaluation of long-lasting humoral responses against VOC including omicron variant in a cohort of patients with SLE. Neutralisation activity was not determined but the threshold of 260 BAU/mL for humoral response was consistent with previous published results and a strong correlation between anti-S IgG BAU/mL, live viral neutralisation and pseudo-neutralisation activity has been reported by our group.⁶ Since our patients with SLE received no immunosuppressive drugs, the poor immune response observed

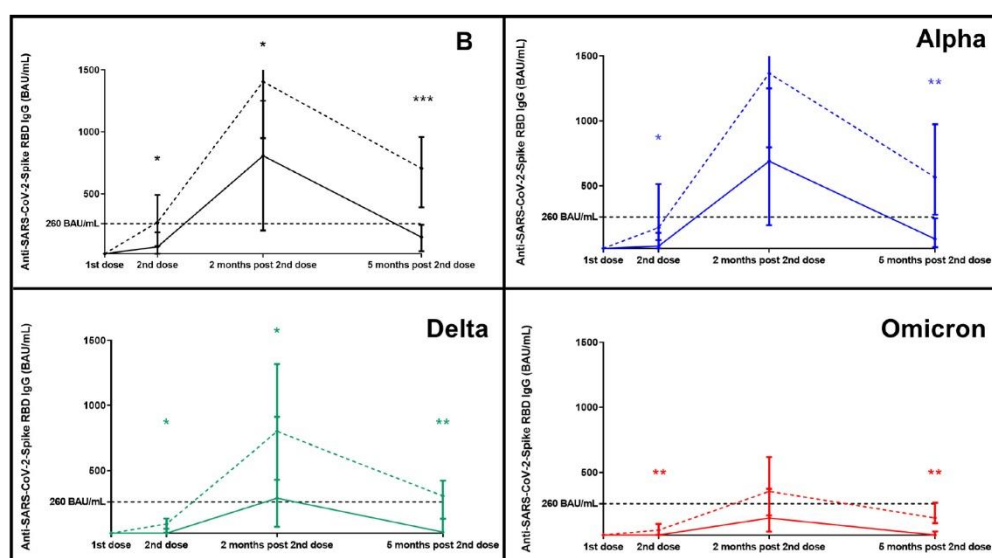


Figure 1 Humoral response following two doses of anti-SARS-CoV-2 mRNA BNT162b2 vaccine in COVID-19-naïve patients with SLE and healthy volunteers. Serum SARS-CoV-2 anti-spike IgG level assessed overtime against B (ancestral), beta, delta and omicron variants by using a specific quantitative ELISA assay (CoVIDiag kit, Innobiochips, Loos, France) in patients with SLE (n=35, solid line) and healthy volunteers (n=9, dotted line). Medians and first and third quartiles were showed at second dose, 2 months and 5 months after second dose. P value was calculated using Mann-Whitney U test (*p<0.05; **p<0.01; ***p<0.001). The value of 260 indicated the threshold for humoral response. BAU, binding antibody units; SLE, systemic lupus erythematosus.

after two vaccine doses could not be ascribed to treatment. Such vaccine failure is worrisome considering the recent onset of highly contagious SARS-CoV-2 variant such as omicron. In patients who were under immunosuppressive drugs and received 3-dose primary series of vaccine, the highly variable humoral responses may reflect the different impact of immunosuppressive agents on the vaccine immunogenicity.

In conclusion, our data show the poor immune long-lasting protection conferred by two doses of BNT162b2 vaccines in patients with SLE. Screening for humoral response to vaccination based on anti-S titres should be performed in all patients with SLE, including those who are not receiving immunosuppressive drugs. The absence of anti-SARS-CoV-2 antibodies after full vaccination might help to identify patients who are candidates for additional strategies, including anti-Sars-COV-2 monoclonal antibody prophylaxis, to protect them from COVID-19

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Handling editor Josef S Smolen

Acknowledgements The authors wish to acknowledge Jean-Francois Alexandra, Laure Delaval, Fatima Farhi, Maureen Marie-Joseph, Diane Rouzaud and Celine Mendes from the Bichat Hospital Internal Medicine Department for their invaluable help.

Contributors KS and TG directed the project. AM, VMF, TG, DD and KS designed the study. AM, VMF, CC and NH-F conducted analysis. ND, CF and TP were involved

in the project development and edited the manuscript. AM and KS wrote the manuscript. All authors reviewed and approved of the final manuscript.

Funding AM was supported by a PhD fellowship provided by Fondation pour la Recherche Médicale (FDM202106013488). This work was supported by Agence Nationale de la Recherche (no ANR-21-COVR-0034 COVALUS) and by the Agence Nationale de la Recherche sur le SIDA et les Maladies Infectieuses Emergentes (ANRS MIE), AC43 Medical Virology and Emergen Programme.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by Institutional Review Board—IRB 00006477—of HUPNVS, Paris 7 University, AP-HP. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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► Additional supplemental material is published online only. To view, please visit the journal online (<http://dx.doi.org/10.1136/annrheumdis-2022-222498>).

AM and VMF contributed equally.



To cite Mageau A, Ferré VM, Goulenok T, et al. *Ann Rheum Dis* 2022;**81**:1194–1196.

Received 16 March 2022

Accepted 31 March 2022

Published Online First 8 April 2022

Ann Rheum Dis 2022;**81**:1194–1196. doi:10.1136/annrheumdis-2022-222498

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SUPPLEMENTARY MATERIALS**Severely impaired humoral response against SARS-CoV-2 variants of concern following 2 doses of BNT162b2 vaccine in systemic lupus erythematosus (SLE) patients**

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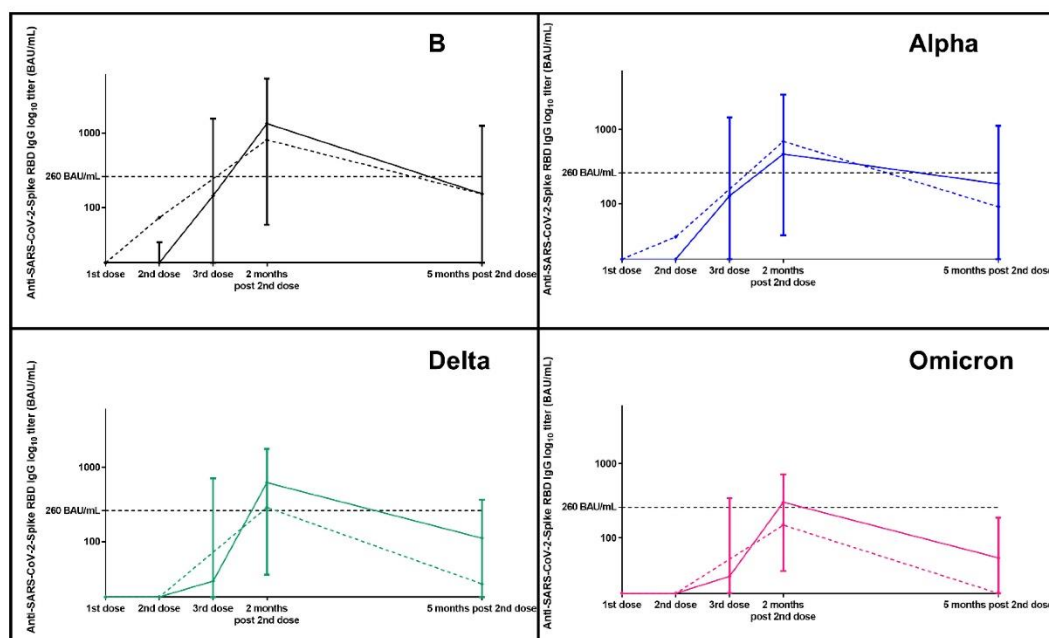
Table S1 Specific anti-S titers against B, alpha, delta and omicron variants in SLE patients

	B (ancestral)	Alpha	Delta	Omicron
BAU/mL at baseline				
SLE 2-dose primary (n=35)	18 [18-18]	18 [18-18]	18 [18-18]	18 [18-18]
SLE 3-dose primary (n=10)	18 [18-18]	18 [18-18]	18 [18-18]	18 [18-18]
SLE prior COVID-19 (n=10)	250 [143-704]	232 [168-545]	96 [73-208]	71 [26-90]
HV (n=9)	18 [18-18]	18 [18-18]	18 [18-18]	18 [18-18]
BAU/mL at 2 nd dose				
SLE 2-dose primary	73 [18-191]	36 [18-139]	18 [18-53]	18 [18-20]
SLE 3-dose primary	18 [18-18]	18 [18-18]	18 [18-18]	18 [18-18]
SLE prior COVID-19	6250 [6074-8657]	6250 [5948-7420]	2926 [1858-5689]	1444 [766-3057]
HV	272 [84-476]	178 [85-457]	90 [26-107]	56 [19-97]
BAU/mL 2 months post-2 nd dose				
SLE 2-dose primary	807 [205-1250]	689 [197-1250]	288 [67-912]	149 [44-375]
SLE 3-dose primary	1338 [79-3637]	466 [77-2639]	621 [72-1428]	302 [36-716]
SLE prior COVID-19	6250 [5854-11781]	6250 [3028-10399]	3213 [564-5964]	1099 [502-2519]
HV	1405 [1074-2500]	1366 [822-2500]	949 [453-1308]	588 [438-650]
BAU/mL 5 months post-2 nd dose				
SLE 2-dose primary	152 [38-250]	91 [26-250]	27 [18-128]	18 [18-45]
SLE 3-dose primary	152 [18-1250]	185 [18-856]	111 [18-354]	54 [18-186]
SLE prior COVID-19	6250 [3437-10 937]	5447[3229-9273]	1190 [1091-2144]	934 [449-1207]
HV	706 [464-837]	566 [311-814]	305 [142-379]	150 [118-205]

BAU, binding antibody units, given in median [IQR]

HV, healthy volunteers

Figure S2 Humoral response following 3-dose primary series of BNT162b2 in COVID-19-naïve SLE patients

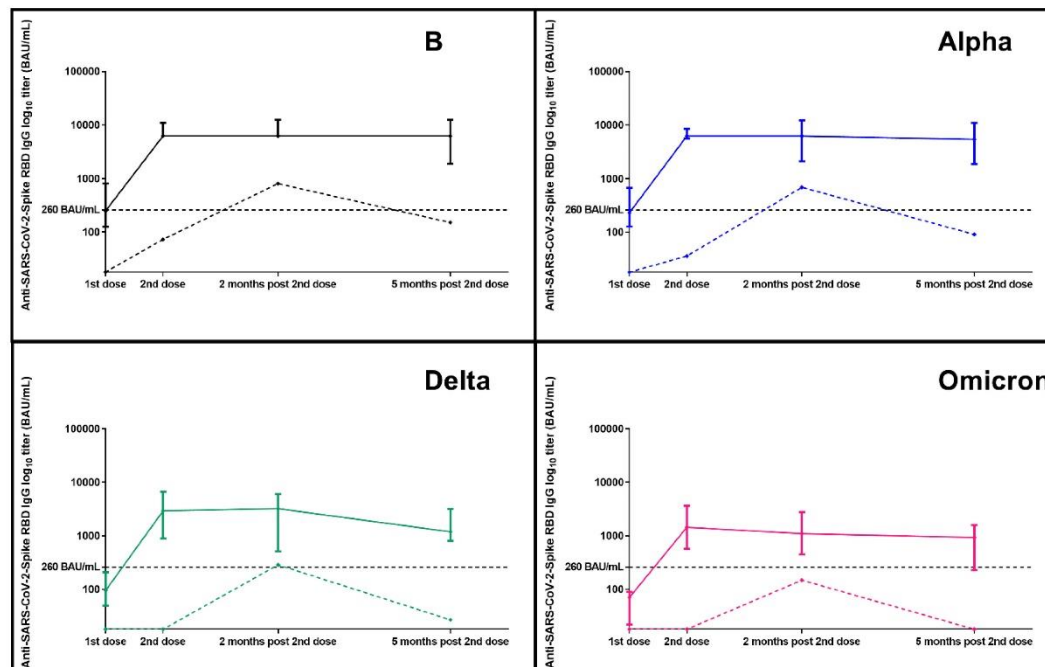


Serum SARS-CoV-2 anti-spike IgG level assessed overtime against B (ancestral), beta, delta and omicron variants by using a specific quantitative ELISA assay (CoViDiag kit, Innobiochips®, Loos, France) in patients with SLE who received 3-dose (n=10, solid line) or 2-dose (n=35, dotted line) primary series of BNT162b2. Medians and first and third quartiles were showed at second dose, 2 months and 5 months after second dose.

BAU, binding antibody units; the value of 260 indicated the threshold for humoral response

According to French guidelines, SLE patients who were under immunosuppressive drugs (azathioprine, mycophenolate mofetil or anti-CD20) received 3-dose primary series of BNT162b2

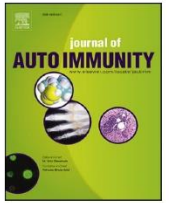
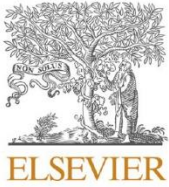
Figure S3 Humoral response following 2-dose primary series of BNT162b2 in SLE patients who experienced prior COVID-19



Serum SARS-CoV-2 anti-spike IgG level assessed overtime against B (ancestral), beta, delta and omicron variants by using a specific quantitative ELISA assay (CoViDiag kit, Innobiochips®, Loos, France) in patients with SLE who experienced (n=10, solid line) or did not experience (n=35, dotted line) prior COVID-19 and received 2-dose primary series of BNT162b2

BAU, binding antibody units; the value of 260 indicated the threshold for humoral response

Study 4



Impact of BNT162b2 mRNA anti-SARS-CoV-2 vaccine on interferon-alpha production by plasmacytoid dendritic cells and autoreactive T cells in patients with systemic lupus erythematosus: The COVALUS project

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ARTICLE INFO

Keywords:

Systemic lupus erythematosus
SARS-CoV-2
mRNA vaccine
Plasmacytoid dendritic cells
Type-1 interferon

ABSTRACT

Objective: To evaluate the specific response of SLE patients to BNT162b2 vaccination and its impact on autoimmunity defined as *in vivo* production of interferon-alpha (IFN α) by plasmacytoid dendritic cells (pDCs) and autoreactive immune responses.

Methods: Our prospective study included SLE patients and healthy volunteers (HV) who received 2 doses of BNT162b2 vaccine 4 weeks apart. Subjects under immunosuppressive drugs or with evidence of prior COVID-19 were excluded. IgG anti-Spike SARS-CoV-2 (anti-S) antibodies, anti-S specific B cells, anti-S specific T cells, *in vivo* INF- α production by pDCs, activation marker expression by pDCs and autoreactive anti-nuclear T cells were quantified before first injection, before second injection, and 3 and 6 months after first injection.

Results: Vaccinated SLE patients produced significantly lower IgG antibodies and specific B cells against SARS-CoV-2 as compared to HV. In contrast, anti-S T cell response did not significantly differ between SLE patients and HV. Following vaccination, the surface expression of HLA-DR and CD86 and the *in vivo* production of IFN α by pDCs significantly increased in SLE patients. The boosted expression of HLA-DR on pDCs induced by BNT162b2 vaccine correlated with the overall immune responses against SARS-CoV-2 (anti-S antibodies: $r = 0.27$ [0.05–0.46], $p = 0.02$; anti-S B cells: $r = 0.19$ [-0.03–0.39], $p = 0.09$); anti-S T cells: $r = 0.28$ [0.05–0.47], $p = 0.016$). Eventually, anti-SARS-CoV-2 vaccination was associated with an overall decrease of autoreactive T cells (slope = - 0.00067, $p = 0.015$).

Conclusion: BNT162b2 vaccine induces a transient *in vivo* activation of pDCs in SLE that contributes to the immune responses against SARS-CoV-2. Unexpectedly BNT162b2 vaccine also dampens the pool of circulating autoreactive T cells, suggesting that vaccination may have a beneficial impact on SLE disease.

1. Introduction

Anti-SARS-CoV-2 vaccination is a major issue in patients with systemic lupus erythematosus (SLE) because of their comorbidities, immunosuppressive treatment and the severity of COVID-19 in this population [1,2]. International boards have however provided

conflicting guidelines regarding mRNA vaccination in autoimmune disorders [3,4]. Vaccination coverage has been challenged by the common belief that vaccination could induce flare of the disease [5,6]. Patients with autoimmune diseases were excluded at first from SARS-CoV-2 vaccine clinical development programs. Although data from the large COVAX registry were reassuring [7], both patients and

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physicians still fear that vaccination could induce SLE flares by boosting innate immunity [8].

Plasmacytoid dendritic cells (pDCs) - the most potent producers of type I IFN (IFN-I) [13] - is a key cell involved in SLE pathogenesis [9,10]. Since type I interferons (IFN) play a role in both SLE pathophysiology and COVID-19 immune response [8–12], a specific risk associated with anti-SARS-CoV-2 vaccine could be postulated. BNT162b2 mRNA anti-SARS-CoV-2 vaccine may activate pDCs in SLE patients and increase the risk of lupus flares.

In this study, we tested the ability of BNT162b2 vaccine to induce interferon-alpha (IFN α) production by pDCs *in vivo* and analysed its putative impact on both autoreactive T cells and B cell-driven immune protection against SARS-CoV-2 in patients with SLE.

2. Methods

2.1. Population

We conducted a prospective observational study that included SLE patients who received a first dose of BNT162b2 mRNA anti-SARS-CoV-2 vaccine between March and May 2021 at our national center for autoimmune diseases [5]. To be included, patients had to give their written consent and fulfilled these criteria: being 18 years old or older, having a SLE defined by the 2019 EULAR/ACR classification criteria [12], having a non-clinically active disease, and being eligible to anti-SARS-CoV-2 vaccination according to French national guidelines [13]. Patients were secondarily excluded from the analysis if they were under immunosuppressive treatment (including cyclophosphamide, mycophenolate mofetil, azathioprine or rituximab) or had a prior history of COVID-19 defined by a positive SARS-CoV-2 PCR infection test or by a positive SARS-CoV-2 serology (anti-S or anti-N) before vaccination. As controls, 11 healthy volunteers (HV) among healthcare workers were included and received their first vaccine dose during the same time period.

2.2. Study scheme

All were vaccinated with BNT162b2 mRNA vaccine according to French national guidelines [13]. Briefly, SLE patient and HV received 2 doses of BNT162b2 vaccine 4 weeks apart and were screened at baseline (before first dose), at second dose, and at 3 and 6 months after the first dose. At inclusion and/or at follow-up visits, data on demographics, SLE history, treatment history, SLE disease activity (SLEDAI-2k), COVID-19 infection and/or side effects of the vaccine were recovered. Blood and urine samples were collected at each visit, in order to measure anti-dsDNA auto-antibodies titers, C3 and C4 levels, and anti-S and anti-N SARS-CoV-2 IgG antibodies titers, and proteinuria. Ficoll-Paque isolated peripheral blood mononuclear cells (PBMCs) were divided in two samples: one was freshly used for the pDC stimulation procedure and one was stored at -80°C for further analysis.

2.3. Ethical statement

This study involves human participants and was approved by Institutional Review Board (IRB) 00006477 of HUPNVS, Université Paris Cité, AP-HP, authorization number CER-2020-114. Participants gave informed consent to participate in the study before taking part.

2.4. Protective immune response to BNT162b2 mRNA vaccine

Vaccine efficacy was evaluated through different methods. First, we looked at the B-cell response with a standard quantitative IgG anti-Spike SARS-CoV-2 (anti-S) serology (Alinity-Abbott). According to French guidelines [14], we chose a cut-off value of 260 BAU/mL in anti-S IgG serum level to define “responders” and “non-responders”. We also quantified blood anti-S-specific-B cells induced by the vaccine with tetramers made of biotinylated-Spike protein (Recombinant

SARS-CoV-2 Spike-Prot (HEK)-Biotin, Miltenyi-Biotec) and fluorescent streptavidin (PE and PE-Cy7 streptavidin, BioLegend) in a flow cytometry assay (according to manufacturer instructions [15], Fig. S1). Then, we looked at the T-cell response using a 6-h stimulation with a pool of peptides covering the full sequence of the spike protein. T cell vaccine response was assessed by using the percentages of CD154⁺CD4⁺ T cells among IFN- γ -secreting cells [21] after stimulation with a pool of peptides covering the whole SARS-CoV-2 wild-type spike protein (PepTivator[®] SARS-CoV-2 Prot_S, Miltenyi Biotec). Results were normalized by subtracting at each time point, and for each patient, the percentage of responses observed at time 0.

2.5. Interferon- α 2b production by plasmacytoid dendritic cells

Freshly isolated PBMCs were counted and resuspended at $10^6/\text{mL}$ in complete medium (RPMI 1640 GlutaMax [Gibco] supplemented with 10% fetal calf serum, 10 mM HEPES buffer, 1% sodium pyruvate, 1% minimum essential medium non-essential amino acids (all from ThermoFisher scientific), and $37.5\ \mu\text{M}$ of β -mercaptoethanol (Sigma-Aldrich)). One million cells (1 mL) were then added to a 48-well plate supplemented with $2\ \mu\text{g}/\text{mL}$ brefeldin A (BFA) in a 37°C incubator with 5% CO₂ for 6 h. At the end of the incubation, cells were harvested, washed with phosphate buffered saline (PBS), and stained with a viability marker (Ghost Dye BV510; Tonbo biosciences) for 20 min at 4°C . After washing with FACS buffer (PBS, 1% bovine serum albumin, 1 mM EDTA, and 0.05% sodium azide), unspecific antibody-binding sites were saturated with an Ig blocking buffer containing $100\ \mu\text{g}/\text{mL}$ of polyclonal human IgG, polyclonal rat IgG and polyclonal mouse IgG (Innovative Research, Inc., Novi, MI, USA). Then, PBMCs were stained with a panel of fluorophore-conjugated antibodies (Ab) targeting surface markers: CD303-Alexa Fluor (AF) 488, CD141-PerCP-Cy5.5, CRTH2-AF647, CD1c-AF700, Fc ϵ R1 α -APC/Fire750, CCR3-Brilliant Violet (BV) 605, HLA-DR-BV785, CD123-PE-Dz594 (all from BioLegend) and CD3/CD19/CD56/CD14 Brilliant Ultra Violet (BUV) 395 (T, B, NK, classical monocyte lineages, all from BD Biosciences) in FACS buffer for 20 min. After a PBS wash, cells were fixed for 20 min using a fixation buffer according to the guidelines of the manufacturer (BioLegend). PBMCs were then permeabilized and stained with IFN α 2b-PE (from BD Biosciences) in Permeabilization and wash (Perm/wash) buffer (BioLegend) supplemented with $20\ \mu\text{l}$ of Ig blocking buffer for 20 min at 4°C . Finally, PBMCs were washed in Perm/wash buffer and resuspended in FACS buffer until acquisition. We also monitored the activation markers CD86 and HLA-DR expression levels on pDCs with a flow cytometry assay performed on whole blood cells, after ACK lysis. For assessment of the CD86 and HLA-DR expression levels, the ratio of the geometric mean fluorescence intensity (gMFI) of CD86 and HLA-DR to the corresponding fluorophore-conjugated isotype control gMFI was calculated and expressed in arbitrary units (A.U.). Flow cytometry data acquisition was realized using a Becton Dickinson 5-lasers LSR Fortessa X-20 and data analysis using Flowjo vX (BD Biosciences, Franklin Lakes, NJ, USA). Plasmacytoid dendritic cells (pDCs) were defined among living cells as (CD3/CD19/CD56/CD14)⁻CD123⁺Fc ϵ R1^{lo}CD303⁻HLA-DR⁺ cells (gating strategy presented in ESM, Fig. S2).

2.6. Autoreactive T cells

Quantification of specific autoreactive T cells was realized by defining the proportion (%) of activated (double positive CD154⁺/CD69⁺) cells among non-naïve CD45⁻RA⁻CD4⁺ T cells after stimulation with a pool of nuclear antigens [16] containing an equimolar concentration of Sm/RNP, SS-A, SS-B and histones (all from Immunovision). Briefly, all the PBMCs collected at the different follow-up times for a given individual were thawed and put in complete medium. They were then stimulated in a 96-well U-bottom plate at 2×10^6 per mL with either 1) only a co-stimulating pool containing anti-CD-40 Ab ($1\ \mu\text{g}/\text{mL}$, clone HB14, BioLegend) and anti-CD28 Ab ($1\ \mu\text{g}/\text{mL}$, clone CD28.2,

BioXCell-InVivoMab) in complete medium (non-stimulated condition) or 2) the costimulating pool and SARS-CoV-2 Prot_S PepTivator® (0.6 nmol/mL) or 3) the costimulating pool and the nuclear antigens pool (5 µg/mL) for 6 h at 37 °C in a 5% CO₂ incubator. BFA (2 µg/mL) and Monensin (10 µmol/L) were added 2 h after the beginning of the incubation. At the end of the incubation, cells were harvested, washed with phosphate buffered saline (PBS), and stained with a viability marker (Ghost Dye 510) for 20 min at 4 °C. After washing with FACS buffer, unspecific antibody-binding sites were saturated with Ig blocking buffer. Then, PBMCs were stained with a panel of fluorophore-conjugated Ab targeting surface markers: CD3-AF488, CD69-PerCP-Cy5.5, CD8a-BV605, CD4-BV785 and PE/Cy7-CD45-RA (all from BioLegend) in FACS buffer for 20 min. After a PBS wash, cells were fixed for 20 min using a fixation buffer according to manufacturer's instructions (BioLegend). PBMCs were then permeabilized and unspecific antibody-binding sites were saturated with blocking solution in Perm/Wash buffer and cells were stained with CD154-APC/Fire750 (from BioLegend) in Perm/Wash buffer for 20 min at 4 °C. Finally, PBMCs were washed in Perm/Wash buffer and resuspended in FACS buffer until acquisition. For each analysis the percentage of the non-stimulated condition was subtracted from the one of the stimulated conditions to take into account the background signal.

2.7. Statistical analyses

Data are expressed as median with inter-quartile range (IQR) for quantitative variables or frequency (percentage) for categorical variables. Comparison of quantitative variables between two different time points were made using a paired Wilcoxon test. To establish the significance of the trend observed during follow-up for the autoimmune activity, we used a linear mixed effect model (package lme4) defining time as both a random and a fixed effect (more details in ESM). Two-sided P values of <0.05 were considered to indicate statistical significance. Statistical analyses were performed with R version 4.1.0 and Graphpad v9 softwares.

3. Results

3.1. Population

Between March and May 2021, 57 SLE patients and 11 healthy volunteers (HV) vaccinated with BNT162b2 mRNA vaccine were included in the study. SLE patients were mostly female (86.0%) with a median age at inclusion of 44.0 [38.1, 50.8] years. All patients were under hydroxychloroquine (n = 51, 89.5%) and/or corticosteroids (n = 35, 61.4%) at a median dose of 7 [5–9] mg/day. Among them, 10 (17.5%) patients were excluded from the analysis because they were receiving azathioprine, mycophenolate mofetil or rituximab. Eleven (21.0%) patients were also excluded because of a previous history of COVID-19 infection - assessed by the detection in serum of anti-N SARS-CoV-2 antibodies at screening. Eventually, 36 SLE patients with SLEDAI-2k at 0 [0–2] at inclusion, who were not receiving immunosuppressive drugs, had no previous history of COVID-19 and had received 2 doses of BNT162b2 vaccine 4 weeks apart were considered for the analysis (Table 1). The immune response following vaccine were analysed at baseline before the first dose (T0), at second dose (M1), and 3 (M3) and 6 (M6) months after the first dose.

3.2. Humoral response to SARS-CoV-2 vaccine in SLE patients

SLE patients and HV had no detectable anti-S and anti-N at baseline. At M1, M3 and M6, 9.1% (n = 3/33), 63.3% (n = 19/30), and 8.0% (n = 2/25) of SLE patients had specific anti-S titers >260 BAU/ml, respectively. One month after the last vaccine shot (M3), the percentage of SLE patients able to mount a humoral response against SARS-CoV-2 were lower as compared to HV (63.3% vs 100%, p = 0.038). Accordingly,

Table 1

Characteristics of SLE patients at baseline.

	SLE patients n = 36
Male gender, n (%)	5 (13.9)
Age, in years (median [IQR])	43.7 [36.3, 49.7]
Duration of SLE disease, years (median [IQR])	9.3 [4.1, 13.2]
SLE characteristics, n (%)	
Class III/IV nephritis	9 (25.0)
Skin lesions,	22 (61.1)
Arthritis	26 (72.2)
Pleural/pericardial effusion	10 (27.8)
Immune cytopenia	12 (33.3)
CNS involvement	4 (11.1)
Anti dsDNA at baseline	
<1 N	20 (55.6)
1–3 N	9 (25.0)
>3 N	7 (19.4)
Antiphospholipid biology	13 (36.1)
Associated disease, n (%)	
Antiphospholipid syndrome	6 (16.7)
Sjögren syndrome	6 (16.7)
Anti-IFNα Ab detected at baseline (%)	6 (16.7)
SLEDAI-2k at baseline (median [IQR])	0 [0–2]
Treatment at baseline, n (%)	
Corticosteroids	17 (47.2)
daily dose, mg/d (median [IQR])	7.0 [5.0, 9.0]
Hydroxychloroquine	31 (86.1)
[HCQ] <500 µg/L	10 (27.8)
[HCQ] 500–1500 µg/L	21 (58.3)
[HCQ] >1500 µg/L	4 (11.1)
Belimumab	1 (2.8)

CNS, central nervous system; [HCQ], hydroxychloroquine concentration measured in whole blood.

anti-S antibodies titers were also lower in SLE patients as compared to HV at M1 (37.1 [8.9–88.9] BAU/mL in SLE vs 120.4 [64.3–251.9] BAU/mL in HV, p = 0.005), M3 (350 [130.7–769.4] vs 877.3 [531.7–1334.2], p < 0.001) and M6 (59.1 [28.9–124.4] vs 219.8 [140.4–521.6], p < 0.0001) (Fig. 1A). Those data confirmed the poor immune protection conferred by 2 doses of BNT162b2 vaccines in SLE patients, even though they were not treated with immunosuppressive drugs [17],

3.3. Cellular immune response to SARS-CoV-2 vaccine in SLE patients

We next analysed the cellular immune response induced by BNT162b2 vaccine. Among SLE patients, the absolute count of circulating anti-Spike specific B cells measured by flow cytometry increased overtime and appeared maximal 6 months after the first vaccine shot (5 [4–10].10⁵/mL anti-S specific B cells at T0 vs 16 [6–29] at M6, p = 0.009). Consistent with the poor humoral response, the absolute count of anti-S specific B cells was significantly lower in SLE patients as compared to HV at M1 (5 [4–10].10⁵/mL anti-S specific B cells in SLE vs 14 [11–23].10⁵/mL in HV; p = 0.004), M3 (11 [6–19].10⁵/mL vs 30 [18–53].10⁵/mL, p = 0.008) and M6 (16 [6–29].10⁵/mL vs 27 [25–82].10⁵/mL, p = 0.02) (Fig. 1B). Interestingly, anti-S antibodies titers correlated with anti-S specific B cell counts in blood (Fig. 1C) suggesting that the humoral response reflects the overall B cell response to SARS-CoV-2 vaccine in SLE.

The anti-SARS-CoV-2 T cell response to vaccine was then assessed by measuring the frequency of CD154⁺CD4⁺T cells producing IFN-γ after *in vitro* stimulation with a pool of peptides covering the full sequence of the SARS-CoV-2 spike protein. Anti-SARS-CoV-2 CD154⁺IFN-γ⁺CD4⁺T increased overtime after vaccination in SLE patients. However, in contrast to the B cell responses to vaccine, anti-SARS-CoV-2 T cell response did not significantly differ between SLE patients and HV (Fig. 1D). Such findings confirmed that despite evidence for impaired humoral response, SARS-CoV-2 vaccine still induces a robust T-cell response in patients with autoimmune diseases [18,19].

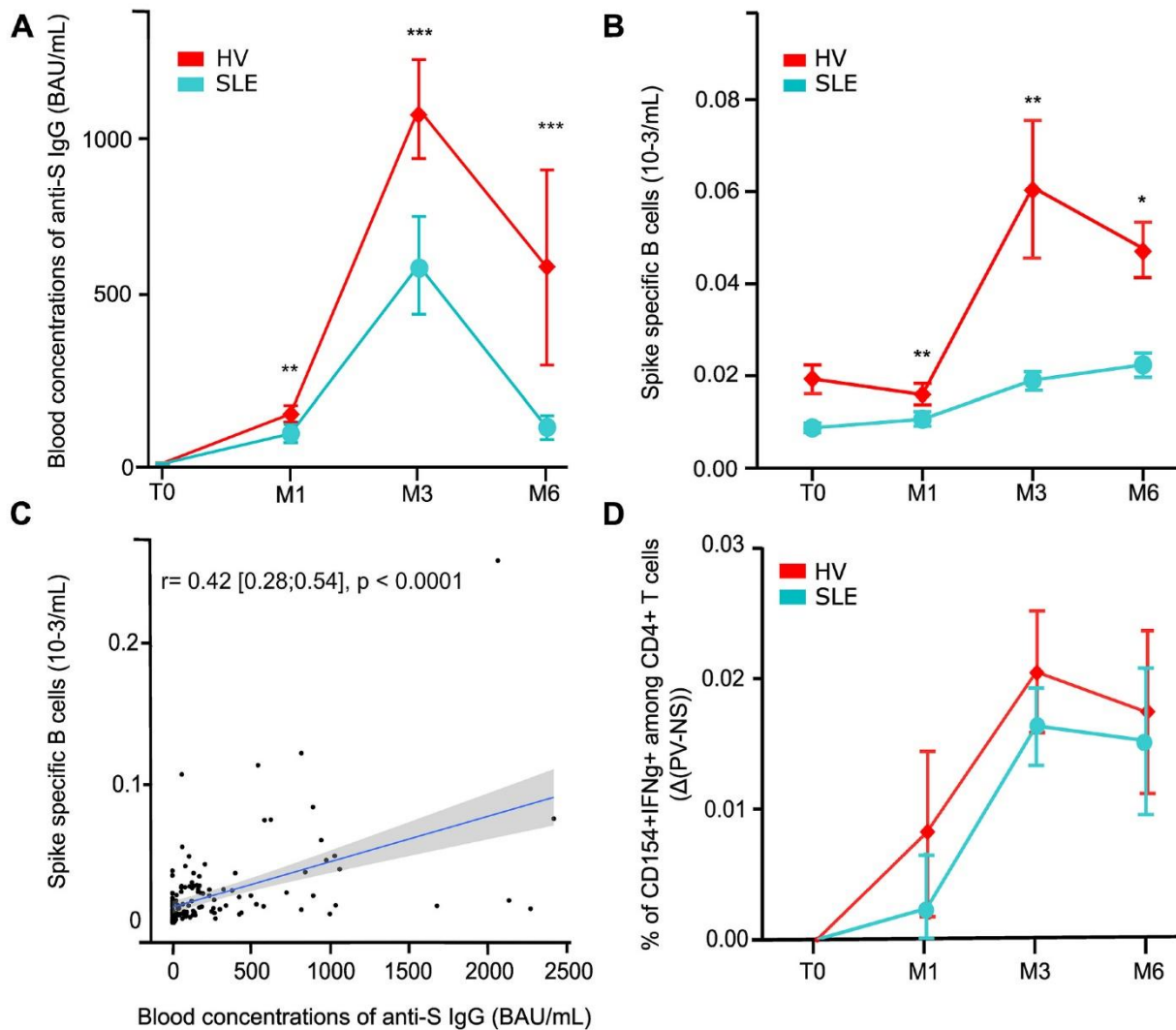


Fig. 1. SARS-CoV-2-specific immune responses following vaccination

Anti-Spike IgG blood titer measured in BAU/mL by ELISA in SLE patients (in blue) compared to HV (in red). Points represents the mean and error bars the standard error of the mean (A). Blood concentrations of anti-S specific B cell measured by flow cytometry using tetramers of biotinylated spike-protein associated to fluorescent streptavidin. Points represented the mean and error bars the standard error of the mean (B). Correlation between anti-spike IgG blood level and anti-S specific B cells in SLE and HV at all the time points. Pearson's coefficient is provided (C). T cell response to SARS-CoV-2 vaccine measured by flow cytometry as the percentage of CD154⁺/IFN γ ⁺ among CD4 cells after stimulation with a pool of peptides covering the sequence of Spike protein. For each time Ti, we represented here the delta Ti- T0 to take into account background and basal signal (D). Points represented the mean and error bars the standard error of the mean* $p < 0.05$ ** $p < 0.001$ *** $p < 0.001$.

3.4. Impact of anti-SARS-CoV-2 vaccination on IFN-alpha production by plasmacytoid dendritic cells and specific autoreactive T cells

We next analysed the impact of BNT162b2 mRNA anti-SARS-CoV-2 vaccine on pDCs in SLE patients. At T0, the ability for unstimulated pDCs to spontaneously produce IFN α *in vivo* was stronger in SLE patients as compared to HV (0.64 [0.27–1.09] % of pDCs⁺IFN α ⁺ in the SLE versus 0.32 [0.25–0.47] % of pDCs⁺IFN α ⁺ in the HV, $p = 0.04$) (Fig. 2A). Following anti-SARS-CoV-2 vaccine, the frequency of pDCs⁺IFN α ⁺ raised at M1 in both groups (1.27% [0.6–2.6] in SLE, $p < 0.001$; 1.5% [0.95–2.12] in HV, $p = 0.03$) but remained high at M3 in SLE patient only (1.25% [0.85–1.83], $p = 0.004$) to next return to baseline at M6. Consistent with the activation of pDCs induced by anti-SARS-CoV-2 vaccine, the amount of both CD86 (2.9 [2.6–3.4] MFI ratio versus 2.3 [1.8–30] at T0, $p = 0.002$) and HLA-DR (41.9 [34.2–61.3] versus 24.4 [16.4–32.8] at T0, $p < 0.001$) markers were increased on pDCs at M3 in SLE (Fig. 2 B, C). Interestingly, anti-S antibodies titers, ($r = 0.27$ [0.05–0.46], $p = 0.02$), anti-S specific B cells ($r = 0.19$ [–0.03–0.39], $p = 0.09$) and anti-S specific T cells ($r = 0.28$ [0.05–0.47], $p = 0.016$)

correlated with the enhanced expression of HLA-DR on pDCs boosted by BNT162b2 mRNA vaccine at M1 and M3 (Fig. 2 D, E, F).

We next sought to determine whether BNT162b2 mRNA vaccine had an impact on the pool of autoreactive T cells in SLE. Specific autoreactive T cells - defined as the percentages of CD154⁺ CD69⁺ CD45⁺ RA⁺ CD4⁺ T cells identified after *ex vivo* stimulation with a pool of nuclear antigens including Sm/RNP, SS-A, SS-B and histones were measured at T0, M1, M3 and M6. As expected, the amount of autoreactive T cells at T0 were higher in SLE patients than in HV in whom those cells were barely detected (0.125% [0.042–0.38] vs 0.05 [0–0.26], $p = 0.03$). In line with the activation of pDCs 4 weeks after the first vaccine shot, we observed a 1.6-fold increase - but not significant - of specific autoreactive T cells at M1 as compared to T0 (0.200% [0.07–0.41] vs 0.125% [0.042–0.38], $p = 0.50$) that eventually dampened from M1 to M6. Overall, anti-SARS-CoV-2 vaccination was associated with a decrease of specific autoreactive T cells in SLE overtime (β for fixed-effect of time in the linear mixed-effect model = - 0.00067, $p = 0.015$) (Fig. 3A). We found no association between the activation of pDCs and anti-dsDNA titers, serum C3/C4 levels and autoreactive T cell

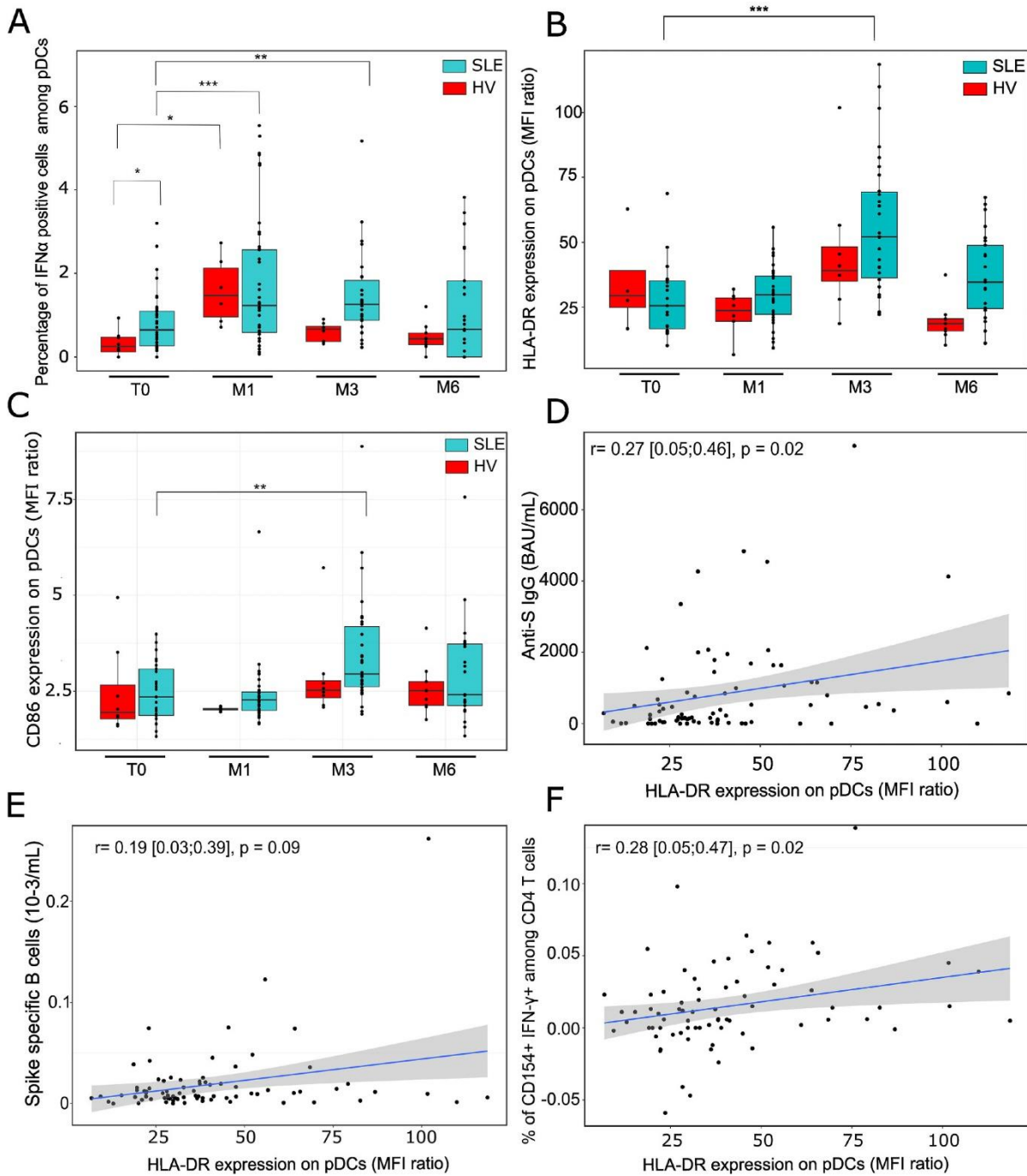


Fig. 2. Impact of BNT162b2 vaccine on *ex vivo* IFN α production by pDCs and pDCs activation. Percentage of IFN α 2b production by circulating pDCs during follow-up. In blue, SLE patients, in red HV (A). Activation markers on circulating pDCs during study follow-up measured by mean fluorescence intensity ratio of HLA-DR (B) and CD86 (C) in flow cytometry. Correlation between pDCs activation measured by HLA-DR gMFI on pDCs at M1 and M3 in SLE and HV and anti-S IgG blood level (D), anti-S specific B cells (E) and anti-S specific T cells (F) *p < 0.05 **p < 0.001 ***p < 0.001.

counts (Fig. S3).

3.5. Clinical outcome

During the 6-months study time, one SLE patient (2.8%) experienced PCR-confirmed COVID-19 that did not require admission to hospital. Two (5.5%) SLE patients experienced lupus flare: one had a relapse of immune thrombocytopenia between T0 and M1 and one had a relapse of a class III lupus nephritis between M3 and M6. In both cases, SLE flares occurred after corticosteroids were tapered by the clinician. Except for these 2 patients, we did not observe any modification of SLEDAI-2k scores, serum levels of anti-dsDNA IgG and serum levels of

complement during follow-up (Fig. 3B, C, D).

4. Discussion

In the present study, we first confirmed the results of previous studies showing a B cell defect that impairs immune protection following anti-SARS-CoV-2 vaccine in SLE patients [17]. Second, we showed that BNT162b2 mRNA induces a short-term *in vivo* activation of the pDCs that contributes to the immune response against SARS-CoV-2 vaccine. Third, and most strikingly, BNT162b2 mRNA appears to dampen the pool of circulating autoreactive T cells, suggesting that vaccine may actually protect SLE patients from lupus flare.

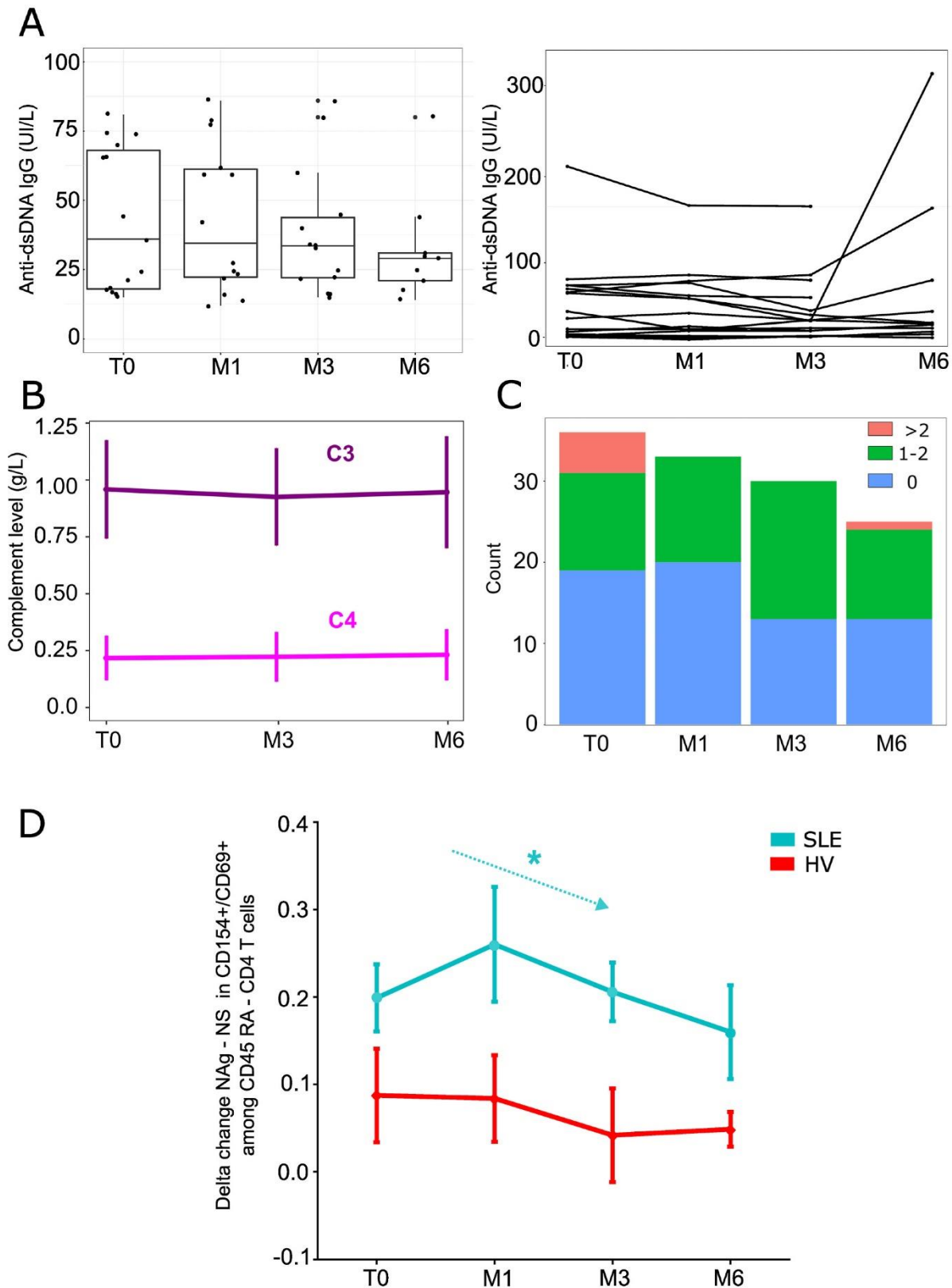


Fig. 3. Autoreactive-specific immune responses following vaccination

Anti-dsDNA IgG blood levels among SLE patients during follow-up. Box plot represents the median and the interquartile range of patients with detectable anti-dsDNA Ab at baseline [left-panel]. Points and lines represent the individual levels of each included patients at each visit [right-panel] (A). Complement fraction C3 and C4 blood level among SLE patients during follow-up. Points represents the mean and error bars the standard deviation (B). SLE disease activity measured by SLEDAI-2k during follow-up (C). Autoreactive anti-nuclear specific T cell activity among SLE patients and HV during follow-up defined as the percentages of activated (double positive CD154+/CD69+) cells among non-naïve CD4 T cells after stimulation with a pool of nuclear antigens. Time-associated slope is significantly negative in a linear mixed-effect model in the SLE group: (β for fixed-effect of time in the linear mixed-effect model = -0.00067, $p=0.015$). Points represented the mean and error bars the standard error of the mean (D).

In order to avoid treatment-related bias, we selected SLE patients who were not receiving immunosuppressive drugs. The observed B cell defect preventing a strong immune response to BNT162b2 mRNA could not be ascribed to drug-induced immunosuppression. Such poor immune response to vaccine is probably related to SLE – as our group previously reported in the setting of anti-pneumococcal vaccination [20–22]. Because SLE entails a risk for severe COVID-19 [1,2], SLE patients are obvious candidates for alternative vaccination strategies [23].

Besides concern for poor immune responses to vaccine, vaccination also appears to increase disease activity. RNA vaccines against SARS-CoV-2 may trigger Toll-like receptors-9 and -7 constitutively expressed on pDCs to induce further production of type I IFN, known to play a key role in SLE pathogenesis [10]. Indeed in our study, RNA vaccines activated pDCs *in vivo* which contributed to the overall protective response against SARS-CoV-2, in line with a previous study in mice [24]. Unexpectedly, specific auto-reactive anti-nuclear T cells blood levels decreased following BNT162b2 mRNA, leaving the possibility that the vaccine exert an anti-inflammatory and protective effect on lupus disease. Concordant with this intriguing result, a previous study has shown that vaccination (i.e. anti-pneumococcal vaccination) improves lupus disease in MRL/lpr mice probably by modifying the T follicular helper cells/T follicular regulatory cells balance in secondary lymphoid organs [25]. Overall, there was no change in SLEDAI score pre- and post-vaccination in all but 2 patients, supporting the safety of the vaccination in SLE patients [26]. These data should hopefully reduce vaccine hesitancy and encourage both patients and physicians to support vaccination.

Our study has several limitations. The findings were based on a small number of patients. There was vaccine hesitancy among SLE patients in our cohort [5] and the patients in this study may not be fully representative. Last, our study was not designed to determine the in-depth immune process that mechanistically linked the vaccine to the decrease of specific auto-reactive T cells.

This study has several strengths. First, our design selected homogeneous SLE patients who were not receiving immunosuppressive drugs, had no disease high activity at vaccination and no prior SARS-CoV-2 infection. Second, the study assessed BNT162b2 mRNA vaccine' effects on lupus-specific disease activity pre- and post-vaccination by using several markers including diseases score activity, anti-dsDNA, complement level but also pDCs activation *in vivo* and autoreactive T cells quantification *ex vivo*. Third, the protective immune response to vaccine was assessed by analysing not only anti-SARS-CoV-2 antibodies but also SARS-CoV-2 specific B and T cells.

In conclusion, BNT162b2 mRNA vaccine induces IFN-alpha production by pDCs that contributes to the immune protective response against SARS-CoV-2 and appears to have an unexpected beneficial protective impact on autoimmunity in SLE.

Funding

Arthur Mageau was supported by a PhD fellowship provided by Fondation pour la Recherche Médicale (FDM202106013488). This work was supported by the Agence Nationale de la Recherche (n°ANR-21-COVR-0034 COVALUS), the Agence Nationale de la Recherche sur le SIDA et les Maladies Infectieuses Emergentes (ANRS MIE), AC43 Medical Virology and Emergen Program, the University Paris Cité and the Assistance Publique Hôpitaux de Paris.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Obtained.

Author contributions

KS and NC directed the project. AM, TG, NC and KS designed the study. AM, JT, PNR, and VMF conducted analysis. DD, ND, CF, CM and TP were involved in the project development. AM and KS wrote the manuscript. All authors reviewed and approved of the final manuscript.

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.

Acknowledgment

The authors wish to acknowledge Jean-Francois Alexandra, Laure Delaval, Fatima Farhi, Maureen Marie-Joseph, and Diane Rouzaud from the Bichat Hospital Internal Medicine Department; Luc de Chaisemartin and Vanessa Granger from the Bichat Hospital Immunology Department; Nadhira Houhou-Fidouh and Charlotte Charpentier from the Bichat Hospital Virology Department; and Alexandra Lavalley-Morelle from INSERM UMR 1137 IAME, team BIPID for their invaluable help and advices.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jaut.2022.102987>.

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Impact of BNT162b2 mRNA anti-SARS-CoV-2 vaccination on interferon-alpha production by plasmacytoid dendritic cells and autoreactive T cells in patients with systemic lupus erythematosus: the COVALUS Project.

ELECTRONIC SUPPLEMENTARY MATERIALS

1- Linear mixed effect model.

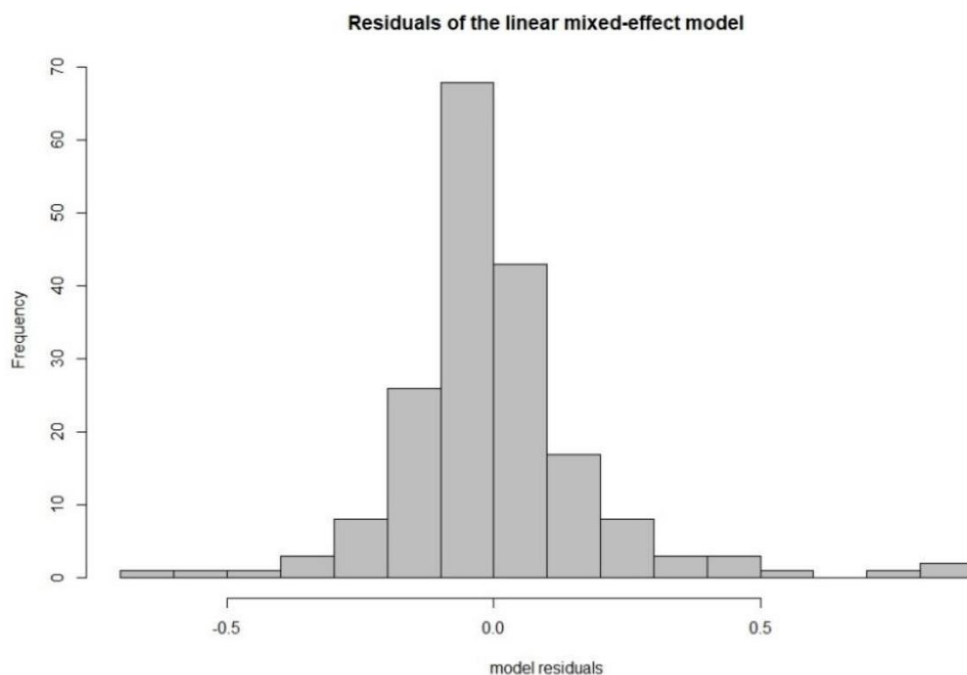
To establish the significance of the trend observed during follow-up for the autoimmune activity, we used a linear mixed effect model (package lme4) defining time as both a fixed and a random effect. The model had also a random intercept to take into account the difference at time 0 between each individual.

So, the model was written as following:

- `library(lme4)`
- `mod <- lmer(delta_IFNg ~ (1 + time | Id) + time, data = df)`

We verified the validity of the model by plotting the model residuals:

- `hist(resid(mod), col = "grey", xlab = "model residuals", breaks = 15, main = "Residuals of the linear mixed-effect model")`



2- Gating strategies

Spike-specific-B Cells

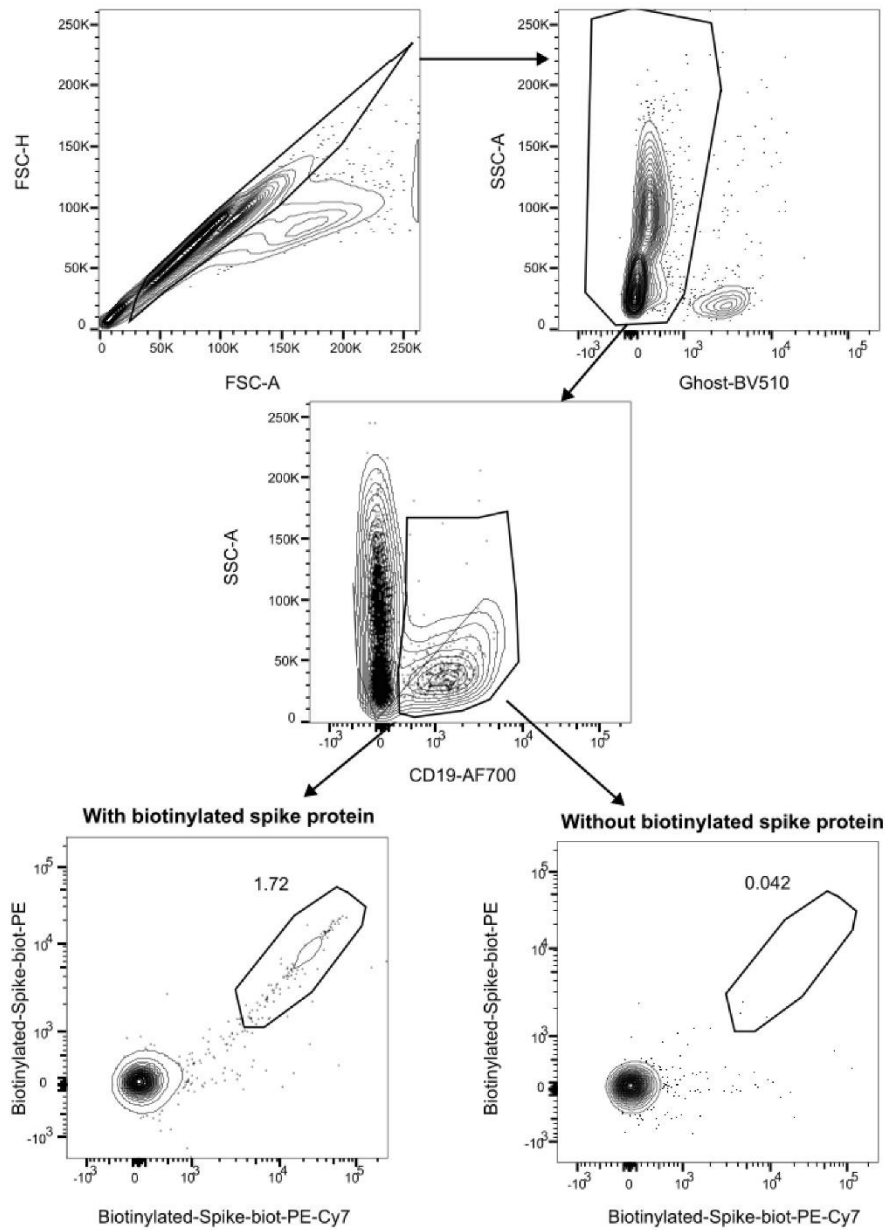


Figure S1: Gating strategy of B cells and detection of Spike-specific B cells.

PBMCs were stained with two kinds of tetramers: one made of PE-Streptavidin associated with biotinylated-Spike protein and the other one made of PE-Cy-7-Streptavidin associated with biotinylated-Spike protein. Spike-specific B cells were defined as cells positive for both PE and PE-Cy7. As a control, we added the same amount of PE-Streptavidin and PE-Cy-7 Streptavidin without biotinylated spike protein.

Plasmacytoid dendritic cells

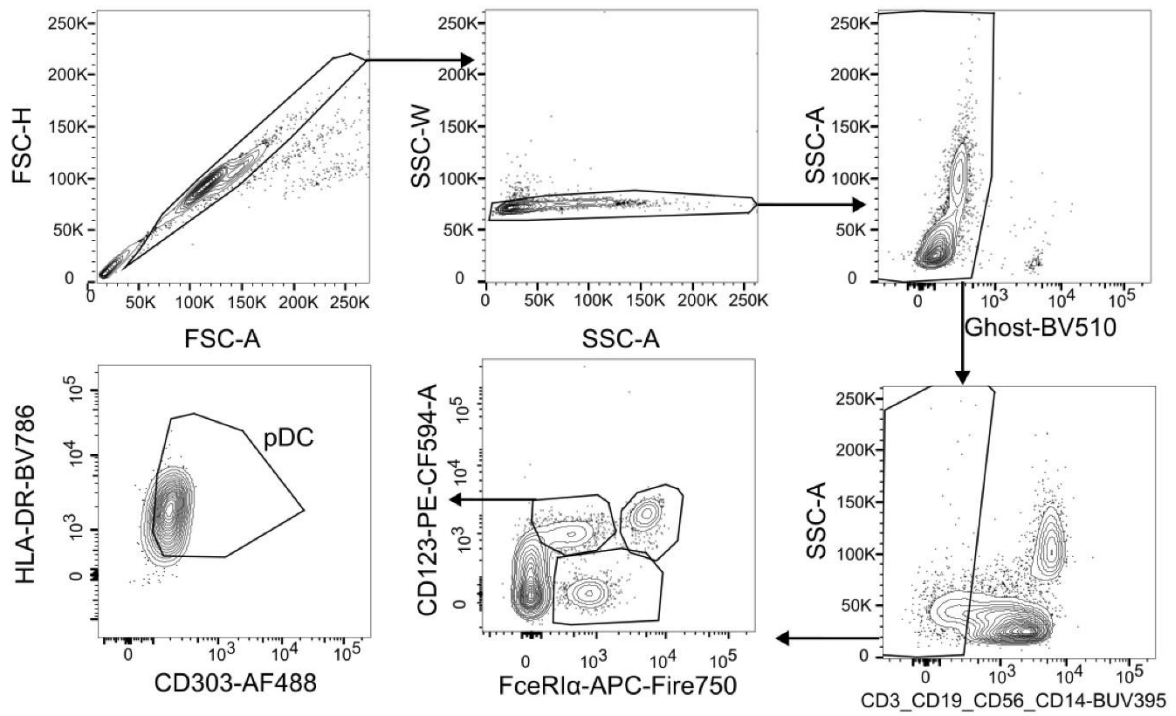


Figure S2: Gating strategy for the plasmacytoid dendritic cells (pDCs)

3- Assessment of the correlation between the activation of pDCs measured by the expression of HLA-DR on pDCs and autoimmunity biomarkers

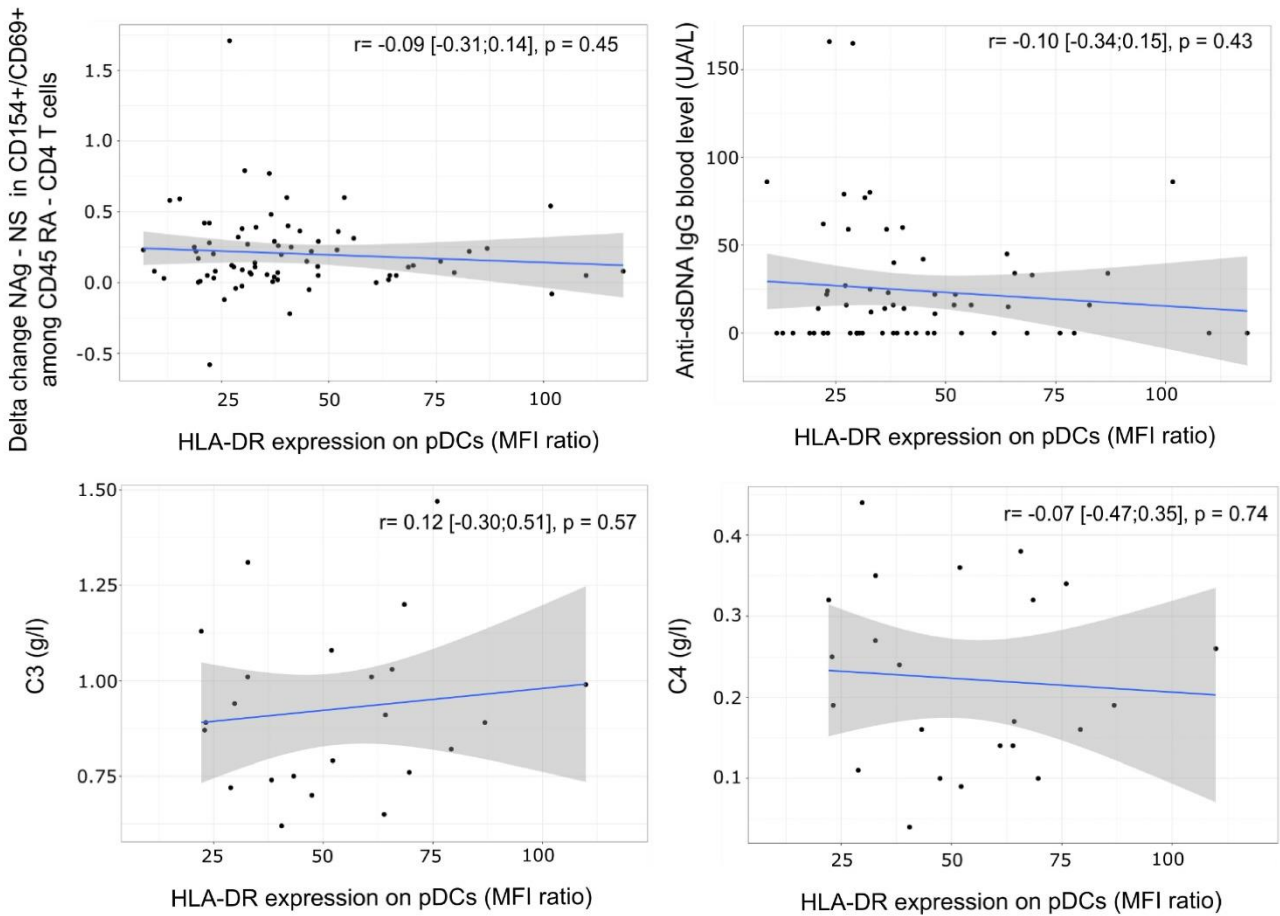


Figure S3: Correlation between the activation of pDCs measured by the expression of HLA-DR on pDCs among SLE patients and HV at M1 and M3 with -Upper left panel: autoreactive T cells -Upper right panel: Anti ds-DNA IgG blood level – Bottom left panel: C3 blood level – Bottom right panel: C4 blood level. Pearson's coefficient is provided

Anti-SARS-CoV-2 vaccination among patients living with SLE in Sweden: coverage and clinical effectiveness. Study 5.

Data on the immunogenicity of the anti-SARS-CoV-2 vaccine in SLE patients have been rapidly published in studies of varying sample sizes. However, the concentration of vaccine-induced anti-Spike (anti-S) antibodies vaccine is only one facet of vaccine immunogenicity which is itself only a surrogate marker of vaccine effectiveness. In fact, according to the WHO, vaccine effectiveness could be defined as a measure of how well the vaccine works in the real world, with clinical outcomes. Furthermore, there could be no vaccine effectiveness without vaccine administration, and the preliminary question of vaccination coverage has unfortunately not been studied on a large scale and with long-term follow-up in SLE.

We used Swedish population-based, nationwide registers to describe coverage progression and assess the effectiveness of the anti-SARS-CoV-2 vaccination in SLE patients. In Sweden, the healthcare system is tax-funded and universally accessible to residents. Data generated by interaction with the healthcare system are recorded in registers and can be linked using an individual's unique identification number. We were able to link the National Patient Register to the vaccination Register and to other registers in order to create a cohort of SLE patients and matched controls living in Sweden on the beginning of 2021.

In the following study, which has been submitted to *Rheumatology* on the 8th of September, we aimed to determine whether, to which extent and among which patients, anti-SARS-CoV2 mRNA vaccination clinical effectiveness is affected by SLE. Specifically, we aim to answer the following questions: i) Was the progression of the vaccination coverage similar between SLE patients and the general population? ii) Do vaccinated SLE patients have an increased risk of hospitalization for COVID-19 compared to vaccinated people without SLE from the general population? iii) Among patients with SLE, does the risk of COVID-19 hospitalization vary by immunosuppressive treatment?

Study 5

Anti-SARS-CoV-2 mRNA vaccination among patients living with SLE in Sweden: coverage and clinical effectiveness

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ABSTRACT

Objectives: To describe the uptake of anti-SARS-CoV2 vaccination in 2021 and investigate vaccine effectiveness in systemic lupus erythematosus (SLE) patients in Sweden.

Methods: The cumulative incidence of first anti-SARS-CoV2 vaccination was estimated among SLE patients from the Swedish National Patient Register and matched comparators living in Sweden on January 1, 2021. To assess vaccine effectiveness, we included the individuals who received two doses of anti-SARS-CoV2 mRNA vaccines before January 1, 2022, with no COVID-19 diagnosis code before the 2nd vaccine dose. Hospitalization rates with COVID-19 as main diagnosis during the year after second dose were compared between SLE patients and comparators in multivariable-adjusted marginal Cox models, overall and stratified by immunosuppressive treatment received during the year before second vaccine dose.

Results: Vaccination uptake was similar between SLE patients and comparators. By December 2021, around 10% of both SLE and comparators had not received any vaccine doses. Among 5,585 SLE patients and 37,102 comparators we observed 11 COVID-19 hospitalizations in the SLE group and 20 in the comparators. SLE was associated with a higher risk of COVID-19 hospitalization (HR=3.47, 95%CI 1.63 to 7.39). The HR was higher for immunosuppressive-treated SLE (7.03 95%CI 3.00-16.5) than for immunosuppressive-untreated (1.50 95%CI 0.34-6.60).

Conclusion Anti-SARS-CoV2 vaccination coverage was similar between SLE patients and the general population in Sweden. Even though the incidence of post-vaccination COVID-19 hospitalization was very low, vaccine effectiveness was diminished in SLE patients compared to the general population and lowest in those treated with immunosuppressants.

INTRODUCTION

The COVID-19 pandemic has raised particular concerns for patients with systemic lupus erythematosus (SLE) who are often immunocompromised, more prone to infection and may have several comorbidities such as chronic kidney disease [1,2]. Furthermore, SLE has been shown to be associated with a poor prognosis after a COVID-19-associated organ failure, independently of major comorbidities [3]. Therefore, anti-SARS-CoV-2 vaccination was quickly recommended in the SLE population [4]. Unfortunately, several immunological reports showed that the production of a humoral response following vaccination was lower in SLE patients than the general population, even for patients without immunosuppressive treatments [5,6]. However, the humoral response measured by the concentration of vaccine-induced anti-spike (anti-S) antibodies, which has been the most studied, is only a surrogate marker of vaccine effectiveness. Thus, some studies showed that immunocompromised patients could have a T-cell-driven vaccine response even without a humoral response [7]. Unfortunately, real-world data assessing the effectiveness [8] of the vaccination using clinical outcomes in this population are currently lacking. Furthermore, the impact of immunosuppressive treatments has not been studied at a large scale and with long-term follow-up. A better understanding of the vaccination effectiveness and of the factors associated with a decreased effectiveness could help to improve the vaccination guidelines in this population.

Our overall aim is to determine whether, to which extent and among which patients, anti-SARS-CoV2 mRNA vaccination clinical effectiveness is affected by SLE. Specifically, we aim to answer the following questions: i) Was the uptake of the SARS-CoV2 mRNA vaccination similar between SLE patients and general population? ii) Do vaccinated SLE patients have an increased risk of hospitalization for COVID-19 compared to vaccinated people without SLE from the general population? iii) Among patients with SLE, does the risk of COVID-19 hospitalization vary by immunosuppressive treatment?

METHODS

Study settings and data source

In Sweden, the healthcare system is tax-funded and universally accessible to residents. Data generated by interaction with the healthcare system are captured in registers and can be linked using an individual's unique identification number. We created a large cohort of individuals with and without SLE by linking several nationwide and population-based registers. Ten randomly sampled comparators from the general population without SLE were identified in the Total Population Register, and matched with SLE cases on age, sex, calendar time, and county of residence. We collected information on

hospitalizations and outpatient visits to specialist care from the National Patient Register (NPR; nationwide coverage of hospitalizations since 1987 and of outpatient visits since 2001). Data quality is high [9], but results of biological, histological or imaging examinations are not available in the NPR. Prescription medication dispensations were obtained from the Prescribed Drug Register (PDR) - which was available starting July 2005 - and from the Swedish Rheumatology Quality (SRQ) register [10], which covers a part of the SLE population in Sweden since 2007. Anti-SARS-CoV2 vaccination data were obtained from the National Vaccine Register. Offspring data (number of children, date of their birth) were obtained from the Multigeneration Register (MGR). Follow-up in all of the registers was through Dec 31, 2022.

Study populations

Using inpatient and outpatient visit data in the NPR, SLE was defined according to the previously-established definition [11] as ≥ 2 ICD-coded visits with ≥ 1 code from a specialist who typically treats or diagnoses SLE (i.e., rheumatology, dermatology, nephrology, internal medicine, or pediatrics). General population comparators had no SLE codes before the date of first observed SLE ICD-coded visit of their matched case. We included only individuals ≥ 18 years old living in Sweden at the start of the vaccination campaign (January 1st, 2021).

We studied two different populations: one to describe uptake of the vaccination (Population 1) and another one to assess vaccine effectiveness (Population 2).

In population 1, we included all individuals who fulfilled the definition of SLE before January 2021 and their matched comparators.

In population 2, we applied additional criteria restricting population 1 in order to study individuals who were vaccinated according to the standard scheme. Individuals (SLE and matched comparators) were selected from population 1 if they received two doses of anti-SARS-CoV2 mRNA vaccines before January 1st, 2022, if there were more than 10 days and less than 90 days between the two injections and if they did not receive any COVID-19 diagnosis code in the NPR before the 2nd vaccine dose.

Outcomes

For the description of vaccination uptake, the main outcome was first vaccine injection.

For the vaccine effectiveness assessment, the main outcome was a first hospitalization with COVID-19 (defined as ICD-10 codes U07.1 or U07.2) as main diagnosis for the hospitalization listed in the inpatient component of the NPR. The secondary outcome was defined as first COVID-19 diagnosis in inpatient or outpatient care, as main or secondary diagnosis.

Follow-up

For the description of the vaccination coverage, the follow-up period was the year 2021 (January 1st - December 31st).

For vaccine effectiveness assessment, start of follow-up was defined as the date of the second dose of the anti-SARS-CoV-2 mRNA vaccine. End of follow-up was the date of the first in-hospital admission for COVID-19, death, emigration, third vaccine dose or 12 months after start of follow-up, whichever comes first. We censored individuals at third vaccine dose because our main interest was the clinical effectiveness of the first two doses and because the time between the second and the third dose varied considerably between patients. We defined a global censoring at 12 months after second dose if none of the listed events occurred because we assumed that the effect of the first two doses was not supposed to last longer.

Covariates

Among all the included individuals, we defined subpopulations according to the disease-modifying treatments that they received and according to their comorbidities. We defined the use of an oral treatment if a patient had two dispensations in the Prescribed Drug Register of the same drug during the year before start of follow-up (i.e. January 1st 2021 for vaccination coverage description and date of second dose for vaccine effectiveness assessment). For treatment given by infusion (belimumab, rituximab and cyclophosphamide) we defined the use if a patient had one infusion during the last 6 months before inclusion. Data on infusions were obtained from both the NPR (infusion procedure code associated with a ATC code of interest) and SRQ. Of note, these registers do not have complete coverage of infusions as some of them might not be reported in the NPR and SRQ does not have 100% coverage of SLE patients in Sweden. Out-of-hospital dispensations of belimumab were also retrieved from the PDR, and considered as infusions.

Comorbidities (chronic kidney disease, obesity, and arterial hypertension) were defined as any history of relevant ICD codes and at any time before inclusion. Diabetes was defined as any ICD code or any use of an antidiabetic drug before inclusion.

Civil status from the Total Population Register and age of offspring from the Multigeneration Register were used to derive a three-level variable for household composition: i) living alone, ii) living with a partner, without any child < 18 years old, and iii) having child(ren) < 18 years old, with or without partner. See electronic supplementary materials (ESM), table S1.

Statistical analyses

Characteristics of the study populations were compared by exposure (SLE versus general population) using frequencies and median with first (q1) and third quartile (q3).

To describe the vaccination campaign course, we calculated and plotted a cumulative incidence function using first vaccine injection as outcome of interest and death or emigration as censoring events. We described the characteristics of the SLE population remaining unvaccinated on December 31st, 2021, with descriptive statistics and compared them to those SLE patients who get vaccinated.

We studied the vaccine effectiveness with a time-to-event analysis using a marginal Cox proportional hazard model that considers the matching between SLE and matched comparators [12]. The Cox model estimated the hazard ratio (HR) and 95% confidence intervals (95%CI) of COVID-19 associated with SLE diagnosis compared to non-SLE comparators. The model was adjusted for age, sex, health administrative region and household composition.

To study the risk according to the treatment received, we stratified SLE patients by use of immunosuppressive treatment in the year before the second vaccine dose was received. Hydroxychloroquine was not considered an immunosuppressive drug. We plotted the survival without COVID-19-related hospitalization in these three groups according to the Kaplan-Meier method. Then, we ran a standard Cox regression model to calculate the HR of COVID-19 hospitalization associated with SLE with or without immunosuppressive treatment, using general population without immunosuppressive treatment use at start of follow-up as reference. Here, we took age, sex, health administrative region, household composition and number of contacts with the healthcare system in 2020 as covariates. Finally, we described more precisely which immunosuppressive drugs were used by patients that experienced the main outcome with descriptive statistics.

Sensitivity analyses

We ran several sensitivity analyses. First, to examine whether informative censoring affected our results, we used inverse probability censoring weighting (IPCW) [13]. We modelled the probability of being censored because of a third vaccine dose using age, place of birth (Sweden or another country), household composition, type of vaccine (Comirnaty[®] versus Spikevax[®]) and number of contacts with the healthcare system in 2020 as baseline covariates. Calendar period (before or after January 1st, 2022) was used as a time-dependent covariate. Weights obtained using this modelling were used in the marginal Cox model. Second, we did not censor patients at third vaccine dose and kept following them until date of the first in-hospital admission for COVID-19, death, emigration, or 12 months after start of follow-up, whichever came first.

In another sensitivity analysis, we added a time-dependent covariate in the marginal Cox model to take into account the COVID-19 wave that took place in Sweden between November 18th, 2021 and April 20th, 2022 [14]. We looked for an interaction between SLE and the wave period.

The study protocol was registered to OSF registries <https://doi.org/10.17605/OSF.IO/RSCBZ>. Ethical approval was provided by the Regional Ethics Review Board in Stockholm (DNR 2021-01148). Informed consent was not required.

RESULTS

Vaccine coverage progression (population 1)

We identified 7,429 adults living in Sweden and diagnosed with SLE according to our definition on January 1st, 2021. These patients were matched to 64,568 comparators living in Sweden and ≥ 18 years old on the same date. A more detailed flow chart of the study is presented in **Figure 1**. The median [q1-q3] age was 57 [44.0-70.5] years at start of follow-up in the SLE group and 56.0 [43.1-68.9] among comparators. 86.1% were female in the SLE group and 87.1% in the non-SLE group.

The cumulative incidence of anti-SARS-CoV-2 vaccination in the SLE and comparator groups is displayed in **Figure 2**. Few doses were administered as early as December 27th, 2020 but most of the first doses were administered in spring 2021. We observed similar trends in vaccine uptake in SLE and comparators. The maximum difference between the two groups was observed at the end of May 2021 when 70% of the SLE patients and 60% of the comparators had received a first dose (10% difference). After the end of September 2021 very few first doses were newly administered and the slope of the cumulative incidence function became almost flat for both groups.

On December 31st, 2021, 650 SLE patients remained unvaccinated. The characteristics of these patients compared to the vaccinated SLE patients at that time are presented in ESM, **table S2**. Briefly, we observed that unvaccinated SLE patients were younger (median [q1-q3]: 47.4 [35.6-58.5] years compared with 57.9 [45.0-71.0] years in the vaccinated group) and more frequently born outside of Sweden (34.8% in the unvaccinated group versus 16.3% in the vaccinated group). One possible reason for not being vaccinated at that time was having a previous COVID-19 infection. We observed that 6.0% of the unvaccinated and 3.0% of the vaccinated had a previous COVID-19 diagnosis code reported in the NPR. It should be noted that we do not have information on positive tests in this study, nor visits in primary care, and are likely underestimating previous COVID-19 infection.

Vaccine effectiveness (population 2)

For the assessment of vaccine effectiveness, we included 5,585 SLE patients and 31,102 matched comparators from population 1 who also met the following criteria: having received two mRNA vaccine doses before January 1st, 2022, with >10 days and <90 days between the two doses and without any COVID-19 diagnosis in the NPR before second dose (**Table 1**). Both groups received mostly the Comirnaty® vaccine (87.4% in the SLE group and 87.1% in the comparator group). As expected, the individuals with SLE had more contact with the healthcare system in 2020 and more comorbidities, such as chronic kidney disease (5.8% in the SLE group versus 0.6% in the comparator group). Half (49.7%) of the SLE patients were using an immunosuppressive treatment before their 2nd vaccine dose, the majority of whom had received corticosteroids (76.5%). Only 2,466 (44.1%) SLE patients had been dispensed hydroxychloroquine twice during the year before second vaccine dose.

For the main outcome (first hospitalization with COVID-19 as main diagnosis), the median duration of follow-up was 196 days in both groups. The SLE group had 3,339 patients-years of follow-up versus 22,745 in the comparator group. Most of the patients were censored because of a third dose (86.0% in the SLE group and 85.0% in the control group). The number of patients censored because of death or emigration during follow-up was very low in both groups (1.8% in the SLE group and 0.6% in the control group). We observed 20 COVID-19 hospitalizations (0.05%) in the non-SLE comparator versus 11 (0.20%) in the SLE group (**Table 2**). The Kaplan-Meier curve representing the survival without COVID-19 hospitalization is displayed in **Figure 3**. The crude HR of hospitalization with COVID-19 as main diagnosis associated with SLE during the follow-up was 3.76 [95%CI 1.80-7.85]. After adjusting for age, sex, household composition and administrative health region, the HR remained almost unchanged (HR 3.47 [95%CI 1.63-7.39]). We observed more secondary outcomes (any first COVID-19 diagnoses in inpatient or outpatient care during follow-up): 57 (0.15%) in the control group and 29 (0.52%) in the SLE group (ESM, figure S3). However, the unadjusted and adjusted HRs associated with SLE were very close to those observed for the primary hospitalization outcome: 3.52 [95%CI 2.26-5.48] and 3.58 [95%CI 2.30-5.59], respectively.

Of note, we observed only seven COVID-19 related deaths (COVID-19 reported as a cause of death in the Cause of Death Register), six in the comparator group and one in the SLE group. Among these seven deaths, four occurred during a hospital stay with COVID-19 as the main diagnosis.

Vaccine effectiveness according to the immunosuppressive treatment

Among population 2, there were 36,065 comparators individuals with no immunosuppressant treatment, 2,783 SLE patients not treated with immunosuppressants and 2,802 SLE patients treated with immunosuppressants during the year before second vaccine dose. We observed that 9 out of 11 (81.8%) COVID-19 hospitalizations in the SLE group occurred among those treated with immunosuppressants. Outcome-free survival was very similar between the non-SLE comparator and SLE patients without immunosuppression (**Figure 4**). This was supported by the results of the Cox model which estimated an unadjusted HR of 1.73 [95%CI 0.40-7.57] for SLE patients without IS and of 8.22 [95%CI 3.60-18.8] for SLE patients treated with IS, compared to comparators without IS. After adjusting for age, sex, household composition, health administrative region and number of NPR contacts in 2020, the HRs were qualitatively similar to the unadjusted (1.50 [95%CI 0.34-6.60] for SLE patients without IS and 7.03 [95%CI 3.00-16.5] for SLE patients treated with IS compared to non-SLE comparators). The number of events were too low for us to be able to look for differences according to specific IS treatment (ESM Table S4).

Sensitivity analyses

When using IPCW to account for the censoring mechanism, we did not observe any major differences in the results: the crude HR was 4.47 [95%CI 1.59-12.6] and the adjusted HR was 4.40 [95%CI 1.55-12.5]. When patients were not censored at third dose, we observed 44 COVID-19 hospitalizations (0.12%) in the comparator group and 38 (0.68%) in the SLE group. Using the same marginal Cox model as in the main analysis, the adjusted HR associated with SLE was 5.32 [95%CI 3.42-8.27].

Investigating the effect of the winter 2021-2022 COVID-19 wave in Sweden by adding a time dependent covariate in the model, we observed that the wave period was indeed associated with an increased risk of COVID-19 hospitalization (HR comparing winter 2021-2022 to other time periods 8.16 [95%CI 3.30-20.2]) but we did not find any significant interaction between SLE and the COVID-19 wave period ($p=0.18$).

DISCUSSION

We leveraged Swedish population-based, nationwide registers to describe coverage and assess the effectiveness of anti-SARS-CoV-2 vaccination in SLE patients. We found that the uptake of the vaccine was very similar between individuals with and without SLE. The incidence of COVID-19 related hospitalization after vaccination was low in both SLE and comparators, suggesting an overall good effectiveness of the vaccination. However, mRNA vaccines were still less effective in the SLE patients, especially after 6 months of follow-up. The increased risk was observed mainly in the group with a history of immunosuppressive treatment, while SLE patients without immunosuppressive treatment had a risk of COVID-19 hospitalization very similar to that of the general population.

Although this is the first study to assess the anti-SARS-CoV-2 mRNA vaccine's clinical effectiveness in a real-life setting in SLE patients, our findings are in line with the pre-existing literature about vaccine (anti-SARS-CoV-2 or others) immunogenicity in SLE patients [6,15,16]. In a previous prospective cohort study [6], we observed that after BNT162b2 vaccination, SLE patients had a dramatically decreased humoral response against SARS-CoV-2 variants of concern such as omicron, which was involved in the winter 2021-2022 pandemic wave. However, we found in the current study that patients without immunosuppression had similar COVID-19 hospitalization risk to general population comparators even though the vaccine-induced humoral response is decreased in SLE. This finding could suggest an important role of the cellular, T-cell driven protection induced by the vaccine that was found to be still effective in patients with autoimmune diseases, despite a low humoral response [7,17].

We observed a very similar pattern in the vaccine uptake between SLE patients and the general population. This demonstrates how the organization of the vaccination was conducted in Sweden where vaccination was scheduled by the central administration and not by the physicians in charge of the patient. At the beginning of fall 2021, vaccination coverage reached a peak. Although this was true for our study population and similar to what was reported by the Swedish health authorities for the Swedish population [18], 10% of SLE patients remaining unvaccinated is an issue given the risk that these patients face regarding COVID-19. Our study was not designed to study the barriers to vaccination in SLE but physicians should be aware that the proportion of unvaccinated people was notably elevated among people born out of their country of residency and young patients who have already be shown to be more prone to vaccine hesitancy, either with or without autoimmune disease [19,20].

The maximum difference in vaccine effectiveness between SLE patients and comparators was observed after six months of follow-up, which was when the third vaccine dose was recommended, after the protection provided by the first two doses began to decrease over time. It is likely that this

decrease was more marked among immunocompromised individuals such as SLE patients. To account for bias associated with the censoring mechanism, we performed sensitivity analyses using IPCW and removed the third dose from the reason of censoring, which did not change the conclusions of our analysis. Because the six months period after the second dose coincided with a COVID-19 wave in Sweden, we looked for an interaction between this wave and SLE, which would have indicated that the wave affected SLE patients and general comparators differently. This interaction was not significant but interaction tests are known to lack power [21].

Our study was limited by the small number of events observed during the follow-up. Even though this is good news for patients and physicians, it impaired our ability to perform subgroup analysis and to investigate the effect of different immunosuppressive treatments. This work also has the usual limitations of register studies that rely on ICD-10 codes. Some comorbidities like obesity and diabetes could be under-reported. However, misclassification of these covariates should have only a limited impact on our estimates. We had no information on the SARS-CoV-2 variant involved in the COVID-19 episode. More importantly, we captured diagnoses for COVID-19 only from hospital care, which misses less severe infection. Nevertheless, we believe that it is a strength to examine the more severe outcome, which the vaccine was developed to address. We assumed that the only reason that drove the decision to admit was the immediate severity of the patient, but patients with SLE might be more likely to be hospitalized with COVID-19, or to test and seek medical care if they are infected than people without SLE. This would lead to a differential misclassification bias of the outcome and an overestimation of the HRs. However, our secondary outcome used diagnoses from outpatient visits and results were similar to the primary outcome. The dispensation of immunosuppressive treatment in the year before vaccination might not reflect the state of immunosuppression at time of vaccination and during follow-up. Besides, some patients on immunosuppressive medications could have been told to pause their treatment around vaccination and for some time after. However, we observed that almost all the events in the SLE group occurred in the group using immunosuppressives at second vaccine dose, meaning that our definition was a good proxy for immunosuppression status at vaccination. We cannot exclude that people on immunosuppressive drug might have had a lower threshold for hospitalization which would cause differential outcome misclassification, leading to an overestimation of the true effect. In order to have a homogenous population, we excluded patients with a previous COVID-19 diagnosis in the vaccine effectiveness assessment analysis, it is possible that our results could not apply to the whole SLE population and that patients most prone to COVID-19 had already been infected at that time.

In conclusion, we found that vaccination uptake and coverage was similar in Sweden between individuals with SLE and general population comparators of the same age and sex, but that it could still

be improved. Even though we observed a very low number of post-vaccination COVID-19 hospitalizations, vaccine effectiveness was diminished in SLE patients, especially among those who were using immunosuppressive medication. The vaccination scheme could possibly be tailored among patients treated with immunosuppressants. The use of other prophylactic treatment such as monoclonal antibodies should be proposed to immunosuppressant-treated SLE patients in case of reactivation of the pandemic or if mRNA vaccines were developed for other indications.

TABLES & FIGURES

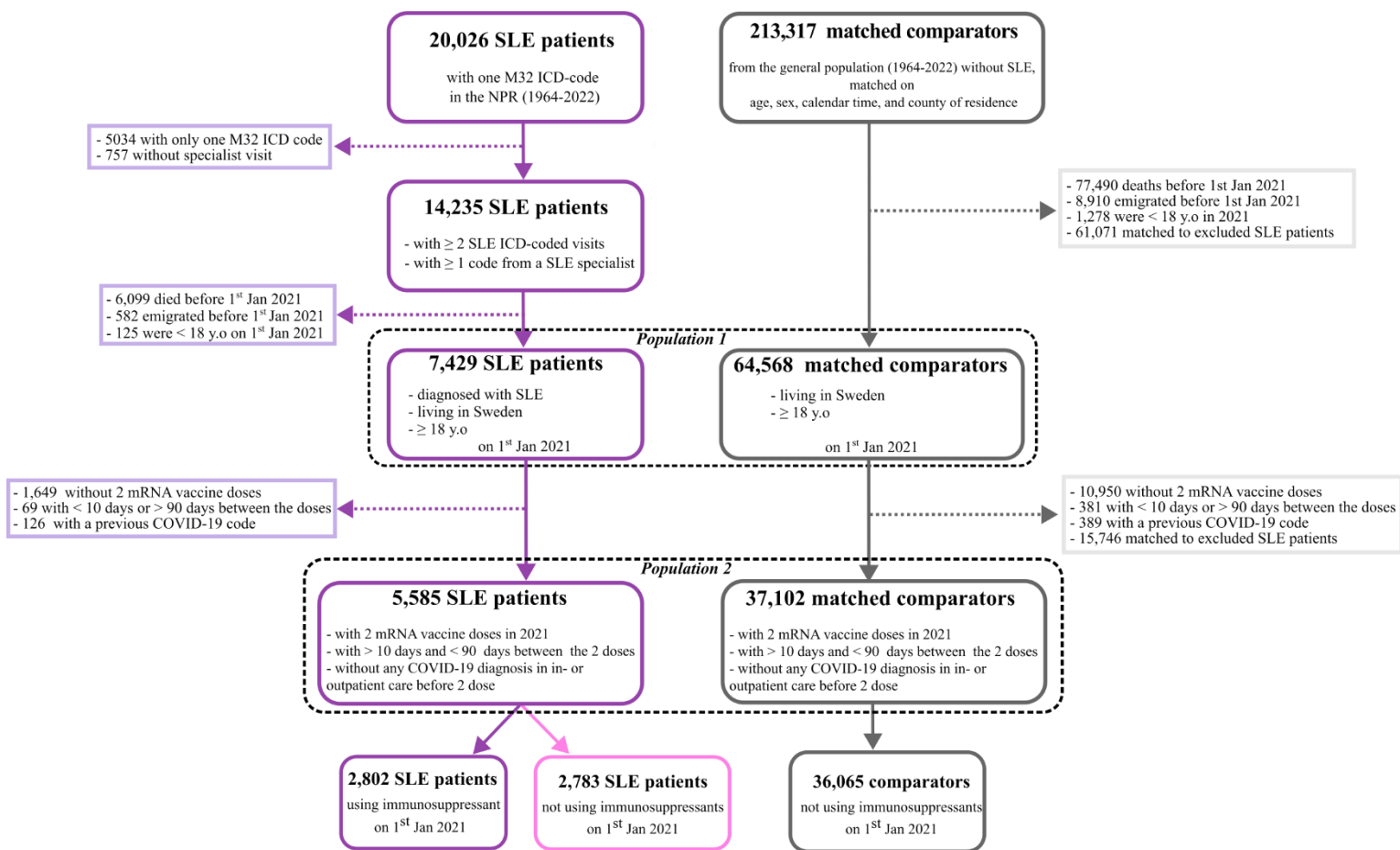
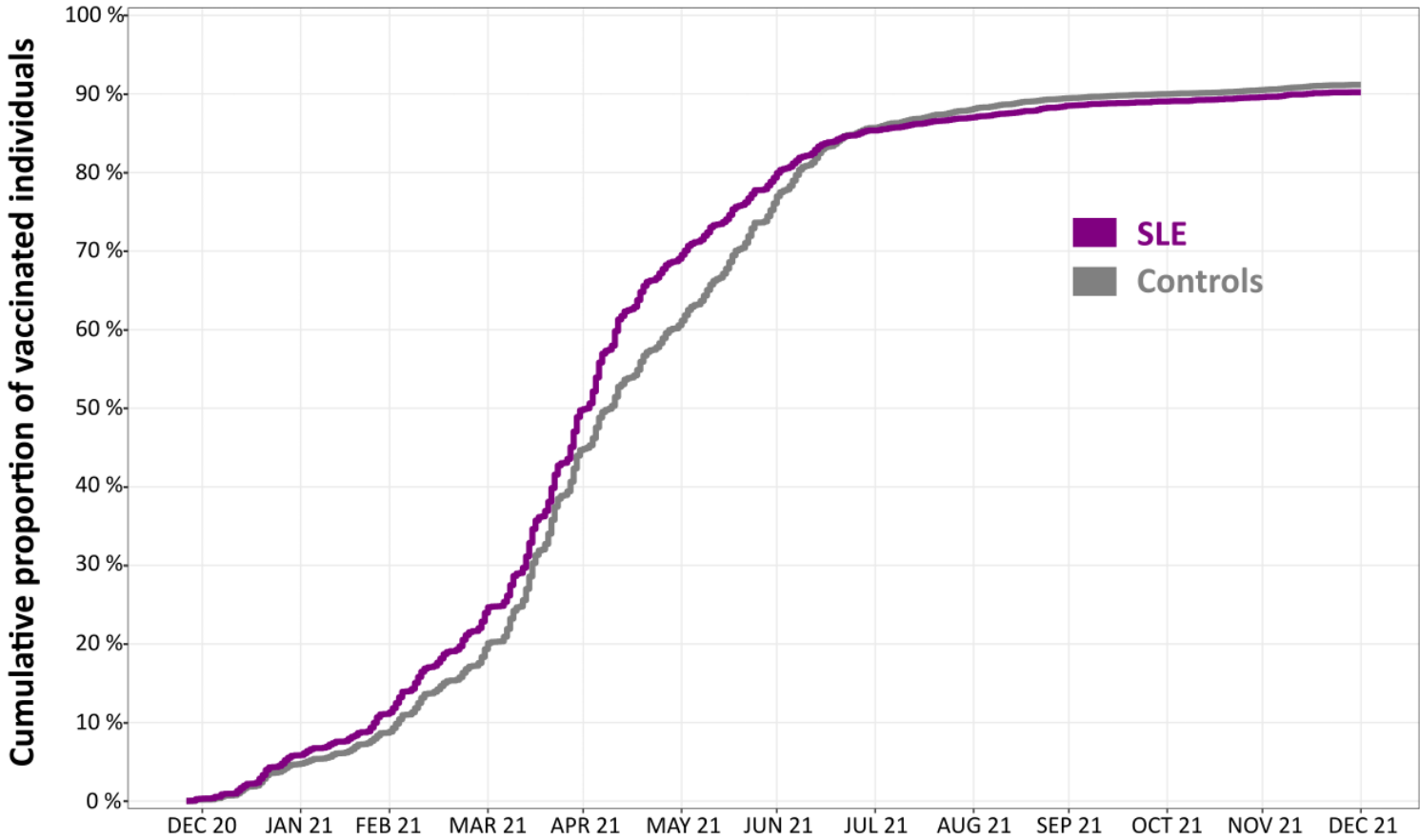


Figure 1: Flow-chart of the study

NPR: National Patient Register; SLE: Systemic lupus erythematosus; Jan: January; y.o : years old; ICD: International Classification of Disease

Figure 2: Progression of the vaccine coverage in SLE patients compared to matched comparators in Sweden December 2020 to December 2021.



Matched comparators

At risk	64568	61478	58860	51945	35559	25282	15237	9024	7506	6565	6204	5870	5424
Events	125	3081	5708	12983	28941	39486	49710	55333	56897	57771	58110	58445	58866

SLE

At risk	7429	6972	6567	5604	3684	2247	1475	1023	899	783	741	699	650
Events	24	435	839	1833	3706	5166	5939	6341	6466	6576	6617	6657	6703

Table 1: Baseline characteristics of the SLE patients and matched non-SLE comparators from the general population in Sweden who received two doses of mRNA vaccines in Sweden in 2021 before January 1st, 2022, and before any COVID-19 diagnosis in in- or outpatient care (population 2).

	SLE n= 5 585	non-SLE n= 37 102
Demographics		
Age on January 1 st , 2021, years, median [q1-q3]	57.0 [44.7-70.4]	55.2 [44.0-66.7]
Female, n (%)	4 819 (86.3)	32 113 (86.5)
Born out of Sweden, n (%)	914 (16.4)	4 772 (12.9)
Education level, n (%):		
0-9 years	980 (17.5)	4 978 (13.4)
10-12 years	2 358 (42.2)	15 952 (43.0)
≥ 10-13 years	2 213 (39.6)	16 004 (43.1)
missing	34 (0.6)	168 (0.45)
Household composition, n (%):		
Living alone	2 412 (43.2)	14 715 (39.7)
Having child(ren) < 18 years old	1 246 (22.3)	10 587 (28.5)
Living with a partner, without having any child < 18 years old	1 927 (34.5)	11 800 (31.8)
Health administrative region, n (%):		
Stockholm	1 137 (20.4)	7 145 (19.3)
Uppsala-Örebro	1 215 (21.8)	8 187 (22.1)
South	913 (16.3)	5 840 (15.7)
West	1 038 (18.6)	7 047 (19.0)
North	551 (9.9)	3 847 (10.4)
Southeast	731 (13.1)	5 036 (13.6)
Number of contacts in inpatient or non-primary outpatient care in 2020, median [q1-q3]	3 [1-7]	0 [0-2]
Vaccine		
Comirnaty® (Pfizer)	4 879 (87.4)	32 335 (87.1)
Time between the two doses, in days	42 [34-43]	42 [40-47]
SLE		
Time since SLE diagnosis, in years, median [q1-q3]	13.0 [6.6-19.2]	
Comorbidities		
High blood pressure, n (%):	1 813 (32.5)	5 693 (15.3)
Chronic kidney disease, n (%):	324 (5.8)	219 (0.6)
Obesity, n (%):	357 (6.4)	1 900 (5.1)
Diabetes, n (%):	524 (9.4)	3 062 (8.3)
Treatment received in the year prior to 2nd vaccine dose		
Hydroxychloroquine, n (%):	2 466 (44.1)	33 (0.1)
Immunosuppressive drug, n (%):	2 802 (50.2)	1 036 (2.8)
Prednisone	2 123 (38.0)	732 (2.0)
Azathioprine	584 (10.5)	63 (0.2)
Mycophenolic acid	561 (10.0)	49 (0.1)
Methotrexate	462 (8.3)	358 (1.0)
Belimumab	136 (2.4)	0
Cyclophosphamide	8 (0.1)	1 (0.0)
Anti-CD20 mAb	41 (0.7)	0

SLE: systemic lupus erythematosus; q1: first quartile; q3: third quartile; Anti-CD20 mAb: monoclonal antibodies targeting the CD20 (rituximab, ofatumumab, obinutuzumab).

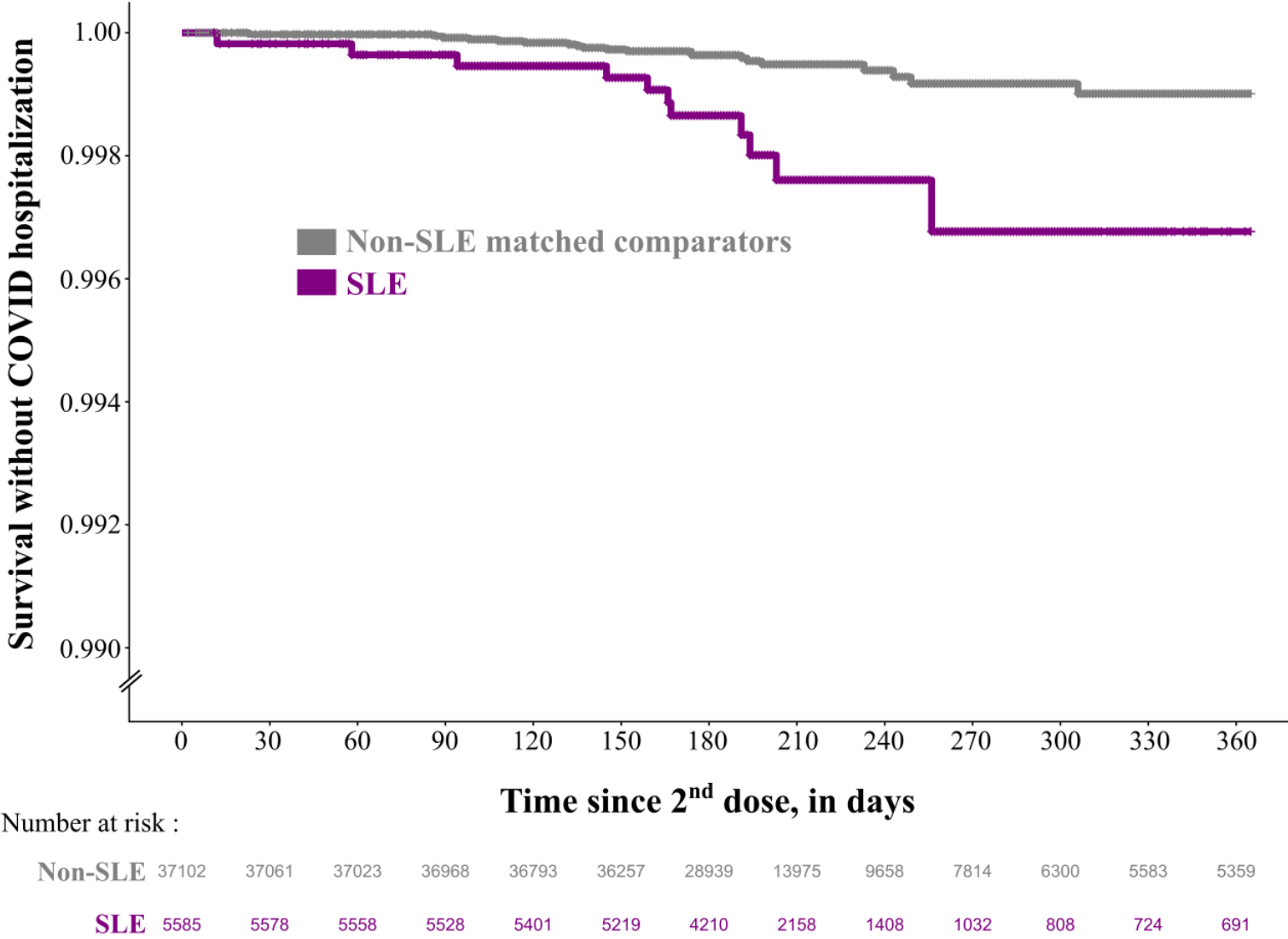
Table 2: SLE patients and non-SLE matched comparators from general population received 2 doses of mRNA vaccines in Sweden before January 1st, 2022, and before any COVID-19 diagnosis in inpatient or outpatient care (population 2).

	SLE n=5,585	non-SLE comparators n=37,102
Main outcome		
Events	11	20
Patients-years	3 339	22 745
Incidence (per 1000 PY) [95CI]	3.29 [1.82-6.00]	0.88 [0.57-1.36]
Unadjusted HR	3.76 [1.80-7.85]	ref
Adjusted* HR	3.47 [1.63-7.39]	ref
Secondary outcome		
Events	29	57
Patients-years	3 333	22 734
Incidence (per 1000 PY) [95CI]	8.70 [6.05-12.5]	2.51 [1.93-3.25]
Unadjusted HR	3.52 [2.26-5.48]	ref
Adjusted* HR	3.58 [2.30-5.59]	ref

HR: hazard ratio; SLE = systemic lupus erythematosus; PY: patients-years; ref: reference; [95CI]: 95% confidence interval; main outcome: first hospitalization with COVID as main diagnosis; secondary outcome: any first COVID-19 diagnoses in inpatient our outpatient care during follow-up.

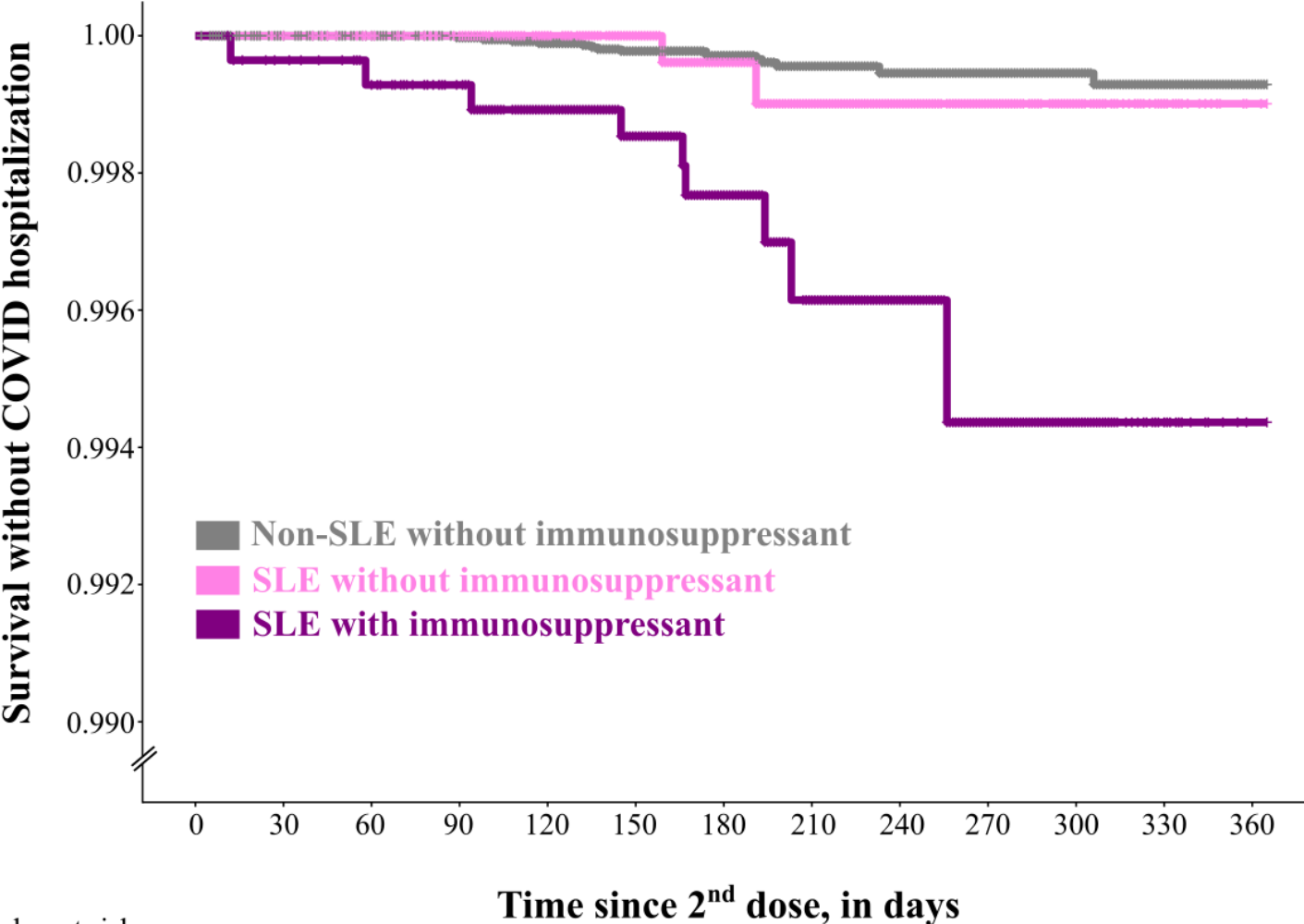
*HRs are calculated using a marginal Cox model adjusting for age, sex, household composition and administrative health region.

Figure 3: Survival without COVID-19 as a main diagnosis in inpatient care among SLE patients and non-SLE matched comparators from general population who received two doses of mRNA vaccines in Sweden before January 1st, 2022, and before any COVID-19 diagnosis in in-or outpatient care (population 2).



SLE: systemic lupus erythematosus.

Figure 4: Survival without COVID-19 as a main diagnosis in inpatient care according to the use of immunosuppressant on January 1st, 2021 among SLE patients and non-SLE matched comparators from the general population who received 2 doses of mRNA vaccines in Sweden before January 1st, 2022, and before any COVID-19 diagnosis in in-or outpatient care.



Number at risk :

	0	30	60	90	120	150	180	210	240	270	300	330	360
Non-SLE without IS	36065	36026	35994	35952	35798	35289	28153	13631	9453	7701	6216	5521	5302
SLE without IS	2783	2782	2774	2766	2727	2661	2174	1129	742	553	451	408	390
SLE with IS	2802	2796	2784	2762	2674	2558	2036	1029	666	479	357	316	301

SLE: systemic lupus erythematosus; w/o: without; IS: immunosuppressant.

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Anti-SARS-CoV-2 mRNA vaccination among patients living with SLE in Sweden: coverage and clinical effectiveness

ELECTRONIC SUPPLEMENTARY MATERIALS

Table S1. Definitions of variables used in analyses including International Classification of Diseases (ICD) Swedish revision codes and Anatomical Therapeutic Chemical (ATC) classification system codes.

Variable	Definition	ICD-10 codes
Exposure		
Systemic lupus erythematosus	≥2 inpatient or outpatient visits in the NPR with ≥1 visit in a rheumatology, internal medicine, nephrology, dermatology, or pediatric clinic	M32.1–M32.9
Outcome		
COVID-19	- main outcome: hospitalization as main diagnosis in inpatient register - secondary outcome: any diagnoses in inpatient our outpatient care	U071, U072
Covariates (diagnoses)		
Hypertension	≥1 visit in the NPR before start of follow-up	I10.X
Chronic kidney disease	≥1 visit in the NPR before start of follow-up	N18.3, N18.4, N18.5
Obesity	≥1 visit in the NPR before start of follow-up	E66.X
Diabetes mellitus	≥1 visit in the NPR or ≥1 dispensation of an antidiabetic drug (see below) before start of follow-up	E10.X, E11.X, E12.X, E13.X, E14.X, O24.X
Drugs		
Hydroxychloroquine	≥2 dispensations in the year before first dose	P01BA02
Prednisone	≥2 dispensations in the year before first dose	XXX
Azathioprine	≥2 dispensations in the year before first dose	L04AX01
Mycophenolic acid	≥2 dispensations in the year before first dose	L04AA06
Methotrexate	≥2 dispensations in the year before first dose	L04AX03
Belimumab	≥1 dispensation in the PDR OR ≥1 infusion (infusion procedure "DT016" + ATC code) in the NPR or in the SRQ during the last 6 months before first dose	L04AA26
Cyclophosphamide	≥1 dispensation in the PDR OR ≥1 infusion (infusion procedure "DT016" + ATC code) in the NPR or in the SRQ during the last 6 months before first dose	L01AA01
Anti-CD20 antibody	monoclonal ≥1 dispensation in the PDR OR ≥1 infusion (infusion procedure "DT016" + ATC code) in the NPR or in the SRQ during the last 6 months before first dose	L01FA01, L04AA52, L01FA03
Antidiabetic drug	≥1 dispensation in the PDR before first dose	A10.X
Other variables		
Household composition	- If one child < 18 years old on January 1, 2021, in the MR → living with (a) child(ren) - If no child < 18 years but married or living with a partner in 2020 in the TPR → "Living with a partner, without having any child < 18 years old " - else: "living alone"	
Number of contacts in inpatient or non-primary outpatient care in 2020	Number of visits in the NPR in 2020	

Table S2: Characteristics of SLE patients on Jan 1, 2021 who received or did not receive any anti-SARS-CoV-2 vaccine dose by December 31, 2021, in Sweden.

	SLE NOT VACCINATED N= 650	SLE VACCINATED N= 6 703
Demographics		
Age at January 1st 2021, years, median [q1-q3]	47.4 [35.6-58.5]	57.9 [45.0-71.0]
Female, n (%)	576 (88.6 %)	5 801 (86.5%)
Born out of Sweden, n (%)	226 (34.8)	1 096 (16.3)
Education level, n (%) :		
<i>0-9 years</i>	131 (20.1)	1 184 (17.7)
<i>10-12 years</i>	302 (46.5)	2 850 (42.5)
<i>≥ 10-13 years</i>	202 (31.1)	2 626 (39.2)
<i>missing</i>	15 (2.3)	43 (0.6)
Number of children, median [q1-q3]	1 [0-2]	2 [1-2]
Household composition, n (%) :		
<i>Living alone</i>	313 (48.1)	2 895 (43.2)
<i>Living with children</i>	210 (32.3)	1 426 (21.3)
<i>Living with partner and without child</i>	127 (19.5)	2 382 (35.6)
Health administrative region, n (%):		
<i>Stockholm</i>	172 (26.5)	1 392 (20.8)
<i>Uppsala-Örebro</i>	114 (17.5)	1 469 (21.9)
<i>North</i>	46 (7.1)	642 (9.6)
<i>West</i>	129 (19.8)	1 221 (18.2)
<i>South</i>	123 (18.9)	1 114 (16.6)
<i>Southeast</i>	66 (10.0)	865 (12.9)
SLE-related variables		
Time since SLE diagnosis, in years, median [q1-q3]	9.8 [4.4-17.9]	12.8 [6.3-18.9]
Hydroxychloroquine*, n (%):	244 (37.5)	2964 (44.2)
Corticosteroids*, n (%):	230 (35.4)	2 609 (38.9)
DMARDs*, n (%):	142 (21.9)	1 857 (27.7)
COVID-19		
Previous COVID-19 diagnosis in inpatient or outpatient care, n (%):	39 (6.0)	198 (3.0)
Comorbidity history		
High blood pressure, n (%):	162 (24.9)	2 244 (33.5)
Chronic kidney disease, n (%):	27 (4.2)	392 (5.8)
Diabetes, n (%):	50 (7.7)	593 (8.8)
Obesity, n (%):	49 (7.5)	433 (6.5)

SLE: systemic lupus erythematosus; q1: first quartile; q3: third quartile; DMARDs: disease modifying anti-rheumatic drug (azathioprine, methotrexate, or mycophenolic acid). * 2 or more dispensations in the year prior to start of follow-up (Jan 1, 2021)

Figure S3: Survival without COVID-19 as any diagnosis in in- or outpatient care (secondary outcome) among SLE patients and matched general population comparators who received two doses of mRNA vaccines in Sweden before January 1st, 2022, and before any COVID-19 diagnosis in in- or outpatient care (population 2).

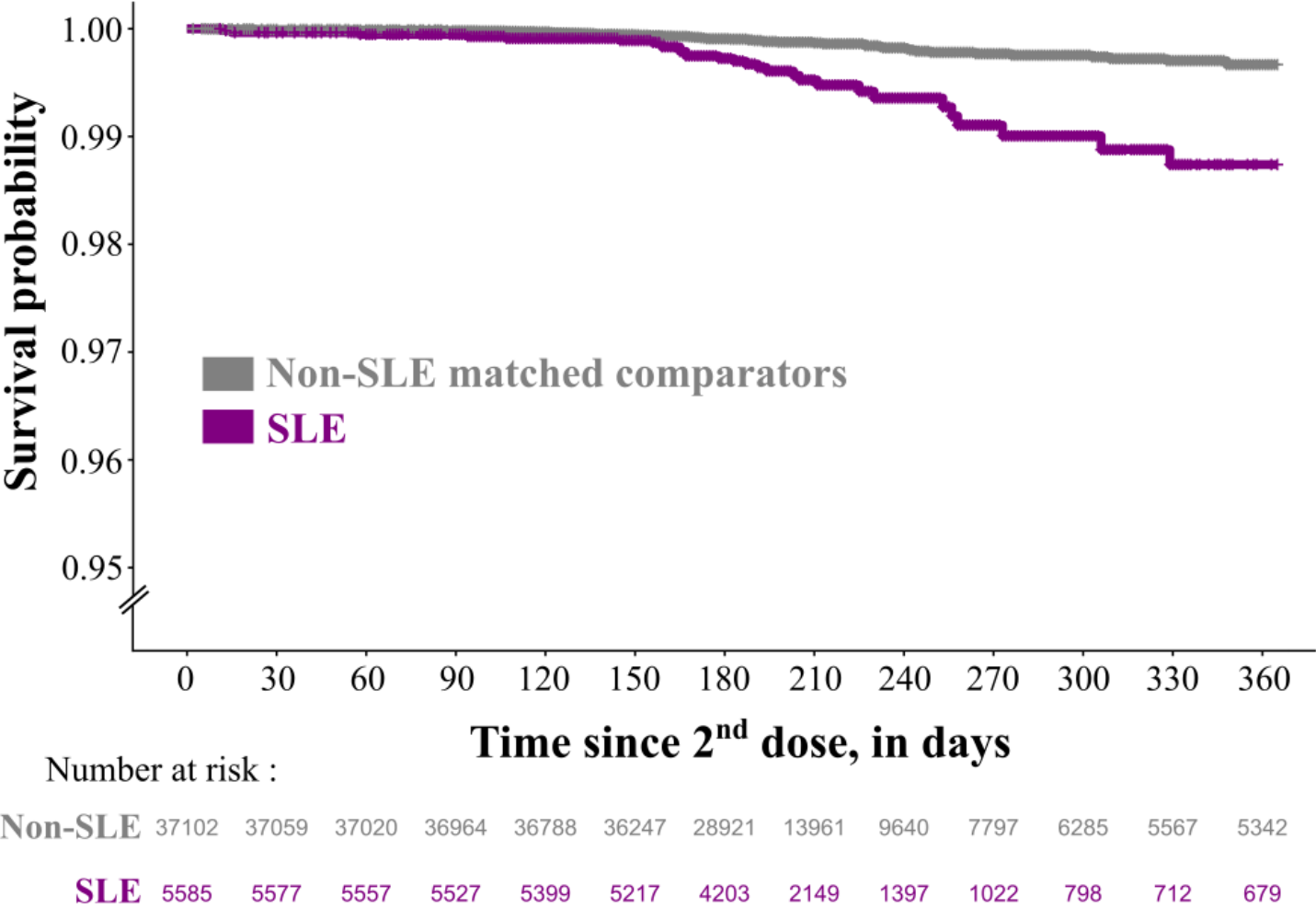


Table S4: Comparison of immunosuppressant use between SLE patients who experienced or who did not experience the main outcome (COVID-19 hospitalization) among those who had received an immunosuppressive drug within the first year before first vaccine dose.

	Not hospitalized for COVID-19 n=2,793	Hospitalized for COVID-19 n=9
Hydroxychloroquine, n (%):	1 497 (53.6)	3 (33.3)
Immunosuppressive drug, n (%):		
Prednisone	2 115 (75.7)	8 (88.9)
Azathioprine	582 (20.8)	2 (22.2)
Mycophenolic acid	559 (20.0)	2 (22.2)
Methotrexate	460 (16.5)	2 (22.2)
Belimumab	135 (4.8)	1 (11.1)
Cyclophosphamide	8 (0.3)	0
Rituximab	41 (1.5)	0

The risk of lupus flare after admission for COVID-19. Study 6.

If the initial concern for SLE patients during the SARS-CoV-2 pandemic was their increased risk of severe COVID-19, that of COVID-19-induced lupus flare also quickly emerged. In the internal medicine department of Bichat Hospital, we were intrigued by a probable case of such a COVID-19-induced lupus flare in a 20-year-old woman. This case, reported as a Letter to the Editors in *Clinical and Experimental Rheumatology*, led us to hypothesize that SLE, among all other IMIDs, may interact differently with SARS-CoV-2 because of the importance of type 1 IFN and the presence of anti-type 1 IFN autoantibodies in the pathophysiology of both diseases. The risk of an infection-induced SLE flare is challenging to study with register data, as it is imperative to perfectly assess the temporal sequence between infection and flare to avoid reverse causation.

Therefore, we decided to use the Assistance Publique - Hôpitaux de Paris (APHP) Clinical Data Warehouse which routinely collects and aggregates on a daily basis all the anonymized data generated through hospitalizations and consultations in a group of 39 public hospitals located in the Greater Paris area, France. The database gathers structured medical, biological and administrative information prospectively collected from 11 million patients. The main differences between this database and the PMSI of the Swedish nationwide registers are that here we had access to laboratory measurements and to the electronic health records (EHRs) written in natural language by the medical staff in charge of the patient.

In this study, which was submitted to *Rheumatology* on August 22, 2023, we included 4,533 SLE patients who received an SLE ICD-10 code at one of the 39 university hospitals in the Greater Paris area between July 15, 2017, and February 9, 2022. I personally reviewed the medical records of the 128 patients who also received a COVID-19 diagnosis code during one of their hospitalizations to verify the validity of the SLE and SARS-CoV-2 diagnoses. We were able to match 79/81 of the verified cases with 79 matched controls whose EHRs were also reviewed. In this matched population, we examined the absolute and relative risk of flares during follow-up.

Systemic lupus erythematosus flare following SARS-CoV2 infection: the implication of IFN α and anti-IFN α autoantibodies

Sirs,

The SARS-CoV2 pandemic brought back the unresolved question of whether and how a viral infection may trigger autoimmune diseases¹. Type 1-interferon and autoantibodies to IFN α (anti-IFN α) are involved in both systemic lupus erythematosus (SLE) and COVID-19 pathogeny (2-5). To give insight into the complex relationship between COVID-19 and SLE, IFN α , anti-IFN α and anti-dsDNA antibodies were tested overtime in a patient who experienced a SLE flare following COVID-19. In January 2019, a 20-year-old woman was admitted for acute pericarditis. Testing for antinuclear antibodies (ANA) was not performed at this time. She was treated with colchicine and aspirin then discharged. In April 2020, the patient was hospitalised for a mild COVID-19 that recovered without treatment. In August 2020, she presented malar rash, sore mouth, chest pain and arthritis. Laboratory tests showed elevated levels of anti-dsDNA antibodies at 159 IU/ml and SLE was diagnosed. Serum complement levels and urinary protein/creatinine ratio were normal. Oral glucocorticoids (starting at 0.5 mg/kg/day) and hydroxychloroquine (HCQ) led to a complete clinical remission. In January 2021, the patient was admitted for a severe infection with SARS-Cov-2 α variant, while still under steroids and HCQ. Supplemental oxygen was required. The patient recovered without SLE relapse.

Serum specimens from January 2019 until June 2021 could fortunately be retrieved and analysed (Fig. 1). In January 2019, serum was already positive for ANA, anti-Sm and anti-dsDNA antibodies, confirming that pericarditis was the heralding manifestation of SLE. Interestingly, high titre of anti-IFN α was also detected in January 2019 prior to COVID-19 (Fig. 1). Consistent with a potential protective role of anti-IFN α in SLE³, lupus disease remitted without specific treatment at that time. Conversely, the presence of anti-IFN α may predispose to COVID-19 by blocking the action of this crucial antiviral cytokine (2, 5) and the patient displayed a first SARS-Cov-2 infection in April 2020. As an apparent consequence of type I interferon overproduction induced by the virus (5), the titre of anti-IFN α decreased after COVID-19 while IFN α level remained high (Fig. 1). The decrease in anti-IFN α titre may have contributed in turn to the lupus flare observed 4 months after COVID-19. Eventually, while the patient was still receiving steroids and HCQ, IFN α levels decreased and paralleled both diminished lupus activity and anti-dsDNA titres. Unfortunately, the patient suffered highly symptomatic COVID-19 reinfection during the "second wave" of the pandemic in France in December 2020. Thus, the first infection failed to induce a protective humoral immu-

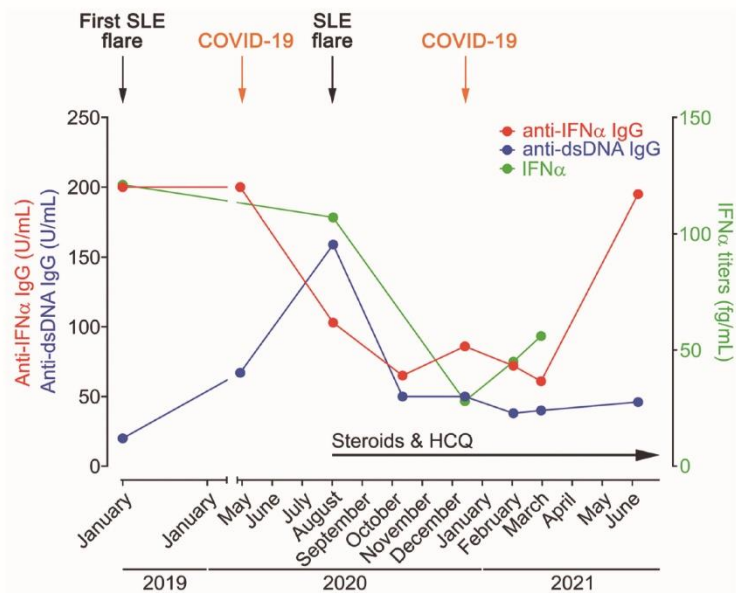


Fig. 1. IFN α , anti-IFN α and anti-dsDNA time course in a 20-year-old SLE patient with COVID-19. IFN α was measured by SIMOA technology (threshold 32 fg/ml), anti-IFN α by in house ELISA as described² (positivity threshold >10 UA/ml), anti-dsDNA by FEIA (positivity threshold >15 UI/ml).

nity as assessed by the lack of circulating N-protein and S-protein specific IgG detected in October 2020. The second infection occurred while the patient was under steroids and HCQ making it more difficult to decipher the variation causes of circulating IFN α and anti-IFN α at this time. However, the second COVID-19 happened while anti-IFN α were still detectable in serum and was followed by an apparent rebound of IFN α level in March 2021. Eventually, in June 2021 anti-IFN α titre rose to its "protective" level for SLE (195 U/ml) while SARS-CoV-2 seroconversion had occurred and SLE was still in remission (Fig. 1).

Although a causative link cannot be demonstrated, the chronology of events indicates an original mechanism by which a viral infection may promote SLE flares. Indeed, a high titre of anti-IFN α – known to inhibit IFN α signalling (3) – may protect against lupus flare but predispose to COVID-19. In such setting, strong IFN α production induced by a virus like SARS-Cov-2 may overpass the protective role of anti-IFN α in SLE and thus contribute to lupus flare. Although our group reported no clear-cut evidence for a higher risk of severe COVID-19 in SLE (6), this observation suggests that SLE patients with anti-IFN α may be at risk for lupus flare following COVID-19.

Acknowledgements

We are thankful to Professors S. Chollet Martin, D. Descamps and T. Papo for their help with the manuscript preparation.

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Funding: this work was supported by the French Agence Nationale de la Recherche (ANR) [grants no. ANR-19-CE17-282 0029 BALUMET to N. Charles and ANR-21-COVR-0034 COVALUS to K. Sacre], by the Centre National de la Recherche Scientifique (CNRS), by Université de Paris, by the Assistance Publique-Hôpitaux de Paris (AP-HP) and by the Institut National de la Santé et de la Recherche Médicale (INSERM).

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Study 6

Increased risk of systemic lupus erythematosus flare after COVID-19: a multicenter matched cohort study coupling medico-administrative and clinical databases.

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Financial support Arthur Mageau was supported by a PhD fellowship provided by Fondation pour la Recherche Médicale (FDM202106013488). This work was supported by the Agence Nationale de la Recherche (n°ANR-21-COVR-0034 COVALUS), the University Paris Cité and the Assistance Publique Hôpitaux de Paris

Disclosures None

ABSTRACT

Objective: We analyzed the risk of systemic lupus erythematosus (SLE) flare after admission for COVID-19.

Methods: We performed a matched cohort study using the Assistance Publique - Hôpitaux de Paris Clinical Data Warehouse which collects structured medical, biological and administrative information from 11 million patients in Paris area, France. Each SLE patient hospitalized with a COVID-19 diagnosis code between March 2020 and December 2021 was matched to one SLE control patient with an exact matching procedure using age ± 3 years, gender, chronic kidney disease, end-stage renal disease, and lupus biology. The main outcome was a lupus flare during the 6 months follow-up. A flare was considered if a) documented by the treating physician in the patient's EHR and b) justifying a change in SLE treatment. The electronic health records (EHRs) were individually checked for data accuracy.

Results: Among 4,533 SLE patients retrieved from the database, 81 (2.8%) have been admitted for a COVID-19 between March 2020 and December 31, 2021 and 79 (n=79/81,97.5%) were matched to a unique unexposed SLE. During follow-up, a flare occurred in 14 (17.7%) SLE patients from the COVID-19 group as compared to 5 (6.3%) in the unexposed control group, including 4 lupus nephritis in the exposed group and 1 in the control group. After adjustment for HCQ use at index date and history of lupus nephritis, the risk of flare was higher in exposed SLE patients (hazard ratio [95% confidence interval] of 3.79 [1.49-9.65]).

Conclusions: COVID-19 increases the risk of lupus flare in SLE patients.

KEY POINTS

What is already known on that topic: SLE patients are prone to face severe COVID-19 episodes. The impact of these episodes on the risk of subsequent flare is unknown.

What this study adds: In this matched cohort study that included 158 SLE patients, the risk of flare was higher in SLE patients exposed to COVID-19 as compared to unexposed SLE patients. (hazard ratio [95% confidence interval] = 3.79 [1.49-9.65]).

How this study might affect research, practice or policy: SLE patients are at increased risk of lupus flare following symptomatic COVID-19. Physicians should be aware of such risk when managing a COVID-19 episode in order to set up short term follow-up after hospital discharge.

INTRODUCTION

The SARS-CoV2 pandemic reopened the unresolved question of whether and how a viral infection can trigger flares of immune-mediated inflammatory diseases such as systemic lupus erythematosus (SLE). Different elements may contribute to a higher risk of lupus flare following COVID-19. First, type 1-interferon and neutralizing anti-type I interferon (IFN-I) autoantibodies - both involved in SLE and COVID-19- have a Janus effect on the activity of SLE and the control of SARS-CoV-2 infection: a high titer of neutralizing anti- IFN-I protects against lupus flare-ups but predisposes to severe COVID-19 [1–5]. In such setting, strong IFN-I production induced by SARS-CoV-2 may overpass the protective role of anti-I IFN-I in SLE and contribute to lupus flare as previously reported [6]. Second, severe COVID-19 is associated with a poor prognosis among patients with SLE [7,8]. Tapering immunosuppressive (IS) drugs because of ongoing severe COVID-19 may increase the risk of SLE flare. So far SLE flares following COVID-19 have been reported in case reports [6,9–11] but such association has not been assessed through larger systematic studies.

Assistance Publique–Hôpitaux de Paris (APHP) is the largest university hospital system in Europe and sees more than 8.3 million patients per year in 39 hospitals in Paris and its surroundings. We herein leverage the APHP Clinical Data Warehouse – a population-based register combined with clinical databases built from electronic health records - to collect information on SLE patients admitted for COVID-19 and perform a matched cohort study investigating the relationship between COVID-19 and lupus flare onset.

METHODS

Data source

The Assistance Publique - Hôpitaux de Paris (APHP) Clinical Data Warehouse routinely collects and aggregates on a daily basis all the anonymized data generated through hospitalizations and consultations in a group of 39 public hospitals located in the Greater Paris area, France. The database gathers structured medical, biological and administrative information prospectively collected from 11 million patients. Diagnoses and procedures identified during the hospital stays are coded according to the International Classification of Diseases, 10th Revision [12] (ICD-10) and the *classification commune des actes médicaux* [13] (CCAM), respectively. In addition to data identified through ICD/CCAM codes, APHP Clinical Data Warehouse gives access to all the anonymized medical reports and prescriptions written in natural language in the electronic health records (EHRs) as well as all the medical notes and biological exams performed overtime during routine care.

Study population and definitions

All patients older than 16 years of age admitted between July 15, 2017 and February 9, 2022 in any of the 39 French public hospitals located in the greater Paris area who received at least one international classification of diseases, M32.X ICD-10 code (SLE) were retrieved from the database. Among them, 1) all SLE patients admitted for a first COVID-19 before January 1st, 2022 defined the “exposed group” and 2) all matched SLE patients without evidence for a COVID-19 prior the index date defined the “unexposed group”. The follow-up of each exposed patient started the day of admission for COVID-19 (index date). Follow-up of each unexposed patient began on the index date of his or her matched exposed counterpart.

The initial selection of patients was made using M32.X and U07.1 ICD-10 codes for SLE and COVID-19, respectively. The medical charts of the selected patients were next individually reviewed to confirm that i) all patients fulfilled the 2019 EULAR/ACR classification criteria for SLE [14], ii) all SLE patients identified with COVID-19 (exposed) had a proven infection (i.e. positive PCR for SARS-CoV-2), iii) COVID-19 was the main reason for admission of exposed patients and iv) all SLE patients identified without COVID-19 (unexposed) had no evidence for any COVID-19 before the index date. The medical charts were reviewed by a physician specialized in clinical immunology (AM)

Demographic characteristics, comorbidities, anti-SARS-CoV2 vaccine status, SLE features including lupus biology, and treatment received prior and during index date were retrieved from medical records. Serum C3 levels and anti-dsDNA IgG titers measured within 6 months prior to the index visit were considered for lupus biology. When performed, lupus biology was defined as either normal - when both C3 level and anti-dsDNA IgG titer were into the normal range – or abnormal – when C3 level was low and/or anti-dsDNA IgG titer was high. A SLE flare was defined if was 1) considered by the physician in the medical record and ii) followed by a change in treatment adjusted for SLE flare in the setting of care.

Matching procedure

Each SLE patient who experienced a COVID-19 episode during the period of study was randomly matched with one SLE control patient. A random exact matching procedure (without replacement) using the prespecified following matching variables: age ± 3 years, gender, chronic kidney disease, end-stage renal disease (chronic dialysis or renal transplant), and lupus biology was used. Matching accuracy and efficacy were estimated by calculating the absolute mean standardized differences (SMD) between the characteristics of the matched populations.

Survival analyses

The primary outcome was the occurrence of a SLE flare during follow-up. Follow-up began the first day of the index date and ended after 6 months, another COVID-19-episode, death or lost to follow-up. Kaplan-Meier method was used to analyze the 6-months survival without flare. We used a marginal Cox proportional hazard model [15], accounting for the matching, to calculate the hazard ratio of the exposed population, using the unexposed population as reference. We adjusted the model on the remaining relevant differences between the two matched populations (i.e. use of hydroxychloroquine at index date and a history of a lupus nephritis). In order to look for factors associated with the occurrence of flare in the exposed group while taking account of the high mortality rate in this population, we ran univariate Fine and Gray's competing risk models [16] using either occurrence of flare or death during follow-up as outcomes of interest.

Statistical analyses

Categorical variables are given as number (percentage). Quantitative variables are given as median (first quartile–third quartile). HRs are given with their 95% CI. The evolution of lupus biology - C3 levels in all and anti-dsDNA IgG titers among in those with positive anti-dsDNA IgG - following index date were fitted and plotted with a LOESS approach. We looked for a difference in the evolution of these biomarkers within the two groups by running linear mixed models (one for each biomarker, package lme4) with a patient-level random effect. We considered that the evolutions were different between the two groups if the interaction term time * group was significant according to Wald test. All analyses were performed using SAS V.9.4 and R V.4.0.3 softwares.

Ethical aspects

The study and its experimental protocol were approved by the AP-HP Scientific and Ethical Committee (IRB00011591 decision number CSE-210014). Patients were informed that their EHR information could be reused after an anonymization process and those who objected to the reuse of their data were excluded. All methods were carried out in accordance with relevant guidelines (reference methodology MR-004 of the CNIL: Commission Nationale de l'Informatique et des Libertés).

Data availability

The datasets analyzed during the current study are not publicly available due the confidentiality of data from patient records, even after de-identification. However, access to the AP-HP data warehouse's raw data can be granted following the process described on its website:

www.eds.aphp.fr, contacting the Ethical and Scientific Committee at secretariat.cse@aphp.fr. A prior validation of the access by the local institutional review board is required. In the case of non-APHP researchers, the signature of a collaboration contract is mandatory.

RESULTS

Population selection

A SLE diagnosis ICD-10 code was reported in the electronic health records of 4,533 patients admitted in one of the 39 university hospitals of the Greater Paris area, France between July 15, 2017 and February 9, 2022. Among them, 128 (2.8%) had an admission stay tagged with a COVID-19 diagnosis ICD-10 code between March 2020 and December 31, 2021. After individual review of the medical charts, 47 patients were excluded because 2019 EULAR/ACR classification criteria for SLE were not met (n=22), SARS-CoV-2 infection occurred after December 2021 (n=10) or was not proven (n=7), data following COVID-19 infection were missing (n=6), patients were younger than 16 (n=1), or had a SLE diagnosed after COVID-19 (n=1) (details provided in **Figure 1**).

Overall, 81 SLE patients (76 (96.2%) female, median [Q1-Q3] age 56.3 [40.6-68.3] years old) with COVID-19 fulfilling the selection criteria were included in the study. The characteristics of the COVID-19 in those patients are given **Table S1**. Around 30% (n=25/81) of admissions for COVID-19 occurred before August 2020 **Figure S2**. Eleven patients died during (n=8) or shortly after (n=3) discharge from the COVID-19 stay. Among COVID-19 survivors, the median [Q1-Q3] follow-up time after COVID-19 was of 289 [42-502] days.

Matching procedure

We were able to match 79/81 (97.5%) COVID-19 patients to 79 unique unexposed SLE patients through our matching procedure. Despite matching, significant differences were still remained between groups regarding hydroxychloroquine (HCQ) treatment (51 (65.4 %) SLE in the COVID group were receiving HCQ at index date as compared to 60 (75.9%) in the unexposed group; SMD = 0.251) and history of lupus nephritis (37 (48.1%) SLE patients in the COVID group had past history of lupus nephritis at index date as compared to 31 (39.7 %) in the unexposed group; SMD= 0.153). The characteristics of the matched populations are given **Table 2**.

Risk of SLE flare after COVID-19

During follow-up, 14 (17.7%) SLE patients from the COVID-19 group experienced a lupus flare as compared to 5 (6.3%) from the unexposed control group. Overall, lupus flare ups included lupus nephritis relapses (n=5, 4 in the COVID-19 group and 1 in the control group), severe immune cytopenia

(n=4, 3 in the COVID-19 group and 1 in the control group) and pleuritis (n=3, 2 in the COVID-19 group and 1 in the control group). Unadjusted HR showed that risk of lupus flare during a 6-month follow-up period were higher in SLE patients who experienced COVID-19 as compared to unexposed control (HR 3.62 [1.39-9.41])

After adjustment for HCQ use at index date and history of lupus nephritis, HR was 3.79 [1.49-9.65]. The median delay between the index date and lupus flare was shorter (47 [19-129] versus 77 [46-83] days) in the COVID-19 group than in the control group. The Kaplan-Meier curve of survival without lupus flare in the two matched groups is given **Figure 2**. The proportional hazard assumption was met for the whole period of analysis (Data not shown).

Immunological biomarkers for SLE after COVID19

During follow up, 85 SLE patients (46 COVID and 39 controls) and 44 SLE patients positive for anti-dsDNA autoantibodies (17 COVID and 27 controls) had at least one measurement of C3 levels and anti-dsDNA IgG titers, respectively. Using the mixed model approach to analyze 184 measurements of C3 levels overtime, we observed that C3 levels decreased after the index date in COVID-19 patients and remained unchanged in the control groups ($p=0.085$). Based on the analysis of 85 measurements, no difference was observed between groups regarding the evolution of anti-dsDNA IgG titers during follow-up. The fitted outcome of these immunological biomarkers in each group of interest is shown in **Figure 3**.

Sensitivity analyses

We also observed unbalanced mortality between groups since 8 SLE patients died during the index stay in the COVID-19 group and none in the non-exposed group. To analyze the impact of competing risks, we performed a sensitivity analysis excluding the pairs (exposed and matched control) of exposed patients who died of COVID-19. The same proportion of events was observed in each group and the adjusted hazard ratio remained almost unchanged: 3.45 [1.35-8.81].

We also performed an analysis after extending the follow-up to 9 months after the index date. The number of events observed in both groups was the same as in the main analysis, and the adjusted HR was very similar: 3.79 [1.49-9.65].

Risk factors for lupus flare after COVID-19.

Factors associated with the occurrence of a lupus flare after COVID-19 were analyzed using competing risk models in the exposed populations. Death during follow-up was considered as the competing event and factors associated with such risk were studied (**Table 2**). The only factor associated with the occurrence of a flare after COVID-19 was a prior anti-SARS-CoV2 vaccine with a HR of 4.00 [1.09-14.6].

Interestingly, tapering the SLE immunosuppressive drugs during COVID stay was not associated with an increased risk of flare (HR=0.86 [0.23-3.18]). Results are given **Table 2**.

DISCUSSION

Using the APHP Clinical Data Warehouse, we leveraged more than 4,000 electronic health records of SLE patients admitted in one of the 39 university hospitals of Paris area to investigate the link between COVID-19 and lupus flare. Our analysis demonstrated that SLE patients are at increased risk of lupus disease flare after COVID-19. Lupus flares were severe, including lupus nephritis in almost 30% of cases and occurred shortly after COVID-19, suggesting a causal relationship between COVID-19 and flares. Our findings are consistent with the published evidence supporting a link between COVID-19 and lupus flares in case reports and short series [6,9–11,17,18] and with a recent self-controlled case series study which observed an increased risk of flare after influenza infections [19].

Type 1-interferon (IFN-1) play a key role in both SLE and COVID-19. IFN-1 is produced by plasmacytoid dendritic cells (pDCs) in response to SARS-CoV2 infection and contributes to the macrophage-induced cytokine storm (6) observed during COVID-19 episodes. IFN-1 and pDCs also play a central role in SLE, being involved in the pathogenesis and activity of the disease (4). In such setting, the persistence of a low-grade inflammatory type 1-interferon activity in SLE patients who survive severe COVID-19 could play a role in subsequent lupus flares. The occurrence of various auto-antibodies following severe COVID-19 suggests a defect in tolerance mechanisms as a result of the rapid and exaggerated inflammatory responses to Sars-CoV-2 (14). Critically ill patients with severe infection caused by SARS-CoV-2 display intense extrafollicular B cell responses enriched in autoreactive potential similar to those previously reported in SLE [20,21]. On one hand, uncensored extrafollicular expansion may be considered a dominant and adapted immune response that controls severe COVID-19 through acute inflammation; on the other hand, it may promote flare-ups in SLE patients.

Unexpectedly, the only significant risk factor for lupus flare following COVID-19 was a prior anti-SARS-CoV2 vaccine. This finding is clearly challenging— considering the demonstrated benefit of vaccination in SLE [22]. Severe SLE patients are usually treated with immunosuppressive drugs. Since anti-SarS-CoV-2 vaccination is highly recommended in patients treated with immunosuppressive (IS) drugs, vaccinated SLE patients may have a higher risk of relapse because they have more severe disease. Although such selection bias is plausible it should also be pointed out that 1) humoral response against SARS-CoV-2 following vaccination may be dramatically high in SLE patients with evidence of prior COVID-19 [23] and 2) SARS-CoV-2 vaccination was followed by increased *in vivo* production of IFN α by pDCs in SLE patients [24].

Our work has several limitations. First, only SLE patients admitted for COVID-19 have been considered and our results might not be generalizable to mild or asymptomatic COVID-19 outpatients. Additionally, some patients may have had symptoms related to a lupus flare but wrongly ascribed to incident COVID-19; such confusion appears very unlikely considering the long median delay that was observed between admission for COVID-19 and lupus flare of 47 [19-129] days. Third, the high mortality rate at the early phase of COVID-19 may have artificially inflated the hazard ratio due to informative censoring, despite our sensitivity analyses considering competing risk of death. Fourth, although all SLE patients appeared to be followed on a regular basis regardless of COVID-19, our analysis might suffer from a surveillance bias where patients benefited from a reinforced follow-up after COVID-19. Fifth, SLE is a rare disease and admission for COVID-19 was a rather uncommon exposure. The limited number of patients may have particularly affected the analysis of anti-dsDNA titers after the index date or the search for risk factors for flare that are both based on restricted subsets of patients. Our study is however the largest on this matter and has sufficient power for significant results. Sixth, we did not provide any mechanistic evidence of the link between COVID-19 and lupus flare. Interestingly, a causal link between COVID-19 and lupus flare was suggested by the clinician in most cases as specified in the medical records.

Our study also has several strengths. We had access to a comprehensive clinical database that drew from electronic health records, detailed information on medical history, biology, treatments, procedures, and outcomes. Furthermore, we thoroughly examined the full text of medical reports that were generated by the medical staff on a daily basis as part of the standard of care. Additionally, our matching process, which took into account factors such as age, sex, lupus activity parameters (anti-dsDNA IgG titers and C3 levels), and organ damage (chronic kidney disease), helped mitigate the risk of selection bias. Lastly, we used a clinically relevant definition of flares based on the assessment of the patient by the treating physician.

In conclusion, SLE patients are at increased risk of lupus flare following symptomatic COVID-19. Short-term follow-up is warranted after hospital discharge.

ACKNOWLEDGEMENTS

The authors would like to thank the AP-HP data warehouse, which provided the data and the computing power to carry out this study under good conditions. We wish to thank all the medical colleges from the APHP departments of internal medicine, rheumatology, dermatology, and nephrology that gave their agreements for the use of the clinical data.

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TABLES

	COVID-19 n = 79	No COVID-19 n=79	Absolute SMD
Age, in years*, median (Q1-Q3)	56.3 [40.6-68.3]	55.9 [39.7-68.2]	0.003
Female gender*, n (%)	76 (96.2)	76 (96.2)	0.000
Afro-Caribbean ethnicity, n (%)	30 (45.4)	24 (36.4)	0.185
Comorbidities			
CKD*, n (%)	22 (27.9)	22 (27.9)	0.000
ESRD*, n (%)	15 (18.9)	15 (18.9)	0.000
SLE disease			
Years from SLE diagnosis, median [Q1-Q3]	14.2 [5.6-22.3]	11.8 [6.8-24.8]	0.035
History of lupus nephritis, n (%)	37 (48.1)	31 (39.7)	0.153
<i>class III/IV nephritis, n (%)</i>	24 (31.2)	22 (28.6)	0.056
Lupus biology during the last 6 months* [†] , n (%)			0.022
<i>Normal</i>	29 (36.7)	30 (36.7)	
<i>Abnormal</i>	35 (44.3)	34 (43.0)	
<i>Not performed</i>	15 (18.9)	15 (18.9)	
SLE treatment at index date			
Hydroxychloroquine, n (%)	51 (65.4)	60 (75.9)	0.251
Steroids, n (%)	53 (67.9)	54 (68.3)	0.027
<i>Prednisone equivalent daily dose, if any (mg/d)</i>	5 [5-9]	7 [5-10]	0.109
IS drug, n (%)	31 (39.2)	32 (40.5)	0.025
<i>Mycophenolate mofetil</i>	22 (28.2)	20 (25.3)	
<i>Azathioprine,</i>	5 (6.4)	9 (11.4)	
<i>Rituximab</i>	6(7.7)	5(6.4)	
Recent modification of SLE treatment ‡, n (%)	24 (30.4)	23 (29.1)	0.028
Follow-up			
Death during follow-up, n (%)	11 (14.0)	3 (3.8)	

Table 1 Characteristics of the matched populations.

Q1: first quartile; Q3: third quartile; CKD: Chronic kidney disease defined as an eGFR < 60mL/min and no end-stage renal disease; ESRD: End-stage renal disease defined as chronic dialysis or renal transplantation; IS: immunosuppressive; SMD: standardized mean differences.

Lupus nephritis classes refer to the ISN/RPSWG classification [25].

[†]C3 levels and anti-dsDNA IgG titers measured in the serum at the latest 6 months prior the index date were considered. When performed, lupus biology was defined as either normal - when both C3 level and anti-dsDNA IgG titer were into the normal range – or abnormal – when C3 level was low and/or anti-dsDNA IgG titer was high.

* Matching variables. ‡ SLE treatment modification during the six months before the index date or during COVID episode.

	Risk of SLE flare		Risk of death	
	sdHR [95 CI]	p	sdHR [95 CI]	p
Age, in years	0.98 [0.95-1.01]	0.11	1.05 [1.02-1.09]	0.003
Male gender	2.12 [0.22-20.3]	0.51	NA	
Comorbidities				
Chronic kidney disease	0.66 [0.17-2.50]	0.54	3.65 [1.06-12.6]	0.041
End-stage renal disease	1.21 [0.32-4.64]	0.78	0.98 [0.22-4.42]	0.98
COVID-19				
> 6l.min-1 of oxygen during COVID	0.24 [0.05-1.11]	0.07	16.2 [2.05-129.1]	0.008
Prior anti-SARS-CoV2 vaccine	4.00 [1.09-14.6]	0.04	NA	
SLE disease				
Years from SLE diagnosis,	0.97 [0.90-1.03]	0.28	1.05 [1.01-1.09]	0.019
History of lupus nephritis	0.60 [0.20-1.80]	0.60	1.02 [0.30-3.45]	0.98
<i>class III/IV lupus nephritis</i>	0.90 [0.27-3.02]	0.86	1.45 [0.42-5.06]	0.56
Lupus biology during the last 6 months [†]				
<i>Normal</i>	ref	ref	ref	ref
<i>Abnormal</i>	2.64 [0.73-9.54]	0.14	0.53 [0.09-3.06]	0.53
<i>Not performed</i>	0.59 [0.06-5.83]	0.65	3.76 [0.95-14.9]	0.06
SLE treatment				
Steroids at index date	0.82 [0.28-2.41]	0.73	1.92 [0.41-9.09]	0.41
IS drugs at index date	0.38 [0.10-1.39]	0.14	0.61 [0.16-2.36]	0.47
Tapering of IS drugs during COVID	0.86 [0.23-3.18]	0.86	0.75 [0.16-3.42]	0.75

Table 2: Factors associated with the occurrence of a flare or death during follow-up.

CKD: Chronic kidney disease defined as an eGFR < 60mL/min and no end-stage renal disease; ESRD: End-stage renal disease defined as chronic dialysis or renal transplantation; IS: immunosuppressive [†]C3 levels and anti-dsDNA IgG titers measured in the serum at the latest 6 months prior the index date were considered. When performed, lupus biology was defined as either normal - when both C3 level and anti-dsDNA IgG titer were into the normal range – or abnormal – when C3 level was low and/or anti-dsDNA IgG titer was high.

sdHR = sub-distribution hazard ratio ; 95CI: 95 % confidence interval

FIGURE

Figure 1: Selection of the exposed population

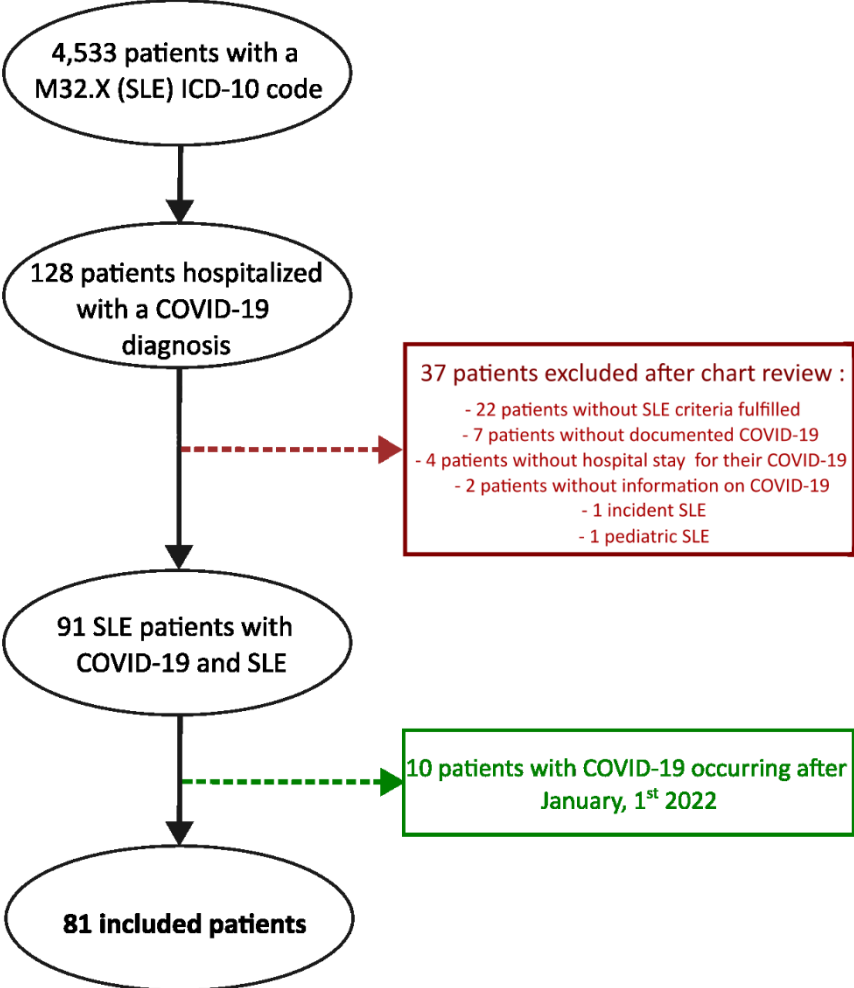
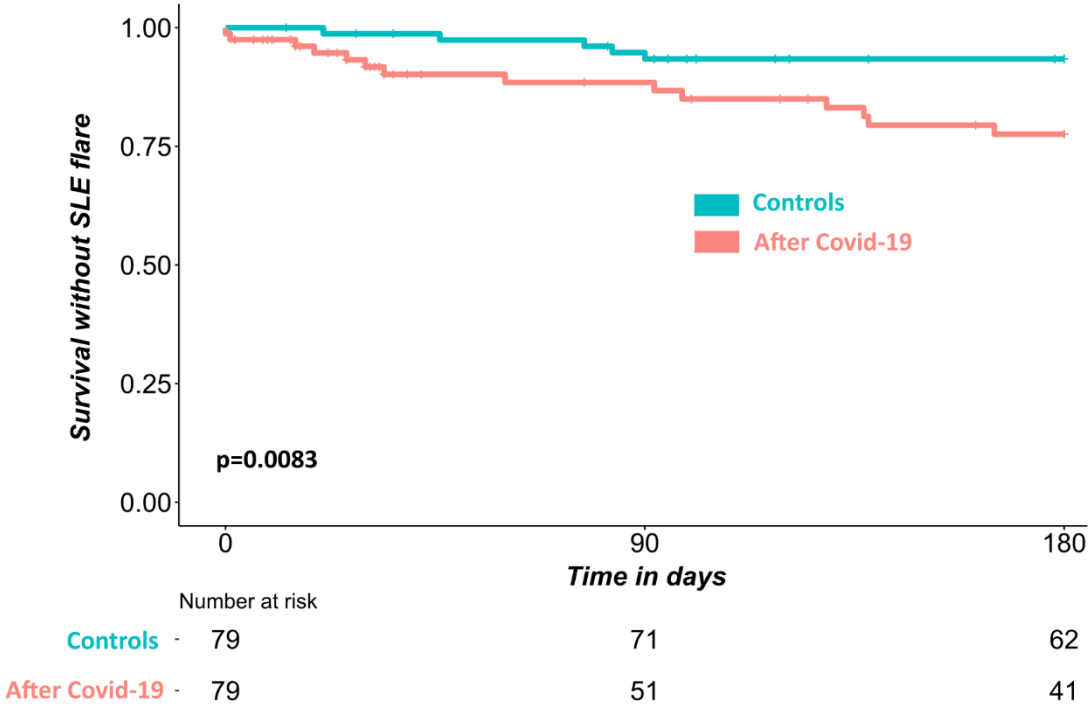
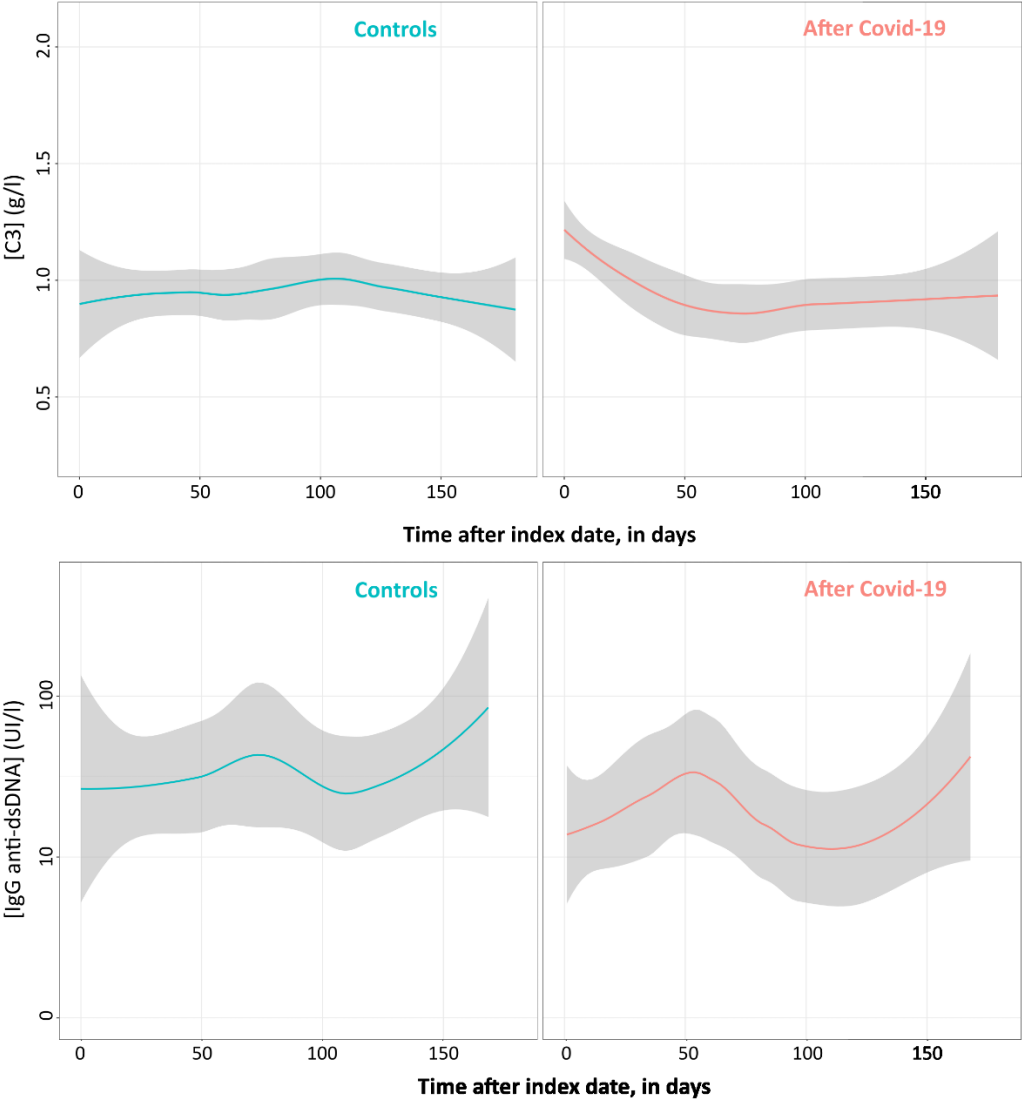


Figure 2: Kaplan-Meier curves of the survival without flare among the matched populations.



P value was calculated with the log rank test.

Figure 3: C3 levels and anti-dsDNA IgG titers



C3 levels after index date in the matched populations (upper panel). Anti-dsDNA IgG titers after index date among patients positive for anti-dsDNA autoantibodies (lower panel) in the matched populations. Lines represent the fitted LOESS model with its confidence interval. A log10 scale is used for the Y axis in the lower panel.

ELECTRONIC SUPPLEMENTARY MATERIALS

SLE patients with COVID-19	
n = 81	
Age, in years, median (Q1-Q3)	56.4 [42.2-68.3]
Female gender, n (%)	76 (93.8)
COVID-19 episode	
Prior anti-SARS-CoV2 vaccine, n (%)	9 (11.1)
CT-severity score, (33 missing), n (%) :	
< 10 %	8 (16.7)
10-25%	17 (35.4)
25-50 %	12 (25.0)
50-75%	9 (18.8)
> 75%	2 (4.2)
Treatment of COVID-19	
Oxygen, n (%)	54 (66.7)
More than > 6l.min ⁻¹ of oxygen, n (%)	31 (38.3)
Non-invasive mechanical ventilation*, n (%)	18 (27.8)
Invasive mechanical ventilation, n (%)	14 (17.5)
ECMO, n (%)	1 (1.3)
Dexamethasone , n (%)	23 (28.8)
Anti-cytokine mAb, n (%)	5 (6.3)
Anti-SARS-CoV2 specific mAb, n (%)	6 (7.6)
Anticoagulant treatment, n (%)	27 (35.1)
Convalescent plasma therapy, n (%)	2 (2.5)
Outcome	
Length of the hospital stay, in days (median [Q1-Q3])	9.5 [6.0-20.0]
Thrombosis, n (%)	6 (7.8)
Death during hospital stay, n (%)	8 (9.8)

Table S1: Characteristics of the COVID-19 episode

Q1: first quartile; Q3: third quartile; ECMO: extracorporeal membrane oxygenation; mAb: monoclonal antibody; *non-invasive mechanical ventilation includes high flow oxygen therapy.

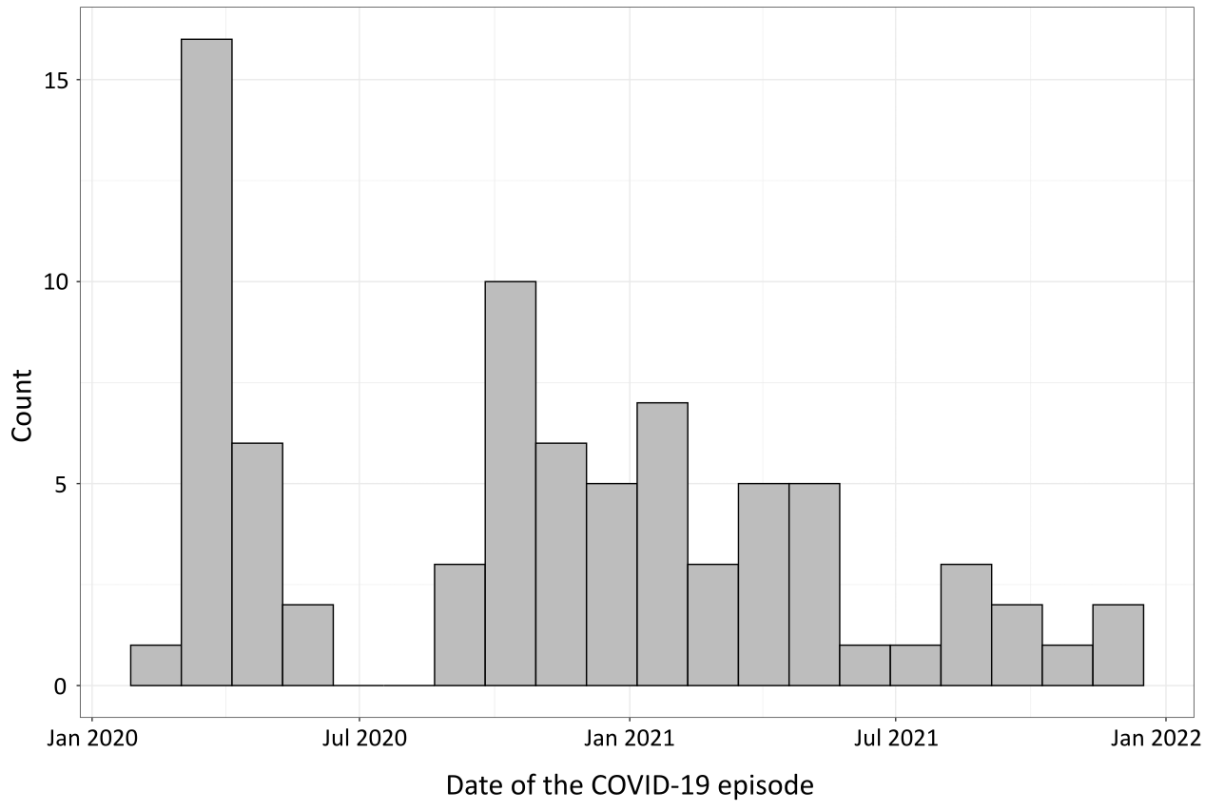


Figure S2: Temporal distribution of the COVID-19 episodes.

Incidence of immune-mediated inflammatory diseases in sepsis survivors. Study 7.

The previous studies of this thesis focused mostly about the interplay between SARS-CoV-2 (either infection or vaccination) and SLE. However, these two conditions are just a particular case of the more general relationship that links infectious diseases and IMIDs. We saw in the COVALUS project and in the case report of the COVID-19 induced SLE flare that one possible way for these two entities to communicate is through pro-inflammatory cytokines. Then, we hypothesized that the pro-inflammatory cytokines produced by the immune system during an infection could trigger IMID onset.

To test our hypothesis, we decided to go back to the French nationwide medico-administrative hospital database (the PMSI) to study the risk of IMID onset after severe infections. To do so, we studied the rate of systemic IMID onset among sepsis survivors compared to acute myocardial infarction (AMI) survivors, after excluding patients with previously diagnosed IMIDs. We chose sepsis as a marker of severe infection and because it implies the release of pro-inflammatory cytokines which are responsible for most of the systemic symptoms observed in sepsis.

We included 62,257 who experienced a sepsis in France in 2020 and the same number of AMI patients matched on age ± 2 years, gender, and comorbidities thanks to a random, exact matching process. In these patients we compared the rate of IMID onset overall and for each IMID with a marginal Cox model. We observed an intriguing, and extremely high incidence of IMIDs among survivors of severe infections. I conducted this study together with Aloïs Hélyary, who were realizing his master thesis in our research unit. We submitted the manuscript as an Original Article on July 31, 2023, to the *Journal of Internal Medicine*.

Study 7

High incidence of immune-mediated inflammatory diseases in sepsis survivors: a nationwide exposed-non-exposed epidemiological study

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Financial support Aloïs Helary was supported by a research grant from the Année Recherche, Ministère de la Santé. Arthur Mageau was supported by a PhD fellowship provided by Fondation pour la Recherche Médicale (FDM202106013488). This work was supported by the Agence Nationale de la Recherche (n°ANR-21-COVR-0034 COVALUS), the University Paris Cité and the Assistance Publique Hôpitaux de Paris

Disclosures None

Key words Sepsis; immune-mediated inflammatory diseases; incidence; post-sepsis

ABSTRACT

Importance: Can sepsis, a life-threatening organ dysfunction caused by a dysregulated host response to infection, trigger immune-mediated inflammatory diseases (IMIDs) onset?

Objective: To analyze the incidence of IMIDs in patients who survived sepsis.

Design: Nationwide exposed-non-exposed epidemiological study.

Setting: Comprehensive data collected from the national medical-administrative database, the PMSI (Programme de Médicalisation des Systèmes d'Information, Information system medicalization program) that provides a summary of diagnoses, procedures, and individual medical conditions at discharge from all French healthcare facilities.

Participants: All data on adult patients admitted for sepsis between January to November 2020, in any of the French healthcare facilities were retrieved from the database.

Exposure: Exposure was sepsis requiring hospitalization. Sepsis was defined by the combination of at least one code of infection and one code referring to an organ failure diagnosis or procedure. Patients with a first sepsis (i.e. exposed) diagnosed in a French hospital in 2020 were randomly matched (ratio 1/1) with patients admitted during the same period for acute myocardial infarction (i.e. non-exposed). An exact matching procedure taking age ± 2 years, gender, and comorbidities as matching variables was performed.

Main Outcome and Measure: The main outcome was a diagnosis of IMID based on specific ICD-10 codes during a 9-month follow up. Only patients with i) a first diagnosis of sepsis (exposed) or AMI (non-exposed) in 2020 and ii) no history of IMIDs reported in PMSI between January 1, 2010 and the index stay were included.

Results: In France, the incidence rate of IMIDs after a sepsis in 2020 - analyzed in 62,257 patients – was of 7,956 [95CI 7,392-8,520] per 100,000 patient-years. As compared to the non-exposed admitted population, the IMID-free survival analysis showed an increased risk for IMIDs of 2.80 (HR; 95%CI [2.22-3.54]) starting from day 16 after admission. Risk of IMIDs following severe infection differed according to the nature of the autoimmune disease and were higher for immune thrombocytopenia (5.51 [1.97-15.4]), autoimmune hemolytic anemia (4.83 [1.45-16.1]) and ANCA associated vasculitis (4.66 [2.05-10.6]).

Conclusions and Relevance: Our study shows an unexpectedly high incidence of IMIDs among sepsis survivors.

KEY POINTS

Question: Are sepsis survivors at risk of immune-mediated inflammatory diseases?

Findings: In this matched cohort study that included more than 120,000 patients, the risk of IMIDs was higher in patients exposed to sepsis as compared to unexposed (hazard ratio [95% confidence interval] = 2.80 [2.22-3.54])

Meaning: Sepsis survivors are at increased risk of IMIDs. IMIDs contribute to the burden of noncommunicable diseases occurring in patients who survived the acute phase of sepsis.

INTRODUCTION

Sepsis affects 50 million individuals worldwide and is associated with more than 10 million deaths annually ¹. Most sepsis survivors experience long-term morbidity with significant increased healthcare needs and one third will still die within one year of hospital discharge ². Although the long-term consequences of sepsis are increasingly recognized, epidemiologic data on the incidence and nature of sequelae in survivors are limited.

Several elements support a link between severe infections and immune-mediated inflammatory diseases (IMIDs). First, overproduction of proinflammatory cytokines is central to the pathogenesis of both IMIDs and severe infections ³⁻⁹. Second, neutralizing anti-cytokine autoantibodies, reported in the setting of both IMIDs (such as systemic lupus erythematosus) and severe infections (such as severe COVID-19), play a Janus effect on IMIDs activity and infection risk ¹⁰⁻¹². Third, patients with sepsis exhibit a high prevalence of autoantibodies against self-antigens that, which, because of their role in autoimmune diseases, may pave the way for the development of IMIDs in sepsis survivors ¹³⁻¹⁵. Fourth, the association between some specific pathogens and some IMIDs has been well demonstrated, as recently with Epstein-Barr virus and multiple sclerosis ¹⁶.

Previous studies on the temporal immune dynamics in sepsis have shown that immune dysregulation associated with severe infection diminishes over time with recovery but persists after discharge in two-thirds of surviving patients and is associated with worse long-term outcomes ^{17,18}. Hypothesizing that persistent immune dysregulation associated with sepsis may be involved in the development of IMIDs, we sought for this association using a nationwide database to analyze the incidence of IMIDs after sepsis.

MATERIAL AND METHODS

Data source

Comprehensive data on all exposed and non-exposed patients admitted to all French hospitals from January 2011 to November 2020 were collected from the national medical-administrative database, the PMSI (*Programme de Médicalisation des Systèmes d'Information*, Information system medicalization program). The PMSI database provides a summary of diagnoses, procedures, and individual medical conditions at discharge from all French healthcare facilities ¹⁹. Each facility produces its own anonymous standardized data, which are then aggregated at the national level. Routinely collected medical data include principal and secondary diagnoses, coded according to the International Classification of Diseases, tenth revision (ICD-10), and medical procedures (e.g., radiological exams, technical care, surgical procedures) coded according to the *Classification Commune des Actes Médicaux* (CCAM, French common classification of medical procedures). Administrative data include

age, sex, year, length of hospital stay, and hospital site. In-hospital deaths are also reported. Since 2004, the budget of each hospital depends on the medical activity described in this specific program. The social insurance authority carries out regular checks to ensure that the data are correctly attributed. For patients admitted to intensive care units (ICUs), the severity illness at admission was assessed by using the Simplified Acute and Physiology Score II (SAPS II). The reliability and validity of PMSI data have been assessed elsewhere^{20–22}.

Definitions and study population

All diagnosis codes are listed in the **electronic supplementary material (ESM)**. Sepsis (exposed) was defined by the combination of i) a diagnosis code for infection (ICD-10 code A00-B99 + others) and ii) a diagnosis and/or procedure code consistent with organ failure, as previously reported^{21–23}. The comparator condition for sepsis must i) be common, ii) be severe enough to require admission and prolonged follow-up after discharge, iii) be captured by a clear and specific ICD-10 code, and iiiii) not require prescription of immune system-modifying treatment. Patients who experienced an acute myocardial infarction (AMI) meet all of these criteria and were considered as the unexposed control group. AMI was defined by ICD-10 code I21. IMIDs (outcomes) included immune thrombocytopenia (ITP), autoimmune hemolytic anemia (AHAI), systemic lupus erythematosus (SLE), systemic sclerosis (SSs), Sjögren's syndrome (SS), antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, giant cell arteritis (GCA), polymyalgia rheumatica (PMR), rheumatoid arthritis (RA), spondyloarthritis (SpA), multiple sclerosis (MS), inflammatory bowel disease (IBD), Behçet's disease (BD). Only patients with i) a first diagnosis of sepsis (exposed) or AMI (non-exposed) in 2020 and ii) no history of IMIDs reported in PMSI between January 1, 2010, and the index stay were included. Demographics, underlying comorbidities, medical history (including diagnoses and procedures) and the updated Charlson comorbidity index (CCI)^{24,25} associated with the index stay were assessed.

Matching Procedure

Exact 1/1 random matching without replacement of exposed (i.e. sepsis) and unexposed (i.e. AMI) patients was performed on the basis of on age ± 2 years, sex, active cancer, active malignant hemopathy, HIV infection and organ transplant history (**Table S1**). Matching variables were putative confounding factors chosen *a priori* in all cases. Matching accuracy and efficacy were assessed by calculating the standardized differences for the matching variables between the two populations.

9-month IMIDs-free survival analysis

The first day of index stay for sepsis (exposed) or AMI (unexposed) in 2020 was defined as Day 0 (D_0). Censoring was performed at 9-month follow up, at last hospital stay or at death, whichever occurred first. The incidence of IMIDs was first assessed in the exposed and unexposed populations and compared with the incidence of IMIDs reported in the general population. Hazard ratios (HRs) of IMIDs-free survival between exposed (sepsis) and matched nonexposed (AMI) patients were then estimated. As the proportionality of the hazard - assessed graphically (**Figure S1**) – did not hold for the main outcome (IMDs), survival analyses were run starting i) from D_0 (whole period analysis) or ii) from D_{16} after admission, to the end of follow-up. Further sensitivity analyses were performed including i) a 6-month censoring (to account for follow-up gaps between the study groups) (**Table S2**), ii) the exclusion of patients with IMIDs diagnosed during the index stay (to account for death gaps between the study groups) (**Table S3**), and iii) the exclusion of patients with no evidence of prior hospital stay (to optimize the exclusion of patients with unreported IMIDs prior to the index stay) (**Table S4**). As requested during the reviewing process we did a post hoc analysis using competing risk models for clustered data taking into account death during the follow up as a competing event (more details in ESM, **Table S5**)²⁶.

Statistical analyses

Categorical variables are presented as counts (percentages). Quantitative variables are presented as mean (standard deviation) or median (first quartile–third quartile) for time variables. Differences between matched groups were assessed using standardized mean differences. The number of patient-years - defined as the sum of the duration of follow-up (in years) for each patient – and the incidence rate – defined as the number of events divided by the number of patient-years - were calculated for each group. Wald 95% confidence intervals (95CI) were calculated for the proportions. Hazard ratios (HRs) and their respective 95CIs were estimated using a marginal Cox proportional hazards model²⁷, according to populations matching. To account for remaining differences between groups despite matching, the estimated HRs were adjusted for ICU admission during the index stay. The Kaplan-Meier method was used to present 9-month IMID-free survival. All analyses were performed with SAS V.9.4 software. Kaplan-Meier curves were generated using R V.4.2.0 software with survival package.

Ethical aspects

In accordance with the French regulatory system for personal and medical data and with the approval of the French data protection authority (*Commission nationale de l'informatique et des libertés*, CNIL), our institution was granted access to the PMSI database according to MR-005.

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

RESULTS

Characteristics of patients experiencing sepsis

From January to November 2020, a diagnosis of sepsis and AMI was reported in 460,707 and 62,258 patients, respectively. According to the inclusion criteria, no patient had prior evidence of sepsis, AMI, or IMIDs. The overall characteristics of patients with sepsis and AMI were different, highlighting the need for a matching process for further comparison (**Table S1**). The matching process between sepsis (i.e. exposed) and AMI (i.e. unexposed) patients was successful in all but one case (n=62,257 sepsis patients matched with n=62,257 AMI patients among 62,258 patients with AMI in 2020). Notably, in-hospital mortality was higher in sepsis patients at both the index hospitalization (12.1% vs 4.5% in non-exposed patients) and 9-month follow-up (16.9% vs 6.0%). Rates of 9-month censoring differed between exposed (n=49,405; 79.4%) and unexposed (n=57061; 91.6%) patients. Remaining differences between exposed and unexposed matched populations are shown in **Table 1**.

Incidence of IMIDs following sepsis in 2020

In 2020, a total of 704 IMIDs occurred a median time of 19 days (IQR, 10.5-42.5) after a diagnosis of sepsis in 8849 patient-years (i.e. 9-month censoring) thus defining an overall incidence rate [95CI] of 7,956 [7,392-8,520] IMIDs per 100,000 patient-years in sepsis survivors. Using the incidence of IMIDs reported in the literature in the general population as a reference, we found that the incidence of IMIDs in sepsis survivors appeared to be 50- to 300-fold higher, depending on the type of IMID²⁸⁻⁴⁰. For example, the incidence of ITP, GCA, and SS in sepsis survivors was 938 [737-1139], 655 [487-824], and 339 [218-460] per 100 000 patient-years respectively compared with 2.92 [2.8-3.0]²⁸, 7.6 [5.9-9.8]³⁶, and 5.3 [4.5-6.1]³¹ in the general population (**Figure 1**).

9-month IMIDs-free survival analysis

9-month-free survival Kaplan-Meier curves comparing IMIDs onset between exposed and non-exposed patients showed that the proportional hazards assumption did not hold for the main analysis (**Figure 2, Figure S1**). Interestingly, the survival analysis showed, after adjustment for ICU admission and using IMIDs onset after AMI as reference, an increased risk for IMIDs after sepsis of 2.80 (HR; 95%CI [2.22-3.54]) starting from day 16 after admission. The adjusted HRs for the different IMIDs onset following sepsis are shown in **Figure 3**. Sensitivity analyses, performed after i) a 6-month censoring, ii) exclusion

of patients with IMIDs diagnosed during the index stay, iii) exclusion of patients without evidence of prior hospitalization were consistent with the main analysis (**Tables S2, S3, S4**). The post hoc analysis using competing risk models for clustered data taking death during follow up as a competing event showed a sub-distribution Hazard Ratio (sdHR) of 2.17 [1.43-3.27] for the period starting after day 16 for the risk of IMIDs onset after sepsis (**Table S5**). Of note, the risk of IMIDs after a sepsis depended on the type of the autoimmune disease. Indeed, the risk of IMIDs onset in sepsis survivors was higher for ITP (5.51 [1.97-15.4]), AIHA (HR 4.83 [1.45-16.1]), AAV (4.66 [2.05-10.6]), SLE (4.32 [1.49-12.5]), GCA (3.02 [1.26-7.22]), SpA (2.63 [1.16-5.98]), and IBD (2.36 [1.51-3.71]). Notably we found that the association between sepsis and IMIDs onset appeared well balanced across pathogen categories (**Figure 4**).

DISCUSSION

All patients with sepsis admitted to French hospitals over a 1-year period were enrolled in a study cohort to capture the incidence of IMIDs following sepsis. Our primary analysis of 60,167 patients with sepsis and 60,167 matched controls showed a dramatically high incidence rate of IMIDs after severe infection. To our knowledge, no large-scale comparative study of IMIDs after sepsis has been published so far.

The onset of IMIDs onset following sepsis was delayed over time and became apparent only after day 16 after admission. Such a time lag may reflect a transient immunosuppressive phase at the onset of sepsis, as previously reported⁴¹. Although bias in the survival analysis cannot be completely ruled out, sensitivity analyses confirmed the strong association between sepsis and IMIDs onset.

The choice of the control group was key in ensuring the reliability of our study. The control group had i) to be wide enough, ii) to involve inpatients with a pathology relatively severe, with a precise diagnosis, iii) to require the least possible involvement of immune system-modifying treatment and iv) to have enough follow-up. We figured out that acute myocardial infarction (AMI) was a good option. Although up to 30 % of the patients admitted for an AMI are readmitted in the 30 days following initial discharge⁴² medical monitoring and follow-up might also have been different between the two study groups. Our sensitivity analysis reducing the follow-up period to 6 months (**Table S2**) was consistent with the main analysis and thus limits the risk of a surveillance bias. On the other hand, the majority of patients in both groups were censored at 5 months follow-up, meaning that for most of them, information on the occurrence of IMIDs, whether positive or negative, were not available. However, and regardless of the AMI or sepsis group, IMIDs like ANCA-associated vasculitis or autoimmune hemolytic anemia – the most frequently IMIDs diagnosed after a sepsis - are severe condition that led directly to hospitalization in most cases. If some incident IMIDs have been missed in the follow-up, there is no reason for this hypothetical bias to be more pronounced in one group.

The validity of the IMIDs diagnoses need to be questioned. The coding list for the sepsis and the comorbidities is extensive but, PMSI data being strictly anonymous, we have no access to medical charts to gain more granularity. This may be particularly true when there is no specific marker for the diagnosis of IMIDs such as polymyalgia rheumatica (PMR). However, we tested the accuracy of the PMR coding diagnosis (M353) by reviewing the medical records of 227 consecutive patients admitted to our institution between 2017 and 2021 and confirmed the accuracy of the coding procedure in almost all cases (n = 212, 93.4%).

The majority of IMIDs occurred in the short-term post-infection period. The strength and temporal pattern of the association between sepsis and increased risk of IMIDs suggest a causal relationship. Some IMIDs have been associated with specific pathogens, such as SLE and multiple sclerosis with Epstein-Barr virus, or polyarteritis nodosa with hepatitis B ^{16,43–45}. No study to date examined the specific risk for IMIDs following sepsis in general, regardless of the pathogen involved. The association between sepsis and IMIDs onset appeared well balanced across pathogen categories and viruses, bacteria and parasites all induce multiple inflammatory cascades leading to the activation of innate and adaptive immune cells ⁴⁶. Pathogens can induce autoimmune disease through mechanisms involved in the breakdown of self-tolerance such as bystander activation, pathogen-induced necroptosis, epitope spreading, superantigen cross-linking and molecular mimicry ^{46,47}. Alternatively, patients who suffered from severe infection and IMIDs may share a common genetic susceptibility background. Our main analysis is based on admissions for sepsis in 2020 and thus used data collected during the first wave of COVID-19. Although this may have resulted in different follow-up of patients from usual, particularly those with long COVID, and less than usual follow-up for patients admitted with AMIs, our sensitivity analyses performed in comparison to patients with a sepsis stay in 2019 (i.e. prior the COVID-19 pandemics) remain unchanged (**Table S6**).

IMIDs differ in their clinical phenotype, tissue distribution and response to treatment ⁴⁸. Interestingly, the risk for IMIDs seems to be higher for ANCA-associated vasculitis, immune thrombocytopenia and autoimmune hemolytic anemia. Although thrombocytopenia is common in patients with sepsis ⁴⁹, the identification of antiplatelet autoantibodies already reported in this setting supports an immune-related process ⁵⁰. ANCA are an important biomarker for ANCA-associated vasculitis ⁵¹. ANCA target different components of human neutrophils. Pathogenic ANCA may be secondary to the release of neutrophilic enzymes triggered by infection. Production of other autoantibodies such as rheumatoid factor, antinuclear and antiphospholipid antibodies has also been described after severe infection ^{52–54}.

This study has several limitations. First, although the PMSI database links all hospital stays at the individual level, only in-hospital diagnoses and procedures are captured by the database. Second, IMIDs may have been diagnosed in outpatients before the index stay and a classification bias cannot

be excluded. However, our sensitivity analysis focusing on patients admitted before the index stay confirmed the main analysis. Third, we did not have access to medical records and cannot rule out misclassification bias. Fourth, we did not have access to immune-modifying treatments such as steroids that patients may have received during sepsis care. Fifth, our cohort consists only of admitted patients and an information bias cannot be excluded. This may indeed contribute to the higher incidence rate of IMIDs observed in our study as compared with the general population. The studies used as reference from the general population had different methods and populations: not only in-hospital like ours and coming, for some of them, from countries other than France. Finally, the exact delay between the diagnosis of sepsis and the diagnosis of IMIDs diagnosis was difficult to determine using the PMSI database.

In conclusion, our study shows an intriguing, unexpected and extremely high incidence of IMIDs among survivors of severe infections. Further studies are needed to investigate the relationship between severe infections and IMIDs. Coupling sound epidemiologic evidence with a comprehensive immune-monitoring approach should help to characterize the patterns of immune activation at sepsis onset that may pave the way to autoimmunity.

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TABLES

Table 1: Characteristics of the matched populations

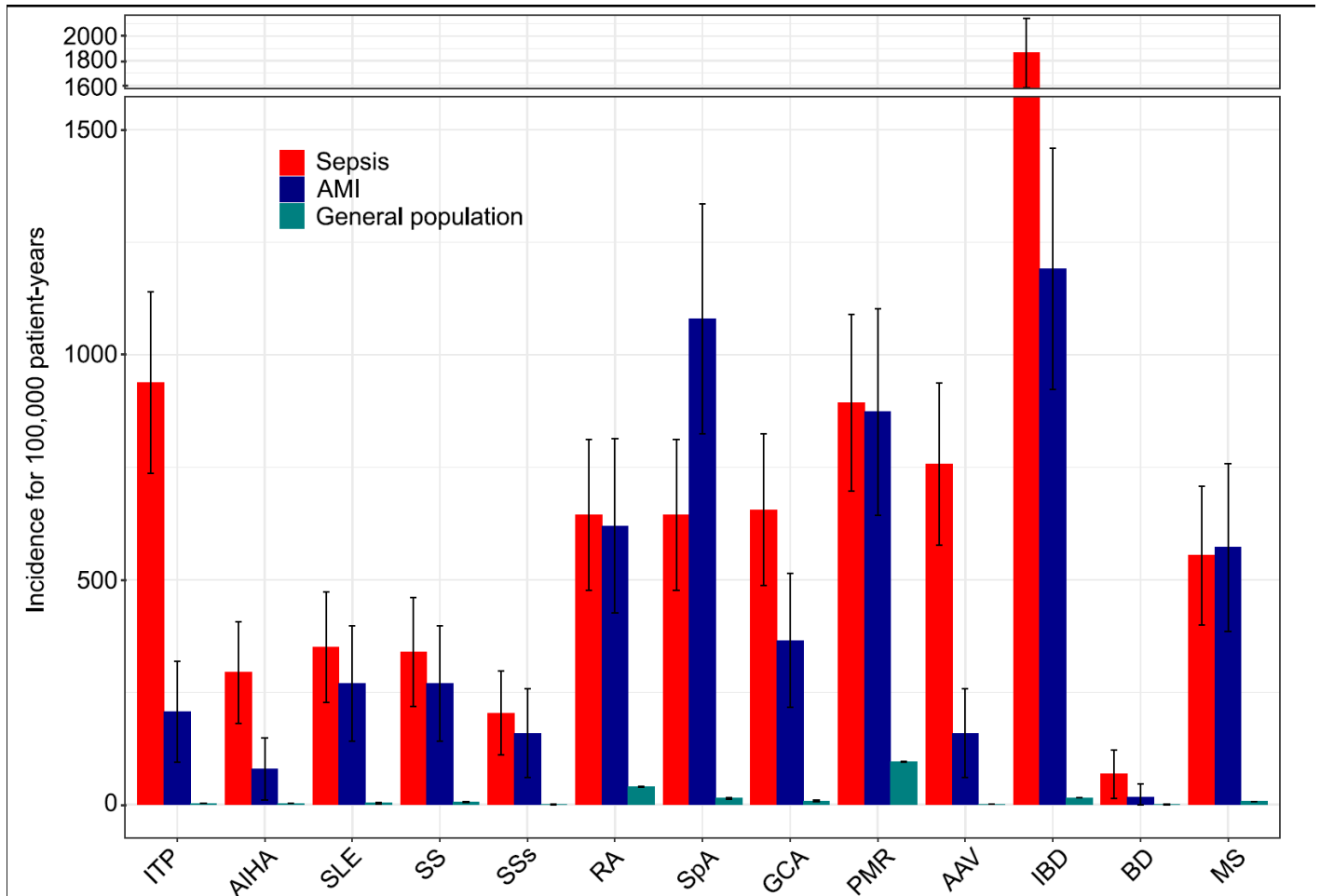
	Sepsis n = 62,257	Myocardial infarction n = 62,257	Absolute SMD
Age, years, mean (std) §	62.8 (14.0)	62.8 (14.0)	0.004
Gender, female, n (%) §	19,968 (32.1)	19,968 (32.1)	0.000
Event-associated hospital stay			
Duration of stay, days, median (Q1-Q3)	11 (6-18)	5 (3-7)	0.767
Intensive care unit admission, n (%)	47,135 (75.7)	21,756 (34.9)	0.900
SAPS-II score, mean (std) *	39.5 (22.1)	29.3 (20.3)	0.480
Organ failure associated procedures			
- Mechanical ventilation, n (%)	12,075 (19.4)	1,687 (2.7)	0.552
- Noninvasive ventilation, n (%)	10,091 (16.2)	715 (1.2)	0.552
- Hemodialysis for AKI, n (%)	2,216 (3.6)	160 (0.3)	0.243
- Pressor amine use, n (%)	10,288 (16.5)	1,697 (2.7)	0.481
Death during index hospital stay	7,525 (12.1)	2,813 (4.5)	0.277
Pathogens involved			
Bacteria, n (%)	22,207 (35.7)	NA	
Viruses, n (%)	35,248 (56.6)	NA	
- SARS-CoV2, n (%)	22,185 (35.6)	NA	
Other, n (%)	7,657 (12.3)	NA	
Unidentified, n (%)	27,284 (43.8)	NA	
Comorbidities/medical history			
CCI, mean (std)	3.2 (2.4)	2.2 (1.8)	0.472
Modified CCI, mean (std)	2.9 (2.1)	2.1 (1.7)	0.392
Obesity, n (%) †	6,683 (10.7)	4,938 (7.9)	0.100
Hypertension, n (%)	23,499 (37.8)	11,468 (18.4)	0.440
Diabetes mellitus, n (%)	10,481 (16.8)	4,510 (7.2)	0.298
Ischemic cardiopathy, n (%)	10,633 (17.1)	NA	0.457
Congestive heart failure, n (%)	9,664 (15.5)	1,684 (2.7)	0.642
Stroke or transient ischemic attack, n (%),	5,153 (8.3)	1,925 (3.1)	0.224
Chronic kidney disease, n (%)	3,973 (6.4)	989 (1.6)	0.247
- End-stage renal disease, n (%)	8864 (1.4)	259 (0.4)	0.103
HIV infection, n (%) §	189 (0.3)	189 (0.3)	0.000
Chronic pulmonary disease, n (%)	6,913 (11.1)	2,123 (3.4)	0.300
Active cancer, n (%) §	1,272 (2.0)	1,2172 (2.0)	0.000
Active malignant hemopathy, n (%) §	229 (0.4)	229 (0.4)	0.000
Hepatopathy, n (%)	3,370 (5.4)	641 (1.0)	0.250
Organ transplantation, n (%) §	25 (0.1)	25 (0.1)	0.000

*SAPS II is only available for ICU-admitted patients. †Obesity is defined by a body mass index > 30 kg/m².

§Matching variables. S MD, standardized mean difference; AKI, acute kidney injury; SAPS II, simplified acute physiology score; CCI, Charlson comorbidity index; HIV, human immunodeficiency virus; COPD, chronic obstructive pulmonary disease; NA, not appropriate; std: standard deviation; Q1, first quartile; Q3, third quartile.

FIGURE LEGENDS

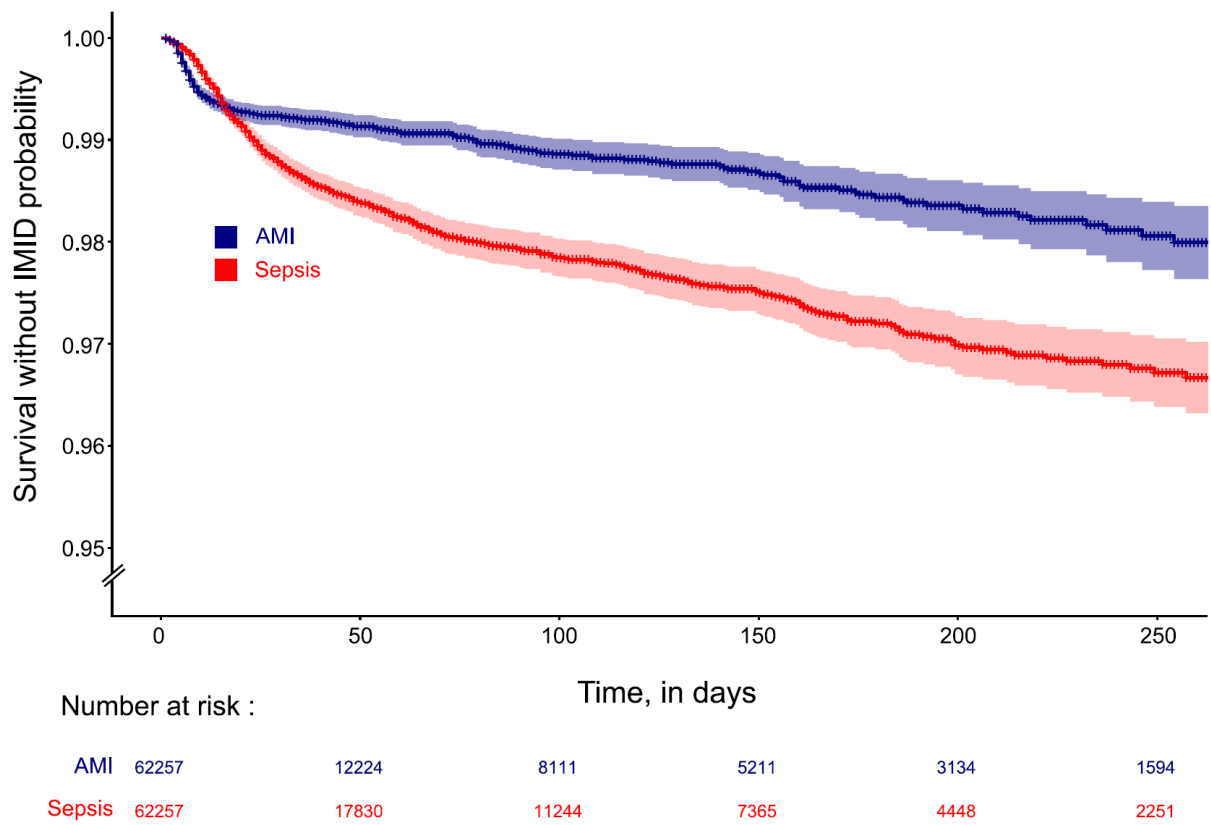
Figure 1 Incidence of immune-mediated inflammatory diseases (IMIDs) after sepsis and acute myocardial infarction (AMI) in patients without previous history of IMIDs.



Incidences are presented per 100,000 patient-years. IMID incidences in general population, as reported in literature is presented as reference (references 36 to 48).

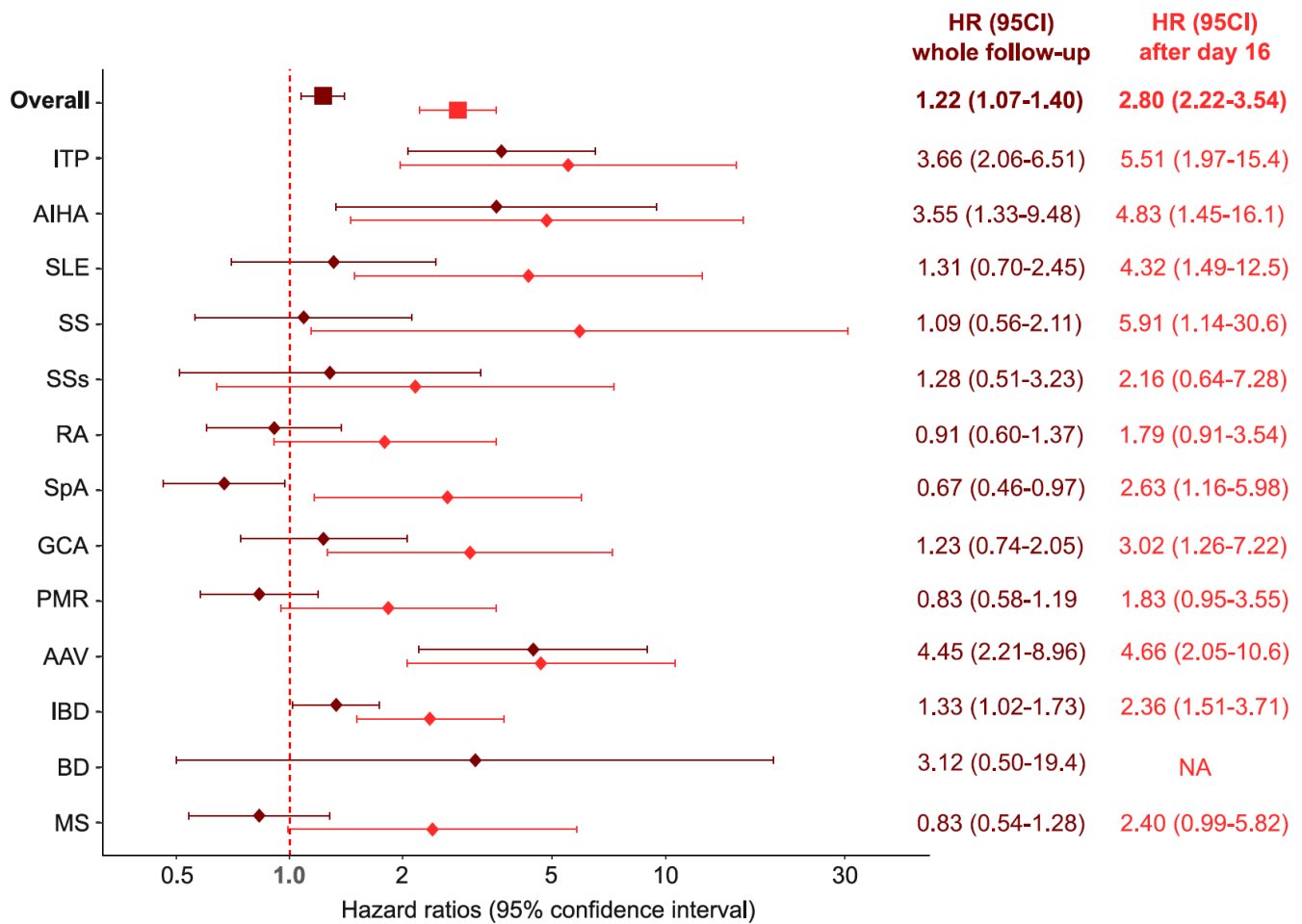
IMIDs, immune-mediated inflammatory diseases; ITP, immune thrombocytopenia; AIHA, autoimmune hemolytic anemia; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; SSs, systemic sclerosis; RA, rheumatoid arthritis; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; IBD, inflammatory bowel disease; BD, Behçet's disease; MS, multiple sclerosis.

Figure 2 Survival without IMIDs among matched populations



Bottom-left panel: un-zoomed Kaplan-Meier curve. AMI, acute myocardial infarction.

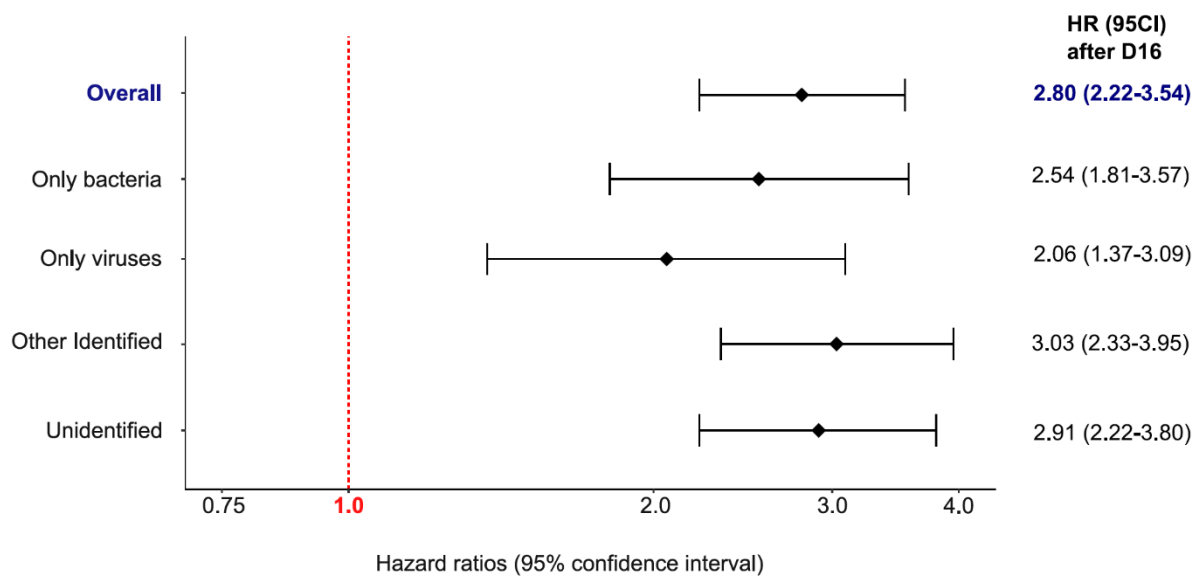
Figure 3 Risk for IMIDs onset after sepsis



Hazard ratios (HR) are given for the risk of IMIDs after sepsis compared to AMI. HR are calculated using a marginal Cox model, adjusting on ICU stay during the first index stay. A log₁₀-scale is used for the X axis. HRs are reported using the risk in non-exposed patients (AMI) as reference.

IMIDs, immune-mediated inflammatory diseases; ITP, immune thrombocytopenia; AIHA, autoimmune hemolytic anemia; SLE, systemic lupus erythematosus; SS, Sjögren’s syndrome; SSs, systemic sclerosis; RA, rheumatoid arthritis; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; IBD, inflammatory bowel disease; UC, ulcerative colitis; MS, multiple sclerosis.

Figure 4 IMIDs-free survival analysis according to the pathogen identified during sepsis.



HRs associated with bacteria (n=1,382 patients-years), virus (n=1,065 patients-years, including SARS-CoV-2 in most (88%) cases), other pathogens than virus or bacteria (n=2,816 patients-years) and no identified pathogen (n=3,585 patients-years) have been calculated considering the overall follow-up time. HRs are reported using the risk in non-exposed patients (AMI) as reference.

ELECTRONIC SUPPLEMENTARY MATERIALS

High incidence of immune-mediated inflammatory diseases in sepsis survivors: a nationwide exposed-non-exposed epidemiological study

1- Codes used for the analysis

1.1 Diagnosis codes used (from ICD-10th classification)

Label	ICD-10 codes
Infection	A00, A000, A001, A009, A01, A010, A011, A012, A013, A014, A02, A020, A021, A022, A028, A029, A03, A030, A031, A032, A033, A038, A039, A04, A040, A041, A042, A043, A044, A045, A046, A047, A048, A049, A05, A050, A051, A052, A053, A054, A058, A059, A06, A060, A061, A062, A063, A064, A065, A066, A067, A068, A069, A07, A070, A071, A072, A073, A078, A079, A08, A080, A081, A082, A083, A084, A085, A09, A090, A099, A15, A150, A151, A152, A153, A154, A155, A156, A157, A158, A159, A16, A160, A161, A162, A163, A164, A165, A167, A168, A169, A17, A170, A171, A178, A179, A18, A180, A181, A182, A183, A184, A185, A186, A187, A188, A19, A190, A191, A192, A198, A199, A20, A200, A201, A202, A203, A207, A208, A209, A21, A210, A211, A212, A213, A217, A218, A219, A22, A220, A221, A222, A227, A228, A229, A23, A230, A231, A232, A233, A238, A239, A24, A240, A241, A242, A243, A244, A25, A250, A251, A259, A26, A260, A267, A268, A269, A27, A270, A278, A279, A28, A280, A281, A282, A288, A289, A30, A300, A301, A302, A303, A304, A305, A308, A309, A31, A310, A311, A318, A319, A32, A320, A321, A327, A328, A329, A33, A34, A35, A36, A360, A361, A362, A363, A368, A369, A37, A370, A371, A378, A379, A38, A39, A390, A391, A392, A393, A394, A395, A398, A399, A40, A400, A401, A402, A403, A408, A409, A41, A410, A411, A412, A413, A414, A415, A418, A419, A42, A420, A421, A422, A427, A428, A429, A43, A430, A431, A438, A439, A44, A440, A441, A448, A449, A46, A48, A480, A481, A482, A483, A484, A488, A49, A490, A491, A492, A493, A498, A499, A50, A500, A501, A502, A503, A504, A505, A506, A507, A509, A51, A510, A511, A512, A513, A514, A515, A519, A52, A520, A521, A522, A523, A527, A528, A529, A53, A530, A539, A54, A540, A541, A542, A543, A544, A545, A546, A548, A549, A55, A56, A560, A561, A562, A563, A564, A568, A57, A58, A59, A590, A598, A599, A60, A600, A601, A609, A63, A630, A6300, A6308, A638, A64, A65, A66, A660, A661, A662, A663, A664, A665, A666, A667, A668, A669, A67, A670, A671, A672, A673, A679, A68, A680, A681, A689, A69, A690, A691, A692, A698, A699, A70, A71, A710, A711, A719, A74, A740, A748, A749, A75, A750, A751, A752, A753, A759, A77, A770, A771, A772, A773, A778, A779, A78, A79, A790, A791, A798, A799, A80, A800, A801, A802, A803, A804, A809, A81, A810, A811, A812, A818, A819, A82, A820, A821, A829, A83, A830, A831, A832, A833, A834, A835, A836, A838, A839, A84, A840, A841, A848, A849, A85, A850, A851, A852, A858, A86, A87, A870, A871, A872, A878, A879, A88, A880, A881, A888, A89, A90, A91, A92, A920, A921, A922, A923, A924, A928, A929, A93, A930, A931, A932, A938, A94, A95, A950, A951, A959, A96, A960, A961, A962, A968, A969, A98, A980, A981, A982, A983, A984, A985, A988, A99, B00, B000, B001, B002, B003, B004, B005, B007, B008, B009, B01, B010, B011, B012, B018, B019, B02, B020, B021, B022, B023, B027, B028, B029, B03, B04, B05, B050, B051, B052, B053, B054, B058, B059, B06, B060, B068, B069, B07, B08, B080, B081, B082, B083, B084, B085, B088, B09, B15, B150, B159, B16, B160, B161, B162, B169, B17, B170, B171, B172, B178, B179, B18, B180, B181, B182, B188, B189, B19, B190, B199, B20, B200, B201, B202, B203, B204, B205, B206, B207, B208, B209, B21, B210, B211, B212, B213, B217, B218, B219, B22, B220, B221, B222, B227, B23, B230, B231, B232, B238, B24, B24+0, B24+1, B24+9, B25, B250, B251, B252, B258, B259, B26, B260, B261, B262, B263, B268, B269, B27, B270, B271, B278,

Label	ICD-10 codes
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Type of pathogen	
SARS-CoV-2	U071, U0710, U711, U0712, U0714, U0715, U109
SARS-CoV-2 with virus identified	U0710, U0714
Gram negative bacilli	A00, A000, A001, A009, A01, A010, A011, A012, A013, A014, A02, A020, A021, A022+, A028, A029, A03, A030, A031, A032, A033, A038, A039, A04, A040, A041, A042, A043, A044, A045, A046, A053, A20, A200, A201, A202, A203, A207, A208, A209, A21, A210, A211, A212, A213, A217, A218, A219, A23, A230, A231, A232, A233, A238, A239, A24, A240, A241, A242, A243, A244, A25, A250, A251, A259, A26, A260, A267, A268, A269, A280, A281, A282, A37, A370, A371, A378, A379, A413, A415, A430, A438, A44, A440, A441, A448, A449, A480, A481, A482, A484, A492, A57, A000, A001, A014, A022, A030, A031, A038, A040, A043, A044, A053, B961, B962, B963, B964, B965, B966, B9680, B9681, B980, G000, J14, J150, J151, J155, J156, J201, M491, M4910, M4911, M4912,

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Gram-positive cocci	A050, A38, A40, A400, A401, A402, A403, A408, A409, A410, A411, A412, A544, A549, A38, A050, A400, A401, A402, A403, A409, A410, A412, A46, A483, A490, A491, B95, B950, B951, B952, B953, B954, B955, B956, B957, B958, G001, G002, G003, J020, J030, J13, J152, J153, J154, J202, L01, L010, L011, M000, M0000, M0001, M0002, M0003, M0004, M0005, M0006, M0007, M0008, M0009, M001, M0010, M0011, M0012, M0013, M0014, M0015, M0016, M0017, M0018, M0019, M002, M0020, M0021, M0022, M0023, M0024, M0025, M0026, M0027, M0028, M0029, M009, M0090, M0091, M0092, M0093, M0094, M0095, M0096, M0097, M0098, M0099, M463, M4630, M4632, M4633, M4634, M4635, M4636, M4637, M4638, M4639
<i>Staphylococcus aureus</i>	A410, B956
<i>Streptococcus pneumoniae</i>	A403, B953, G001, J13, M001
<i>Haemophilus influenzae</i>	A413; A492, B963; G000, J14, J201
<i>Neisseria meningitidis</i>	A39, A391, A392, A393, A394, A395, A398, A399
Tuberculosis	A15, A150, A151, A152, A153, A154, A155, A156, A157, A158, A159, A16, A160, A161, A162, A163, A164, A165, A167, A168, A169, A17, A170, A171, A178, A179, A18, A180, A181, A182, A183, A184, A185, A186, A187, A188, A19, A190, A191, A192, A198, A199, A15, A150, A151, A152, A153, A154, A155, A156, A157, A158, A159, A16, A160, A161, A162, A163, A164, A165, A166, A167, A168, A169, A17+, A170+, A171+, A178+, A179+, A18, A180+, A181, A182, A183, A184, A185, A186, A187+, A188, A19, A190, A191, A192, A198, A199
Fungal infections	B35, B350, B351, B352, B353, B354, B355, B356, B358, B359, B36, B360, B361, B362, B363, B368, B369, B37, B370, B371, B372, B373, B373+, B374, B375, B375+, B376, B376+, B377, B378, B379, B38, B380, B381, B382, B383, B384, B384+, B387, B388, B389, B39, B390, B391, B392, B393, B394, B395, B399, B40, B400, B401, B402, B403, B407, B408, B409, B41, B410, B417, B418, B419, B42, B420, B420+, B421, B427, B428, B429, B43, B430, B431, B432, B438, B439, B44, B440, B441, B442, B447, B448, B449, B45, B450, B451, B452, B453, B457, B458, B459, B46, B460, B461, B462, B463, B464, B465, B468, B469, B47, B470, B471, B479, B48, B480, B481, B482, B483, B484, B487, B488, B49, C840, J67, L22, P375
Parasite infections	A59, A590, A598, A599, A06, A060, A061, A062, A063, A064, A065+, A066+, A067, A068, A069, A07, A070, A071, A072, A073, A078, A079, J173, K231, O986, O988, A061, A063, A065, A067, A070, A071, A590, A060, A062, A064, A066, A068, A069, A072, A073, A078, A079, A081, A598, A599, B350, B351, B352, B353, B354, B355, B356, B358, B359, B360, B361, B362, B363, B50, B500, B508, B509, B51, B510, B518, B519, B52, B520, B528, B529, B53, B530, B531, B538, B54, B55, B550, B551, B552, B559, B56, B560, B561, B569, B57, B570, B570+, B571, B572, B573, B574, B575, B58, B580, B580+, B581, B581+, B582, B582+, B583, B583+, B588, B589, B59, B59+, B60, B600, B601, B602, B608, B6080, B6088, B64, B65, B650, B651, B652, B653, B658, B659, B66, B660, B661, B662, B663, B664, B665, B668, B669, B67, B670, B671, B672, B673, B674, B675, B676, B677, B678, B679, B68, B680, B681, B689, B69, B690, B691, B698, B699, B70, B700, B701, B71, B710, B711, B718, B719, B72, B73, B74, B740, B741, B742, B743, B744, B748, B749, B75, B76, B760, B761, B768, B769, B77, B770, B778, B779, B78, B780, B781, B787, B789, B79, B80, B81, B810, B811, B812, B813, B814, B818, B82, B820, B829, B83, B830, B831, B832, B833, B834, B838, B839, B85, B850, B851, B852, B853, B854, B86, B87, B870, B871, B872, B873, B874, B878, B879, B88, B880, B881, B882, B883, B888, B889, B89,
Viral infection (except SARS-CoV-2)	A08, A080, A081, A082, A083, A084, A60, A600, A601, A609, A630, A80, A800, A801, A802, A803, A804, A809, A81, A810, A811, A812, A818, A819, A82, A820, A821, A829, A83, A830, A831, A832, A833, A834, A835, A836, A838, A839, A84, A840, A841, A848, A849, A85, A850, A850+, A851, A851+, A852, A858, A86, A87, A870, A870+, A871, A871+, A872, A878, A879, A88, A880, A881,

Label	ICD-10 codes
	A888, A89, A90, A91, A92, A920, A921, A922, A923, A924, A928, A929, A93, A930, A931, A932, A938, A94, A95, A950, A951, A959, A96, A960, A961, A962, A968, A969, A98, A980, A981, A982, A983, A984, A985, A988, A99, B00, B000, B001, B002, B003, B003+, B004, B004+, B005, B007, B008, B009, B01, B010, B010+, B011, B011+, B012, B012+, B018, B019, B02, B020, B020+, B021, B021+, B022, B022+, B023, B027, B028, B029, B03, B04, B05, B050, B050+, B051, B051+, B052, B052+, B053, B053+, B054, B058, B059, B06, B060, B060+, B068, B069, B07, B08, B080, B081, B082, B083, B084, B085, B088, B09, B15, B150, B159, B16, B160, B161, B162, B169, B17, B170, B171, B172, B178, B18, B180, B181, B182, B188, B189, B19, B190, B199, B20, B200, B201, B202, B203, B204, B205, B206, B207, B208, B209, B21, B210, B211, B212, B213, B217, B218, B219, B22, B220, B221, B222, B227, B23, B230, B231, B232, B238, B24, B24+0, B24+1, B24+9, B25, B250, B250+, B251, B251+, B252, B252+, B258, B259, B26, B260, B260+, B261, B261+, B262, B262+, B263, B263+, B268, B268, B269, B27, B270, B271, B278, B279, B30, B300, B300+, B301, B301+, B302, B303, B303+, B308, B308+, B309, B33, B330, B331, B332, B333, B334+, B338, B34, B340, B341, B342, B343, B344, B348, B349, B91, B941, B942, B970, B971, B972, B973, B974, B975, B976, B977, B978, G051, G020, I411, J09, J10, J100, J101, J108, J11, J110, J111, J118, J12, J120, J121, J122, J123, J128, J129, J171, B17.9, J203, J204, J205, J206, J207, J210, J211, K2380, K770, K8700, K871, K93820, K93840, M014, M0140, M0141, M0142, M0143, M0144, M0145, M0146, M0147, M0148, M0149, M015, M0150, M0151, M0159, M0158, M0157, M0156, M0155, M0154, M0153, M0152, O987, O985, O984, P351
Flu (<i>Influenzae virus</i>)	J09, J10, J100, J101, J108, J11, J110, J111, J118
Organ failure (OF)	
Cardiovascular OF	E86, E872, I95, I951, I958, I959, I981, R55, R571, R57, R570, R572, R578, R579, R65, R651, R659, R092
Haematological OF	D65, D689, D695, D696, D762
Kidney OF	N17x, N19, R392, R34
Liver OF	K72, K720, K729, R17
Neurological OF	F05, F050, F058, F059, F079, F09, G934, R40, R400, R401, R4018, R402, R4028, R410, R451
Respiratory OF	J80, J951, J952, J96, J960x, R230
Auto-immune diseases	
Immune thrombocytopenia	D693
Autoimmune hemolytic anemia	D591
Systemic lupus erythematosus	M32x
Systemic sclerosis	M340, M341, M348, M349
Sjogren syndrome	M350
Inflammatory myopathy	M608
Giant cell arteritis	M315, M316
Polymyalgia rheumatica	M353
Rheumatoid arthritis (seropositive)	M05x
Overlap syndrome	M351
ANCA-associated vasculitis	M301, M317, M313
Guillain-Barre syndrome	G610
Sarcoidosis	D86x

Label	ICD-10 codes
Behcet disease	M352
Kawasaki syndrome	M303
Takayasu disease	M314
Crohn disease	K50x
Ulcerative colitis	K51x
Multiple sclerosis	G35
Hashimoto's disease	E063
Grave's disease	E050
Type 1 diabetes	E10x
Still disease	M061
Psoriasis	L40x
Pemphigoid syndrome	L120
Spondyloarthritis	M45x
Comorbidities	
Obesity	E6604, E6605, E6606, E6607, E6614, E6615, E6616, E6617, E6624, E6625, E6626, E6627, E6684, E6685, E6686, E6687, E6694, E6695, E6696, E6697
Hypertension	I10
Diabetes	E10x, E11x, E12x, E13x, E14x, O24x
Complicated diabetes	E100, E101, E102, E103, E104, E105, E106, E107, E108, E110, E111, E112, E113, E114, E115, E116, E117, E118, E1100, E1110, E1120, E1130, E1140, E1150, E1160, E1170, E1180, E1108, E1118, E1128, E1138, E1148, E1158, E1168, E1178, E1188, E120, E121, E122, E123, E124, E125, E126, E127, E128, E130, E131, E132, E133, E134, E135, E136, E137, E138, E140, E141, E142, E143, E144, E145, E146, E147, E148
Ischemic cardiomyopathy	I21x, I20x, I22x, I24x, I25x, Z8671, Z951
Congestive heart failure	I099, I110, I130, I132, I255, I42x, I43x, I50x
Stroke or transient ischemic attack (TIA)	F01x, G45x, G46x, I63x, I64, I693, Z8660, Z8670
Chronic kidney disease	N183, N184, N185, N180, N188, N189
Stage 3	N183
Stage 4	N184
Stage 5	N180, N185, Z49, Z2992
HIV infection	B20x, B21x, B22x, B23x, B24x, Z21x
Severe cognitive impairment	F00x, F01x, F02x, F03x, F051, F1073, F1173, F1273, F1373, F1473, F1573, F1673, F1773, F1873, F1973, F311 G30x
Chronic pulmonary disease	I278, I279, J41x, J42x, J43x, J44x, J45x, J47x, J60x, J61x, J62x, J63x, J64x, J65x, J66x, J67x, J99x, J684, J701, J703, J841, J961
Chronic obstructive pulmonary disease (COPD)	J41x, J42x, J43x

Label	ICD-10 codes
Cancer	C00, C000, C001, C002, C003, C004, C005, C006, C008, C009, C01, C02, C020, C021, C022, C023, C024, C028, C029, C03, C030, C031, C039, C04, C040, C041, C048, C049, C05, C050, C051, C052, C058, C059, C06, C060, C061, C062, C068, C069, C07, C08, C080, C081, C088, C089, C09, C090, C091, C098, C099, C10, C100, C101, C102, C103, C104, C108, C109, C11, C110, C111, C112, C113, C118, C119, C12, C13, C130, C131, C132, C138, C139, C14, C140, C142, C148, C15, C150, C151, C152, C153, C154, C155, C158, C159, C16, C160, C161, C162, C163, C164, C165, C166, C168, C169, C169+0, C169+8, C17, C170, C171, C172, C173, C178, C179, C18, C180, C181, C182, C183, C184, C185, C186, C187, C188, C189, C189+0, C189+8, C19, C20, C21, C210, C211, C212, C218, C22, C220, C221, C222, C223, C224, C227, C229, C23, C24, C240, C241, C248, C249, C25, C250, C251, C252, C253, C254, C254+0, C254+8, C257, C258, C259, C259+0, C259+8, C26, C260, C261, C268, C269, C30, C300, C301, C31, C310, C311, C312, C313, C318, C319, C32, C320, C321, C322, C323, C328, C329, C33, C34, C340, C341, C342, C343, C348, C349, C37, C38, C380, C381, C382, C383, C384, C388, C39, C390, C398, C399, C40, C400, C401, C402, C403, C408, C409, C41, C410, C411, C412, C413, C414, C418, C419, C43, C430, C431, C432, C433, C434, C435, C436, C437, C438, C439, C44, C440, C441, C442, C443, C444, C445, C446, C447, C448, C449, C45, C450, C451, C452, C457, C459, C46, C460, C461, C462, C463, C467, C468, C469, C47, C470, C471, C472, C473, C474, C475, C476, C478, C479, C48, C480, C481, C482, C488, C49, C490, C491, C492, C493, C494, C495, C496, C498, C499, C500, C501, C502, C503, C504, C505, C506, C508, C509, C51, C510, C511, C512, C518, C519, C52, C53, C530, C531, C538, C539, C54, C540, C541, C542, C543, C548, C549, C55, C56, C57, C570, C571, C572, C573, C574, C577, C578, C579, C58, C60, C600, C601, C602, C608, C609, C61, C62, C620, C621, C629, C63, C630, C631, C632, C637, C638, C639, C64, C65, C66, C67, C670, C671, C672, C673, C674, C675, C676, C677, C678, C679, C68, C680, C681, C688, C689, C69, C690, C691, C692, C693, C694, C695, C696, C698, C699, C70, C700, C701, C709, C71, C710, C711, C712, C713, C714, C715, C716, C717, C718, C719, C72, C720, C721, C722, C723, C724, C725, C728, C729, C73, C74, C740, C741, C749, C750, C751, C752, C753, C754, C755, C758, C759, C76, C760, C761, C762, C763, C764, C765, C767, C768, C81, C810, C811, C812, C813, C814, C817, C819, C82, C820, C821, C822, C823, C824, C825, C826, C827, C829, C83, C830, C831, C832, C833, C834, C835, C836, C837, C838, C839, C84, C840, C841, C842, C843, C844, C845, C846, C847, C848, C849, C85, C850, C851, C852, C857, C859, C86, C860, C861, C862, C863, C864, C865, C866, C88, C880, C881, C882, C883, C884, C887, C889, C90, C900, C901, C902, C903, C91, C910, C911, C912, C913, C914, C915, C916, C917, C918, C919, C92, C920, C921, C922, C923, C924, C925, C926, C927, C928, C929, C93, C930, C931, C932, C933, C937, C939, C94, C940, C941, C942, C943, C944, C945, C946, C947, C95, C950, C951, C952, C957, C959, C96, C960, C961, C962, C963, C964, C965, C966, C967, C968, C969, C97
Metastatic cancer	C77x, C78x, C79x, C80x
Malignant hemopathy	B211, C81x, C82x, C83x, C84x, C85x, C86x, C88x, C90x, C91x, C92x, C93x, C94x, C95x, C96x
Chronic liver disease	B18x, I850, I859, I864, I982, K700, K702, K703, K709, K711, K713, K714, K715, K717, K721, K729, K73x, K74x, K76x, Z944,
Chronic liver disease with portal hypertension complication	K711, I850, I982
Hemiplegia or paraplegia	G114, G800, G801, G802, G81x, G82x, G830, G834
Digestive ulcer	K25x, K26x, K27x, K28x

1.2 CCAM codes (Classification Commune des Actes Médicaux, General coding of medical procedures) for the identification of organ failures and transplantation procedures

Label	CCAM codes
Organ failure (OF) associated procedures	
Cardiovascular OF	
Pressor amine use	EQLF0010, EQLF0030
Fluid resuscitation	EQLF0020
Cardiopulmonary resuscitation	DKMD0010, DKMD0020
Renal OF	
Hemodialysis for acute kidney failure	JVJF0020, JVJF0050
Respiratory OF	
Mechanical ventilation	GELD0040, GLLD0050, GLLD0060, GLLD0080, GLLD0130, GLLD0150, ZZLB0040
Noninvasive ventilation	GLLD0020, GLLD0030, GLLD0120, GLLD0190, GLLP0030
Prone position	GLLD0040
Oxygen administration	GLLD0170
Transplantation associated procedures	
Heart transplantation	DZEA002, DZEA003, DZEA001, DZEA004, DZFA004
Kidney transplantation	JAEA0030
Liver transplantation	HLEA002, HLEA001
Lung transplantation	GFEA005, GFEA002, GFEA007, GFEA004, GFEA001, GFEA006

2- Characteristics of the unmatched populations

	Sepsis n = 460,707	AMI n = 62,258
Age, years, mean (std)	63.8 (23.5)	62.8 (14.0)
Gender, female, n (%)	218,101 (47.3)	19,969 (32.1)
Event-associated hospital stay		
Duration of stay, days, median (Q1-Q3)	11 (6-18)	5 (3-7)
Intensive care unit admission, n (%)	110,353 (23.9)	21,728 (34.9)
SAPS-II score, mean (std) *	40.2 (22.0)	29.3 (20.3)
Organ failure associated procedures		
Mechanical ventilation, n (%)	56,628 (12.7)	1,687 (2.7)
Noninvasive ventilation, n (%)	55,653 (12.1)	715 (1.1)
Hemodialysis for AKI, n (%)	10,355 (2.2)	160 (0.3)
Pressor amine use, n (%)	51,369 (11.1)	1,697 (2.7)
Pre-event stay, n (%)	390,991 (84.9)	40,247 (64.5)
Interval between event and last stay, days, median (Q1-Q3)	18 (8-62)	8 (5-32)
Comorbidities/medical history		
CCI, mean (std)	4.2 (2.9)	2.2 (1.8)
Modified CCI, mean (std)	3.9 (2.7)	2.1 (1.7)
Obesity, n (%)†	33,557 (7.3)	4,938 (7.9)
Hypertension, n (%)	182,836 (39.7)	11,468 (18.4)
Diabetes mellitus, n (%)	70,418 (15.3)	4,510 (7.2)
Ischemic cardiopathy, n (%)	70,925 (15.4)	NA
Congestive heart failure, n (%)	73,810 (16.0)	1,684 (2.7)
Stroke or transient ischemic attack, n (%)	40,523 (8.8)	1,936 (3.1)
Chronic kidney disease, n (%)	33,567 (7.3)	989 (1.6)
End-stage renal disease, n (%)	5,767 (1.3)	259 (0.4)
HIV infection, n (%)	2,387 (0.5)	189 (0.3)
Chronic pulmonary disease, n (%)	47,805 (10.4)	2,123 (3.4)
Active cancer, n (%)	75,031 (16.3)	1,272 (2.0)
Active malignant hemopathy, n (%)	13,002 (2.8)	229 (0.4)
Hepatopathy, n (%)	17,810 (3.9)	641 (1.1)
Organ transplantation, n (%)	846 (0.2)	25 (0.04)

*SAPS II is only available for ICU-admitted patients. AKI, acute kidney injury; SAPS II, simplified acute physiology score; CCI, Charlson comorbidity index; HIV, human immunodeficiency virus; COPD, chronic obstructive pulmonary disease; Q1, first quartile; Q3, third quartile.

3- Proportional hazard hypothesis assessment

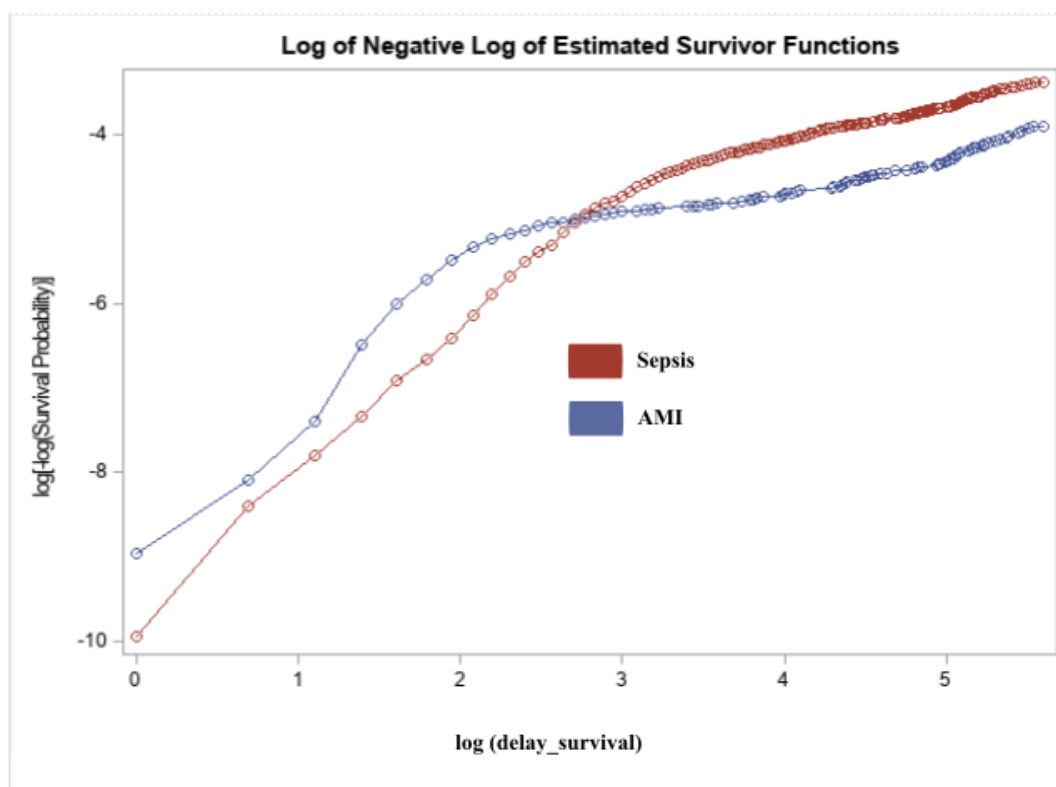


Figure S1: Log-log survival plot for the graphical assessment of the proportional hazard hypothesis for the main outcome (onset of any IMIDs) after sepsis or AMI

4-Sensitivity analyses

4.1- 6-month IMIDs-free survival

	HR (95% CI)	p-value
Overall	1.22 (1.07-1.40)	<0.0001
ITP	3.64 (2.05-6.47)	<0.0001
AIHA	3.55 (1.33-9.48)	0.012
SLE	1.29 (0.69-2.42)	0.43
SS	1.07 (0.55-2.08)	0.85
SSs	1.19 (0.45-3.14)	0.72
RA	0.89 (0.59-1.35)	0.59
SpA	0.68 (0.46-0.99)	0.04
GCA	1.22 (0.73-2.02)	0.45
PMR	0.80 (0.56-1.15)	0.23
AAV	4.98 (2.28-10.9)	<0.0001
IBD	1.38 (1.05-1.81)	0.022
BD	3.12 (0.50-19.4)	0.22
MS	0.84 (0.54-1.30)	0.43

Table S2: 6-months censorship IMID-free survival analysis

Hazard ratios (HR) are given for the risk of IMIDs after sepsis compared to myocardial infarction. HR are calculated using a marginal Cox model, adjusting on ICU stay during the first index stay.

IMIDs, immune-mediated inflammatory diseases; ITP, immune thrombocytopenia; AIHA, autoimmune hemolytic anemia; SLE, systemic lupus erythematosus; SS, Sjögren’s syndrome; SSs, systemic sclerosis; RA, rheumatoid arthritis; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; IBD, inflammatory bowel disease; BD, Behçet’s disease; MS, multiple sclerosis.

4.2- 9-month IMIDs-free survival after exclusion of patients with IMIDs occurring during the index stay

	Whole period		After D16	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Overall	1.05 (0.83-1.32)	0.69	1.40 (1.08-1.81)	0.011
ITP	2.31 (1.05-5.09)	0.037	4.48 (1.45-13.9)	0.009
AIHA	1.88 (0.53-6.62)	0.32	3.52 (0.78-15.8)	0.10
SLE	0.86 (0.29-2.53)	0.78	1.18 (0.34-4.08)	0.79
SS	3.56 (0.39-32.6)	0.26	3.28 (0.34-31.2)	0.30
SSs	0.53 (0.14-1.89)	0.32	0.68 (0.18-2.56)	0.57
RA	0.76 (0.38-1.53)	0.09	1.02 (0.50-2.09)	0.95
SpA	0.44 (0.21-0.91)	0.026	0.75 (0.33-1.70)	0.49
GCA	0.68 (0.26-1.74)	0.42	0.91 (0.32-2.58)	0.83
PMR	0.81 (0.44-1.50)	0.49	0.92 (0.44-1.90)	0.82
AAV	3.91 (1.62-9.43)	0.0024	3.91(1.62-9.43)	0.0024
IBD	1.04 (0.66-1.65)	0.86	1.14 (0.71-1.85)	0.59
BD	NA	NA	NA	NA
MS	0.51 (0.19-1.34)	0.17	1.10 (0.39-3.07)	0.86

HR is given for risk of IMIDs after a sepsis compared to a myocardial infarction and was calculated using a marginal Cox proportional hazard model after adjustment for ICU admission during the index stay.

IMIDs, immune-mediated inflammatory diseases; ICU, intensive care unit; ITP, immune thrombocytopenia; AIHA, autoimmune hemolytic anemia; SLE, systemic lupus erythematosus; SS, Sjögren’s syndrome; SSs, systemic sclerosis; RA, rheumatoid arthritis; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; IBD, inflammatory bowel disease; HR, hazard ratio.

Table S3: IMID-free survival analysis after exclusion of patients with IMIDs onset occurring during the index stay

Hazard ratios (HR) are given for the risk of IMIDs after sepsis compared to myocardial infarction. HR are calculated using a marginal Cox model, adjusting on ICU stay during the first index stay.

4.3- 9-month IMIDs-free survival in patients who had at least one prior admission before the index stay

n= 51,890 in the sepsis group and n= 40,246 in the AMI group

	Whole period		After D16	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Overall	1.16 (1.00-1.35)	0.051	2.50 (1.91-3.28)	<0.0001
ITP	3.37 (1.69-6.74)	0.0006	3.45 (1.12-9.71)	0.019
AIHA	3.41 (0.97-12.0)	0.056	9.44 (1.26-70.9)	0.029
SLE	1.50 (0.71-3.17)	0.29	5.38 (1.26-23.1)	0.023
SS	0.99 (0.47-2.05)	0.97	8.45 (0.94-75.8)	0.057
SSs	1.22 (0.34-4.38)	0.76	2.87 (0.53-15.5)	0.22
RA	0.91 (0.58-1.45)	0.70	1.65 (0.75-3.64)	0.21
SpA	0.75 (0.48-1.18)	0.21	3.31 (1.16-9.44)	0.025
GCA	1.12 (0.65-1.93)	0.69	2.88 (1.15-7.26)	0.024
PMR	0.69 (0.47-1.02)	0.06	1.64 (0.75-3.60)	0.22
AAV	7.17 (2.49-20.7)	0.0003	4.71 (1.59-14.01)	0.005
IBD	1.21 (0.89-1.64)	0.22	1.91 (1.16-3.15)	0.011
BD	1.42 (0.29-6.90)	0.42	NA	NA
MS	0.65 (0.38-1.13)	0.13	1.16 (0.49-2.73)	0.74

HR is given for risk of IMIDs after a sepsis compared to a myocardial infarction and was calculated using a marginal Cox proportional hazard model after adjustment for admission in ICU during index stay.

IMIDs, immune-mediated inflammatory diseases; ICU, intensive care unit; ITP, immune thrombocytopenia; AIHA, autoimmune hemolytic anemia; SLE, systemic lupus erythematosus; SS, Sjögren's syndrome; SSs, systemic sclerosis; RA, rheumatoid arthritis; GCA, giant cell arteritis; PMR, polymyalgia rheumatica; AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; IBD, inflammatory bowel disease; HR, hazard ratio.

Table S4: IMID-free survival analysis in patients with prior admission before the index stay.

Hazard ratios (HR) are given for the risk of IMIDs after sepsis compared to myocardial infarction. HR are calculated using a marginal Cox model, adjusting on ICU stay during the first index stay.

4.4- Competing risk analysis

As presented in Table 1, 12.1 % of patients from the sepsis group died during their index stay versus 4.5 % in the AMI group. After the index stay, 3 054 (5.6%) patients died in the sepsis group versus 901 (1.5 %) in the AMI group. In the presented main results, patients are censored at death. To address competing risk issue, we have run a competing risk analysis (Fine and Gray model adapted to clustered data: Bingqing Zhou, et al, Competing risks regression for clustered data, *Biostatistics*, 2012; R package crrSC) taking death as a competing event. Here are the results of this analysis:

	Whole period	After D16
sdHR (CI 95)*	1.46 (1.17-1.83)	3.38 [2.23-5.10]

Table S5: Results of the competing risk analysis *sub distribution hazard ratio (sdHR) is adjusted on ICU admission during index stay and is given for the risk to experience an IMID onset for patients with sepsis (AMI taken as reference).

4.5- Matching with 2019 sepsis

Our main analysis is based on admissions for sepsis in 2020 and thus used data collected during the first wave of COVID-19. Although this may have resulted in different follow-up of patients from usual, particularly those with long COVID, we performed a sensitivity analysis in comparison to patients with a sepsis stay in 2019 (i.e. prior the COVID-19 pandemics, n = 418811).

In this analysis, we ran the same matching procedure and matched 62257 AMI patients to 62257 patients who had a first sepsis stay in 2019. We observed these results :

	n	Events	HR whole period*	HR after D16*
AMI 2020	62257	361	ref	ref
Sepsis 2019	62257	860	1.03 [0.91-1.17]	1.97 [1.55-2.49]

Table S6: Results of the matching with 2019 sepsis * hazard ratio (sdHR) is adjusted on ICU admission during index stay and is given for the risk to experience an IMID onset for patients with sepsis (AMI taken as reference).

Of note, we observed 5086 IMIDs onset after a 9-months follow-up for the whole 2019 sepsis population (n=418,811 patients). This 1.2 % rate was similar to the one observed in the 2020 sepsis population (4956/460707, 1.08 %).

Synthesis

A summary of the main findings of the thesis is presented in table 1.

Research questions	Findings
<p>Do patients with IMIDs such as SLE have a special risk when facing COVID-19?</p>	<ul style="list-style-type: none"> - Patients with SLE are more likely to develop severe SARS-CoV-2 infection if they have comorbidities already identified as risk factors for severe infection in the general population, such as older age, male gender and hypertension. - COVID-19-associated organ failure is associated with a poor late-onset prognosis in patients with SLE, compared to non-SLE patients matched on comorbidities.
<p>What is the protection conferred by mRNA vaccines in IMIDs such as SLE?</p>	<ul style="list-style-type: none"> - Two doses of BNT162b2 vaccine conferred a poor immune long-lasting response in patients with SLE. The vaccine response was even poorer against SARS-CoV-2 variants of concern other than the historical “Wuhan” strain. - Vaccine effectiveness was diminished in SLE patients, compared with general population comparators and lowest in those treated with immunosuppressants.
<p>What is the impact of a mRNA vaccination during the course of IMIDs such as SLE?</p>	<ul style="list-style-type: none"> - BNT162b2 vaccine induces a transient in vivo activation of pDCs in SLE that contributes to the immune responses against SARS-CoV-2. - BNT162b2 vaccine also dampens the pool of circulating autoreactive T cells, suggesting that vaccination may have a beneficial impact on SLE disease.
<p>What is the impact of a viral infection such as COVID-19 during the course of IMIDs such as SLE?</p>	<ul style="list-style-type: none"> - SLE patients have an increased risk of lupus flare following symptomatic, hospitalized episodes of COVID-19. - Viral infections could trigger autoimmune flare through an interplay between type 1-IFN and anti-type I IFN autoantibodies.
<p>Is severe infection a risk factor for developing IMIDs?</p>	<ul style="list-style-type: none"> - We observed an extremely high incidence of IMIDs after sepsis. This incidence was higher than the one observed in hospital controls admitted for acute myocardial infarction.

Table 1: Summary of the main findings of the thesis

The main objective of this thesis was to provide scientific evidence that would contribute to a better understanding of the interplay between systemic IMIDs such as SLE and infectious diseases. The years 2020, 2021, 2022 and 2023, during which this work took place, were also the years of the emergence and the subsiding of the COVID-19 pandemic which brought up new and urgent questions regarding this very topic. Therefore, I decided to adapt my research efforts to consider the interplay between SLE and COVID-19 as a model of the relationship between IMIDs and infectious diseases. By doing so, my purpose was to provide relevant, up-to-date insights for SLE patients and physicians during the acute crisis of COVID-19 but also to address the broader question of the links between infectious diseases and IMIDs.

The results of this thesis are synthesized in two sections: the infectious risk of patients with IMIDs and the modulation of autoimmunity by infectious stimuli.

1- Infectious risk in patients with SLE.

At the beginning of the pandemic, the main concern for patients with IMIDs such as SLE was the risk of severe forms of COVID-19. Very little data was available on the specific risk for these patients, but they were known to be more susceptible to other infections, especially respiratory infections, such as pneumococcal pneumonia or influenza. However, from an epidemiological perspective, it could have been hypothesized that comorbidities (which are frequent in SLE) are the mediator responsible for their risk of facing severe COVID-19, and that SLE involves no special risk per se. In the first study of this thesis, we were able to confirm that the risk of hospitalization and poor outcome after COVID-19 was mostly associated with comorbidities already identified as risk factors of severe infection in the general population, such as older age, male gender, and hypertension. Our analysis of the risk associated with the different specific features of SLE was limited because the study was based on ICD-10 codes. We observed that a history of lupus nephritis was also associated with a risk of hospitalization and poor outcome of COVID-19. This first study included SLE patients only, meaning that it was impossible for us to compare the risk of SLE patients with the one of non-SLE comparators. Thereafter, we enlarged our scope to include all patients hospitalized with a sepsis in France. Then, we were able to compare the outcome of patients with and without SLE after a COVID-19 sepsis. Of note, we decided to use the term of COVID-19 associated organ failure (AOF) in the paper rather than COVID-19 sepsis on reviewers' request, who found that the word sepsis should be limited to bacterial infections. Our description of the 196 SLE patients with COVID-19 AOF confirmed that these patients had more comorbidities than the 113,371 non-SLE comparators with COVID-19 AOF, even though SLE patients were younger and more frequently female. Interestingly, the crude analysis of the 90-days

survival of these patients after a COVID-19 AOF showed that SLE patients had a better short-term prognosis. However, this observed difference was probably mainly due to age and sex difference between the two groups. Indeed, after matching on age ± 2 years, gender, chronic kidney disease, high blood pressure, cardiovascular history, diabetes mellitus, chronic pulmonary disease, and obesity we unmasked a poor late-onset prognosis in patients with SLE, that could be attributed to SLE. Thus, we were able to isolate the effect of SLE from the one of the main comorbidities. Unfortunately, we did not have access to patients' treatment in this database, so we were unable to study the effect of the immunosuppressive treatments received by these patients.

This work supports the idea that SLE, and more generally IMIDs, should be considered as distinct comorbidities when assessing the risk of severe risk infection. It also confirms that within an age group, patients with IMIDs such as SLE should be prioritized for vaccination.

Unfortunately, IMIDs also interfere with the vaccine-induced protection. Our studies about vaccine immunogenicity and clinical effectiveness in SLE patients showed that the protection conferred by the vaccine is diminished in this population. Together with the virology and the immunology laboratories of Bichat hospital, we conducted the prospective COVALUS project to better describe and understand the immunogenicity and the immune tolerance of the mRNA BNT162n2 vaccine in SLE patients. The COVID-19 pandemic evolved in several waves involving different variants and a lot of questions raised regarding the ability of the initial mRNA vaccines to protect against all. Thus, using a specific multiplex ELISA assay, we assessed the specific humoral vaccine responses against B (ancestral), alpha, delta and omicron variants in SLE patients and in healthy volunteers. We observed a dramatically reduced vaccine response in SLE patients. At that time, the most common variant was Omicron. We observed that, two months after the second dose, only 55.6% of SLE patients without a prior COVID-19 and without a heavy immunosuppressive treatment had a concentration of anti-Omicron IgG considered as protective. Five months after the second dose, only 10 % of SLE patients could be considered as protected. Patients with heavy immunosuppressive drugs (azathioprine, mycophenolate mofetil or anti-CD20) were excluded from this analysis and most of the included patients had only low doses of steroids. Therefore, our findings suggest that the response to the vaccine is not entirely driven by the current immunosuppressive treatment and that vaccine humoral response should be monitored in SLE patients, even without immunosuppressive treatment. This monitoring could help us identify patients who may benefit from other prophylactic strategies, such as pre-exposure monoclonal antibodies, which are effective in this population (136).

Then, we were able to look more in details into the immunogenicity of the vaccine by focusing on the specific, vaccine-induced B and T cells. We observed, in flow-cytometry assays, that the lack of antibody production response was associated with a lack of induction of Spike-specific B cells in SLE patients, compared with healthy volunteers. We also observed a lower T-cell response in SLE patients, compared with healthy volunteers, even though this difference was not significant. These results reinforced our previous findings, suggesting that mRNA vaccines have less immunogenicity in SLE patients. Other studies reported the existence of a T cell response among IMIDs patients, even without humoral response (93). We did not find that to be the case in our cohort, suggesting that studying the T-cell response does not bring additional information regarding the vaccine immunogenicity in patients with IMIDs and that the prophylaxis strategy in patient unresponsive to the vaccine could not be tailored according to the T-cell response. In this prospective study, we lack power to be able to study the vaccine effectiveness, meaning the actual protection against clinical outcomes, of the vaccine.

In order to be able to study the vaccine effectiveness in real-life settings, using clinical outcomes, I had to go back to nationwide register data. However, in France, it was impossible to link vaccination data to the national registers. This led me to the clinical epidemiology division of the Karolinska Institute in Stockholm where I was able to leverage the power of Swedish national registers. Indeed, in Sweden, it was possible to link the National Patient Register to the Vaccination register and to other useful registers.

Since there can be no vaccine effectiveness without vaccine administration, we first sought to compare the pace of the first vaccine dose uptake in SLE patients and age- and sex-matched controls from the general population. We observed that almost all enrolled individuals received their vaccine in the spring of 2021 and that the pace of vaccine uptake was very similar between SLE patients and the general population. This is very informative about the effect of healthcare organization in such time. Because in Sweden the vaccination schedule was centralized, there was no priority based on comorbidities such as IMIDs. Given the risk of severe COVID-19 in patients with IMIDs, we may hypothesize that this organization could have had a negative impact on the morbidity and mortality of the COVID-19 pandemic in the IMID community. However, vaccination coverage increased rapidly and within a few months, 90% of the population, including SLE patients, was vaccinated. Although 90% seems like a high number, it could be improved. Interestingly, we noticed that almost all patients who had not been vaccinated by the end of September 2021 never got vaccinated. Looking at the

differences between vaccinated and unvaccinated SLE patients, we observed that unvaccinated patients were younger and more often born outside of Sweden. Physicians should be aware of this finding in order to better promote the importance of vaccination in these patients.

Looking at the effectiveness of the vaccine, we observed a very low incidence of COVID-19 hospitalizations after 2 mRNA vaccine doses in both SLE and non-SLE individuals. This confirms that SARS-CoV-2 mRNA vaccines are an effective prophylaxis for severe COVID-19. However, when comparing their effectiveness between SLE patients and non-SLE comparators from general population, we found that the hazard ratio [CI 95%] associated with COVID-19 hospitalization was 3.47 [1.63-7.39] for SLE patients. This means that after vaccination, SLE patients have a 3.5-fold risk of being hospitalized because of a COVID-19 episode, compared to general population of same age and sex. This corroborates our previous results based on the vaccine immune response and calls for close monitoring of the vaccine response in SLE patients and IMIDs patients in general, especially as these patients could be offered alternative effective prophylaxis such as monoclonal antibodies. Interestingly, we observed that the risk of COVID-19 hospitalisation of the subgroup of patients non-exposed to immunosuppressive drug was very similar to the one of the general population comparators. These results are in contrast with the ones that we observed looking at the immune response, both humoral and cellular, of SLE patients without immunosuppressive treatment. Several hypotheses could explain this discrepancy. In my opinion, the most likely is that we cannot summarize all the immune protection conferred by the vaccine with our usual tests evaluating the humoral response which is only an imperfect surrogate marker of the vaccine-induced protection. This leads us to urge for the use of clinical outcome, while looking at vaccine real-life effectiveness. The translational nature of this work, looking at both the immune and epidemiological levels, gives us a good opportunity to get a comprehensive overview of this topic.

2- The modulation of autoimmunity by infectious stimuli.

How infectious stimuli modulate autoimmunity is a challenging question to address. The choice of outcome is crucial: biological autoimmune features such as the production of autoantibodies is a relevant surrogate marker that is easier to study, but it doesn't fully match the clinical outcomes of interest, which are the induction of clinical autoimmune activity or the new onset of an IMID. The exposure is also hard to assess since the organism is constantly exposed to infectious pathogens. And, as we already saw, patients with IMIDs are often immunocompromised, therefore more likely to suffer from infections which means that the risk of reverse causation should be cautiously evaluated.

During the COVALUS project, we were able to closely monitor the impact of the vaccine on several autoimmune features. We did not observe a worrisome signal when looking at the number of clinical flares of SLE after vaccination, but our sample size was limited, and we did not have a control group of unvaccinated SLE patients to compare with. Nevertheless, we were able to study the autoimmune activity of each included individuals before and at multiple time points after vaccination. Because we also enrolled healthy volunteers (HV), we had a chance to assess whether or not the modulation of autoimmunity we observed after vaccination was specific to SLE patients. This setting was particularly interesting when we looked at the ex-vivo production of IFN α by pDCs after vaccination since we observed that, 1 month after a first dose (M1), this production was increased compared to baseline in both SLE patients and HV. However, at M3, this production remained elevated only in SLE patients, and was associated with the up-regulation of two activation markers on the surface of pDCs cells (HLA-DR and CD86). Given the importance of IFN α in the pathophysiology of SLE and the accumulated evidence showing that the level of circulating IFN α is correlated with SLE activity, this finding could suggest a deleterious effect of the vaccine in SLE patients. On the other hand, we also found that this vaccine-induced activation of pDCs contributes to the vaccine response since the level of expression of CD86 and HLA-DR at the surface of pDCs is correlated with the immunogenicity of the vaccine. This effect was determined by a few SLE patients with a very high level of HLA-DR on the surface of pDCs at M1 and M3 and a relatively good vaccine response. Interestingly, the activation of the innate immune system was contrasted by a downregulation of autoreactive antinuclear specific T cell activity in SLE patients during follow-up. This finding, combined with the absence of variation in the levels of well-known markers of lupus biological activity (complement and anti-dsDNA IgG levels), led us to conclude that the overall effect of the BNT1362b2 mRNA vaccine on the autoimmunity was not

clinically significant in SLE patients. These findings improved our understanding on how the innate and adaptive immune systems of SLE patients cope with a pro-inflammatory challenge.

It is likely that the impact of a mRNA vaccine agents on the immune system of IMID patients is very different from that of a COVID-19 episode. So, after studying the effects of vaccination in SLE patients, we decided to study the effects of the actual SARS-CoV-2 infection by using the AP-HP Data Warehouse which gave us access to the biological results and electronic medical records of all patients treated for SLE in the Paris area university hospitals. After matching SLE patients with and without a hospitalization for COVID-19 on demographic variables (age, sex), SLE activity markers (complement, anti-dsDNA levels), and SLE damage markers (chronic kidney disease), we observed a significantly increased incidence of lupus flares after COVID-19. Of note, the flare observed in the COVID-19 groups seemed more severe, with more renal flares, than the ones observed in the comparator group. This higher incidence of flares was accompanied by a decrease in the C3 levels after the index date in COVID-19 patients whereas it remained unchanged in the control group. Notably, in the majority of post-COVID-19 flares, the patient's treating physician made a causal link in the electronic medical record between the infection and the lupus flare. These findings confirmed the impression given by the previously reported cases that a viral infection such as COVID-19 could be responsible for autoimmune flares in IMIDs. Even though it seems clear to physicians that infections can trigger autoimmunity in patient with already established IMID, very little data was available in the literature on that subject, and especially in SLE patients. These results raise the question of the adaptation of the immunosuppressive treatment during an infectious episode. The balance between the infectious risk of maintaining treatment and the risk of inducing an autoimmune flare by withdrawing the treatment in a pro-inflammatory context is sometimes very difficult to assess. In our study, we observed that tapering of SLE immunosuppressive drugs during COVID stays was not associated with increased risks of flares. However, we may have been underpowered to see such an association.

After looking at SLE and SARS-CoV-2 interactions, we next broadened the scope of the analysis by studying the risk of IMIDs onset in sepsis survivors. Thanks to the PMSI nationwide database, we were able to match patients who experienced a sepsis in 2020 in France to all the patients who were hospitalized for an acute myocardial infarction (AMI) in the same period. Compared to the incidence of IMIDs in the general population reported in the literature, we observed an extremely high incidence of IMID after sepsis and after AMI. These results could probably be explained by the hospital nature of the sepsis and AMI populations. However, when we compared sepsis with AMI patients, which are

both hospital populations, we observed an increased risk for IMIDs of 2.80 (HR; 95%CI [2.22-3.54]) starting from day 16 after admission in the sepsis group. This important and significant relationship remained stable in multiple sensitivity analyses, and the risk of IMID after sepsis was very similar when we performed the same analysis with sepsis from 2019, before the COVID-19 era. Looking at each IMID individually, we observed that the risk of IMIDs following severe infection differed according to the nature of the autoimmune disease and were higher for immune thrombocytopenia, autoimmune haemolytic anemia and ANCA associated vasculitis., which were already known to be potentially triggered by infectious pathogen. These results confirmed our initial hypothesis that a severe infection, such as sepsis, whatever the pathogen involved, is associated with an increased risk of IMID onset. The PMSI database is not suitable for mechanistic analyses and we could not confirm the involvement of pro-inflammatory cytokines or anti-cytokine autoantibodies in the pathogenesis of IMIDs after sepsis. It is unclear whether these immune-mediated inflammatory diseases that occur after sepsis can be attributed to the well-known post-sepsis syndrome, as the majority of patients experiencing post-sepsis syndrome do not exhibit a clinically-defined IMID. However, physicians should be aware of our findings and easily screen sepsis survivors for IMIDs in the presence of unexplained symptoms.

A recent study from the United Kingdom (137) found that the burden of IMID continued to increase over time in the period 2000-2019 and that environmental factors are likely to be involved in the pathogenesis of the disease. We have already observed that the incidence of sepsis increased in France during the same period (138). This higher rate of sepsis, associated with a post-sepsis risk of IMID onset, may be involved in the increase in IMID incidence reported by the British researchers. However, it should be noted that, although the ratios were high when we compared sepsis with AMI patients or with the general population, the absolute incidence of post-sepsis IMIDs was only 8.0 per 1,000 patient-years, meaning that we should not expect “an IMID pandemic” because of sepsis. The effect of the pandemic on the global incidence of IMIDs remains to be determined, but we did not find a particular effect of SARS-CoV-2 compared with other pathogens in our analysis.

Conclusion

Using a translational approach, both epidemiological and immunological, to study the relationships between infections and IMIDs, and using SLE and SARS-CoV-2 as models, we were able to answer our research questions and validate some of our hypotheses. This work led to a more comprehensive understanding of the crosstalk between infections and IMIDs, which can now be described as shown in Figure 8.

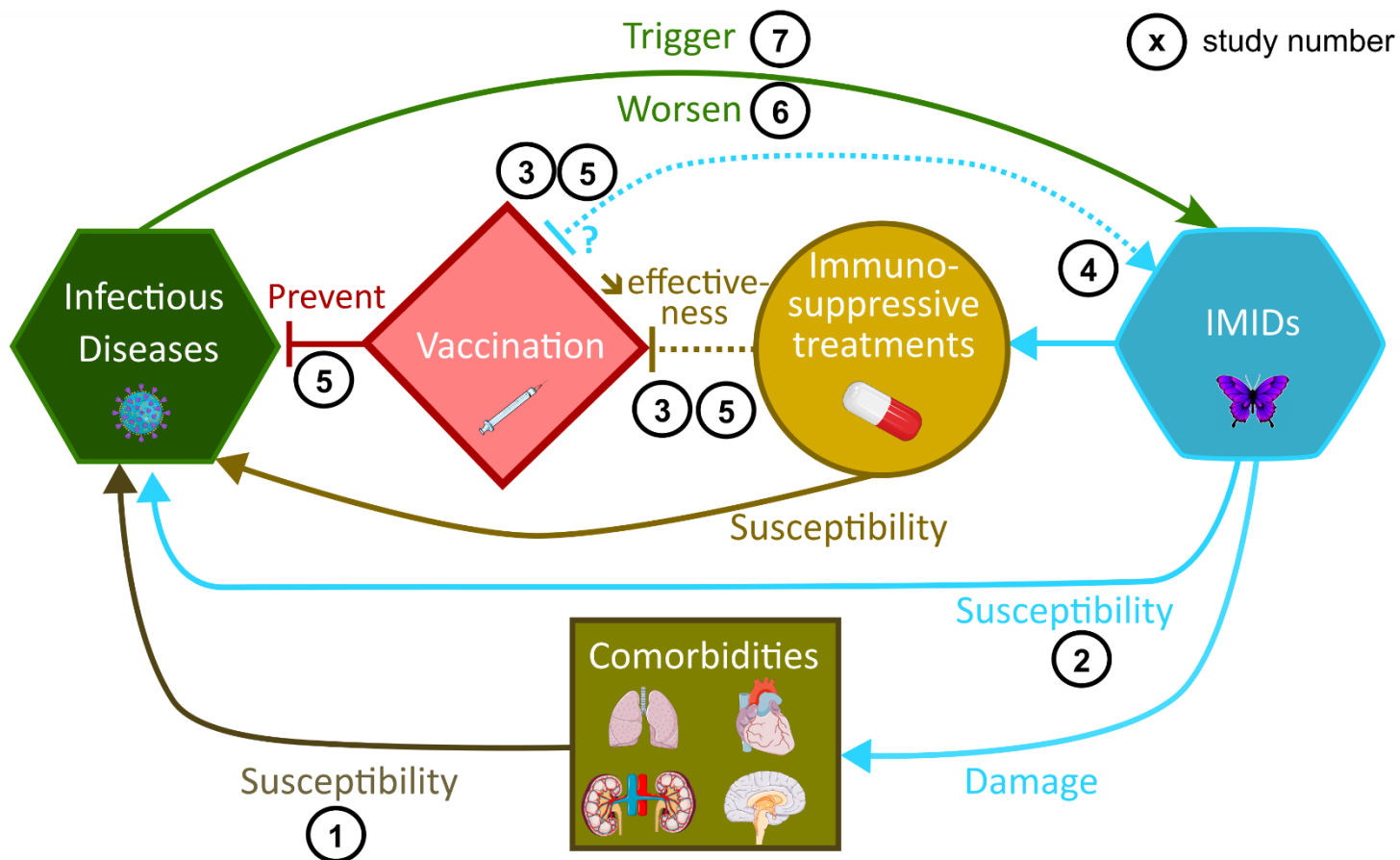


Figure 8: Improved representation of the relationship between infectious and IMIDs.

We validated the circle between infectious diseases and IMIDs mentioned in the introduction by showing that patients with IMIDs such as SLE are more likely to suffer from serious infections and that infectious diseases can trigger or exacerbate IMIDs. However, we also identified other important players in this relationship. We found that vaccination can effectively prevent infectious diseases in patients with SLE, but that vaccine’s immunogenicity and clinical effectiveness are reduced by immunosuppressive treatments. Regarding the effect of SLE, independent of IS treatment, on vaccination outcome, we observed that patients with SLE have reduced immunogenicity of the

vaccine, but that the clinical effectiveness might be preserved. We did not find any clinically meaningful impact of vaccination on the course of SLE but we did observe a significant impact on both innate and adaptive immune system. Comorbidities also play an important role in the interaction between infections and IMIDs, both because they are more common in patients with IMIDs and because they are a risk factor for severe infections in these patients. However, we found that comorbidities do not account for all the risk of infection in patients with SLE, and that SLE is independently a risk factor for serious infections. We observed that the post-infection period is a vulnerable time for patients, whether they have been diagnosed with IMIDs or not. Therefore, clinicians should be aware of the risk of exacerbation or onset of IMIDs during this time.

The results of this work may have several clinical implications. Thanks to a better understanding of the interplay between infectious diseases and IMIDs, we can now propose different interventions to improve the outcome of patients with IMIDs facing infection and to reduce the burden of post-infection autoimmune disorders:

- Vaccination should remain the cornerstone of infection prophylaxis in patients with IMIDs, as it is effective and safe.

- Vaccine uptake could be improved by therapeutic education focusing on patients at risk of low vaccine uptake.

- The vaccination schedule can be tailored for patients on immunosuppressive drugs and other prophylactic strategies can be proposed to reduce the infectious risk that is not entirely handled by vaccination.

- A close medical follow-up should be organized for patients surviving from a severe infection, whether they are diagnosed or not with an IMID.

- IMID onset or exacerbation of already known IMID should be looked for during the time right after surviving from a severe infection.

- The expected benefits of discontinuing an immunosuppressive drug during an episode of severe infection should be weighed against the risk of a post-infectious autoimmune flare.

Perspectives

As I was working on my research projects, many new interrogations arose, and I realised how many unmet issues remain about the interactions between infections and systemic IMIDs such as SLE. Therefore, I consider the findings gathered during this work as a starting point for a research workflow that will be pursued over the next few years, in France and, hopefully in other European countries.

The high incidence of IMID after sepsis that we observed in the French hospital data needs to be confirmed in other settings and to be explained by mechanistic studies. My supervisors and I, together with several other researchers from France, Sweden, Denmark, Belgium, Switzerland and the Netherlands applied for the HORIZON-HLTH-2023-DISEASE-03-07 grant about the relationship between infections and non-communicable diseases. This grant would allow us to initiate several clinical, epidemiological, immunological, and translational research projects to confirm our previous results but also to identify risk factors, biomarkers and mechanistic processes involved in post-infectious autoimmunity.

I also plan on continuing to leverage the power of Swedish nationwide register data to assess the anti-SARS-CoV-2 vaccine immune tolerance by looking at the risk of post-vaccine lupus flare with a self-controlled case series method. First, I need to validate the register-based definition of lupus flare that we developed, using a modification in the immunosuppressive treatment as a proxy for flare. This validation will be done using data from the prospective Kluring clinical cohort, taking modification in clinical scores such as SLEDAI-2k, Physician's Global Assessment, and the SELENA-SLEDAI flare index as the gold standard to define flare. Because validation studies are an important step in register research, I also plan on validating an automatized tool that uses Natural Language Processing to define lupus flare with the electronic health record stored in the AP-HP Data Warehouse.

In this thesis, we did not explore the field of the interaction between chronic and pro-oncogenic viruses and IMIDs. In the next few months, we will use data from the PSMI to study the risk of uterine cervical neoplasms associated with human papillomavirus infection in SLE patients. This topic is crucial in a disease that involves mostly immunocompromised young women.

Finally, on a more personal note, as of November 2023, I will return to clinical work at the Internal Medicine Department of the Bichat University Hospital in Paris as a "Chef de Clinique Assistant". I will take advantage of this university position to conduct and participate in research projects at the IAME Inserm unit in Paris, but also with the international partners I met during this thesis.

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