EPIDEMIOLOGICAL SCIENCE

Influenza outcomes in patients with inflammatory joint diseases and DMARDs: how do they compare to those of COVID-19?

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ABSTRACT

Objectives To estimate absolute and relative risks for seasonal influenza outcomes in patients with inflammatory joint diseases (IJDs) and disease-modifying antirheumatic drugs (DMARDs). To contextualise recent findings on corresponding COVID-19 risks.

Methods Using Swedish nationwide registers for this cohort study, we followed 116 989 patients with IJD and matched population comparators across four influenza seasons (2015–2019). We quantified absolute risks of hospitalisation and death due to influenza, and compared IJD to comparators via Cox regression. We identified 71 556 patients with IJD on active treatment with conventional synthetic DMARDs and biological disease-modifying antirheumatic drugs (bDMARDs)/targeted synthetic disease-modifying antirheumatic drug (tsDMARDs) at the start of each influenza season, estimated risks for the same outcomes and compared these risks across DMARDs via Cox regression.

Results Per season, average risks for hospitalisation listing influenza were 0.25% in IJD and 0.1% in the general population, corresponding to a crude HR of 2.38 (95% CI 2.21 to 2.56) that decreased to 1.44 (95% CI 1.33 to 1.56) following adjustments for comorbidities. For death listing influenza, the corresponding numbers were 0.015% and 0.006% (HR=2.63, 95% CI 1.93 to 3.58, and HR=1.46, 95% CI 1.07 to 2.01). Absolute risks for influenza outcomes were half (hospitalisation) and one-tenth (death) of those for COVID-19, but relative estimates comparing IJD to the general population were similar.

Conclusions In absolute terms, COVID-19 in IJD outnumbers that of average seasonal influenza, but IJD entails a 50%–100% increase in risk for hospitalisation and death for both types of infections, which is largely dependent on associated comorbidities. Overall, bDMARDs/tsDMARDs do not seem to confer additional risk for hospitalisation or death related to seasonal influenza.

INTRODUCTION

Rheumatoid arthritis (RA) and biological disease-modifying antirheumatic drugs (bDMARDs) or targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs) have been linked with increased risks of infections, which in turn constitute one of the reasons behind the increased morbidity and preterm mortality in RA and other inflammatory joint diseases (IJDs).[1][2] Some of these infection

Key messages

What is already known about this subject?
► Patients with rheumatoid arthritis (RA) or other inflammatory joint diseases (IJDs) are at increased risk of infections. Historical studies indicate that this applies also to seasonal influenza. Risks in contemporary patients with IJDs and with modern antirheumatic therapies remain unclear.

What does this study add?
► Patients with RA and other IJDs are at increased risk of hospitalisations and death related to seasonal influenza. Much though not all of these increases can be explained by contextual factors rather than the rheumatic disease diagnosis as such. Taken together, biological disease-modifying antirheumatic drugs (DMARDs)/targeted synthetic DMARDs do not confer additional risks beyond conventional synthetic DMARDs. These patterns of relative risks are largely similar to those recently observed for COVID-19, although the absolute risks with the latter are much higher.

How might this impact on clinical practice or future developments?
► Our results indicate the need and potential to further optimise risk mitigation measures against common and epidemic infections such as seasonal influenza in patients with IJDs, but also suggest that common antirheumatic therapies are not strong drivers of this increase.

risks are relatively specific to infectious agent and clinical context (eg, tuberculosis in patients treated with tumour necrosis factor inhibitors (TNFis). Others are less specific with respect to infectious agent and causative context, and rather arise against a background of suboptimally controlled rheumatic disease activity, comorbid conditions associated with RA and a certain level of perturbated immune competence, be it from oral glucocorticoids or from bDMARDs/tsDMARDs. It is clear, however, that 'infection risk' is a broad entity, that risks may not be directly translatable across infectious agents, and thus that a complete understanding of infection risks in IJD and with disease-modifying

antirheumatic drugs (DMARDs) calls for studies of specific types of infections.

Seasonal influenza is known to lead to significant morbidity and mortality in the general population.[3] Despite the notion that RA, IJD and DMARDs are associated with increased infection risks, that the absolute risk of contracting seasonal influenza in many countries is several times higher than the risks of less prevalent infections such as tuberculosis and other opportunistic infections that have received much (more) attention, and that risk mitigation measures for seasonal influenza, such as annual vaccination, are indeed available,[4 5] surprisingly little is known on influenza outcomes in patients with RA or other IJDs, and in relation to DMARDs as currently used in clinical practice. Cross-sectional self-report studies have indicated an increased occurrence of influenza-like illnesses in patients with RA.[6–8] A claims-data based study from the USA reported increased risks of influenza-related complications in patients with RA, but little impact of bDMARDs, but these studies were all based on data from more than 10 years ago.[9]

For many common infections such as seasonal influenza, clinical risks lie not so much with the infection per se as with its severity and outcome, suggesting that further studies of influenza outcomes are needed. In IJD, this is particularly important since common DMARDs may both reduce effectiveness of vaccines against seasonal influenza[10] (the main intended effect of which is to prevent serious disease rather than infection per se) and impair host immune competence of relevance for the clinical severity of seasonal influenza infection.

Recently, we presented absolute and relative risks of hospitalisation and death following COVID-19 in patients with RA or other IJD and in relation to the general population, and could demonstrate that patients with RA and other IJD are at increased risks of hospitalisation and death following COVID-19, but also that most of these increased risks appear attributable to comorbid conditions associated with IJD rather than to the IJD disease or its DMARD treatment per se.[11] A full interpretation of these risks and the impact of COVID-19 on the IJD population call for contextualisation with risks of other prevalent infections, such as seasonal influenza during the past years.

In this study, we therefore aimed to estimate absolute and relative risks of hospitalisation and death following seasonal influenza in patients with RA, other IJD and with specific DMARDs in Sweden. The second aim was to put risks with seasonal influenza next to those we recently presented for COVID-19.

METHODS
Study population and period
We used an existing multiregister linkage of IJD (Anti-Rheumatic Treatments In Sweden ('ARTIS')), described elsewhere,[11 12] to identify our study population, exposures, outcomes and covariates (see online supplemental tables S1–S3 for details). To enable comparison with our recent COVID-19 study, we used similar methodological approaches and definitions.[11]

We first identified all adult individuals with IJD in Sweden alive at the beginning of at least one of four consecutive influenza seasons (15 September–15 May the following year, as defined by the Swedish National Board of Health and Welfare) 2015/2016, 2016/2017, 2017/2018 and 2018/2019. IJD was identified using the International Classification of Diseases 10th Revision, 10th Revision (ICD-10) codes for RA, psoriatic arthritis, ankylosing spondylitis, other spondyloarthropathies and juvenile idiopathic arthritis via the National Patient Register (NPR) using previously devised algorithms (online supplemental table S2).[11] Each

unique individual was matched on year of birth, sex and region of domicile to five randomly selected population comparator subjects from the Swedish Population Register.

Treatment exposures
DMARD treatment status of the patients with IJD at the start of each influenza season was identified using the closest ongoing treatment on or before 15 September per season recorded in the Swedish Rheumatology Quality Register and the Prescribed Drug Register. These were categorised into the following exposures: conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and bDMARDs/tsDMARDs. The latter was further divided into TNFi, abatacept, tocilizumab, rituximab and janus kinase inhibitors.

Outcomes, follow-up and covariates
We defined the following outcomes: (1) hospitalisation listing influenza (main and contributory diagnoses based on data from the NPR, and with influenza defined as ICD-10=J09 J11), and (2) death from influenza (main and contributory causes based on data from the Cause of Death register). Hospitalisation and deaths listing any cause were also identified to contextualise the influenza-specific outcomes. We followed individuals from the start of the influenza season to the first recorded event of interest (ie, multiple events within each influenza season were not allowed), or censoring at death, migration from Sweden or end of the influenza season.

Information on age, sex, region, socioeconomic factors (education, civil status and country of birth), influenza hospitalisation during the previous year and comorbidities (history of cancer, diabetes, heart failure, ischaemic heart disease, lung disease, stroke, surgery, venous thrombotic event and kidney failure) at the start of each influenza season was obtained from the NPR and the Prescribed Drug Register (online supplemental table S3).

Statistical methods
Absolute risks of outcomes of interest were presented as percentages and calculated as the number of events divided by the number of individuals at risk; this was averaged across seasons for influenza outcomes.

To assess whether the risk of our outcomes was elevated in IJD versus the general population, we estimated crude rates per week (number of events per person−time at risk) for each outcome for each influenza season. We estimated HRs comparing patients with IJD to comparators via Cox proportional hazards models adjusted for influenza season, and with age, sex and region accommodated by the matched design, and further covariate adjustment for socioeconomic factors and comorbidities.

In order to determine the role of DMARDs on the risk of influenza outcomes, we estimated absolute risks and HRs comparing bDMARDs/tsDMARDs to csDMARDs via Cox proportional hazards models. Robust cluster SEs were used in order to account for the fact that one individual could contribute data from more than one influenza season. Cox regressions models were adjusted in the same way as described earlier, plus adjustments for disease duration, Disease Activity Score on 28 joints (DAS28), number of previous bDMARDs/tsDMARDs and concomitant steroid use. No imputation of missing data was performed; sensitivity analyses were performed to determine the effect of missing DAS28 values included in the DMARD treatment analyses (see online supplemental table S10 for details). Comparative analyses were not performed where the number of events in one group was less than five.
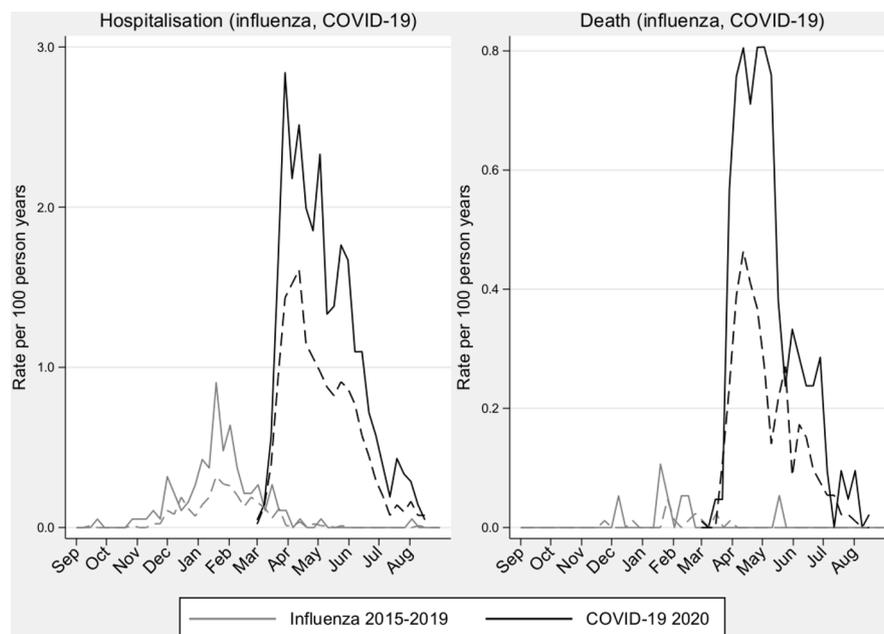
Figure 1 Weekly rate per 100 person-years of hospitalisation and death listing influenza during seasons 2015/2016–2018/2019 and COVID-19 during 2020, for individuals with inflammatory joint diseases (solid lines) and population comparators (dashed lines) in Sweden.

RESULTS

Role of IJD during the influenza seasons 2015–2019

We identified 116 989 unique patients with IJD contributing data to at least one of the four influenza seasons (99 175, 102 811, 106 360 and 109 465 patients during the influenza seasons 2015–2016, 2016–2017, 2017–2018 and 2018–2019, respectively). Descriptive statistics can be found in online supplemental tables S4–S6.

Crude absolute rates (see figure 1) showed an increased rate of hospitalisation listing influenza and death due to influenza for patients with IJD versus the general population. The average absolute risk of influenza outcomes per season in patients with IJD was approximately three times that seen in the general population, although all risks were low (table 1, left panel; for hospitalisation listing influenza: 0.25% and 0.1% for IJD and comparators, respectively (one additional hospitalisation for influenza for every 666 patients with IJD); for death listing influenza: 0.015% and 0.006% (one additional death from influenza for every 11 111 patients with IJD), respectively).

Prior to adjustment for comorbidities and socioeconomic factors, HRs comparing IJD to the general population for hospitalisation listing influenza and death due to influenza were 2.38 (95% CI 2.21 to 2.56) and 2.63 (95% CI 1.93 to 3.58), respectively (table 1, left panel). Following adjustment, the HRs decreased to 1.44 (95% CI 1.33 to 1.56) for hospitalisation listing influenza and 1.46 (95% CI 1.07 to 2.01) for death due to influenza; similar reductions after adjustment were seen for hospitalisation and deaths due to any cause (online supplemental table S7). Using an alternative definition of death due to influenza, defined as any death occurring 30 days after a hospitalisation listing influenza, we obtained similar results (online supplemental table S8).

When considering patients with RA separately (whose mean age was higher than that of other IJDs), absolute risks were slightly higher than for all IJDs, but the pattern of crude and adjusted relative risks (HRs) remained similar (table 1, left panel).

Role of DMARDs during the influenza seasons 2015–2019

Comparing b/tsDMARDs to csDMARDs, we found a 32% increased rate of hospitalisation listing influenza (adjusted HR=1.32, 95% CI 1.06 to 1.64) but no statistically significantly different rates for death from influenza. A minor but statistically significant higher rate of all-cause hospitalisation was found in bDMARDs/tsDMARDs compared with csDMARDs (online supplemental table S9; adjusted HR=1.08, 95% CI 1.05 to 1.12), but no increased risk for death due to any cause. With respect to specific bDMARDs/tsDMARDs, we noted increased HRs for hospitalisation listing influenza for abatacept and for rituximab (table 2).

Contextualising risks with COVID-19

The right panels in tables 1 and 2 and figure 1 display corresponding risk estimates from our study on COVID-19.[11] The pattern of HRs and the impact of adjustment were largely similar for seasonal influenza, although the decline in disease-specific HRs (here: hospitalisation and death specifically from influenza) following adjustment was somewhat less pronounced for seasonal influenza than for COVID-19. The crude rates for hospitalisation and death presented in figure 1 were much higher for COVID-19 outcomes than for influenza outcomes. Results for hospitalisation listing any cause and death due to any cause can be found in online supplemental table S7 (n.b., the study period was 8 months for seasonal influenza vs 6 months for COVID-19, and they further spanned different calendar months).

DISCUSSION

In this study, one of the few to date that have investigated the pattern of absolute and relative risks for hospitalisation and deaths associated with seasonal influenza in patients with IJD and with currently available DMARDs as used in clinical practice, we noted that the absolute risk of each of the four outcomes under study was higher in IJD (in RA in particular) compared with the general population, but also that a large part (though not all) of these increases could be explained

Table 1 Number of events, absolute risk, excess risk and HRs estimated from Cox proportional hazards models comparing patients with IIDs to matched comparators for outcomes hospitalisation listing influenza (during 2015/2016–2018/2019 influenza seasons) or COVID-19 (during the first wave of COVID-19 2020), and death listing influenza (influenza seasons 2015–2019) or COVID-19 (during the first wave of COVID-19 2020)

Influenza, seasons 2015–2019

Outcome	Events (n) (average risk, %) in IID cohort	Events (n) (average risk, %) in the general population	Crude excess risk per 100 patients	HR 1†	HR 2‡
All IID					
Hospitalisation listing influenza	1066 (0.25)	2011 (0.1)	0.15	2.38 (2.21 to 2.56)	1.44 (1.33 to 1.56)
Death listing influenza	64 (0.015)	109 (0.006)	0.009	2.63 (1.93 to 3.58)	1.46 (1.07 to 2.01)
RA					
Hospitalisation listing influenza	743 (0.35)	1312 (0.15)	0.2	2.41 (2.21 to 2.64)	1.47 (1.34 to 1.62)
Death listing influenza	50 (0.02)	78 (0.009)	0.011	2.73 (1.91 to 3.90)	1.56 (1.08 to 2.27)

COVID-19 2020*

Outcome	Risk (%) in IID cohort	Risk (%) in general population	Crude excess risk per 100 patients	HR 1†	HR 2‡
All IID					
Hospitalisation listing COVID-19	(0.5)	(0.3)	0.2	1.77 (1.61 to 1.95)	1.32 (1.19 to 1.46)
Death listing COVID-19	(0.10)	(0.07)	0.03	2.09 (1.73 to 2.52)	1.18 (0.97 to 1.44)
RA					
Hospitalisation listing COVID-19	(0.7)	(0.4)	0.3	2.02 (1.78 to 2.28)	1.40 (1.23 to 1.60)
Death listing COVID-19	(0.30)	(0.11)	0.19	2.28 (1.85 to 2.81)	1.27 (1.02 to 1.59)

*COVID-19 data taken from Bower et al,[11] from Cox models fitted identically to those of ‡. Note that season lengths differ for COVID-19, and for influenza, the former was from March to September (6 months) 2020, whereas the latter was from September to May (8 months) each year 2015–2019.

†HR 1 accounts for age, sex and region via the matching (and for influenza season adjustment for influenza analyses) .

‡HR 2 additionally adjusts for socioeconomic factors (education, civil status and country of birth), influenza hospitalisation in the previous year (in influenza analyses) and comorbidities (history of the following diseases: cancer, diabetes, heart failure, ischaemic heart disease, lung disease, stroke, surgery, venous thrombotic event and kidney failure).

IID, inflammatory joint disease; RA, rheumatoid arthritis.

Table 2 HRs comparing the rates of hospitalisation listing influenza and death listing influenza (during 2015/2016–2018/2019 influenza seasons) in patients with inflammatory joint diseases receiving csDMARDs to patients receiving bDMARDs/tsDMARDs in Sweden

Outcome	Cohort	Events (n)	Absolute risk (%)	HR 1 (95% CI)*	HR 2 (95% CI)†	HR 2 COVID-19 (95% CI)‡
Hospitalisation	csDMARD	327	0.3	1 (ref)	1 (ref)	1 (ref)
	TNFi	110	0.2	0.54 (0.43 to 0.66)	1.18 (0.92 to 1.52)	1.05 (0.67 to 1.64)
	Abatacept	25	0.6	2.05 (1.33 to 3.16)	2.01 (1.26 to 3.19)	0.49 (0.15 to 1.59)
	Tocilizumab	9	0.2	0.74 (0.38 to 1.43)	1.28 (0.65 to 2.51)	–
	Rituximab	42	0.5	1.83 (1.33 to 2.52)	1.49 (1.04 to 2.14)	1.03 (0.58 to 1.81)
	All bDMARDs/tsDMARDs combined§	191	0.2	0.75 (0.62 to 0.89)	1.32 (1.06 to 1.64)	1.08 (0.73 to 1.58)
Death	csDMARD	21	0.02	1 (ref)	1 (ref)	1 (ref)
	TNFi	3	0.004	–	–	1.03 (0.40 to 2.61)
	Abatacept	1	0.02	–	–	–
	Tocilizumab	0	0	–	–	–
	Rituximab	1	0.01	–	–	3.20 (1.19 to 8.57)
	All bDMARDs/tsDMARDs combined§	5	0.006	0.30 (0.11 to 0.81)	0.65 (0.04 to 12.00)	1.26 (0.60 to 2.64)

Note: Results only presented where treatment cohorts have five or more events.
Previously published corresponding HRs for COVID-19 are in the rightmost column.
*Adjusted for influenza season; age, sex and region accounted for via matching.
†Additionally adjusted for disease duration, Disease Activity Score on 28 joints, number of previous bDMARDs/tsDMARDs and concomitant steroid use, socioeconomic factors (education, civil status and country of birth), influenza hospitalisation in the previous year and comorbidities (history of the following diseases: cancer, diabetes, heart failure, ischaemic heart disease, lung disease, stroke, surgery, venous thrombotic event and kidney failure).
‡Taken from the COVID analyses presented in Bower et al,[11] adjusted for the same factors as †, but via inverse probability treatment weighting via propensity score estimation.
§Includes Janus kinase inhibitors.
bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; ref, reference; TNFi, tumour necrosis factor inhibitor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

by socioeconomy and associated comorbidities. Further, and for the same outcomes, we noted no major differences in risk with bDMARDs/tsDMARDs compared with csDMARDs, although we noted signals (for the outcome hospitalisation listing influenza) with abatacept and rituximab. When put next to our previously published data on risks and relative risks with COVID-19, we noted that whereas the absolute risks of influenza outcomes were around half (hospitalisation) and one-tenth (death) those for COVID-19, the pattern of relative risks for influenza-specific outcomes and for COVID-19-specific outcomes comparing IJD to the general population was qualitatively quite similar.

As mentioned, there is a scarcity of data on risks, relative risks and risk determinants for outcomes of seasonal influenza infections in patients with IJD and with DMARDs. Historically, rheumatic disease has been identified as a risk factor for influenza hospitalisation in the elderly.[4 5] Our results suggest that despite marked improvements in the general disease status of patients with IJD during the past decades, the relative risk increase (a 50%–100% increase compared with the general population) remains.

We noted a strong effect on our HRs of adjustment for comorbidities and other contextual factors. Although little studied previously, this is in keeping with observations from at least one previous study.[9] While the increased risks signal a need for clinical vigilance or preventive measures, the marked attenuation of the strength of the association following adjustments suggests that much of the increase is related to the clinical context rather than the rheumatic disease diagnosis itself, although our results

formally do not rule out any level of risk increase in individuals with IJD in remission but otherwise at full health.

With respect to DMARDs, we noted no clear overall difference in influenza outcomes with bDMARDs/tsDMARDs versus csDMARDs, but signals for certain bDMARDs (and too small numbers to make explicit comparisons with tsDMARDs). In the few previous studies, one similarly reported little effect of bDMARDs.[9] While seemingly in keeping, our results are not comparable as that study focused on risks of influenza rather than risks of adverse influenza outcomes, and (using data until 2007) effectively only studied TNFis. By contrast, a small Dutch questionnaire-based study and a small Italian study (both also based on data from more than 10 years ago) indicated no higher and an increased prevalence, respectively, of influenza-like illness in those patients treated with TNFis.[6 7]

Despite the fact that the vulnerable population is similar for COVID-19 and seasonal influenza, direct comparisons of absolute risks in COVID-19 versus seasonal influenza are not straightforward since they hit during different(-ly long) seasons, and since the underlying rates for our outcomes (death and hospitalisation for all causes) also have a seasonal variation. Relative risks, however, should be more directly comparable as they accommodate this seasonal effect. Further, it is important to remember that during our study period, SARS-CoV-2 was a new virus, for which no herd immunity, specific treatment or vaccine existed. For COVID-19, our results thus reflect effects of the virus per se, social distancing, absence of immunity (whether from previous infection or from vaccination) and a largely trial-and-error based treatment of severe COVID-19. By contrast, for influenza, our results are reflective of the impact of seasonal influenza per se,

plus the seasonal public health influenza campaigns and the effects of immunity from previous epidemics or vaccination, and antiviral treatment for severe cases of influenza.

Our study has limitations. We studied outcomes of seasonal influenza but did not have individual-level data to assess risks of acquiring influenza infection in the first place, or individual-level information on host protection against severe influenza outcomes, either through previous influenza infection or from vaccination. In Sweden, the yearly influenza vaccine is recommended for all individuals above 65 years of age and for individuals with certain comorbidities (but not specifically IJD, although Swedish rheumatologists likely encourage their patients to get vaccinated). The proportion vaccinated in the IJD cohort could thus be expected to be somewhat higher than that in the general population, which would make our observed increased risk in IJD an underestimate for what would be observed in a completely unvaccinated population. However, a sensitivity analysis restricted to only those aged 65 years and over showed almost identical results (results not shown), suggesting that differences in vaccination rate have not had a major impact on our data. We also cannot infer whether or to what extent RA, other IJDs or DMARDs increase the susceptibility to influenza infection, only that patients with RA and other IJDs are at increased risk of unfavourable outcomes once infected. Further, since influenza may progress to pneumonia, death (and to some extent also hospitalisation) may be recorded as being due to pneumonia rather than to influenza. This may lead to an underestimation of the influenza-specific outcomes, but we believe this will impact for the IJD and the population comparator subjects equally. Similarly, our influenza definition may be subject to misclassification since we did not have access to data which could confirm the physician-assigned diagnosis. Treatment switches during follow-up are clinically relevant, but were not accounted for in this study to align with the approach taken in our COVID-19 study. However, since <1.1% of patients changed treatment cohort during each influenza season, we do not expect this to measurably alter the results. Although we accommodated many comorbid and contextual factors, our adjusted HRs may contain residual or unmeasured confounding, including (for the drug-specific comparisons, eg, for rituximab) residual confounding by indication.

To conclude, in absolute terms, IJD is a risk factor for hospitalisation and death following seasonal influenza, but the impact of COVID-19 on patients with IJD outnumbers that of seasonal influenza. On the other hand, and compared with the general population, IJD is a risk factor of similar (relative) strength for seasonal influenza as previously observed for COVID-19. In both instances, much of this increase can be explained by other factors suggesting that merely having IJD is in itself not a strong risk factor (although having its comorbid consequences may increase risk). Overall, bDMARD/tsDMARD treatment does not seem to markedly increase risk of adverse influenza outcomes, but signals for abatacept and rituximab call for replication. Our results underscore the continued need to optimise risk-mitigation measures against epidemic infections beyond COVID-19 in the rheumatic disease population.

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Supplemental material

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Supplementary materials

Table S1: Data sources included in the study	
Swedish Rheumatology Quality Register (SRQ)	A nationwide longitudinal clinically integrated register operated by The Swedish Society for Rheumatology, started in 1996. Patients with RA and other rheumatologic diseases are registered in the SRQ by the treating rheumatologist. SRQ contains information about disease activity and additional information such as treatment and smoking status. SRQ covers 95% of all patients with RA treated with b/tsDMARD s in Sweden.
Swedish Patient Register (NPR)	A national register maintained by The National Board of Health and Welfare. Hospital discharges from inpatient care and patients visits in non-primary outpatient care, have been registered, since 1964 and 2001 respectively. Diagnoses are coded according to the Swedish version of the International Classification of Disease (ICD). The coverage of the inpatient part is close to 100%, for the outpatient part, the overall coverage is around 80% (higher for public than for private care-providers).
Prescribed Drug Register (PDR)	A national register maintained by The National Board of Health and Welfare. It contains information about all drugs dispensed on prescription in Sweden and is linked to the personal identification number since 2005. The coverage is close to 100%.
Swedish Population Register	A national register maintained by Swedish Tax agency. Contains information such as home district, civil status and migration data.
Longitudinal database for insurance and labor market-studies (LISA)	A national register maintained by Statistics Sweden. It contains information about sick leave, parental leave and employment status in Sweden from 1990.
Cause of Death Register	The Cause of Death Register is a national register containing information on date and cause of death (underlying and contributory) for all deceased residents, including deaths among Swedish residents who died abroad. The register was started in 1952, and the data is considered complete since 1961. From that year and onward, cause of death is missing for less than 0.5% of deceased individuals, and in 2002, a validation study estimated that only 3.3% had any errors at the three-digit level of the ICD-coded underlying cause of death

Table S2: International Classification of Disease version 10 (ICD10) and Anatomical Therapeutic Chemical (ATC) codes used to define cohorts			
Inflammatory joint disease cohort definitions		**DMARD treatment cohort definitions***	
Disease	**ICD10 code**	**DMARD**	**ATC code**
Rheumatoid arthritis	M05, M06	csDMARD	L04AX01, A07EC01, L04AD01, P01BA01, M01CB01, L04AA06, L04AX03, L01AA01, P01BA02, J01AA08, L04AA13, M01CC01
Psoriatic arthritis	M070, M071, M073, L405	TNFi	L04AB04, L04AB05, L04AB01, L04AB06, L04AB02
Ankylosing spondylitis	M45	Abatacept	L04AA24
Other spondyloarthropathies	M460, M461, M468, M469	Tocilizumab	L04AC07
Juvenile idiopathic arthritis	M08, M09	Rituximab	L01XC02
		JAKi	L04AA29, L04AA37, L04AA44

*As recorded in the Prescribed Drug Register

Table S3: Description of variables included in analyses	
Variable	**Description**
Comorbidity	
History of cancer	History of cancer recorded within 5 years prior to cohort entry. Data retrieved from the Cancer Register. Indicator variable (Y/N). Note that information on cancer diagnoses recorded in the Swedish Cancer Register was only available until December 31st 2018.
History of diabetes	History of diabetes recorded in the 10 years recorded prior to cohort entry. Defined as a record in the National Patient Register (inpatient and outpatient components, ICD10: E10-E11) or dispensation of treatment (ATC: A10) in the Prescribed Drug Register. Indicator variable (Y/N).
History of heart failure	History of heart failure recorded in the 5 years recorded prior to cohort entry. Defined as record in National Patient Register (inpatient component, ICD10: I50). Indicator variable (Y/N).
History of ischemic heart disease	History of ischemic heart disease recorded in the 5 years recorded prior to cohort entry. Defined as record in National Patient Register (inpatient component, ICD10: I20-I25). Indicator variable (Y/N).
History of hospitalised infections	History of infections recorded in the 2 years prior to cohort entry. Defined as recorded in National Patient Register (inpatient component, ICD10: A00-B99, D73.3, E06.0, E32.1, G00-G02, G04.2, G05-G07, H00.0, H44.0, H60.0-H60.3, H66-H67, H70, I30.1, I40.0, J00-J22, J32, J34.0, J36, J38.3, J39.0-J39.1, J44.0, J85, J86, K04.4, K04.6, K04.7, K10.2, K11.3, K12.2, K14.0, K57.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.1, K65.2, K65.9, L00-L08, L30.3, M00-M01, M46.2-M46.5, M60.0, M65.0, M71.0, M71.1, M72.6, M86, N10, N11, N12, N13.6, N15.1, N15.9, N30.0 N30.8, N34.0, N41.2, N43.1, N45.2, N45.3, N45.4, N48.2, N61, N70, N73, N75.1). Indicator variable (Y/N).
History of lung disease	History of lung disease other than infectious pneumonia recorded in the 5 years recorded prior to cohort entry. Defined as record in National Patient Register (inpatient and outpatient components, ICD10: J40-J94). Indicator variable (Y/N).
History of kidney failure	History of kidney failure recorded in the 5 years recorded prior to cohort entry. Defined as record in National Patient Register (inpatient and outpatient components, ICD10:N17-N19). Indicator variable (Y/N).
History of stroke	History of stroke recorded in the 5 years recorded prior to cohort entry. Defined as record in National Patient Register (inpatient and outpatient components, ICD10:I50-I69). Indicator variable (Y/N).
History of joint surgery	History of joint surgery recorded in the 10 years prior to cohort entry. Defined as record in National Patient Register (inpatient and outpatient components, operational codes: NGB, NFB, NBB, NHB, NHC, NHE, NHF, NHG, 8423, 8424, 8426, 8419, 8437, 8436, 8420, 8421, 8422, 8400-8415). Indicator variable (Y/N).
History of venous thrombotic event	History of VTE recorded in the 5 years recorded prior to cohort entry. Defined as record in National Patient Register (inpatient component, ICD10:I82, I26). Indicator variable (Y/N).
Influenza hospitalisation in the previous year	Hospitalisation in the year prior to cohort entry recording influenza (main and secondary diagnoses, ICD10 codes J09, J10, J11) in the inpatient component of the National Patient Register. Indicator variable (Y/N).
Health-care resource utilisation	
Hospital days in the previous year	The number of days spent in hospital during the 365 days prior to cohort entry. Data obtained from the inpatient component of the National Patient Register.

	Categorised into 0, 1-3, and 4+ days.
Hospital days in the previous 10 years	The number of days spent in hospital during the period 10 years to 365 days prior to cohort entry. Data obtained from the inpatient component of the National Patient Register. Categorised into 0, 1-6, and 7+ days.
Socioeconomics	
Education	Highest education achieved as recorded in the year prior to cohort entry. Data obtained from the Longitudinal integrated database for health insurance and labour market studies (LISA). Note that education information was only available to 2018 in LISA so the value in 2018 was assumed for any subsequent years. Categorised into: 1= <9 years 2=9-12years 3=12years+
Civil status	Civil status recorded in the year prior to cohort entry. Data obtained from LISA, Note that civil status information was only available to 2017 in LISA so the value in 2017 was assumed for any subsequent years. Categorised into married/partner, or single.
Country of birth	Country of birth obtained from the Total Population Register categorised as Sweden, rest of Europe, and rest of world.
Disease-related	
DAS28	DAS28 value (ESR) from most recent rheumatology visit recorded in the SRQ within one year prior to start of follow-up. Categorised into remission (<2.6), low (2.6-3.1), moderate (3.2- 5.1), high (5.2+), and missing.
Disease duration	Disease duration in years, taken as the difference between the diagnosis date (defined using the disease selection definition and data in the National Patient register) and entry to cohort. Categorised as <2, 2-4, 5-9, 10+ years.
Treatment-related	
Number of previous b/tsDMARDs	Number of previous b/tsDMARDs prior to the treatment that caused entry to cohort. Identified by combining the PDR and SRQ. Categorised as 0, 1-2, 3+.
b/tsDMARD recorded in the previous 180 days	Identifies if a different b/tsDMARD was recorded in the previous 180 days prior to start. Indicator variable (Y/N).
Concomitant steroid use	Dispensation of steroids (ATC: H02AB06) recorded in the Prescribed Drug Register in the 90 days prior to cohort entry.

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Table S4: Descriptive statistics for patients with inflammatory joint diseases and matched population comparators during influenza seasons 2015/2016 to 2018/2019 in Sweden

	Influenza season 2015-2016		Influenza season 2016-2017		Influenza season 2017-2018		Influenza season 2018-2019	
	IJD	General population	IJD	General population	IJD	General population	IJD	General population
Individuals	99 175	443 776	102 811	459 031	106 360	474 101	109 465	485 987
RA patients (%)	50 652 (51)	-	51 750 (50)	-	52 780 (49)	-	53 704 (49)	-
Age, median years (IQR)	61 (48-71)	59 (46-69)	61 (48-72)	59 (46-70)	61 (48-72)	59 (47-70)	62 (48-72)	60 (47-70)
Female, %	62%	62%	62%	62%	62%	61%	61%	61%
Disease duration, median years (IQR)	7.8 (3.9-12.3)	-	8.4 (4.1-13.0)	-	8.8 (4.4-13.7)	-	9.3 (4.7-14.5)	-
Days hospitalised in past year median (IQR)	5 (3-12)	4 (2-9)	5 (3-12)	4 (2-9)	5 (3-11)	4 (2-9)	5 (3-11)	4 (2-9)
Education 12+ years,	29%	33%	29%	34%	30%	35%	31%	35%
Education missing,	0%	1%	0%	1%	0%	1%	1%	1%
Married/partner	50%	49%	49%	48%	49%	48%	49%	48%
Married/partner missing,	0%	0%	0%	0%	0%	0%	0%	0%
Born in Sweden	89%	85%	89%	85%	89%	85%	89%	85%
Born in Sweden missing,	0%	0%	0%	0%	0%	0%	0%	0%
Comorbidities,								
Cancer	4%	4%	5%	4%	4%	4%	5%	4%
Diabetes	11%	8%	11%	8%	11%	9%	12%	9%
Heart failure	3%	2%	3%	2%	3%	1%	3%	2%
Ischaemic heart disease	6%	3%	6%	3%	6%	3%	6%	3%
Infections	5%	2%	5%	2%	5%	2%	5%	2%
Lung disease	9%	4%	9%	4%	9%	4%	9%	4%
Kidney failure	2%	1%	2%	1%	3%	1%	3%	1%
Stroke	4%	2%	4%	2%	3%	2%	3%	2%
Surgery	13%	5%	13%	5%	13%	5%	13%	5%
Venous thrombotic event	1.0%	0.5%	0.9%	0.5%	1.0%	0.5%	0.9%	0.5%
Influenza hospitalisation in the previous year	0.2%	0.1%	0.1%	0.1%	0.3%	0.1%	0.3%	0.1%
Treatment N								
csDMARD	28244	-	28691	-	29065	-	29810	-
TNFi	16252	-	17333	-	18479	-	20134	-
Abatacept	923	-	1030	-	1112	-	1245	-

Tocilizumab	974	-	1070	-	1161	-	1087	-
Rituximab	1836	-	2010	-	2137	-	2155	-
JAKi	0	-	0	-	157	-	915	-

Table S5: Descriptive statistics for patients with inflammatory joint diseases and population comparators in Sweden during influenza seasons 2015/2016-2018/2019 and March-September 2020

	Average across influenza seasons 2015/2016-2018/2019			2020		
	All inflammatory joint disease	RA (50% of all IJD)	General population	All inflammatory joint disease	RA (48% of all IJD)	General population
Individuals	104276	52149	464819	110567	53455	484277
Age, Median years (IQR)	61 (48-72)	68 (56-76)	59 (47-70)	62 (49-73)	69 (57-77)	60 (47-71)
Females	62%	72%	62%	62%	73%	62%
Comorbidities						
History of cancer	5%	5%	4%	3%	4%	3%
History of diabetes	11%	13%	9%	12%	14%	10%
History of heart failure	3%	4%	2%	3%	4%	2%
History of ischemic heart disease	6%	8%	3%	6%	7%	3%
History of infections	5%	7%	2%	5%	7%	2%
History of lung diseases	9%	11%	4%	9%	11%	4%
History of kidney failure	3%	3%	1%	3%	4%	1%
History of stroke	3%	4%	2%	3%	4%	2%
History of joint surgery	13%	19%	5%	12%	18%	5%
History of VTE	0.9%	1.2%	0.5%	1.0%	1.3%	0.5%
Influenza hospitalisation in the previous year	0.2%	0.3%	0.1%	-	-	-
Highest achieved education						
<9 years	13%	18%	10%	11%	16%	9%
9-12 years	58%	55%	55%	58%	56%	55%
12+ years	30%	26%	35%	31%	28%	36%
Missing	0%	1%	1%	0%	0%	0%
Civil status: Married	49%	50%	48%	49%	50%	48%
Civil status: missing	0%	0%	0%	0%	0%	0%
Born in Sweden	89%	88%	85%	89%	87%	84%
Born in Sweden missing	0%	0%	0%	0%	0%	0%
Hospitalisation days past year, median (IQR)	5 (3-11)	6 (3-13)	4 (2-9)	5 (3-11)	5 (3-12)	4 (2-8)
Number of individuals on treatment						
csDMARD	40572	27757	-	33296	22904	-
TNFi	26028	13257	-	22070	10463	-

Abatacept	2022	1881	-	1324	1221	-
Tocilizumab	1787	1624	-	1037	942	-
Rituximab	2905	2861	-	2180	2150	-
JAKi*	970	864	-	1725	1384	-

*Note JAKi available in Sweden from 2017

Table S6: Descriptive statistics for patients with inflammatory joint diseases on active cs- and b/ts DMARD treatment, and population comparators in Sweden during influenza seasons 2015/2016 to 2018/2019

	csDMARD (N=123 094)	TNFi (N=75 362)	Abatacept (N=4431)	Tocilizumab (N=4405)	Rituximab (N=8203)	JAKi (N=1081)	All b/tsDMARDs (N=93 482)	General population (N=990 467)
Individuals*, N	**40572**	**26028**	**2022**	**1787**	**2905**	**970**	**31077**	**343200**
Age, Median years (IQR)	65 (53-74)	52 (40-64)	61 (50-70)	58 (46-68)	66 (55-73)	59 (48-69)	54 (42-66)	59 (46-69)
Female,	64%	61%	79%	79%	76%	82%	63%	63%
Disease duration, median years (IQR)	5.4 (1.1-10.9)	6.8 (2.5-12.3)	9.4 (4.4-14.1)	8.5 (4.0-13.7)	10.4 (5.8-14.3)	10.2 (5.4-15.9)	7.3 (2.7-12.6)	-
DAS28, median (IQR)	2.7 (1.9-3.6)	2.6 (1.8-3.7)	3.7 (2.7-4.7)	2.6 (1.5-4.2)	3.4 (2.5-4.5)	4.2 (3.0-5.2)	2.7 (1.9-3.8)	
DAS28, % missing	66%	46%	37%	34%	30%	36%	44%	
Previous number of b/tsDMARDs, median (IQR)	0.0 (0.0-0.0)	0.0 (0.0-1.0)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	1.0 (0.0-2.0)	2.0 (1.0-3.0)	0.0 (0.0-1.0)	
Concomitant csDMARD use,	-	42%	48%	34%	45%	28%	42%	-
Concomitant steroid use,	26%	19%	42%	37%	40%	46%	22%	-
Days hospitalised in past year**, median (IQR)	5 (3-12)	4 (2-8)	5 (3-10)	5 (3-9)	5 (3-11)	5 (3-10)	4 (2-9)	4 (2-9)
Highest achieved education,								
≤9 years	17%	6%	11%	9%	14%	7%	8%	11%
10-12 years	58%	60%	60%	60%	59%	60%	60%	55%
≥12 years	26%	34%	29%	31%	27%	33%	33%	34%
Missing	1%	1%	1%	1%	1%	0%	1%	1%
Married/partner	51%	48%	52%	47%	51%	52%	49%	48%
Married/partner missing,	0%	0%	0%	0%	0%	0%	0%	0%
Born in Sweden	89%	88%	87%	88%	85%	88%	88%	85%
Born in Sweden missing,	0%	0%	0%	0%	0%	0%	0%	0%
Comorbidities,								
Cancer	5%	2%	3%	2%	7%	2%	2%	4%
Diabetes	12%	8%	13%	10%	13%	10%	8%	8%
Heart failure	3%	1%	3%	2%	3%	2%	1%	1%
Ischaemic heart disease	7%	3%	7%	3%	8%	5%	4%	3%
Infections	5%	4%	10%	5%	9%	8%	4%	2%
Lung disease	9%	6%	16%	10%	17%	11%	7%	4%
Kidney failure	2%	1%	2%	2%	3%	2%	2%	1%
Stroke	4%	1%	3%	2%	4%	1%	2%	2%
Surgery	13%	13%	24%	24%	29%	25%	15%	5%

Venous thrombotic event	1.1%	0.5%	1.1%	0.8%	1.8%	1.3%	0.6%	0.5%
Influenza hospitalisation in the previous year,	0.1%	0.1%	0.2%	0.2%	0.2%	0.5%	0.1%	0.1%

* Note characteristics presented limiting to one individual per cohort (can be more than one observation per individual due to year cohorts)

**of those hospitalized

Table S7: Number of events, absolute risk, excess risk and hazard ratios (HR) estimated from Cox proportional hazards models comparing 1) patients with inflammatory joint diseases to matched comparators for hospitalisation listing any cause, or death from any cause during influenza seasons 2015-2019.

Outcome	N events (average risk, %) in IJD cohort	N events (average risk, %) in general population	Crude excess risk per 100 patients	HR 1*	HR 2**
All IJD					
All hospitalisations	56 703 (13.6)	152 124 (8.2)	5.4	1.72 (1.70, 1.73)	1.22 (1.21, 1.24)
All death	6751 (1.61)	15 650 (0.84)	0.8	1.92 (1.87, 1.98)	1.13 (1.10, 1.17)
RA					
All hospitalisations	34 802 (16.7)	85 451 (9.7)	5.0	1.80 (1.77, 1.82)	1.26 (1.24, 1.28)
All death	5058 (2.42)	10 595 (1.20)	1.2	2.03 (1.96, 2.10)	1.21 (1.16, 1.25)

*HR1 accounts for age, sex and region (and influenza season for influenza analyses) via the matching.

**HR2 additionally adjusts for socioeconomic factors (education, civil status, country of birth), influenza hospitalisation in the previous year and comorbidities (history of the following diseases: cancer, diabetes, heart failure, ischemic heart disease, lung disease, stroke, surgery, venous thrombotic event, and kidney failure).

Table S8: Hazard ratios (HR) estimated from Cox proportional hazards models comparing 1) patients with inflammatory joint diseases (IJD) to matched comparators for outcomes death listing influenza (influenza seasons 2015-2019), with alternative death due to influenza definition	
Outcome	**HR 2***
All IJD	
Death listing influenza, original definition	1.46 (1.06, 2.01)
Death due to influenza, 30 days after hospitalisation	1.51 (1.10,2.07)
RA	
Death listing influenza	1.56 (1.07, 2.27)
Death due to influenza, 30 days after hospitalisation	1.56 (1.07, 2.26)

*HR2 accounts for age, sex and region and influenza season via matching and additionally adjusts for socioeconomic factors (education, civil status, country of birth), influenza hospitalisation in the previous year and comorbidities (history of the following diseases: cancer, diabetes, heart failure, ischemic heart disease, lung disease, stroke, surgery, venous thrombotic event, and kidney failure).

Table S9: Hazard ratios (HR) comparing the rates of deaths and hospitalisation (all-cause) in patients with inflammatory joint diseases receiving csDMARDs to patients receiving b/tsDMARDs in Sweden. Previously published corresponding HRs for COVID-19 in the right-most column.

Outcome	Cohort	N events	Absolute risk, %	HR1 (95% CI)**	HR2 (95% CI)#	HR2 COVID (95% CI) ***
Hospitalisation	csDMARD	15952	13.8	1 (ref)	1 (ref)	1 (ref)
	TNFi	7480	10.3	0.73 (0.71, 0.76)	1.06 (1.03, 1.10)	0.99 (0.89-1.10)
	Abatacept	777	18.0	1.33 (1.23, 1.45)	1.12 (1.04, 1.22)	0.94 (0.69-1.26)
	Tocilizumab	596	13.9	1.00 (0.92, 1.10)	1.09 (1.00, 1.19)	0.92 (0.64-1.33)
	Rituximab	1610	19.8	1.49 (1.40, 1.58)	1.16 (1.10, 1.23)	1.25 (1.02-1.53)
	All b/tsDMARDs combined*	10671	11.8	0.85 (0.82, 0.87)	1.08 (1.05, 1.12)	0.99 (0.90-1.10)
Death	csDMARD	1880	1.6	1 (ref)	1 (ref)	1 (ref)
	TNFi	319	0.4	0.27 (0.24, 0.30)	0.77 (0.57, 1.06)	0.71 (0.49-1.03)
	Abatacept	44	1.0	0.63 (0.47, 0.85)	0.97 (0.51, 1.85)	1.12 (0.50-2.48)
	Tocilizumab	39	0.9	0.56 (0.41, 0.77)	0.84 (0.34, 2.08)	1.11 (0.41-3.02)
	Rituximab	137	1.7	1.04 (0.87, 1.23)	1.16 (0.76, 1.78)	2.52 (1.56-4.07)
	All b/tsDMARDs combined*	551	0.6	0.38 (0.34, 0.41)	0.90 (0.70, 1.16)	0.91 (0.67-1.24)

Note results only presented where treatment cohorts have 5 or more events.

*Includes Janus kinases inhibitors (JAKi).

**Adjusted for influenza season; age, sex and region accounted for via matching.

#Additionally adjusted for disease duration, disease activity score on 28 joints (DAS28), number of previous b/tsDMARDs and concomitant steroid use, socioeconomic factors (education, civil status, country of birth), influenza hospitalisation in the previous year and comorbidities (history of the following diseases: cancer, diabetes, heart failure, ischemic heart disease, lung disease, stroke, surgery, venous thrombotic event, and kidney failure)

***Taken from the COVID analyses presented in Bower et al.[11], adjusted for the same factors as #, but via inverse probability treatment weighting via propensity score estimation.

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Table S10: Hazard ratios (HR) comparing the rates hospitalisation listing influenza in patients with inflammatory joint diseases receiving csDMARDs to patients receiving b/tsDMARDs in Sweden. A comparison of approaches for dealing with missing DAS28 information in adjusted Cox proportional hazards models

Outcome	Cohort	Original analysis (as displayed in Table 2)*		Complete case	
		N events	HR2** (95% CI)	N events	HR2** (95% CI)
Hospitalisation	csDMARD	327	1 (ref)	72	1 (ref)
	All b/tsDMARDs combined	191	1.32 (1.06, 1.64)	93	1.56 (1.07, 2.27)

*Original analysis assumes one category for missing DAS28 information, the proportion missing is displayed in Supplementary Table S6

**Influenza season; age, sex and region accounted for via matching. Further adjusted for disease duration, disease activity score on 28 joints (DAS28), number of previous b/tsDMARDs and concomitant steroid use, socioeconomic factors (education, civil status, country of birth), influenza hospitalisation in the previous year and comorbidities (history of the following diseases: cancer, diabetes, heart failure, ischemic heart disease, lung disease, stroke, surgery, venous thrombotic event, and kidney failure)

Figure S1: Crude rates for influenza deaths and hospitalisations listing influenza in inflammatory joint disease patients (solid lines) and matched comparators (dashed lines) over four influenza seasons in Sweden.