SUPPLEMENTARY MATERIAL TO THE MANUSCRIPT

Infections in biological and targeted synthetic drug use in rheumatoid arthritis: where do we stand? A scoping review and meta-analysis

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Supplement 1: search strategy and terms

We performed the literature search in two episodes. At first, a search was performed in December 2019 in PubMed with search terms for biological drugs. Immediately thereafter, the COVID-19 pandemic hit and the study was put on hold. In January 2021, an additional search was performed in both PubMed and Cochrane and aside from biological drugs, targeted synthetic drugs were included as well.

Pubmed:

((TNF-alpha inhibitor* [tiab] OR TNF-alpha antagonist* [tiab] OR tumor necrosis factor alpha inhibitor* [tiab] OR tumor necrosis factor alpha antagonist* [tiab] OR tumour necrosis factor alpha inhibitor* [tiab] OR tumour necrosis factor alpha antagonist* [tiab] OR "Infliximab"[Mesh] OR infliximab [tiab] OR Renflexis [tiab] OR Remicade [tiab] OR Inflectra [tiab] OR adalimumab [tiab] OR Humira [tiab] OR amjevita [tiab] OR Cyltezo [tiab] OR "Adalimumab"[Mesh] OR "Etanercept"[Mesh] OR Etanercept [tiab] OR Enbrel [tiab] OR Erelzi [tiab] OR "Certolizumab Pegol"[Mesh] OR certolizumab [tiab] OR certolizumab pegol [tiab] OR Cimzia [tiab] OR "golimumab"[Supplementary Concept] OR golimumab [tiab] OR Simponi [tiab] OR interleukin antagonist* [tiab] "Interleukin 1 Receptor Antagonist Protein"[Mesh] OR anakinra [tiab] OR Kineret [tiab] OR Antril [tiab] OR interleukin 1 receptor antagonist [tiab] OR "canakinumab" [Supplementary Concept] OR canakinumab [tiab] OR ilaris [tiab] OR dupilumab [tiab] OR "dupilumab" [Supplementary Concept] OR Dupixent [tiab] OR secukinumab [tiab] OR "secukinumab" [Supplementary Concept] OR cosentyx [tiab] OR "tocilizumab" [Supplementary Concept] OR tocilizumab [tiab] OR actemra [tiab] OR ustekinumab [tiab] OR "Ustekinumab"[Mesh] OR stelara [tiab] OR ixekizumab [tiab] OR taltz [tiab] OR sarilumab [tiab] OR kevzara [tiab] OR abatacept [tiab] OR "Abatacept"[Mesh] OR belatacept [tiab] OR nulojix [tiab] OR orencia [tiab] OR B-cell inhibitor* [tiab] OR rituximab

[tiab] OR "Rituximab"[Mesh] OR Rituxan [tiab] OR Mabthera [tiab] OR rituximab CD20 antibody [tiab] OR belimumab [tiab] OR benlysta [tiab] OR vedolizumab [tiab] OR "vedolizumab" [Supplementary Concept] OR entyvio [tiab] OR "Janus Kinase Inhibitors"[Mesh] OR janus kinase inhibitor* [tiab] OR JAK-inhibitor* [tiab] OR JAK inhibitor* [tiab] OR tofacitinib [tiab] OR xeljanz [tiab] OR upadacitinib [tiab] OR Rinvoq [tiab] OR peficitinib [tiab] OR smyraf [tiab] OR baricitinib [tiab] OR Olumiant [tiab] OR filgotinib [tiab] OR "Biosimilar Pharmaceuticals"[Mesh] OR biosimilar* [tiab] OR "Antibodies, Monoclonal"[Mesh] OR monoclonal antibod* [tiab] OR biologic* [tiab]) AND ("Arthritis, Rheumatoid"[Mesh] OR "rheumatoid arthritis" [tiab]) AND ("Infections"[Mesh] OR infection* [tiab]))

Cochrane:

ID	Search
#1	(TNF-alpha inhibitor):ti,ab,kw (Word variations have been searched)
#2	(TNF-alpha antagonist):ti,ab,kw (Word variations have been searched)
#3	(Tumor necrosis factor alpha inhibitor):ti,ab,kw (Word variations have been searched)
#4	(Tumor necrosis factor alpha antagonist):ti,ab,kw (Word variations have been searched)
#5	MeSH descriptor: [Infliximab] explode all trees
#6	(infliximab):ti,ab,kw (Word variations have been searched)
#7	(renflexis):ti,ab,kw (Word variations have been searched)
#8	(remicade):ti,ab,kw (Word variations have been searched)
#9	(inflectra):ti,ab,kw (Word variations have been searched)
#10	MeSH descriptor: [Adalimumab] explode all trees
#11	(adalimumab):ti,ab,kw (Word variations have been searched)
#12	(humira):ti,ab,kw (Word variations have been searched)

#13 (amjevita):ti,ab,kw (Word variations have been searched)

#14 (cyltezo):ti,ab,kw (Word variations have been searched)

#15 MeSH descriptor: [Etanercept] explode all trees

#16 (etanercept):ti,ab,kw (Word variations have been searched)

#17 (enbrel):ti,ab,kw (Word variations have been searched)

#18 (erelzi):ti,ab,kw (Word variations have been searched)

#19 MeSH descriptor: [Certolizumab Pegol] explode all trees

#20 (certolizumab pegol):ti,ab,kw (Word variations have been searched)

#21 (certolizumab):ti,ab,kw (Word variations have been searched)

#22 (cimzia):ti,ab,kw (Word variations have been searched)

#23 (golimumab):ti,ab,kw (Word variations have been searched)

#24 (simponi):ti,ab,kw (Word variations have been searched)

#25 (interleukin antagonist):ti,ab,kw (Word variations have been searched)

#26 MeSH descriptor: [Interleukin 1 Receptor Antagonist Protein] explode all trees

#27 (anakinra):ti,ab,kw (Word variations have been searched)

#28 (kineret):ti,ab,kw (Word variations have been searched)

#29 (antril):ti,ab,kw (Word variations have been searched)

#30 (interleukin 1 receptor antagonist):ti,ab,kw (Word variations have been searched)

#31 (canakinumab):ti,ab,kw (Word variations have been searched)

#32 (ilaris):ti,ab,kw (Word variations have been searched)

#33 (dupilumab):ti,ab,kw (Word variations have been searched)

#34 (dupixent):ti,ab,kw (Word variations have been searched)

#35 (secukinumab):ti,ab,kw (Word variations have been searched)

#36 (cosentyx):ti,ab,kw (Word variations have been searched)

#37 (tocilizumab):ti,ab,kw (Word variations have been searched)

#38 (actemra):ti,ab,kw (Word variations have been searched)

#39 MeSH descriptor: [Ustekinumab] explode all trees

#40 (ustekinumab):ti,ab,kw (Word variations have been searched)

#41 (stelara):ti,ab,kw (Word variations have been searched)

#42 (ixekizumab):ti,ab,kw (Word variations have been searched)

#43 (taltz):ti,ab,kw (Word variations have been searched)

#44 (sarilumab):ti,ab,kw (Word variations have been searched)

#45 (kevzara):ti,ab,kw (Word variations have been searched)

#46 MeSH descriptor: [Abatacept] explode all trees

#47 (abatacept):ti,ab,kw (Word variations have been searched)

#48 (belatacept):ti,ab,kw (Word variations have been searched)

#49 (nulojix):ti,ab,kw (Word variations have been searched)

#50 (orencia):ti,ab,kw (Word variations have been searched)

#51 (B-cell inhibitor):ti,ab,kw (Word variations have been searched)

#52 MeSH descriptor: [Rituximab] explode all trees

#53 (rituxan):ti,ab,kw (Word variations have been searched)

#54 (rituximab):ti,ab,kw (Word variations have been searched)

#55 (mabthera):ti,ab,kw (Word variations have been searched)

#56 (rituximab CD20 antibody):ti,ab,kw (Word variations have been searched)

#57 (belimumab):ti,ab,kw (Word variations have been searched)

#58 (benlysta):ti,ab,kw (Word variations have been searched)

#59 (vedolizumab):ti,ab,kw (Word variations have been searched)

#60 (entyvio):ti,ab,kw (Word variations have been searched)

#61 MeSH descriptor: [Janus Kinase Inhibitors] explode all trees

#62 (janus kinase inhibitor):ti,ab,kw (Word variations have been searched)

#63 (JAK-inhibitor):ti,ab,kw (Word variations have been searched)

#64 (tofacitinib):ti,ab,kw (Word variations have been searched)

#65 (xeljanz):ti,ab,kw (Word variations have been searched)

#66 (upadacitinib):ti,ab,kw

#67 (rinvoq):ti,ab,kw

#68 (peficitinib):ti,ab,kw

#69 (smyraf):ti,ab,kw

#70 (baricitinib):ti,ab,kw

#71 (olumiant):ti,ab,kw

#72 (filgotinib):ti,ab,kw

#73 MeSH descriptor: [Biosimilar Pharmaceuticals] explode all trees

#74 (biosimilar):ti,ab,kw (Word variations have been searched)

#75 (biologic):ti,ab,kw (Word variations have been searched)

#76 MeSH descriptor: [Antibodies, Monoclonal] explode all trees

#77 (monoclonal antibodies):ti,ab,kw (Word variations have been searched)

#78 (vaccin*):ti,ab,kw

#79 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees

#80 (rheumatoid arthritis):ti,ab,kw (Word variations have been searched)

#81 juvenile

#82 (infection):ti,ab,kw (Word variations have been searched)

#83 MeSH descriptor: [Infections] explode all trees

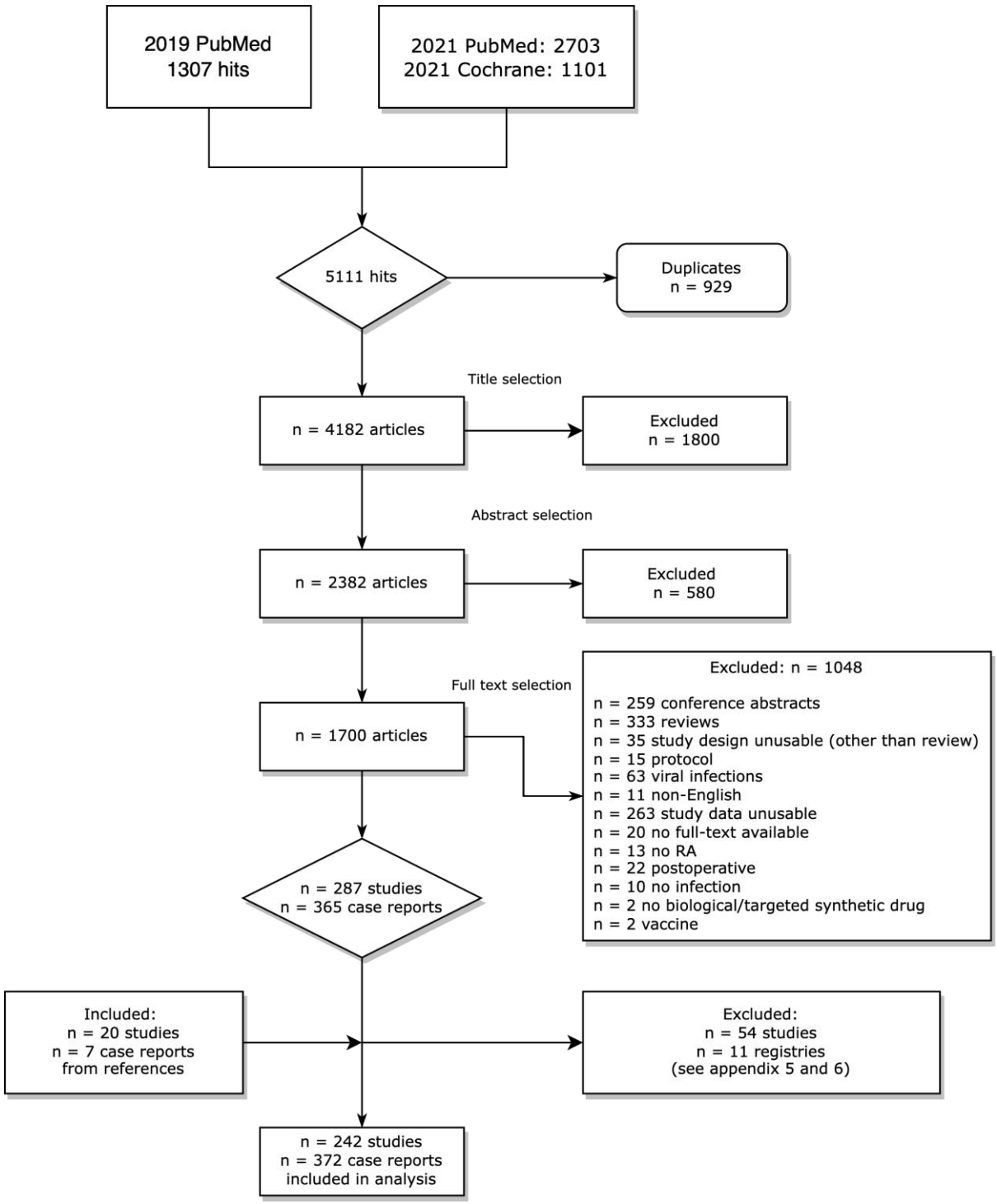
#84 {OR #1-#77} NOT #78

#85 #79 OR #80 NOT #81

#86 #82 OR #83

#87 #84 AND #85 AND #86

Supplement 2: flowchart of study in- and exclusion



Supplement 3: database format for the trials database

In separate excel file

Supplement 4: database format for the case report database

In separate excel file

Supplement 5: Studies making use of the same databases: inclusion, exclusion and reasoning

Studies making use of the same database were grouped, and decisions were made as to which study (arm) to include in the analyses. Table S1 shows the different groups, decisions and reasoning.

Table S1. In- and exclusion of studies making use of the same dataset

Problem	Solution	PMID	Excluded PMID	Included PMID
Multiple updates of same prospective cohort with new inclusions and different outcome measurements	We chose the most recent update of the registry concerning TNF-alpha inhibitors. Included were studies that focused on specific infections rather than a total amount of unspecified infections. The study arm on rituximab from PMDI 28968862 was included as the other studies only used data on TNF-alpha inhibitors. From PMID 20675706 only the serious infection incidence rate was included, since the other studies did not report on that.	20675706 22532633 21784730 17763441 24140761 28968862	17763441 24140761 28968862 TNF-alpha inhibitor study arm	20675706 22532633 21784730 28968862 rituximab study arm
	Include studies that analysed biologicals separately, only included from PMID 21791449 the incidence rates of serious infections 21791449	16255017 21791449		16255017 21791449 only incidence rate of Serious infections

	We chose to include the most recent update of the complete registry	19359261 29329557 31371657 21498482 22422487 24852650 25880658	19359261 31371657 21498482 24852650 25880658 study arm on TNF-alpha inhibitors	29329557 22422487 25880658 study arm on tocilizumab
Registry also used in another study	Use most recent update of registry	27258623 17324968	17324968 Biobadaser study arm	27258623 17324968 Emecar study arm
	Use most recent update of registry	30612115 31764977 17261532	30612115 Danbio study arm 17261532	30612115 Artis study arm 31764977
Same cohort, different biologicals	Include both studies since they focus on different biologicals	31174592 31777822		31174592 31777822
Cohorts used in multiple studies with different inclusion periods	Include individual study arms based on most recent update of registry	17530704 22833479 26315675 28255642 30570833 30679153 30772001	17530704 22833479 28255642 30772001 30679153 study arms on Medicare and MarketScan 26315675 study arm on tocilizumab	26315675 30570833 30679153 study arms on tocilizumab and MarketScan
Multiple updates on same prospective cohort	Choose most recent update	21358439 24470378	21358439	24470378

Supplement 6: RCTs and extension studies: inclusion, exclusion and reasoning

RCTs and associated extension studies were grouped according to the common dataset. Per group, the most recent study describing infectious complications from the start of antirheumatic therapy with biological or targeted synthetic treatment was included.

Table S2. In- and exclusion decisions regarding RCT/OLE clusters

Cluster	Source	Include/exclude	Reasoning	PMID	Design
1	Original search	Exclude	Data unsuitable	23918037	RCT+OLE
	Original search	Exclude	Data unsuitable	22596211	RCT+OLE
	Reference	Exclude	Data unsuitable	19909548	RCT
	Original search	Include		18975346	RCT
2	Original search	Include		26353833	RCT+OLE
	Reference	Include		19015207	RCT
3	Original search	Exclude	Data unsuitable	29219638	RCT+OLE
	Original search	Include		22984173	RCT
4	Original search	Exclude	Data unsuitable	27130908	RCT+OLE
	Reference	Include		23687260	RCT
5	Original search	Exclude	Data unsuitable	26474452	RCT+OLE
	Reference	Include		19644849	RCT
6	Original search	Exclude	Data unsuitable	22798265	RCT+OLE
	Original search	Exclude	Data unsuitable	17921185	RCT+OLE
	Original search	Include		16162882	RCT
7	Original search	Exclude	Data unsuitable	28612179	RCT+OLE
	Reference	Include		27624791	RCT
8	Original search	Exclude	Data unsuitable	29692005	RCT+OLE
	Reference	Exclude	Data unsuitable	26909489	RCT
9	Original search	Include		26199453	RCT+OLE
	Reference	Include		12528101	RCT
	Reference	Exclude	RCT+OLE more recent	12860493	RCT
	Original search	Include		14719195	RCT
	Original search	Include		16308341	RCT+OLE
10	Original search	Exclude	Data unsuitable	27909081	RCT+OLE
	Original search	Include		19297346	RCT
11	Original search	Exclude	Data unsuitable	25627338	RCT+OLE
	Reference	Include		19560810	RCT
	Original search	Exclude	Data unsuitable	22459542	RCT+OLE
12	Original search	Exclude	Data unsuitable	20444749	RCT+OLE
	Original search	Include		19066176	RCT
	Original search	Exclude	Data unsuitable	23678153	RCT+OLE
	Original search	Exclude	Data unsuitable	26669912	RCT+OLE
13	Original search	Exclude	Data unsuitable	23962455	RCT+OLE
	Reference	Include		23169319	RCT
14	Original search	Exclude	Data unsuitable	24241487	RCT+OLE
	Original search	Include		16385520	RCT
15	Original search	Exclude	Data unsuitable	24372225	RCT+OLE
	Original search	Include		24981319	RCT
16	Original search	Exclude	Data unsuitable	31113455	RCT+OLE
	Reference	Include		29259050	RCT
17	Original search	Exclude	Data unsuitable	25005467	RCT+OLE
	Original search	Exclude	Data unsuitable	19273451	RCT+OLE
	Original search	Include		16052582	RCT
18	Original search	Exclude	Data unsuitable	30922373	RCT+OLE
	Reference	Include		28584187	RCT
19	Original search	Include		31452928	RCT+OLE

	Reference	Exclude	Data unsuitable	25733246	RCT
20	Original search	Exclude	Data unsuitable	29657147	RCT+OLE
	Original search	Exclude	Data unsuitable	24584926	RCT+OLE
	Original search	Include		21618201	RCT
21	Original search	Include		25834203	RCT+OLE
	Reference	Exclude	Data unsuitable	23983039	RCT
22	Original search	Exclude	Data unsuitable	27747585	RCT+OLE
	Reference	Exclude	Data unsuitable	23904473	RCT
	Original search	Include		24942540	RCT
23	Original search	Exclude	Data unsuitable	19019888	RCT+OLE
	Reference	Include		15188351	RCT
24	Original search	Exclude	Data unsuitable	30299202	RCT+OLE
	Reference	Include		28622048	RCT
25	Original search	Include		24786925	RCT+OLE
	Original search	Exclude	Data unsuitable	21893583	RCT+OLE
	Reference	Exclude	Data unsuitable	18383390	RCT+OLE
	Original search	Include		16785475	RCT
26	Original search	Exclude	Data unsuitable	31387417	RCT+OLE
	Reference	Include		29514803	RCT
27	Original search	Exclude	Data unsuitable	15996057	RCT+OLE
	Reference	Include		11096165	RCT
28	Original search	Exclude	Data unsuitable	32371430	RCT+OLE
	Reference	Exclude	Data unsuitable	31831079	RCT
29	Original search	Exclude	Data unsuitable	25623393	RCT+OLE
	Original search	Exclude	Data unsuitable	24001888	RCT+OLE
	Reference	Include		22661646	RCT
30	Original search	Exclude	Data unsuitable	22089463	RCT+OLE
	Original search	Include		20131276	RCT
31	Original search	Exclude	Data unsuitable	29361199	RCT+OLE
	Reference	Include		28213566	RCT
	Reference	Exclude	Poster		RCT
32	Original search	Include		23027887	RCT+OLE
	Original search	Include		16947627	RCT
33	Original search	Exclude	Data unsuitable	24429175	RCT+OLE
	Reference	Include		22730366	RCT
34	Original search	Exclude	Data unsuitable	30997153	RCT+OLE
	Reference	Include		30053896	RCT
35	Original search	Include		24441150	RCT+OLE
	Original search	Include		23316080	RCT
36	Original search	Include		17504821	RCT+OLE
	Original search	Exclude	Data unsuitable	17329305	exclude
	Reference	Exclude	Data unsuitable	17504821	exclude
37	Original search	Exclude	Data unsuitable	32164762	RCT+OLE
	Original search	Include		26672064	RCT
	Original search	Include		31350269	RCT
38	Original search	Exclude	Data unsuitable	18050221	RCT+OLE
	Original search	Include		15201414	RCT
	Original search	Exclude	Data unsuitable	11257159	RCT
	Original search	Include		16947627	RCT
39	Original search	Include		12687534	RCT
	Original search	Exclude	Data unsuitable	16396977	RCT+OLE
40	Original search	Exclude	Data unsuitable	29042358	RCT+OLE
	Original search	Include		26318384	RCT
	Reference	Exclude	Data unsuitable	28957563	RCT+OLE
41	Original search	Exclude	Data unsuitable	33164349	RCT+OLE
	Original search	Include		30590833	RCT
42	Original search	Exclude	Data unsuitable	21821865	RCT+OLE
	Original search	Include		19124524	RCT
43	Original search	Exclude	Data unsuitable	22596211	RCT+OLE

	Original search	Include		18975346	RCT
44	Original search	Exclude	Data unsuitable	27334658	RCT+OLE
	Reference	Include		22873531	RCT
45	Original search	Exclude	Data unsuitable	29439289	RCT+OLE
	Reference	Include		28950421	RCT
46	Original search	Include		24026258	RCT+OLE
	Original search	Exclude	Data unsuitable	30666826	RCT+OLE
	Reference	Include		23348607	RCT
	Reference	Include		21584942	RCT
	Reference	Include		25496464	RCT
47	Original search	Exclude	Data unsuitable	26568428	RCT+OLE
	Reference	Include		22923753	RCT
48	Original search	Exclude	Data unsuitable	29247149	RCT+OLE
	Original search	Include		24942540	RCT
49	Original search	Exclude	Data unsuitable	31410787	RCT+OLE
	Original search	Include		28118538	RCT
	Original search	Include		27748083	RCT
50	Original search	Exclude	Data unsuitable	27006728	RCT+OLE
	Original search	Include		24356474	Open label trial
51	Original search	Include		31287230	RCT
	Original search	Exclude	Data unsuitable	33123205	RCT+OLE
	Reference	Exclude	Data unsuitable	31362993	RCT+OLE
52	Original search	Include		28584187	RCT
	Original search	Exclude	Data unsuitable	30922373	RCT+OLE
	Original search	Exclude	Data unsuitable	30922373	RCT+OLE

PMID, PubMed ID; RCT, randomised controlled trial; RCT+OLE, randomised controlled trial and open label extension. Source = how the article was found during literature search. Include/exclude = the decision we made to in- or exclude the article in the analysis. Data unsuitable = data in the original article not presented in a way that made inclusion possible, e.g., no mention of infectious adverse events, infectious adverse events not reported per biological class, OLE that did not report adverse events from initial inclusion of patients. Multiple articles from the same group could be included, if they reported infectious adverse events in a different manner (e.g., incidence rate versus the total number of infected patients). Such studies were not included in the same analyses.

Supplement 7: composite variables related to infection

Specific infections that were reported by studies were grouped into composite variables by organ system as specified in table S3.

Table S3. Infectious adverse event composite variables and individual infections they contain

Composite variable	Contains
Upper respiratory tract infection	Upper respiratory tract infection Nasopharyngitis Pharyngitis Rhinitis Sinusitis Bronchitis Common cold Tonsillitis Otitis
Lower respiratory tract infection	Lower respiratory tract infection Pneumonia Empyema Viral pneumonia Influenza like illness Influenza PJP Pulmonary aspergillosis CMV pneumonitis Infected bronchiectasis
Genitourinary tract infection	Genitourinary tract infection Urinary tract infection Pyelonephritis Epididymitis Vaginal infection Vaginal candidiasis Endometritis
Gastrointestinal infection	Gastrointestinal infection Gastroenteritis Enteritis Colitis Cholecystitis Diverticulitis Appendicitis Peritonitis Gastritis Whipple's disease Salmonellosis
Skin- and soft tissue infections	Skin- and soft tissue infections Cellulitis Erysipelas Abscess

	Wound infection Necrotising fasciitis
Bone and joint infections	Bone and joint infections Osteomyelitis Arthritis Bursitis Spondylodiscitis Prosthetic joint infection
Sepsis	Sepsis
Mycobacterial infections	TB NTM infection
Neurological infections	Herpes zoster Meningitis Encephalitis Viral meningitis Herpetic encephalitis
Fungal infections	Fungal infection Mycotic skin infection Oral mycosis Onychomycosis Endocarditis fungal Histoplasma infection
Viral infections	Viral infection Herpes virus infection Herpes simplex Oral herpes Hepatitis A infection Hepatitis B infection de novo Hepatitis B reactivation Hepatitis C infection Hepatitis E infection Dengue fever Varicella infection EBV reactivation
Other	Dental infection Eye infection Stomatitis Catheter related infection Bartonella henselae infection Mastitis Myositis Parasitic infection Sialoadenitis Borrelia infection Hand foot mouth disease Localised infection Extradural abscess

PJP, Pneumocystis jirovecii pneumonia; CMV, cytomegalovirus; TB, tuberculosis; NTM, non-tuberculous mycobacteria; EBV, Epstein-Barr virus

Supplement 8: Subgroup construction

We observed a considerable level of heterogeneity between studies included in this review for both the total number of infected patients and the number of seriously infected patients. To create subgroups of relatively homogeneous studies, we grouped studies based on study design and follow-up duration, as explained in Table S4 below.

Table S4. Theoretical basis for subgroups created in this review

Potential effect modifiers	Evaluation	Evidence
Study design	RCTs comprise a highly selected population, a double-blind design and an intensive follow-up where patients are carefully monitored for every sign of adverse events. Registries contain real-world data with large study populations; these are secondary data extracted from electronic patient or insurance records. Registries mainly report on serious infections. Patients were not subjected to harsh in- and exclusion criteria like in RCTs, registries therefore contain patients with a higher number of comorbidities than RCTs. Open-label studies are usually performed in one centre. Patients are subjected to selection before inclusion, the design is not double-blind.	Evans SR. Clinical trial structures. J Exp Stroke Transl Med. 2010 Feb 9;3(1):8-18. doi: 10.6030/1939-067x-3.1.8. PMID: 21423788; PMCID: PMC3059315. https://clinicaldevice.typepad.com/cdg_whitepapers/2011/07/registry-studies-why-and-how.html
Follow-up duration	It is likely that the longer a study takes, the more information on ADRs is lost. The incidence of infections in biological treatment is higher in the first 3-6 months after treatment initiation.	Sakai, R., Komano, Y., Tanaka, M., Nanki, T., Koike, R., … Nagasawa, H. (2012). Time-dependent increased risk for serious infection from continuous use of TNF antagonists during three years in rheumatoid arthritis patients. Arthritis Care & Research, n/a–n/a. doi:10.1002/acr.21666 Strangfeld, A., Eveslage, M., Schneider, M., Bergerhausen, H. J., Klopsch, T., Zink, A., & Listing, J. (2011). Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Annals of the Rheumatic Diseases, 70(11), 1914–1920. doi:10.1136/ard.2011.151043 Ranza, R., de la Vega, M.C., Laurindo, I.M.M. et al. Changing rate of serious infections in biologic-exposed rheumatoid arthritis patients. Data from South American registries BIOBADABRASIL and BIOBADASAR. Clin Rheumatol 38, 2129–2139 (2019).

		https://doi.org/10.1007/s10067-019-04516-2

ADR – adverse drug reaction; RCT– randomised controlled trial

As presented in the manuscript, we assessed how heterogeneity metrics changed as we formed subgroups. We first evaluated the relationship between follow-up duration and infection prevalence, by incorporating the follow-up duration as a moderator in a multivariate meta-regression model. I^2, i.e., the percentage of the total variability in a set of effect sizes due to true heterogeneity, was used as primary criterion to assess the change in the level of heterogeneity. The σ_1^2 and σ_2^2, being the between-study and between-study-arms variance respectively, were used to support our I^2 based decision as subgroups were created. Cochran's Q is a weighted sum of squares that uses the deviation of each study's observed effect from the summary effect, weighted by the inverse of the study's variance.

First, we computed the heterogeneity metrics for all studies taken together, then, studies were divided by study design, and finally also by follow-up duration (please see Figure 2 in the manuscript).

All subgroups based on study design – except the registry subgroup (which is based on only three studies) – showed significant heterogeneity. We therefore formed subgroups based on study design and follow-up duration after exploring how the follow-up duration influences the proportion of infected patients (Table S5, Figures S1 & S2). Following the patterns observed in Figures 2 and 3, we defined three subgroups: ≤18 weeks, 19-38 weeks, and 39-60 weeks. Because of the small number of studies per study design, only RCT studies were further sub-grouped according to follow-up duration.

Although the level of heterogeneity was reduced subsequently after subgroups were formed, a moderate to higher level of heterogeneity that needs to be explained or controlled (if possible) remained. For that, we employed a multivariate meta-regression model (see Appendices 10, 19 and 20).

Table 5: Multivariate meta-regression results using follow-up duration as moderator (RCTs only)

		β (SE)	Test for moderator	σ_1^2	σ_2^2	I^2	Cochran's Q test (P)
Total number of infected patients	Intercept	-0.9426(0.0850)	<0.0001	0.2210	0.0035	87.7992	< 0.001
	Follow up length (weeks)	0.0106 (0.0023)	<0.0001				
Number of seriously infected patients	Intercept	-3.8412(0.0948)	<0.001	0.1322	0.0285	36.3202	0.0218
	Follow up (weeks)	0.0054(0.0023)	<0.001				

β, meta-regression coefficient estimate; SE, Standard error; I^2, variation (%) explained by differences in studies; σ_1^2, variance (between study); σ_2^2, variance (within study); Cochran's Q test (P), Cochran's Q test p-value.

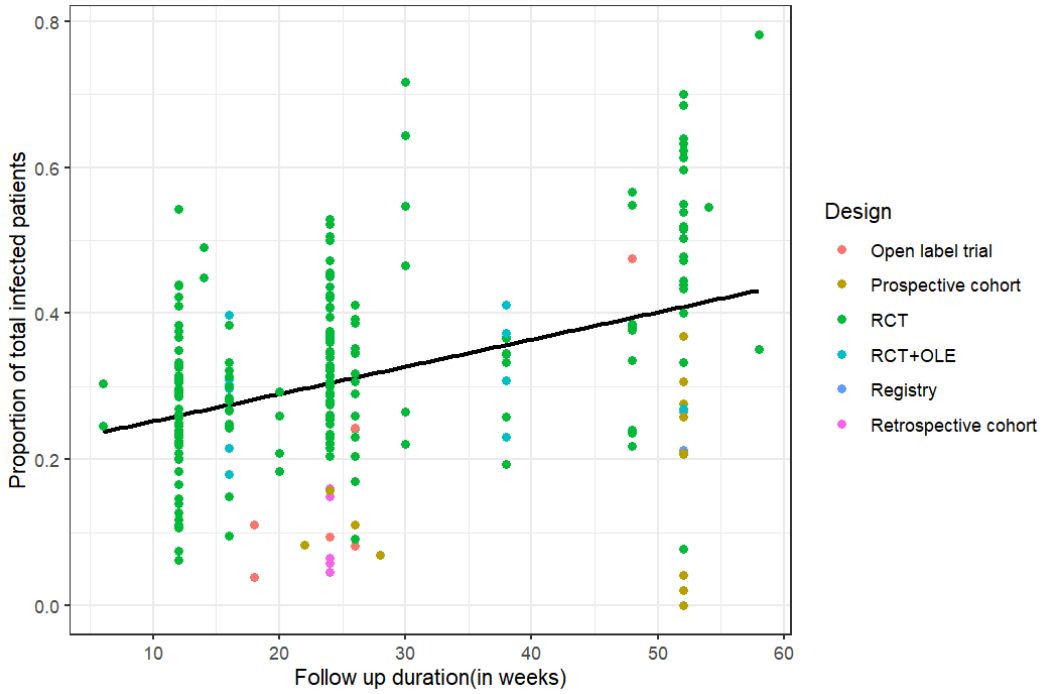


Figure S1: Infection proportion of total number of infected patients vs follow-up duration.
RCT, randomised controlled trial; RCT+OLE = randomised controlled trial open-label extension

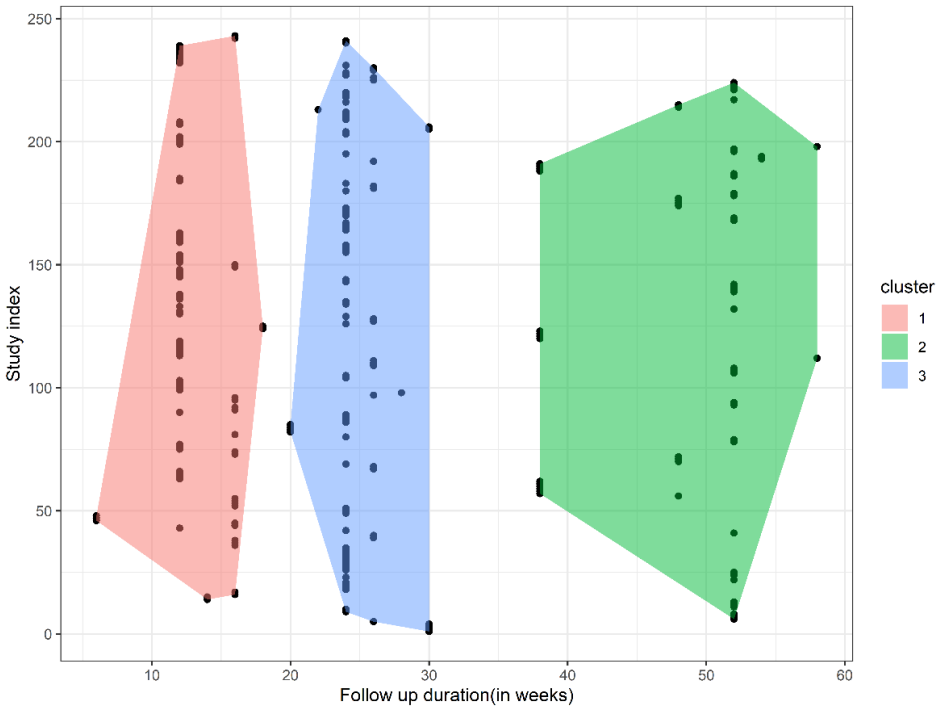


Figure S2: clusters in the follow-up length of included studies
Study index is a unique identification number (row label) assigned to each study and study arm.

Specifying inputs to the rma.mv() function

We used the *rma.mv* function of the *metafor package* with the input of the observed effect sizes(y_i) and the corresponding sampling variances(v_i). For the proportion of the total(seriously) infected patients, for the i^{th}study $(i = 1, \dots, n)$, the observed effect size was $log[\frac{\hat{p}_i}{1-\hat{p}_i}]$ and the corresponding sampling variance was $\frac{1}{x_i} + \frac{1}{L_i - x_i}$, where $\hat{p}_i$ = the reported proportion of the total(seriously) infected patients, x_i = the total number of (seriously) infected patients, and L_i is the sample size of the i^{th}study, n = the number of studies/study arms included in this review. For the event rates, the observed effect size and the corresponding sampling variance were $\frac{e_i}{t_i}$ and $\frac{e_i}{t_i^2}$ respectively, where e_i = the (total) number of (seriously) infectious events and t_i = the total exposure time in patient-year in the i^{th} study. In the *rma.mv* function, we specified the random effect as ~ 1| study_id/study_arm_id where study_id is the unique identifying number for each study and study_arm_id is the unique identifying number for each study arms within the study. This specification of the random effect allows the effect size to vary within and between study arms and by studies.

Supplement 9: Variable selection

A multivariate meta-regression model was fitted for the three subgroups of RCT studies (grouped by study design and follow-up duration, see figure S1 in supplement 8). We identified 51 potential moderators that have a theoretical basis (literature supported) and that were also extractable from the studies included in this review. From these, we selected only those features that had at least been reported in 10 studies per subgroup (table S6). The estimated coefficient together with other relevant information for the selected moderators are presented in the result section of the manuscript, and supplement 10.

Table S6. Variables selected for the multivariate meta-regression model

Variable	Reference(s)	Included/excluded	Reasoning
Age	KOMANO, Y., TANAKA, M., NANKI, T., KOIKE, R., SAKAI, R., … KAMEDA, H. (2011). Incidence and Risk Factors for Serious Infection in Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor Inhibitors: A Report from the Registry of Japanese Rheumatoid Arthritis Patients for Longterm Safety. The Journal of Rheumatology, 38(7), 1258–1264. doi:10.3899/jrheum.101009	Include age	Increasing age increases the risk of serious infection
Sex	Bechman, K., Halai, K., Yates, M., Norton, S., Cope, A. P., British Society for Rheumatology Biologics Register for Rheumatoid Arthritis Contributors Group, Hyrich, K. L., & Galloway, J. B. (2021). Nonserious Infections in Patients With Rheumatoid Arthritis: Results From the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Arthritis & rheumatology (Hoboken, N.J.), 73(10), 1800–1809. https://doi.org/10.1002/art.41754	Include sex	Does not appear to influence the risk of serious infection, but does influence the risk of non-serious infection (female sex)
Chronic pulmonary diseases: COPD, Asthma, ILD	KOMANO, Y., TANAKA, M., NANKI, T., KOIKE, R., SAKAI, R., … KAMEDA, H. (2011). Incidence and Risk Factors for Serious Infection in Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor Inhibitors: A Report from the Registry of Japanese Rheumatoid Arthritis Patients for Longterm Safety. The Journal of	Include COPD, Asthma, ILD	Presence of chronic pulmonary diseases increases the risk of serious infection, particularly pneumonia

	Rheumatology, 38(7), 1258–1264. doi:10.3899/jrheum.101009		
Advanced disease stage of RA (steinbroker stage III or IV)	KOMANO, Y., TANAKA, M., NANKI, T., KOIKE, R., SAKAI, R., … KAMEDA, H. (2011). Incidence and Risk Factors for Serious Infection in Patients with Rheumatoid Arthritis Treated with Tumor Necrosis Factor Inhibitors: A Report from the Registry of Japanese Rheumatoid Arthritis Patients for Longterm Safety. The Journal of Rheumatology, 38(7), 1258–1264. doi:10.3899/jrheum.101009	Include Steinbroker stage	Advanced disease stage of RA increases the risk of serious infection
Dosage of MTX, particularly > 8 mg/week	Sakai, R., Komano, Y., Tanaka, M., Nanki, T., Koike, R., … Nagasawa, H. (2012). Time-dependent increased risk for serious infection from continuous use of TNF antagonists during three years in rheumatoid arthritis patients. Arthritis Care & Research, n/a–n/a. doi:10.1002/acr.21666	Include MTX dosage	Higher MTX dosage increases the risk of infection
Biological class/target/name	Singh, J. A., Wells, G. A., Christensen, R., Tanjong Ghogomu, E., Maxwell, L. J., MacDonald, J. K., … Buchbinder, R. (2011). Adverse effects of biologics: a network meta-analysis and Cochrane overview. Cochrane Database of Systematic Reviews. doi:10.1002/14651858.cd008794.pub2 10.1002/14651858.CD008794.pub2 Strangfeld, A., Eveslage, M., Schneider, M., Bergerhausen, H. J., Klopsch, T., Zink, A., & Listing, J. (2011). Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Annals of the Rheumatic Diseases, 70(11), 1914–1920. doi:10.1136/ard.2011.151043	Include biological class, target and individual drugs	Biological class/target/name may increase or decrease the risk of contracting a serious infection. TNF-alpha inhibitors seem more likely to cause serious infections than other biological classes. Etanercept seems less likely to cause serious infection, and infliximab/adalimumab/certolizumab/tocilizumab/anakinra seem more likely to do so Also influences risk of non-serious infections

	Bechman, K., Halai, K., Yates, M., Norton, S., Cope, A. P., British Society for Rheumatology Biologics Register for Rheumatoid Arthritis Contributors Group, Hyrich, K. L., & Galloway, J. B. (2021). Nonserious Infections in Patients With Rheumatoid Arthritis: Results From the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Arthritis & rheumatology (Hoboken, N.J.), 73(10), 1800–1809. https://doi.org/10.1002/art.41754		
Disease activity - Mean DAS28-CRP - Mean CDAI - HAQ - TJC28 - VAS pain score Functional status FFbH	Sakai, R., Komano, Y., Tanaka, M., Nanki, T., Koike, R., … Nagasawa, H. (2012). Time-dependent increased risk for serious infection from continuous use of TNF antagonists during three years in rheumatoid arthritis patients. Arthritis Care & Research, n/a–n/a. doi:10.1002/acr.21666 Au, K., Reed, G., Curtis, J. R., Kremer, J. M., Greenberg, J. D., … Strand, V. (2011). High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Annals of the Rheumatic Diseases, 70(5), 785–791. doi:10.1136/ard.2010.128637 Van Dartel, S. A. A., Fransen, J., Kievit, W., Dutmer, E. A. J., Brus, H. L. M., Houtman, N. M., … van Riel, P. L. C. M. (2013). Predictors for the 5-year risk of serious infections in patients with rheumatoid arthritis treated with anti-tumour necrosis factor therapy: a cohort study in the Dutch Rheumatoid Arthritis Monitoring (DREAM) registry. Rheumatology, 52(6), 1052–1057. doi:10.1093/rheumatology/kes413 10.1093/rheumatology/kes413 Bechman, K., Halai, K., Yates, M., Norton, S., Cope, A. P., British Society for Rheumatology Biologics Register for Rheumatoid Arthritis Contributors Group, Hyrich, K. L., & Galloway, J. B. (2021). Nonserious Infections in	Include DAS-28 CRP, CDAI, HAQ, TJC28, VAS pain score separately No FFbH included in database	Higher disease activity may lead to higher infection risk, however, data are conflicting Increasing functional status is associated with decreased infection risk DAS28 and HAQ-DI also influence risk of nonserious infection

	Patients With Rheumatoid Arthritis: Results From the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Arthritis & rheumatology (Hoboken, N.J.), 73(10), 1800–1809. https://doi.org/10.1002/art.41754		
DAS-28 ESR TJC68 SJC28 SJC66 Physicians VAS Patient's VAS FACIT SDAI mTSS Morning stiffness duration SF-36		Include composite variable of DAS28-CRP, DAS28-ESR, CDAI, TJC28, TJC68, SJC28, SJC66, Physicians VAS, Patient's VAS, Pain VAS, FACIT	DAS-28 CRP and TJC28 are associated with increased infection risk. By extension, DAS-28 ESR and TJC68 could be predictors of infection risk. Swollen joint count and physicians and patients VAS are also important measures of disease activity and should be included separately. We also included a composite disease activity variable
Chronic renal disease	Strangfeld, A., Eveslage, M., Schneider, M., Bergerhausen, H. J., Klopsch, T., Zink, A., & Listing, J. (2011). Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Annals of the Rheumatic Diseases, 70(11), 1914–1920. doi:10.1136/ard.2011.151043	Include renal disease	Presence of chronic renal disease increases the risk of serious infection
History of serious infections	Strangfeld, A., Eveslage, M., Schneider, M., Bergerhausen, H. J., Klopsch, T., Zink, A., & Listing, J. (2011). Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for	Include history of serious infections	A history of serious infections increases the risk of serious infections during the study period

	the individual patient? Annals of the Rheumatic Diseases, 70(11), 1914–1920. doi:10.1136/ard.2011.151043		
Baseline ESR	Favalli, E. G., Desiati, F., Atzeni, F., Sarzi-Puttini, P., Caporali, R., Pallavicini, F. B., … Marchesoni, A. (2009). Serious infections during anti-TNFα treatment in rheumatoid arthritis patients. Autoimmunity Reviews, 8(3), 266–273. doi:10.1016/j.autrev.2008.11.002 10.1016/j.autrev.2008.11.002	Include baseline ESR	Increasing ESR correlates with increasing risk of serious infection
Concomitant use of corticosteroids and dose-dependent risk Mean dosage of prednisone >10 mg/day ("high-dose corticosteroids")	Favalli, E. G., Desiati, F., Atzeni, F., Sarzi-Puttini, P., Caporali, R., Pallavicini, F. B., … Marchesoni, A. (2009). Serious infections during anti-TNFα treatment in rheumatoid arthritis patients. Autoimmunity Reviews, 8(3), 266–273. doi:10.1016/j.autrev.2008.11.002 10.1016/j.autrev.2008.11.002 Wolfe, F., Caplan, L., & Michaud, K. (2006). Treatment for rheumatoid arthritis and the risk of hospitalization for pneumonia: Associations with prednisone, disease-modifying antirheumatic drugs, and anti–tumor necrosis factor therapy. Arthritis & Rheumatism, 54(2), 628–634. doi:10.1002/art.21568 Sakai, R., Komano, Y., Tanaka, M., Nanki, T., Koike, R., … Nagasawa, H. (2012). Time-dependent increased risk for serious infection from continuous use of TNF antagonists during three years in rheumatoid arthritis patients. Arthritis Care & Research, n/a–n/a. doi:10.1002/acr.21666 Schneeweiss, S., Setoguchi, S., Weinblatt, M. E., Katz, J. N., Avorn, J., Sax, P. E., … Solomon, D. H. (2007). Anti–tumor necrosis factor α therapy and the risk of serious bacterial infections in elderly patients with rheumatoid arthritis. Arthritis & Rheumatism, 56(6), 1754–1764. doi:10.1002/art.22600	Include concomitant corticosteroid Include corticosteroid dose	Concomitant use of corticosteroids and their increasing dosage both increase the risk of serious infection Use of corticosteroids increases the risk of non-serious infection

	Strangfeld, A., Eveslage, M., Schneider, M., Bergerhausen, H. J., Klopsch, T., Zink, A., & Listing, J. (2011). Treatment benefit or survival of the fittest: what drives the time-dependent decrease in serious infection rates under TNF inhibition and what does this imply for the individual patient? Annals of the Rheumatic Diseases, 70(11), 1914–1920. doi:10.1136/ard.2011.151043 Bechman, K., Halai, K., Yates, M., Norton, S., Cope, A. P., British Society for Rheumatology Biologics Register for Rheumatoid Arthritis Contributors Group, Hyrich, K. L., & Galloway, J. B. (2021). Nonserious Infections in Patients With Rheumatoid Arthritis: Results From the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Arthritis & rheumatology (Hoboken, N.J.), 73(10), 1800–1809. https://doi.org/10.1002/art.41754		
Diabetes mellitus	Curtis, J. R., Xie, F., Chen, L., Muntner, P., Grijalva, C. G., Spettell, C., Fernandes, J., McMahan, R. M., Baddley, J. W., Saag, K. G., Beukelman, T., & Delzell, E. (2012). Use of a disease risk score to compare serious infections associated with anti-tumor necrosis factor therapy among high- versus lower-risk rheumatoid arthritis patients. Arthritis care & research, 64(10), 1480–1489. https://doi.org/10.1002/acr.21805 Crowson, C. S., Hoganson, D. D., Fitz-Gibbon, P. D., & Matteson, E. L. (2012). Development and validation of a risk score for serious infection in patients with rheumatoid arthritis. Arthritis and rheumatism, 64(9), 2847–2855. https://doi.org/10.1002/art.34530	Include diabetes mellitus	Presence of diabetes mellitus increases the risk of serious infection

Several other comorbidities: - Alcoholism - Coronary heart disease - Peripheral vascular disease	Crowson, C. S., Hoganson, D. D., Fitz-Gibbon, P. D., & Matteson, E. L. (2012). Development and validation of a risk score for serious infection in patients with rheumatoid arthritis. Arthritis and rheumatism, 64(9), 2847–2855. https://doi.org/10.1002/art.34530	Include coronary heart disease, include congestive heart failure Include alcoholism Include peripheral vascular disease	Presence of these comorbidities increases the risk of serious infection
Smoking	Bechman, K., Halai, K., Yates, M., Norton, S., Cope, A. P., … Hyrich, K. L. (2021). *Nonserious Infections in Patients With Rheumatoid Arthritis: Results From the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. Arthritis & Rheumatology*. doi:10.1002/art.41754	Include smoking status (current, former, ever)	Smoking seems to be associated with an increased risk of serious infection, but a decreased risk of nonserious infection
Extra-articular manifestations of RA, organic brain disease	Doran, M. F., Crowson, C. S., Pond, G. R., O'Fallon, W. M., & Gabriel, S. E. (2002). Predictors of infection in rheumatoid arthritis. Arthritis and rheumatism, 46(9), 2294–2300. https://doi.org/10.1002/art.10529	Include extra-articular manifestations of RA Organic brain disease not included in database	Extra-articular manifestations of RA and organic brain disease are associated with increasing risk of serious infection
RA duration	Lang, V. R., Englbrecht, M., Rech, J., Nüsslein, H., Manger, K., Schuch, F., … Zwerina, J. (2011). Risk of infections in rheumatoid arthritis patients treated with tocilizumab. Rheumatology, 51(5), 852–857. doi:10.1093/rheumatology/ker223 10.1093/rheumatology/ker223	Include disease duration	Longer RA duration is associated with increased risk of serious infection

Previous exposure to >3 DMARDs	Lang, V. R., Englbrecht, M., Rech, J., Nüsslein, H., Manger, K., Schuch, F., … Zwerina, J. (2011). Risk of infections in rheumatoid arthritis patients treated with tocilizumab. Rheumatology, 51(5), 852–857. doi:10.1093/rheumatology/ker223 10.1093/rheumatology/ker223	Include no of prior DMARDs 0->3 Include mean number of prior DMARDs	Exposure to 3 or more prior DMARDS is associated with an increased risk of serious infection
Concomitant leflunomide use	Lang, V. R., Englbrecht, M., Rech, J., Nüsslein, H., Manger, K., Schuch, F., … Zwerina, J. (2011). Risk of infections in rheumatoid arthritis patients treated with tocilizumab. Rheumatology, 51(5), 852–857. doi:10.1093/rheumatology/ker223 10.1093/rheumatology/ker223 Morel, J., Constantin, A., Baron, G., Dernis, E., Flipo, R. M., Rist, S., … Sibilia, J. (2017). Risk factors of serious infections in patients with rheumatoid arthritis treated with tocilizumab in the French Registry REGATE. Rheumatology, 56(10), 1746–1754. doi:10.1093/rheumatology/kex238 10.1093/rheumatology/kex238	Include percentage of patients on concomitant leflunomide	Concomitant leflunomide use is associated with an increased risk of serious infections in tocilizumab use
Negative anti-CCP	Morel, J., Constantin, A., Baron, G., Dernis, E., Flipo, R. M., Rist, S., … Sibilia, J. (2017). Risk factors of serious infections in patients with rheumatoid arthritis treated with tocilizumab in the French Registry REGATE. Rheumatology, 56(10), 1746–1754. doi:10.1093/rheumatology/kex238 10.1093/rheumatology/kex238	Include percentage of patients with positive anti-CCP	Negative anti-CCP at baseline is associated with an increased risk of serious infection in tocilizumab use
Baseline B-cell count, IgM, IgG, neutrophils		Include	Decreased B-cell and immunoglobulin counts at baseline are associated with increased risk of serious infection.
Prior bDMARD use	Salmon JH, Gottenberg JE, Ravaud P on behalf of all the investigators of the ORA registry and the French Society of Rheumatology, et alPredictive risk factors of serious infections in patients with rheumatoid arthritis treated with abatacept in common practice: results from the Orencia	Include	A lower number of prior bDMARDs seems to increase the risk of serious infection

	and Rheumatoid Arthritis (ORA) registry Annals of the Rheumatic Diseases 2016;75:1108-1113.		
Mean number of prior bDMARs	Salmon JH, Gottenberg JE, Ravaud P on behalf of all the investigators of the ORA registry and the French Society of Rheumatology, et alPredictive risk factors of serious infections in patients with rheumatoid arthritis treated with abatacept in common practice: results from the Orencia and Rheumatoid Arthritis (ORA) registry Annals of the Rheumatic Diseases 2016;75:1108-1113.	Include	A lower number of prior bDMARDs seems to increase the risk of serious infection
Number of prior bDMARDs 0->3	Salmon JH, Gottenberg JE, Ravaud P on behalf of all the investigators of the ORA registry and the French Society of Rheumatology, et alPredictive risk factors of serious infections in patients with rheumatoid arthritis treated with abatacept in common practice: results from the Orencia and Rheumatoid Arthritis (ORA) registry Annals of the Rheumatic Diseases 2016;75:1108-1113.	Include	A lower number of prior bDMARDs seems to increase the risk of serious infection

Anti-CCP, anti-cyclic citrullinated protein antibodies; bDMARD, biological DMARD; CDAI, clinical disease activity index; COPD, chronic obstructive pulmonary disease; CRP, c-reactive protein; ILD, interstitial lung disease; DAS28-CRP, disease activity score in 28 joints using CRP; DAS28-ESR, disease activity score in 28 joints using ESR; DMARD, disease modifying anti-rheumatic drug; ESR, erythrocyte sedimentation rate; FACIT, functional assessment of chronic illness therapy-fatigue; FFbH, Funktionsfragebogen Hannover; HAQ-DI, health assessment questionnaire-disability index; mTSS, modified total Sharp score; MTX, methotrexate; RA, rheumatoid arthritis; SDAI, simplified disease activity index; SF-36, 36-item short form survey; SJC-28/66, swollen joint count in 28 or 66 joints; TJC,-28/68 tender joint count in 28 or 68 joints; VAS, visual analogue scale. Included/excluded: the decision whether the variable was included in the analysis, based on previously published literature. Included variables were analysed if they were reported in at least 10 studies.

Supplement 10: Multivariate meta-regression

This section presents the results of the multivariate meta-regression analysis for the total number of infected patients and the number of seriously infected patients for studies grouped by study design.

Table S7. Multivariate meta-regression results for the total number of infected patients; RCT studies

Moderators	N	$\boldsymbol{\beta}$ ($\boldsymbol{SE}$)	95%CI	Cochran's Q test (P)	Test for moderator (P)	$\boldsymbol{\sigma_1^2}$	$\boldsymbol{\sigma_2^2}$	$\mathbf{I^2}$
Biological target (reference: TNF alpha inhibitor)	203			<0.001	**0.048**	0.26	0.002	89.41
Constant		-0.62(0.07)	[-0.77, -0.48]					
B-cell inhibitor		0.05(0.16)	[-0.26, 0.36]					
Rituximab		-0.13(0.25)	[-0.61, 0.36]					
BTK-inhibitor		-0.91(0.28)	[-1.46, -0.36]					
IL-17 inhibitor		-0.48(0.39)	[-1.24, 0.28]					
IL-6 inhibitor		0.08(0.13)	[-0.17, 0.33]					
JAK1/2 inhibitor		0.17(0.13)	[-0.09, 0.43]					
JAK1/3 inhibitor		-0.43(0.32)	[-1.07, 0.21]					
JAK1 inhibitor		0.11(0.13)	[-0.15, 0.38]					
Pan-JAK inhibitor		-0.43(0.54)	[-1.49, 0.63]					
T-cell inhibitor		0.09(0.12)	[-0.15, 0.33]					
Biological class (reference: TNF alpha inhibitor)				<0.001	**0.0310**	0.27	0.002	89.60
Constant		-0.65(0.07)	[-0.79, -0.51]					
Interleukin antagonists		0.06(0.12)	[-0.18, 0.30]					
JAK-inhibitor		0.10(0.09)	[-0.08, 0.28]					
Other		-0.90(0.28)	[-1.45, -0.35]					
B-cell inhibitor		0.02(0.14)	[-0.25, 0.30]					
T-cell inhibitor		0.09(0.12)	[-0.14, 0.33]					
Follow up duration (weeks)	211	0.01(0.002)	[0.01, 0.02]	<0.001	**<.0001**	0.22	0.004	89.28
Age (mean)	192	-0.005(0.01)	[-0.03, 0.02]	<0.001	0.72	0.26	0.004	89.42
MTX dose (mg/week) (mean)	101	0.02(0.01)	[-0.01, 0.05]	<0.001	0.16	0.22	0.002	88.59
DAS28-CRP (mean)	131	-0.0001(0.09)	[-0.17, 0.17]	<0.001	1.0	0.17	0.002	83.64
CDAI (mean)	51	-0.01(0.01)	[-0.03, 0.02]	<0.001	0.53	0.11	0.003	73.24
HAQ-DI (mean)	175	-0.01(0.01)	[-0.02, 0.01]	<0.001	0.53	0.24	0.004	88.93

TJC-28 (mean)	38	-0.05(0.03)	[-0.11, 0.02]	<0.001	0.15	0.14	0.01	78.82
Pain VAS (mean)	107	0.01(0.01)	[-0.01, 0.03]	<0.001	0.47	0.20	0.01	87.98
Exclusion serious/recurrent infection	208	-0.05(0.10)	[-0.25, 0.16]	<0.001	0.65	0.27	0.004	89.27
ESR (mm/h) (mean)	85	-0.004(0.011)	[-0.03, 0.02]	<0.001	0.68	0.25	0.01	89.38
Corticosteroid use (percent)	135	-0.002(0.003)	[-0.01, 0.004]	<0.001	0.56	0.23	0.004	90.15
Corticosteroid dose (mg/day) (mean)	40	-0.004(0.07)	[-0.13, 0.13]	<0.001	0.95	0.19	0	88.49
RA duration (years) (mean)	173	-0.005(0.01)	[-0.03, 0.02]	<0.001	0.74	0.20	0.003	87.85
3 or more prior DMARDs (percent)	15	0.0003(0.01)	[-0.03, 0.03]	<0.001	0.98	0.30	0.02	93.56
Number of prior DMARDs (mean)	26	0.14(0.17)	[-0.19, 0.46]	<0.001	0.41	0.20	0.02	89.62
Number of prior DMARDs (SD)	19	0.1(0.39)	[-0.67, 0.87]	<0.001	0.80	0.22	0.02	91.56
Leflunomide use (percent)	15	0.09(0.04)	[0.02, 0.17]	<0.001	**0.01**	0.03	0.02	81.26
Anti-CCP positive (percent)	121	0.003(0.003)	[-0.002, 0.01]	<0.001	0.26	0.24	0.003	86.73
Previous bDMARD use (percent)	140	0(0.0013)	[-0.002, 0.002]	<0.001	0.99	0.21	0	87.05
1 previous bDMARD (percent)	24	-0.012(0.004)	[-0.02, -0.003]	<0.001	**0.01**	0.06	0	65.93
2 previous bDMARD (percent)	24	0.01(0.011)	[-0.011, 0.03]	<0.001	0.36	0.10	0	76.28
3 or more previous bDMARD (percent)	15	-0.002(0.015)	[-0.03, 0.03]	<0.001	0.92	0.11	0	79.57
Disease activity composite variable	194	-0.15(0.17)	[-0.48, 0.18]	<0.001	0.37	0.25	0.003	89.27
Exclusion criteria composite variable	211	0.012(0.03)	[-0.05, 0.07]	<0.001	0.71	0.27	0.004	89.91

Anti-CCP, anti-citrullinated protein antibodies; BTK, Bruton tyrosine kinase; CDAI = clinical disease activity index; CI, confidence interval; CRP, c-reactive protein; csDMARD, conventional synthetic disease modifying anti rheumatic drug; DAS28-CRP, disease activity score using c-reactive protein; ESR, erythrocyte sedimentation rate; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; JAK, Janus kinase; MTX, methotrexate; n, number of study arms; RA, rheumatoid arthritis; RCT, randomised controlled trial; Reference, a category to which the coefficient estimates for the categorical predictors are compared to ; SE, standard error; TNF-alpha, tumour necrosis factor alpha; VAS, visual analogue scale. Statistically significant moderators in bold.

Table S8. Multivariate meta-regression results for the total number of infected patients; prospective cohort studies

Moderators	n	$\boldsymbol{\beta}$ $(\boldsymbol{SE})$	95%CI	Cochran's Q test (P)	Test for moderator (P)	$\boldsymbol{\sigma_1^2}$	$\boldsymbol{\sigma_2^2}$	$\mathbf{I^2}$
Biological class (reference: TNF-alpha inhibitor)	15			<0.001	0.07	0.92	0	98.92
Constant		-1.43(0.29)	[-2.00, -0.85]					
Interleukin antagonist		-0.26(0.14)	[-0.53, 0.02]					
Biological target (reference: TNF-alpha inhibitor)	7			0.16	0.07	0.92	0.0	98.92
Constant		1.43 (0.29)	[-0.26, 0.14]					
IL-6 inhibitor		-0.26 (0.14)	[-0.53, 0.02]					
Followup duration	15	0.001(0.001)	[-0.001, 0.002]	<0.001	0.27	0.85	0.03	98.87
Age (mean)	17	-0.06(0.06)	[-0.19,0.06]	<0.001	0.32	0.53	0.02	98.49
Corticosteroid use (percent)	16	-0.016(0.01)	[-0.03,0.001]	<0.001	0.07	0.98	0	99.0
RA duration (mean) (years)	15	-0.031(0.07)	[-0.17,0.11]	<0.001	0.67	0.58	0.02	98.12
Previous bDMARD use (percent)	14	-0.002(0.01)	[-0.02, -0.01]	<0.001	0.72	0.54	0.01	98.71
Disease activity composite variable	15	-7.73(2.33)	[-12.30, -3.16]	<0.001	**0.001**	0.33	0.02	97.82
Exclusion criteria composite variable	19	-0.15(0.49)	[-1.11, 0.81]	<0.001	0.76	0.87	0.01	98.96

bDMARD, biological synthetic disease modifying anti rheumatic drug; CI, confidence interval; RA, rheumatoid arthritis; Reference, a category to which the coefficient estimates for the categorical predictors are compared to; SE, standard error; TNF-alpha, tumour necrosis factor alpha. Statistically significant moderators in bold.

Table S9. Multivariate meta-regression results for the total number of infected patients; RCT+OLE studies

Moderators	n	$\boldsymbol{\beta}$ $(\boldsymbol{SE})$	95%CI	Cochran's Q test(P)	Test for moderator(P)	$\boldsymbol{\sigma_1^2}$	$\boldsymbol{\sigma_2^2}$	$\mathbf{I^2}$
Biological class (reference: TNF-alpha inhibitor)				<0.0001	0.32	0.66	0.01	94.15
Constant		-0.29(0.48)	[-1.24, 0.66]					
Interleukin antagonist		-0.75(0.76)	[-2.24, 0.74]					
Biological target (reference: TNF-alpha inhibitor)				<0.0001	0.32	0.81	0.11	94.15
Constant		-0.29(0.48)	[-1.24, 0.66]					
IL-17 inhibitor		-0.75(0.76)	[-2.24, 0.74]					
Follow up duration		0.002(0.0004)	[0.001, 0.003]	0.0275	**<0.001**	0.08	0.01	67.67
Age (mean)	12	-0.003(0.10)	[-0,19, 0.18]	<0.0001	0.97	0.69	0.02	94.41
HAQ-DI (mean)	12	1.94(1.69)	[-1.37, 5.24]	<0.001	0.25	0.54	0.03	93.19
Pain VAS (mean)	11	0.001(0.07)	[-0.13, 0.14]	<0.001	0.99	0.827	0.02	95.47

Exclusion serious/recurrent infection	12	-0.75(0.76)	[-2.24, 0.74]	<0.001	0.32	0.66	0.012	94.15
Disease activity composite variable	12	-6.17(14.55)	[-34.70, 22.35]	<0.001	0.67	0.67	0.021	94.28
Exclusion criteria composite variable	12	-0.14(0.17)	[-0.48, 0.19]	<0.001	0.40	0.71	0.01	94.53

Anti-CCP, anti-citrullinated protein antibodies; HAQ-DI, health assessment questionnaire-disability index; IL, interleukin; n, number of study arms; RA, rheumatoid arthritis; RCT, randomised controlled trial; RCT+OLE, randomised controlled trial and open label extension; Reference, a category to which the coefficient estimates for the categorical predictors are compared to; SE, standard error; TNF-alpha, tumour necrosis factor alpha; VAS, visual analogue scale. Statistically significant moderators in bold.

Table S10. Multivariate meta-regression results for seriously infected patients; RCT studies

Moderators	n	$\boldsymbol{\beta}$ ($\boldsymbol{SE}$)	95%CI	Cochran's Q test (P)	Test for moderator (P)	$\boldsymbol{\sigma_1^2}$	$\boldsymbol{\sigma_2^2}$	$\boldsymbol{I^2}$
Biological class (reference: TNF- alpha inhibitor)	250			0.001	0.08	0.13	0.03	39.97
Constant		-3.65(0.09)	[-3.82, -3.47]					
B-cell inhibitor		0.22(0.19)	[-0.15, 0.58]					
Interleukin antagonist		0.15(0.15)	[-0.14, 0.43]					
JAK-inhibitor		-0.21(0.14)	[-0.48, 0.07]					
Other		-0.55(0.44)	[-1.42, 0.32]					
T-cell inhibitor		-0.2(0.19)	[-0.61, 0.15]					
Biological target (reference: TNF-alpha inhibitor)	245			<0.001	0.08	0.14	0.03	39.57
Constant		-3.66(0.09)	[-3.84, 3.48]					
B-cell inhibitor		0.24(0.24)	[-0.23, 0.70]					
Rituximab		0.19(0.28)	[-0.35, 0.74]					
BTK-inhibitor		-0.51(0.64)	[-1.77, 0.75]					
GM-CSF-inhibitor		-0.56(0.62)	[-1.77, 0.65]					
IL-1 inhibitor		-0.03(0.37)	[-0.76, 0.70]					
IL-17 inhibitor		-0.23(0.46)	[-1.14, 0.67]					
IL-6 inhibitor		0.21(0.16)	[-0.10, 0.52]					
JAK1/2 inhibitor		-0.09(0.24)	[-0.55, 0.38]					
JAK1/3 inhibitor		-0.15(0.21)	[-0.57, 0.27]					
JAK1 inhibitor		-0.31(0.25)	[-0.82, 0.19]					
Pan-JAK inhibitor		-0.36(0.34)	[-1.03, 0.30]					
T-cell inhibitor		-0.23(0.20)	[-0.62, 0.16]					
Followup duration (weeks)	253	0.005(0.002)	[0.001, 0.01]	<0.001	**0.02**	0.13	0.03	39.47
Age (mean)	233	0.01(0.02)	[-0.03, 0.05]	<0.001	0.51	0.18	0.004	38.68
MTX dose (mg/week) (mean)	115	-0.031(0.03)	[-0.08, 0.02]	0.0001	0.25	0.15	0.05	44.40
DAS28-CRP (mean)	147	-0.04(0.11)	[-0.25, 0.18]	0.95	0.74	0.06	0	13.9
CDAI (mean)	69	-0.03(0.02)	[-0.07, 0.02]	0.67	0.21	0.11	0	20.15

HAQ-DI (mean)	208	-0.011(0.011)	[-0.03, 0.01]	0.002	0.31	0.15	0.003	35.88
TJC-28 (mean)	50	0.02(0.05)	[-0.08, 0.11]	0.88	0.72	0.02	0.02	7.61
Pain VAS (mean)	151	0.003(0.01)	[-0.02, 0.03]	0.04	0.82	0.16	0	34.17
Exclusion serious/recurrent infection	253	0.05(0.11)	[-0.26, 0.17]	<0.001	0.68	0.15	0.02	38.96
ESR (mm/h) (mean)	121	0.04(0.011)	[0.02, 0.06]	<0.001	**0.001**	0.16	0.003	39.23
Corticosteroids (percent)	148	0.01(0.005)	[-0.001, 0.02]	0.001	0.07	0.13	0.03	41.42
Corticosteroids dose (mg/day) (mean)	44	0.15(0.14)	[-0.14, 0.43]	<0.001	0.31	0.41	0.01	66.01
RA duration (years) (mean)	213	-0.01(0.02)	[-0.04, 0.03]	<0.001	0.68	0.17	0.01	39.12
3 or more prior DMARDs (percent)	16	-0.01(0.01)	[-0.03, 0.02]	0.63	0.64	0.13	0	37.15
Number of prior DMARDs (mean)	38	0.11(0.14)	[-0.17, 0.38]	0.005	0.45	0.06	0.09	42.84
Number of prior DMARDs (SD)	26	0.28(0.32)	[-0.36, 0.91]	0.03	0.39	0.09	0.03	40.44
Leflunomide use (percent)	15	0.04(0.05)	[-0.06, 0.14]	0.58	0.44	0	0	0
Anti-CCP positive (percent)	128	0.01(0.01)	[0.002, 0.02]	0.72	**0.02**	0.07	0.01	17.53
Previous bDMARD use (percent)	162	0.0001(0.002)	[-0.003, 0.003]	0.01	0.94	0.14	0.001	33.19
1 previous bDMARD (percent)	29	-0.01(0.01)	[-0.02, 0.004]	0.92	0.22	0	0	0
2 previous bDMARD (percent)	29	0.01(0.01)	[-0.02, 0.004]	0.87	0.66	0.03	0	7.48
3 or more previous bDMARD (percent)	22	-0.01(0.01)	[-0.03, 0.02]	0.83	0.67	0	0	0
Disease activity composite variable	233	-0.22(0.22)	[-0.65, 0.21]	0.0001	0.31	0.18	0	39.29
Exclusion criteria composite variable	253	0.01(0.03)	[-0.05, 0.06]	<0.001	0.83	0.15	0.02	38.54

Anti-CCP, anti-citrullinated protein antibodies; bDMARD, biological synthetic disease modifying anti rheumatic drug; BTK, Bruton tyrosine kinase; CDAI = clinical disease activity index; CI, confidence interval; CRP, c-reactive protein; csDMARD, conventional synthetic disease modifying anti rheumatic drug; DAS28-CRP, disease activity score using c-reactive protein; ESR, erythrocyte sedimentation rate; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; JAK, Janus kinase; MTX, methotrexate; n, number of study arms; RA, rheumatoid arthritis; RCT, randomised controlled trial; Reference, a category to which the coefficient estimates for the categorical predictors are compared to; SE, standard error; TNF-alpha, tumour necrosis factor alpha; VAS, visual analogue scale. Statistically significant moderators in bold.

Table S11. Multivariate meta-regression results for seriously infected patients; prospective cohort studies

Moderators	n	$\boldsymbol{\beta}$ ($\boldsymbol{SE}$)	95%CI	Cochran's Q test (P)	Test for moderator (P)	$\boldsymbol{\sigma_1^2}$	$\boldsymbol{\sigma_2^2}$	$\mathbf{I^2}$
Biological class (reference: TNF-alpha inhibitor)	15			<0.0001	0.36	0.26	0.01	88.94
Intercept		-2.97(0.21)	[-3.38, -2.55]					
Interleukin antagonist		-0.26(0.28)	[-0.81, 0.29]					
Biological target (reference: TNF-alpha inhibitor)	15			<0.0001	0.36	0.26	0.01	88.94
Intercept		-2.97(0.21)	[-3.38, -2.55]					
IL-6 inhibitor		-0.26(0.28)	[-0.81, 0.29]					
Follow-up duration (weeks)	15	0.0003(0.0004)	[-0.0004, 0.001]	< 0.0001	0.39	0.24	0.02	88.42
Age (mean)	16	0.04(0.05)	[-0.06, 0.15]	< 0.0001	0.43	0.27	0.03	89.66
Exclusion history of serious infection	18	1.05(0.85)	[-0.62, 2.71]	< 0.0001	0.22	0.20	0.05	86.37
ESR (mm/h) (mean)	10	0.025(0.01)	[0.01, 0.05]	0.0871	**0.014**	0	0.06	50.02
Corticosteroid use (percent)	12	-0.01(0.02)	[-0.04, 0.03]	< 0.0001	0.69	0.25	0.06	91.29
RA duration (years) (mean)	15	0.12(0.06)	[-0.004, 0.25]	< 0.0001	0.06	0.29	0	87.75
Previous bDMARD use (percent)	12	0.002(0.005)	[-0.01, 0.012]	< 0.0001	0.77	0.11	0.16	88.15
Disease activity composite variable	15	2.63(3.24)	[-3.73, 8.98]	< 0.0001	0.42	0.28	0.05	90.45
Exclusion criteria composite variable	18	0.14(0.13)	[-0.11, 0.40]	< 0.001	0.28	0.21	0.05	86.87

Anti-CCP, anti-citrullinated protein antibodies; bDMARD, biological synthetic disease modifying anti rheumatic drug; IL, interleukin; JAK, Janus kinase; MTX, methotrexate; n, number of study arms; RA, rheumatoid arthritis; RCT, randomised controlled trial; Reference, a category to which the coefficient estimates for the categorical predictors are compared to; SE, standard error; TNF-alpha, tumour necrosis factor alpha. Statistically significant moderators in bold.

Table S12. Multivariate meta-regression results for seriously infected patients; registry studies

Moderators	n	$\boldsymbol{\beta}$ ($\boldsymbol{SE}$)	95%CI	Cochran's Q test (P)	Test for moderator (P)	$\boldsymbol{\sigma_1^2}$	$\boldsymbol{\sigma_2^2}$	$\mathbf{I^2}$
Biological class (reference: TNF-alpha inhibitor)	34			< 0.0001	0.24	0.12	0.27	98.51
Constant		-2.63(0.17)	[-2.95, -2.30]					
B-cell inhibitor		0.31(0.28)	[-0.23, 0.86]					
T-cell inhibitor		-0.22(0.27)	[-0.74, 0.30]					
Biological class (reference: TNF-alpha inhibitor)	34			< 0.001	0.24	0.12	0.27	98.51
Constant		-2.63(0.17)	[-2.95, -2.30]					
B-cell inhibitor		0.31(0.28)	[-0.23, 0.86]					
T-cell inhibitor		-0.22(0.27)	[-0.74, 0.30]					
Follow-up duration (weeks)	34	-0.0001(0.0004)	[-0.001, 0.001]	<0.001	0.83	0.16	0.27	98.64
Age (mean)	31	0.02(0.05)	[-0.07, 0.11]	<0.001	0.63	0.18	0.29	98.74
COPD (percent)	20	0.003(0.03)	[-0.06, 0.06]	<0.001	0.91	0.20	0.35	99.12
HAQ-DI (mean)	11	0.76(0.43)	[-0.08, 1.61]	<0.001	0.08	0.30	0.01	98.31
Renal disease (patients)	18	-0.0004(0.001)	[-0.003, 0.002]	<0.001	0.70	0.10	0.40	98.91
Renal disease (percent)	18	0.21(0.13)	[-0.03, 0.47]	<0.001	0.09	0	0.40	98.67
Previous severe infection (patients)	19	0.0004(0.001)	[-0.001, 0.002]	<0.001	0.51	0.04	0.40	98.84
Previous severe infection (percent)	19	0.047(0.04)	[-0.03, 0.13]	<0.001	0.25	0.08	0.35	98.82
Exclusion serious/recurrent infection	37	-0.08(0.53)	[-1.11, 0.95]	<0.001	0.88	0.15	0.26	98.51
Corticosteroid use (percent)	35	0.005(0.01)	[-0.01, 0.02]	<0.001	0.54	0.16	0.27	98.57
Diabetes mellitus (patients)	32	-0.0003(0.0002)	[-0.001, 0.0001]	<0.001	0.13	0.10	0.28	98.54
Diabetes mellitus (percent)	32	-0.02(0.02)	[-0.06, 0.02]	<0.001	0.29	0.12	0.28	98.61
CHF (percent)	15	0.02(0.03)	[-0.04, 0.08]	<0.001	0.45	0.13	0.44	99.08
Smoking. Ever (percent)	12	0.001(0.002)	[-0.003, 0.005]	<0.001	0.56	0.25	0.02	98.24
Smoking. current (percent)	10	0(0.03)	[-0.06, 0.06]	<0.001	1	0.38	0.02	98.72
Previous bDMARD use (percent)	18	0.01(0.01)	[-0.004, 0.02]	<0.001	0.21	0.05	0.58	99.17
Disease activity composite variable	18	2.55(1.38)	[-0.15, 5.24]	<0.001	0.06	0.18	0.01	96.40
Exclusion criteria composite variable	37	-0.09(0.17)	[-0.42, 0.23]	<0.001	0.58	0.14	0.26	98.48

Anti-CCP, anti-citrullinated protein antibodies; bDMARD, biological synthetic disease modifying anti rheumatic drug ; CHF, congestive heart failure; CI, confidence interval; COPD, chronic obstructive pulmonary disease; HAQ-DI, health assessment questionnaire-disability index; IL, interleukin; n, number of study arms; RA, rheumatoid arthritis; Reference, a category to which the coefficient estimates for the categorical predictors are compared to ; SE, standard error; TNF-alpha, tumour necrosis factor alpha; VAS, visual analogue scale. Statistically significant moderators in bold

Supplement 11: Creation of composite disease severity score

The following individual disease severity scores, when available, were used to create a composite variable:

Disease Activity Score using CRP or ESR (DAS28-CRP/ESR)
Clinical Disease Activity Index for RA (CDAI)
Health Assessment Questionnaire – Disability Index (HAQ-DI)
Swollen Joint Count in 66 joints (SJC66)
Tender Joint Count in 68 Joints (TJC68)
Patient's Global Assessment (Visual Analogue Scale 0-100)
Physicians Global Assessment (Visual Analogue Scale 0-100)
Pain score (Visual Analogue Scale 0-100)
Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-fatigue)

The composite variable 'disease severity score' was created by scaling each separate disease activity index and taking the mean of all these scaled values together.

Supplement 12: Creation of exclusion criteria composite variable

Studies could exclude patients from participating based on certain criteria. Exclusion criteria often entailed a history of serious infection or significant comorbidities, which influence infection risk. We therefore found it appropriate to include information on exclusion criteria in the analyses. To that end, we extracted exclusion criteria per study arm, and found studies use a combination of different exclusion criteria. Since the combination of exclusion criteria was not the same across studies, we decided to create a composite variable of exclusion criteria. This composite variable is the sum of the number of exclusion criteria that was used in the study.

Table S13. Exclusion criteria and frequency of use across studies

Exclusion criterion	Frequency (study arms)	Percentage (study arms)
Significant comorbidity	118	23,0
History of malignancy	111	21,7
Previous serious infection or recurrent infections	188	36,7
Other inflammatory disease	128	25,0
TB	149	29,1
Chronic viral infection	61	11,9
Leukopenia	77	15,0
Lab abnormalities	88	17,2
High dose corticosteroids	75	14,6
Prior bDMARD failure	42	8,2
Recent or future surgery	8	1,6
Organ transplantation	6	1,2
Disability	4	0,8
Immunodeficiency	4	0,8

bDMARD, biological disease modifying anti rheumatic drug; TB, tuberculosis. Studies could use multiple exclusion criteria mentioned in this table.

Supplement 13: characteristics of included registries and trials

Characteristics of studies expressed as the number of included studies and patients they contain per study design and geographical location. We also registered information on the mode of infectious adverse event reporting and follow up duration. The last table describes demographic characteristics of patients.

Table S14. Characteristics of included studies

	N (studies)	%	patients	%*
total	**242**	**100.0**	**293431**	**100.0**
RCT	150	62.0	52352	17.8
Registry	34	14.0	172892	58.9
Prospective cohort	26	10.7	42399	14.4
Retrospective cohort	7	2.9	4798	1.6
RCT+OLE	13	5.4	16569	5.6
Open label studies	12	5.0	4421	1.5
North America	122	50.4	149308	50.9
Latin America	58	24.0	27457	9.4
Europe	152	62.8	124421	42.4
East-Asia	82	33.9	70562	24.0
South-Asia	16	6.6	5363	1.8
Africa	8	3.3	2676	0.9
Middle East	8	3.3	2050	0.7
Oceania	16	6.6	15540	5.3
Reporting				
Total number of infected patients	129	53.3	58789	20.0
Total number of seriously infected patients	157	64.9	168042	57.3
Total number of infectious events	25	10.3	13937	4.7
Total number of serious infectious events	38	15.7	90204	30.7
Incidence rate total number of infected pateitns	18	7.4	22647	7.7
Incidence rate total number of seriously infected patients	48	19.8	155217	52.9
Event rate total number of infections	6	2.5	2753	0.9
Event rate total number of serious infections	13	5.4	26344	9.0
individual infections	166	68.6	97082	33.1
individual infectious events	29	12.0	90443	30.8
	median	IQR		
Follow-up duration (weeks)	24	16-48		
Follow-up duration (Patient years)	747	303-2534		

RCT, randomised controlled trial; RCT+OLE, randomised controlled trial and open label extension

Table S15. Number of included studies, study arms and patients across different biological classes

	TNF alpha	% of total	Interleukin antagonists	% of total	IL-6	% of Interleukin antagonists	B-cell inhibitors	% of total	RTX	% of B-cell inhibitor	T-cell inhibitors	% of total	JAK-inhibitors	% of total	Tofacitinib	% of JAK-inhibitor
studies	117	48,3	57	23,6	46	80,7	34	14,0	23	67,6	26	10,7	29	12,0	10	34,5
study arms	205	40,0	115	22,5	84	73,0	59	11,5	26	44,1	35	6,8	70	13,7	24	34,3
patients	170826	58,2	49182	16,8	45379	92,3	22685	7,7	19149	84,4	40098	13,7	9243	3,1	3845	41,6

IL, interleukin; JAK, Janus kinase; TNF, tumour necrosis factor

Table S16. Characteristics of included patients

	N	%*
Total	**293,431**	**100**
Female	231,893	79.0
Male	59,597	20.3
RF positive	58,953	20.1
Anti-CCP positive	22,911	7.8
MTX	146,859	50.0
Corticosteroid use	151,837	51.7
Previous biological use	77,385	26.4
	N	%**
total	43,790	100
Caucasian	39,064	89.2
Black	1,107	2.5
Hispanic	506	1.2
Asian	1,468	3.4
Native American	191	0.4
Other	1,454	3.3
	Weighted mean	
Age	56.6	
Weight	60.2	
RA duration	9.31	
RF titre	276	
Anti-CCP titre	464	
CRP	26.2	
ESR	45.1	

Anti-CCP, anti-citrullinated protein antibodies; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; MTX, methotrexate; n, number of patients; RA, rheumatoid arthritis; RF, rheumatoid factor.
**percentage of the total number of patients, since not all studies reported on all characteristics*
***percentage of the number of patients for whom race was reported*

Supplement 14: geographical location of trials and case reports

We extracted information on the geographical location where included studies were conducted. Case reports and registry studies usually originated in a single country, RCTs and open label (extension) studies, on the other hand, were performed in multiple countries across different continents. For case reports, we included individual countries. For the other studies, we included the continents where the study took place. One study could therefore account for multiple continents on the map.

Figure S3A. Geographical location of case reports

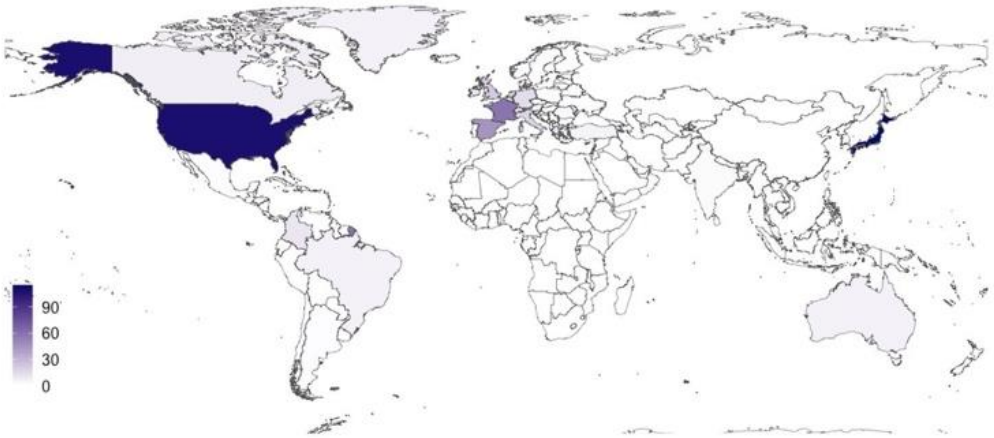
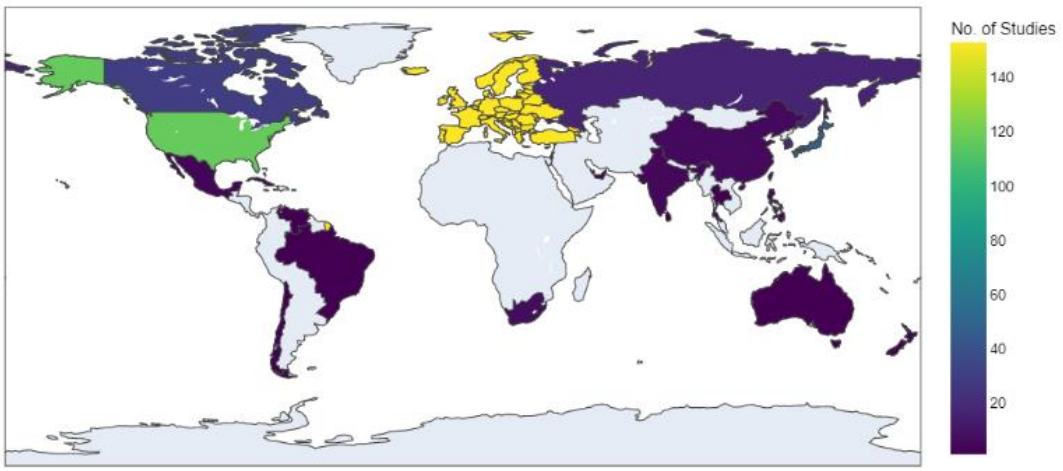


Figure S3B. Geographical location of studies



Supplement 15: Multivariate meta-regression for the total number of (seriously) infected patients in RCT studies with a follow-up duration of 18 weeks or less and between 19-38 weeks

Table S17. Multivariate meta-regression of RCT studies with a follow-up duration of 18 weeks or less and between 19-38 weeks

	Total number of infected patients: follow-up duration of 18 weeks or less						Total number of infected patients: follow-up duration of 19-38 weeks					
Moderators	n	β	95%CI	Test for moderator(P)	Cochran's Q test(P)	I^2	n	β	95%CI	Test for moderator(P)	Cochran's test(P)	
Biological target	75			0.10	<0.001	67.58	92			**<0.001**	0.51	84.69
(reference: TNF-alpha inhibitor)												
Constant		-0.86	[-1.09, -0.63]					-0.71	[-0.87, -0.55]			
Anti-LT-alpha		-0.27	[-0.88, 0.33]					-	-			
B-cell inhibitor		0.22	[-0.43, 0.87]					-0.18	[-0.52, 0.15]			
Rituximab								-0.18	[-0.65, 0.30]			
BTK-inhibitor		-0.91	[-1.43, -0.38]					-	-			
IL-17 inhibitor		-0.19	[-0.98, 0.61]					-0.46	[-1.26, 0.35]			
IL-20 inhibitor		-0.39	[-1.42, 0.64]					-	-			
IL-6 inhibitor		-0.02	[-0.57, 0.52]					0.04	[-0.21, 0.29]			
IL-1 inhibitor								-0.002	[-0.69, 0.68]			
JAK1/2 inhibitor		-0.33	[-1.23, 0.56]					0.30	[-0.17, 0.77]			
JAK1/3 inhibitor		-0.19	[-0.71, 0.33]					-	-			
JAK1 inhibitor		0.01	[-0.44, 0.46]					0.21	[-0.10, 0.52]			
Pan-JAK inhibitor		-0.19	[-1.01, 0.62]					-	-			
T-cell inhibitor		-	-					0.12	[-0.33, 0.58]			
Age (mean)	68	0.04	[-0.01, 0.09]	0.11	<0.001	56.17	84	0.01	[-0.02, 0.05]	0.45	<0.001	78.32
MTX dose (mg/week, mean)	41	-0.03	[-0.08, 0.02]	0.23	0.002	54.22	41	0.03	[-0.003, 0.06]	0.08	<0.001	83.36
DAS28-CRP (mean)	48	-0.20	[-0.58, 0.19]	0.31	<0.001	52.87	65	-0.01	[-0.15, 0.13]	0.88	<0.001	75.50
CDAI (mean)	22	-0.04	[-0.09, 0.01]	0.09	0.24	43.78	22	-0.01	[-0.03, 0.02]	0.68	<0.001	77.54
HAQ-DI (mean)	55	-0.21	[-0.61, 0.19]	0.31	<0.001	61.65	83	-0.003	[-0.02 ,0.01]	0.60	<0.001	80.95
TJC-28 (mean)	19	0.01	[-0.07, 0.09]	0.79	0.42	29.14	17	-0.03	[-0.10, 0.03]	0.32	<0.001	76.06
Pain (mean VAS)	36	0.01	[-0.02, 0.03]	0.60	0.03	47.20	50	-0.004	[-0.03, 0.022]	0.76	<0.001	84.04
Exclusion serious infection	77	0.09	[-0.21, 0.39]	0.55	<0.001	65.60	89	0.09	[-0.124, 0.30]	0.41	<0.001	85.01
ESR (mm/h, mean)	24	-0.02	[-0.06, 0.02]	0.41	<0.001	67.25	37	-0.006	[-0.03, 0.02]	0.61	<0.001	82.53
Corticosteroids (percent)	48	0.01	[0.002, 0.02]	**0.01**	0.15	3.71	62	-0.005	[-0.01, 0.00]	0.20	<0.001	88.43
Corticosteroid dose (mg/day, mean)	24	-0.05	[-0.17, 0.06]	0.35	0.61	25.07	10	0.10	[-0.15, 0.35]	0.42	0.002	72.46
RA duration (years, mean)	54	0.02	[-0.04, 0.08]	0.46	0.01	44.07	81	0.04	[0.01, 0.07]	**0.01**	<0.001	79.89
Number of prior csDMARDs (mean)	-	-	-	-	-	-	12	0.81	[0.40, 1.23]	**<0.001**	<0.001	83.81
Number of prior	-	-	-	-	-	-	12	0.68	[-0.54, 1.9]	0.27	<0.001	92.65

csDMARDS (SD)												
Leflunomide (percent)	-	-	-	-	-	-	10	0.09	[0.003, 0.18]	0.04	<0.001	87.60
Anti-CCP positive (percent)	43	0.002	[-0.004, 0.01]	0.54	0.001	58.49	50	-0.001	[-0.01, 0.01]	0.93	<0.001	67.48
Previous biological use (percent)	46	0.002	[-0.001, 0.004]	0.21	0.24	27.74	66	0.001	[-0.001, 0.004]	0.35	<0.001	79.13
1 previous biological (percent)	-	-	-	-	-	-	16	-0.02	[-0.03, -0.01]	<0.001	0.02	48.57
2 previous biologicals (percent)	-	-	-	-	-	-	16	0.01	[-0.02, 0.04]	0.37	<0.001	82.04
Disease activity composite variable (mean)	67	-0.63	[-211, 0.85]	0.41	<0.001	63.90	88	-0.09	[-0.33, 0.14]	0.44	<0.001	81.70
Exclusion criteria composite variable	77	0.06	[-0.04, 0.15]	0.24	<0.001	65.25	92	0.001	[-0.06, 0.06]	0.97	<0.001	84.65
Total number of seriously infected patients: follow-up duration of 18 weeks or less							**Total number of seriously infected patients: follow-up duration of 19-38 weeks**					
Moderators	n	β	95%CI	Test for moderator(P)	Cochran's Q test(P)	I^2	n	β	95%CI	Test for moderator(P)	Cochran's Q test(P)	I^2
Biological target (reference: TNF-alpha inhibitor)	91			**0.03**	0.99	0	105			0.3127	0.01	39.74
Constant		-3.57	[-3.86, -3.27]					-3.77	[-4.01, -3.54]			
BTK-inhibitor		-0.7219	[-1.75, 0.31]					-	-			
GM-CSF inhibitor		-0.6557	[-1.75, 0.44]					-	-			
IL-17 inhibitor		-0.02	[-0.80, 0.77]					-0.77	[-2.38, 0.84]			
IL-6 inhibitor		0.2532	[-0.39, 0.90]					0.15	[-0.24, 0.54]			
IL-1 inhibitor		0.1793	[-0.72, 1.08]					-	-			
JAK1/2 inhibitor		-0.3263	[-1.75, 1.10]					-0.09	[-0.73, 0.56]			
JAK1/3 inhibitor		-0.3437	[-1.01, 0.32]					-	-			
JAK1 inhibitor		-0.4253	[-0.99, 0.14]					-	-			
Pan-JAK inhibitor		-0.9455	[-1.70, -0.19]					-	-			
B-cell inhibitor		0.9679	[0.14, 1.79]					-0.69	[-1.53, 0.16]			
T-cell inhibitor		-	-					-0.23	[-0.83, 0.37]			
Rituximab		-	-					0.40	[-0.21, 1.01]			
Age (mean)	85	0.085	[-0.003, 0.17]	0.06	0.99	13.62	94	-0.0002	[-0.07, 0.07]	**0.004**	0.99	40.87
MTX dose (mg/week, mean)	41	-0.0774	[-0.14, -0.02]	**0.01**	0.99	0.42	54	0.041	[-0,05, 0,13]	**0.001**	0.36	51.83
DAS28-CRP (mean)	58	-0.3723	[-1.13, 0.39]	0.34	0.99	3.50	64	0.08	[-0.16, 0.33]	0.515	0.50	18.09
CDAI (mean)	30	-0.0999	[-0.18, -0.02]	**0.02**	0.99	1.88	30	0.009	[-0.04, 0.06]	0.26	0.75	28.46
HAQ-DI (mean)	71	0.1243	[-0.84, 1.09]	0.80	0.98	18.55	92	-0.01	[-0.03, 0.01]	0.063	0.47	30.18
TJC-28 (mean)	24	-0.0066	[-0.18, 0.16]	0.94	0.94	0	25	0.03	[-0.08, 0.14]	0.903	0.61	0
Pain (mean VAS)	60	-0.0166	[-0.07, 0.03]	0.50	0.99	8.98	65	0.02	[-0.02, 0.06]	**<0.001**	0.30	52.28
Exclusion serious infection	91	0.0257	[-0.46, 0.51]	0.92	0.95	16.41	105	0.25	[-0.08, 0.57]	**0.002**	0.13	40.56
ESR (mm/h, mean)	35	0.0197	[-0.07, 0.10]	0.65	0.81	23.93	57	0.04	[0.01, 0.07]	0.16	0.01	24.0
Corticosteroids (percent)	51	0.0291	[0.01, 0.04]	**<0.001**	0.99	0	67	0.01	[-0.01, 0.02]	**0.01**	0.34	37.88
Corticosteroid dose	22	-0.1375	[-0.55, 0.28]	0.52	0.48	25.49	14	0.35	[-0.06, 0.76]	**0.003**	0.09	73.084

(mg/day, mean)												
RA duration (years, mean)	70	0.0313	[-0.08, 0.14]	0.58	0.97	19.63	92	0.03	[-0.02, 0.09]	**0.01**	0.21	36.69
Anti-CCP positive (percent)	44	0.0086	[-0.01, 0.03]	0.33	0.93	10.52	48	0.01	[-0.01, 0.03]	0.81	0.44	10.75
Previous bDMARD use (percent)	55	0.0042	[-0.003, 0.01]	0.24	0.89	14.56	72	0.002	[-0.001, 0.005]	0.65	0.18	9.60
1 previous bDMARD (percent)	13	0.0137	[-0.01, 0.04]	0.21	0.99	0	15	-0.02	[-0,03, -0.003]	0.93	0.01	0
2 previous bDMARD (percent)	13	0.0333	[-0.03, 0.10]	0.33	0.98	0	15	0.001	[-0,034, 0.04]	0.48	0.95	13.47
3 or more previous bDMARD (percent)	10	0.0265	[-0.03, 0.08]	0.36	0.98	0	11	-0.01	[-0,04, 0.02]	0.65	0.66	0
Disease activity composite variable (mean)	83	-1.2384	[-3.99, 1.51]	0.38	0.96	17.17	102	-0.12	[-0.55, 0.30]	**0.01**	0.57	36.89
Exclusion criteria composite variable	91	-0.0103	[-0.16, 0.14]	0.89	0.95	15.94	108	0.01	[-0.06, 0.08]	**0.001**	0.78	41.69
Number of prior DMARDs (mean) -		-	-	-	-	-	21	0.27	[0.02, 0.52]	0.55	0.04	0
Number of prior DMARDs (SD) -		-	-	-	-	-	19	0.48	[-0.10, 1.07]	0.65	0.10	8.41
Leflunomide use (percent) -		-	-	-	-	-	10	0.07	[-0.05, 0.19]	0.51	0.29	0

Anti-CCP, anti-citrullinated protein antibodies; bDMARD, biological disease modifying anti rheumatic drug; BTK, Burton tyrosine kinase; CDAI, clinical disease activity index; CI, 95% confidence interval; CRP, c-reactive protein; csDMARD, conventional synthetic disease modifying anti rheumatic drug; DAS28-CRP, disease activity score using c-reactive protein; ESR, erythrocyte sedimentation rate; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; JAK, Janus kinase; MTX, methotrexate; n, number of study arms; RA, rheumatoid arthritis; Reference, a category to which the coefficient estimates for the categorical predictors are compared to ; TNF-alpha, tumour-necrosis factor alpha; VAS, visual analogue scale.
Statistically significant moderators in bold.

Supplement 16: Multivariate meta-regression of the total number of (seriously) infected patients in RCT's with a follow-up duration of 38-60 weeks

Table S18 presents the results of the multivariate meta-regression for the total number of infected patients in RCTs with a follow-up duration of 39-60 weeks.

Table S18: Multivariate meta-regression results for the total number of infected patients in RCT studies with a follow-up duration of 39-60 weeks

Moderators	n	β (SE)	95%CI	Test for moderator (P)	Cochran's Q test (P)	I^2
Biological target (reference: TNF-alpha inhibitor)	26			0.97	<0.001	96.80
TNF-alpha inhibitor (reference)		-0.03(0.27)	[-0.56, 0.51]			
B- cell inhibitor		0.18(0.62)	[-1.04, 1.39]			
IL-6 inhibitor		0.12(0.49)	[-0.83, 1.08]			
T-cell inhibitor		-0.04(0.13)	[-0.30, 0.22]			
Age (mean)	34	-0.03(0.03)	[-0.09, 0.03]	0.26	<0.001	95.33
MTX dose (mg/week, mean)	19	-0.01(0.08)	[-0.16, 0.14]	0.92	<0.001	93.58
Biological class	36	0.07(0.50)	[-0.90, 1.05]	0.88	<0.001	96.19
Biological target	36	-0.59(0.82)	[-2.20, 1.02]	0.47	<0.001	95.97
Biological name	36	-0.06(0.17)	[-0.39, 0.27]	0.71	<0.001	96.96
DAS28-CRP (mean)	18	-0.27(0.40)	[-1.05, 0.52]	0.50	<0.001	86.92
HAQ-DI (mean)	32	-0.38(0.55)	[-1.46, 0.70]	0.49	<0.001	95.70
Pain (mean VAS)	16	-0.06(0.03)	[-0.12, 0.01]	0.09	<0.001	91.09
Exclusion serious infection	36	0.11(0.34)	[-0.55, 0.77]	0.75	<0.001	95.80
ESR (mm/h, mean)	19	0.02(0.02)	[-0.02, 0.06]	0.35	<0.001	89.80
Corticosteroids (percent)	25	0.001(0.01)	[-0.01, 0.01]	0.95	<0.001	90.10
RA duration (years, mean)	32	-0.03(0.03)	[-0.08, 0.03]	0.34	<0.001	88.93
Anti-CCP positive (percent)	28	-0.002(0.013)	[-0.03, 0.023]	0.89	<0.001	90.79
Previous biological use (percent)	22	-0.003(0.01)	[-0.01, 0.01]	0.57	<0.001	95.87
Disease activity composite variable (mean)	34	-1.32(2.37)	[-5.97, 3.33]	0.58	<0.001	95.94
Exclusion criteria composite variable	36	0.10(0.13)	[-0.16, 0.3583]	0.45	<0.001	95.69

Anti-CCP, anti-citrullinated protein antibodies; BTK, Burton tyrosine kinase; CDAI = clinical disease activity index; CI, confidence interval; CRP, c-reactive protein; csDMARD, conventional synthetic disease modifying anti rheumatic drug; DAS28-CRP, disease activity score using c-reactive protein; ESR, erythrocyte sedimentation rate; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; JAK, Janus kinase; MTX, methotrexate; n, number of study arms; RA, rheumatoid arthritis; RCT, randomised controlled trial; Reference, a category to which the coefficient estimates for the categorical predictors are compared to; SE, standard error; TNF-alpha, tumour necrosis factor alpha; VAS, visual analogue scale. Statistically significant moderators in bold.

The following table presents the results of seriously infected patients in multivariate-meta regression for RCT 39-60 weeks.

Table S19. Multivariate meta-regression results for RCT studies with follow up duration between 39 and 60 weeks (seriously infected patients)

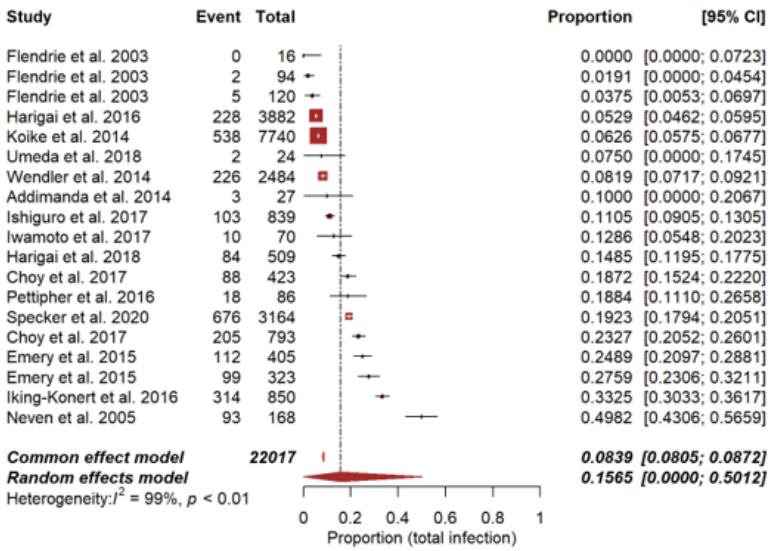
Moderators	k	$\boldsymbol{\beta(SE)}$	95%CI	Test for moderator (P)	Cochran's Q test (P)	$\boldsymbol{\sigma_1^2}$	$\boldsymbol{\sigma_2^2}$	$\mathbf{I^2}$
Biological target (reference: TNF-alpha	36			0.35	0.003	0.09	0.07	54.75
Contact		-	[-3.73, -3.02]					
B-cell inhibitor		0.26(0.35)	[-0.42, 0.95]					
IL-6 inhibitor		0.29(0.30)	[-0.29, 0.88]					
JAK1/3 inhibitor		0.01(0.35)	[-0.67, 0.69]					
T-cell inhibitor		-0.34(0.28)	[-0.90 0.21]					
Age (mean)	45	0.004(0.04)	[-0.06, 0.08]	**0.002**	0.91	0.05	0.08	46.69
MTX dose (mg/week) (mean)	20	-0.04(0.06)	[-0.17, 0.08]	**0.002**	0.47	0.03	0.17	56.82
HAQ-DI (mean)	40	-0.22(0.44)	[-1.08, 0.64]	**0.003**	0.62	0.04	0.08	45.41
Pain VAS (mean)	21	-0.04(0.02)	[-0.08, 0.01]	0.74	0.10	0.003	0	2.204
Exclusion of serious and recurrent infection	45	-0.06(0.18)	[-0.42, 0.2874]	**0.003**	0.72	0.04	0.08	45.65
ESR (mm/h) (mean)	22	0.03(0.02)	[-0.0101, 0.07]	**<0.001**	0.15	0.12	0.05	61.40
Corticosteroid use (percent)	30	-.002(0.01)	[-0.02, 0.01]	**0.002**	0.83	0.07	0.06	50.46
RA duration (years) (mean)	43	-0.02(0.02)	[-0.06, 0.03]	**0.002**	0.48	0.04	0.09	46.89
Anti-CCP positive (percent)	33	0.01(0.01)	[-0.01, 0.04]	0.33	0.27	0.03	0.03	23.36
Previous bDMARD use (percent)	28	-0.005(0.006)	[-0.02, 0.01]	**0.002**	0.36	0.10	0.07	52.80
Disease activity composite variable (mean)	43	-0.82(1.45)	[-3.66, 2.02]	**0.001**	0.57	0.04	0.09	47.63
Exclusion criteria composite variable	45	0.16(0.07)	[0.01, 0.30]	**0.01**	0.03	0.04	0.07	41.69

Anti-CCP, anti-citrullinated protein antibodies; bDMARD, biological synthetic disease modifying anti rheumatic drug; CI, confidence interval; CRP, c-reactive protein; ESR, erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire-disability index; IL, interleukin; JAK, Janus kinase; MTX, methotrexate; n, number of study arms; RA, rheumatoid arthritis; RCT, randomised controlled trial; Reference, a category to which the coefficient estimates for the categorical predictors are compared to; SE, standard error; TNF-alpha, tumour necrosis factor alpha; VAS, visual analogue scale. Statistically significant moderators in bold.

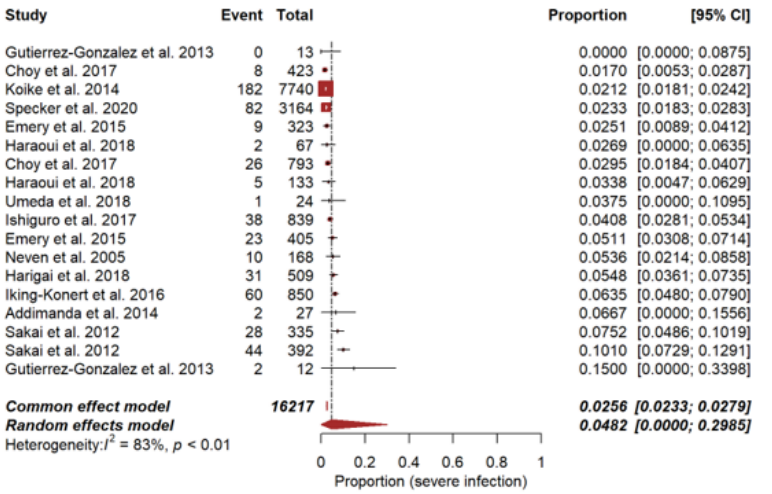
Supplement 17: additional forest plots

Below the forest plots are shown that were created to separately assess inconsistencies for the total number of infected patients and the number of seriously infected patients by study design.

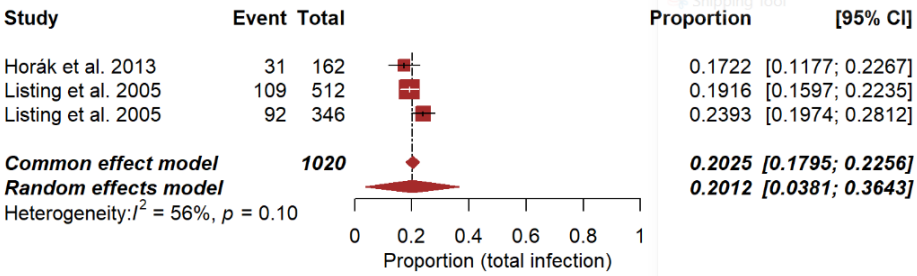
Prospective cohorts
(total number of infected patients)



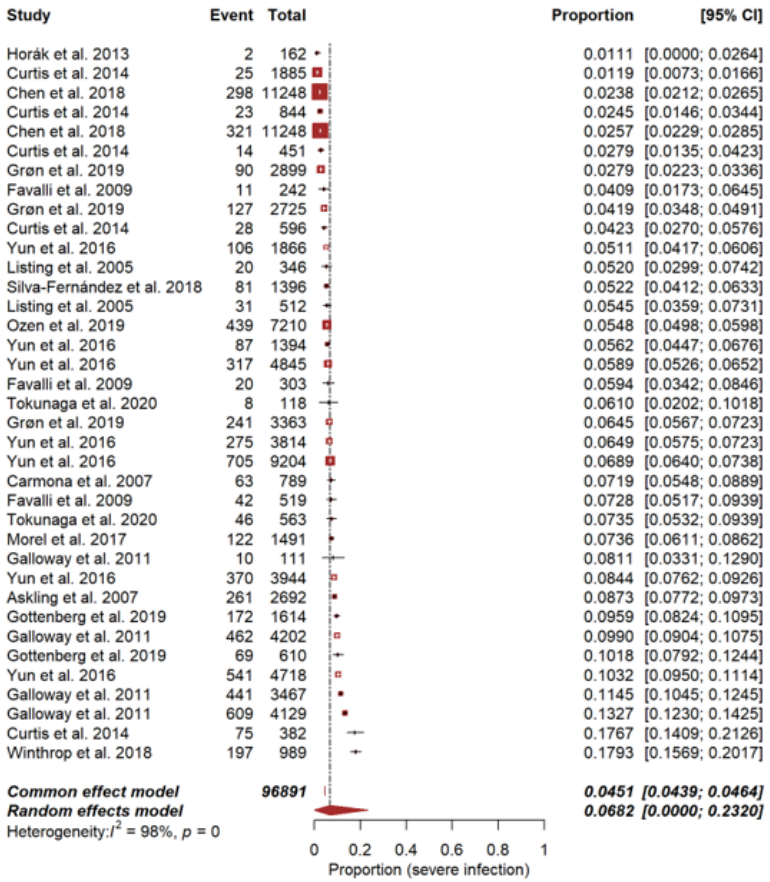
(number of seriously infected patients)



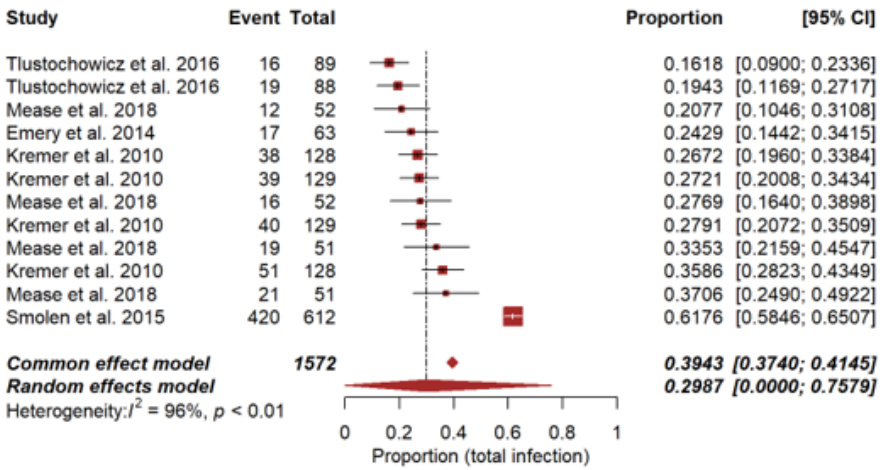
Registry studies
(total number of infected patients)



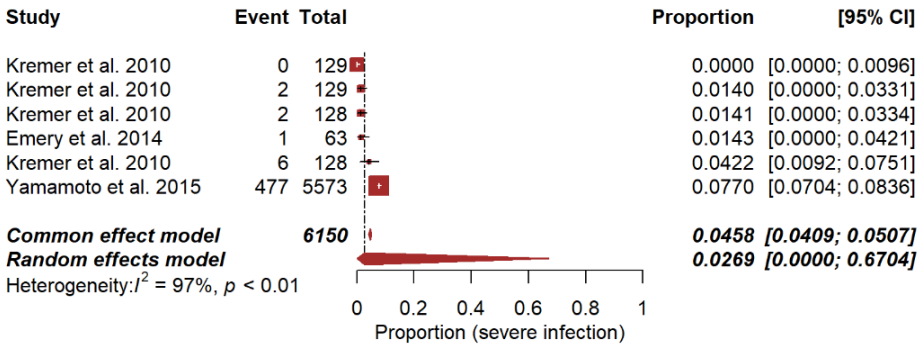
(number of seriously infected patients)



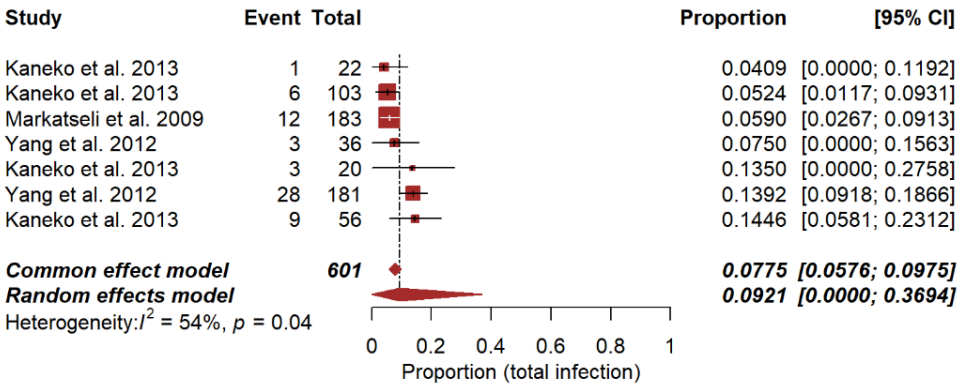
RCT + OLE
(number of infected patients)



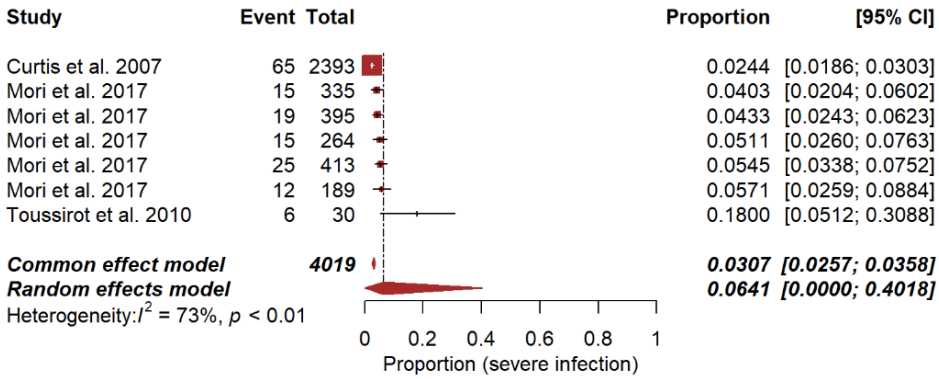
(number of seriously infected patients)



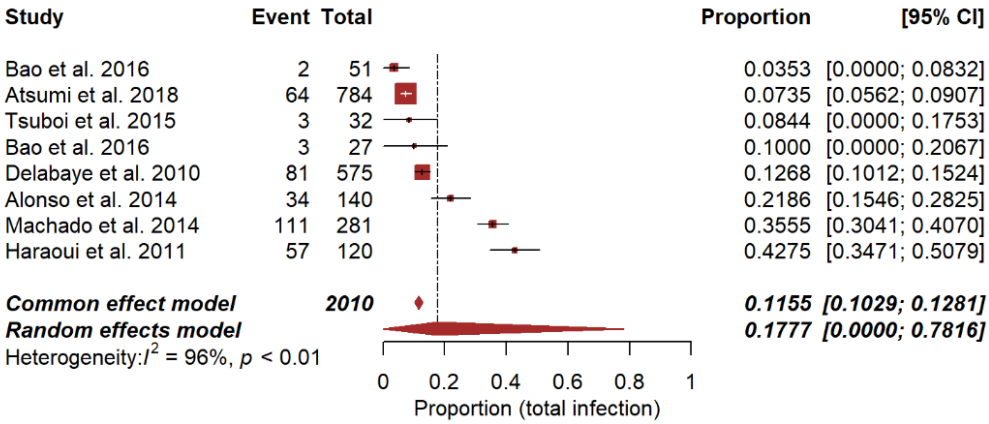
Retrospective cohorts
(total number of infected patients)



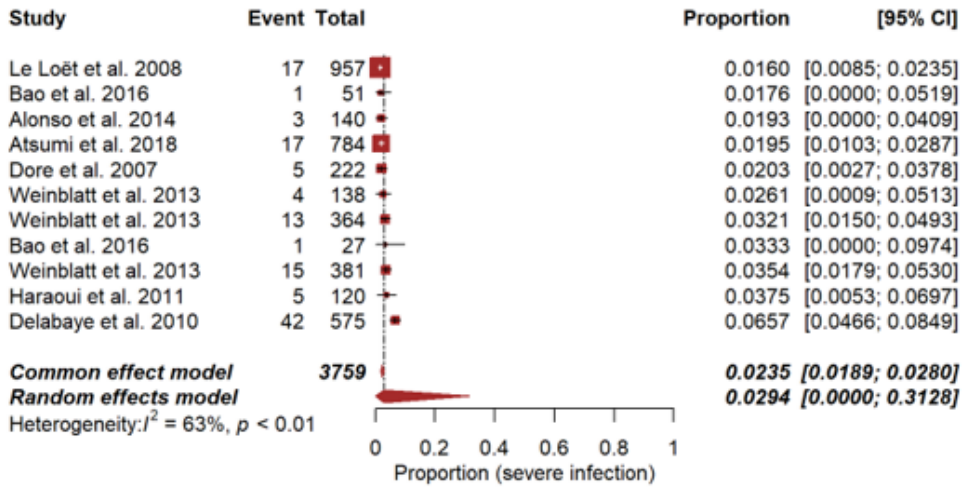
(number of seriously infected patients)



Open Label Trials
(total number of infected patients)



(number of seriously infected patients)



Supplement 18: Characteristics of case reports

In supplement 18, we present characteristics of patients from case reports at the time of the infection. This includes patient demographic characteristics, comorbidities, biological and csDMARD use, and also case characteristics such as outcome, details about treatment, hospitalisation and what happened to the bDMARD after infection. Geographical location of case reports was also extracted.

Table S20. Case report patient characteristics

	N	Percent	mean	SD
Female	336	66.8		
Male	142	28.2		
Unknown sex	25	5.0		
Age			61.02	11.7
RA duration (years)			12.3	9.2
Any comorbidity	155	30.8		
No comorbidity	40	8.0		
Comorbidity unspecified	298	59.2		
Corticosteroids use	210	41.8		
No corticosteroid use	188	37.4		
Corticosteroid use unspecified	105	20.9		
csDMARD use	285	56.7		
No csDMARD use	107	21.3		
csDMARD use unspecified	111	22.1		
csDMARD				
Azathioprine	15	4.7		
Bucillamine	1	0.3		
Cyclophosphamide	2	0.6		
Dapsone	1	0.3		
Hydroxychloroquine	13	4.0		
Iguratimod	1	0.3		
Leflunomide	23	7.1		
Methotrexate	246	76.4		
Sulfasalazine	14	4.3		
Tacrolimus	6	1.9		
Biological class				
B-cell inhibitor	19	3.8		
Interleukin antagonist	53	10.5		
JAK-inhibitor	3	0.6		

T-cell inhibitor	17	3.4		
TNF-alpha inhibitor	411	81.7		
Biological name				
Abatacept (T-cell)	17	3.4		
Adalimumab	102	20.3		
Anakinra (IL-1)	5	1.0		
Certolizumab	7	1.4		
Etanercept	119	23.7		
Golimumab	6	1.2		
Infliximab	173	34.4		
Rituximab (B-cell)	19	3.8		
Sarilumab (IL-6)	1	0.2		
Tocilizumab (IL-6)	48	9.5		
Tofacitinib (JAK-inhibitor)	3	0.6		
<NA>	3	0.6		

csDMARD, conventional synthetic disease modifying anti rheumatic drug; IL, interleukin; JAK, Janus kinase; n, number of patients; NA, not available; SD, standard deviation; RA, rheumatoid arthritis

Table S21. Case report patient comorbidities

comorbidity	N	Percent
Alzheimer's disease	1	0.4
Amyloidosis	3	1.1
Anaemia	1	0.4
Ankylosing spondylitis	2	0.7
Aorta valve replacement	1	0.4
Aortic regurgitation	1	0.4
Arteriosclerosis obliterans	1	0.4
Asthma	7	2.6
Atrial fibrillation	9	3.3
Autoimmune hepatitis	1	0.4
Barrett's oesophagus	1	0.4
Bone sarcoma	1	0.4
Breast cancer	2	0.7
Brucellosis	1	0.4
Cerebellar ataxia	1	0.4
Cervical arthrodesis	2	0.7
Cervical cancer	1	0.4
Chronic kidney disease	2	0.7
Chronic stable thrombocytopenia	1	0.4
CML	1	0.4
Coccidioidomycosis (past infection)	2	0.7

Colectomy	1	0.4
COPD	11	4.0
Corneal transplant	1	0.4
Coronary artery disease	2	0.7
Crohn's disease	2	0.7
Degenerative spondylosis	1	0.4
Depression	2	0.7
Diabetes mellitus	36	13.2
Diverticulitis	1	0.4
Dyslipidaemia	1	0.4
Endovascular prosthesis	1	0.4
Fibromyalgia	1	0.4
Gallstones	1	0.4
Gastric cancer	1	0.4
Gastric ulcer	4	1.5
Gastroesophageal reflux disease	4	1.5
Hashimoto hypothyroidism	2	0.7
Hepatitis	2	0.7
Hepatitis B	1	0.4
Hiatal hernia	1	0.4
Hip prosthesis	7	2.6
HTLV-1	1	0.4
Hyper IgG4-syndrome	1	0.4
Hyperlipidaemia	9	3.3
Hypertension	40	14.7
Hypertensive cardiomyopathy	1	0.4
Hypertrophic cardiomyopathy	1	0.4
Hypothyroidism	7	2.6
Interstitial lung disease	1	0.4
Intracerebral haemorrhage	1	0.4
Ischaemic heart disease	9	3.3
Leishmaniasis (past infection)	1	0.4
Lichen planus	1	0.4
LPD	1	0.4
Lumbar fusion	2	0.7
Lumbar spinal canal stenosis	1	0.4
Lung fibrosis	1	0.4
Myasthenia gravis	2	0.7
Mycobacterium xenopi septic arthritis	1	0.4
OSAS	2	0.7
Osteopenia	2	0.7
Osteoporosis	4	1.5

PJP	1	0.4
Prostatic adenoma resection	1	0.4
Psoriasis	2	0.7
Pulmonary embolism recurrent	1	0.4
Pulmonary micronodules	1	0.4
Pulmonary NTM infection	2	0.7
RA lung involvement	1	0.4
Recent dental examination	1	0.4
Recent gastroenteritis	1	0.4
Recurrent UTIs	1	0.4
Recurrent uveitis	1	0.4
Shoulder prosthesis	1	0.4
Sjögren syndrome	4	1.5
Skin ulcer	1	0.4
Spinal stenosis	1	0.4
Splenectomy	2	0.7
Spondylodesis	1	0.4
Squamous cell carcinoma of tongue	1	0.4
Systemic sclerosis	2	0.7
Thyroid carcinoma	1	0.4
Total hip replacement	2	0.7
Total knee replacement	18	6.6
Tuberculosis	1	0.4
Tuberculosis, pulmonary	9	3.3
Ulcerative colitis	1	0.4
Vasculitis	1	0.4

CML, chronic myeloid leukaemia; COPD, chronic obstructive pulmonary disease; csDMARD, conventional synthetic disease modifying anti rheumatic drug; HTLV-1, human T lymphotropic virus type 1; JAK, Janus kinase; LPD, lymphoproliferative disease; n, number of patients; NTM, non-tuberculous mycobacteria; OSAS, obstructive sleep apnea syndrome; PJP, Pneumocystis jirovecii pneumonia; RA, rheumatoid arthritis; TNF, tumour necrosis factor; UTI, urinary tract infection. Patients could have more than one comorbidity.

Table S22. Case characteristics

Hospitalisation	**N**	**Percent**	**mean**	**SD**
Yes	185	36.78		
No	9	61.43		
Not specified	309	1.79		
Hospitalisation duration (n=59)			27.05	31.68
Treatment				
Targeted therapy	183	36.38		
Discontinuation immunosuppression	16	3.18		
Both	243	48.31		
Neither	4	3.18		
Case outcome				
Chronic illness	3	0.6		
Death	53	10.54		
Progression	6	1.19		
Resolution	391	77.73		
Stabilisation	1	0.2		
Not specified	49	9.74		
bDMARD outcome				
Continued	16	3.18		
Continued lower dose	1	0.2		
Discontinued	148	29.42		
Reinitiation	43	8355		
Reinitiation different biological	17	3.38		
Not specified	278	55.27		
Relapse				
Yes	14	2.78		
No	94	18.69		
Not specified	395	78.53		
Follow-up duration (n = 82)			11.74	9.31

bDMARD, biological disease modifying anti rheumatic drug; n, number of patients; SD, standard deviation

Table S23. Case report countries

Country	N
USA	83
Japan	77
France	39
Spain	28
UK	20
Italy	17
Netherlands	14
Germany	12
Greece	11
Ireland	7
Brazil	6
Australia	5
Canada	5
Turkey	5
Belgium	4
Colombia	4
Switzerland	4
Austria	3
Denmark	3
Romania	3
South Korea	3
Croatia	2
India	2
Israel	2
Taiwan	2
Not available	2
Argentina	1
Burkina Faso	1
Lebanon	1
Malaysia	1
Mexico	1
Poland	1
Portugal	1
Puerto Rico	1
Sweden	1

N = number of case reports

Supplement 19: Identified micro-organisms in the case reports

We extracted information on the causative micro-organisms in each case. One patient could be infected by multiple micro-organisms.

Table S24. All identified micro-organisms in all case reports per biological (class)

Micro-organism	TNF-alpha inhibitors	Tocilizumab (IL-6)	Anakinra (IL-1)	Abatacept	Rituximab	JAK-inhibitors
Acinetobacter baumannii	1					
Actinobacillus ureae	1					
Actinomyces spp	1					
Adenovirus	1					
Aspergillus spp	10	1		1		
Babesia microtii	1				1	
Bacteroides spp	1	1				
Bartonella henselae	1	2		1		
Borrelia Afzelii	1					
Brachiola algerae	1					
Brucella spp	2					
Campylobacter fetus					2	
Candida spp	5			1		
Candidatus Neoehrlichia mikurensis					1	
Capnocytophaga cynodegmi	1					
Cladophialophora bantiana						1
Coagulase-negative staphylococci		1				
Coccidioides spp	11					
Coxiella burneti	1				1	
Cryptococcus supp	12			1	1	
Cutibacterium acnes	1					
Cytomegalovirus	2	1		1	1	
Echinococcus multilocularis	1				1	
Enterobacter aerogenes		1				
Enterobacter cloacae	1					
Epstein-Barr virus	3	1		3		
Escherichia coli	2	2	1			
Finegoldia magna	1					
Francisella tularensis	1					

Gram-positive cocci				1		
Gram-positive streptococci	1	1	1			
Haemophilus influenzae		2				
HHV-6	1					
Hepatitis E virus		2		1	1	
Histoplasma capsulatum	20	1		1		
HSV1	1					
HSV2	1					
Influenza virus		1				
JC virus	1					
Klebsiella pneumoniae		1				
Kocuria kristinae	1					
Legionella pneumophila	17	1				
Leishmania spp	19		1		1	
Listeria monocytogenes	23	1				
Measles morbillivirus	1					
Molluscum contagiosum virus	1					
Moraxella catarrhalis	1					
Mucor spp	3					
Mycobacterium abscessus	4	1				
Mycobacterium avium	10	2				
Mycobacterium avium-intracellulare	1	1		1		
Mycobacterium bovis	3					
Mycobacterium chelonae	7					
Mycobacterium fortuitum	2					
Mycobacterium haemophilum	3					
Mycobacterium heckeshornense	2					
Mycobacterium intracellulare	4					
Mycobacterium kansasii	1					
Mycobacterium leprae	4	1				
Mycobacterium mageritense	1					

Mycobacterium marinum	5					
Mycobacterium mucogenicum	2					
Mycobacterium szulgai	1					
Mycobacterium tuberculosis	81		2		2	
Mycobacterium xenopi	2					
Neisseria meningitidis	1					
Nocardia spp	3	1		1	1	
Paracoccidioides spp	1					
Parvimonas micra	1					
Parvovirus B19		1			1	
Pasteurella multocida	1	1			1	
Pentatrichomonas hominis	1					
Peptostreptococcus spp	1					
Phaeoacremonium spp	1					
Plasmodium falciparum	1					
Pneumocystis jirovecii	24			1	1	2
Polymicrobial	3					
Pseudomonas spp	2	1				
Rhodococcus erythropolis					1	
Rickettsia rickettsi	1					
Roseomonas mucosa	1					
Rothia dentocariosa	1					
Salmonella spp	28					
Sarcoptes scabiei	1	1				
Scedosporium apiospermum	1					
Serratia marcescens		1				
Staphylococcus aureus	15	8	2		1	
Stenotrophomonas maltophilia	1	2				
Streptobacillus monilliformis		1				
Streptococcus agalactiae	1					
Streptococcus constellatus	2					
Streptococcus pneumoniae	6	2				

Streptococcus pyogenes	5	3		1		
Streptococcus viridans	2					
Strongyloides stercoralis	3					
Toxoplasma gondii	7					
Treponema pallidum	1					
Tropheryme whipplei	1					
Varicella zoster virus	3	1		1		
West Nile virus	12				1	

HHV-6, human herpes virus 6; HSV 1/2, herpes simplex virus type 1/2; IL, interleukin; JAK, Janus kinase; JC virus, John Cunningham virus; TNF, tumour necrosis factor

Supplement 20: figures related to the case reports

Per case, information on the anatomical location of the infection was obtained. Reported causative micro-organisms were subdivided into viral, parasitic, mycobacterial, intracellular bacterial, and other bacterial pathogens.

Figure S4. Number of cases with an affected organ, for different organ systems, in case reports

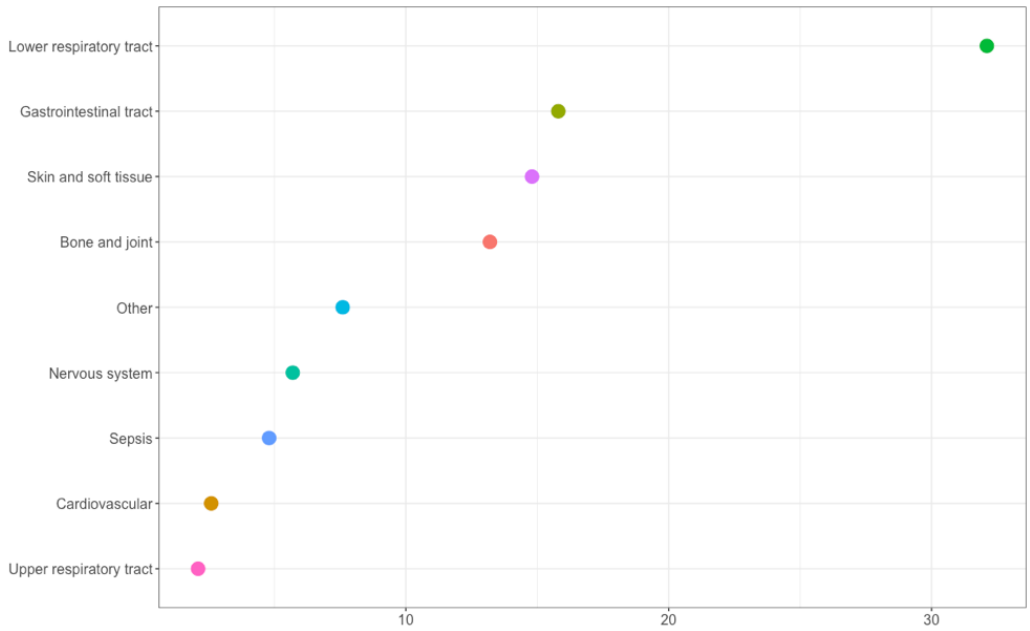


Figure S5. Percentage of different types of infections per biological