APPROCCI INTERDISCIPLINARI IN REUMATOLOGIA

4ª edizione

INFETTIVOLOGIA E MALATTIE REUMATICHE

APPLICAZIONE DELLE EVIDENZE SCIENTIFICHE REAL LIFE NELLA VALUTAZIONE DEL RISCHIO INFETTIVO

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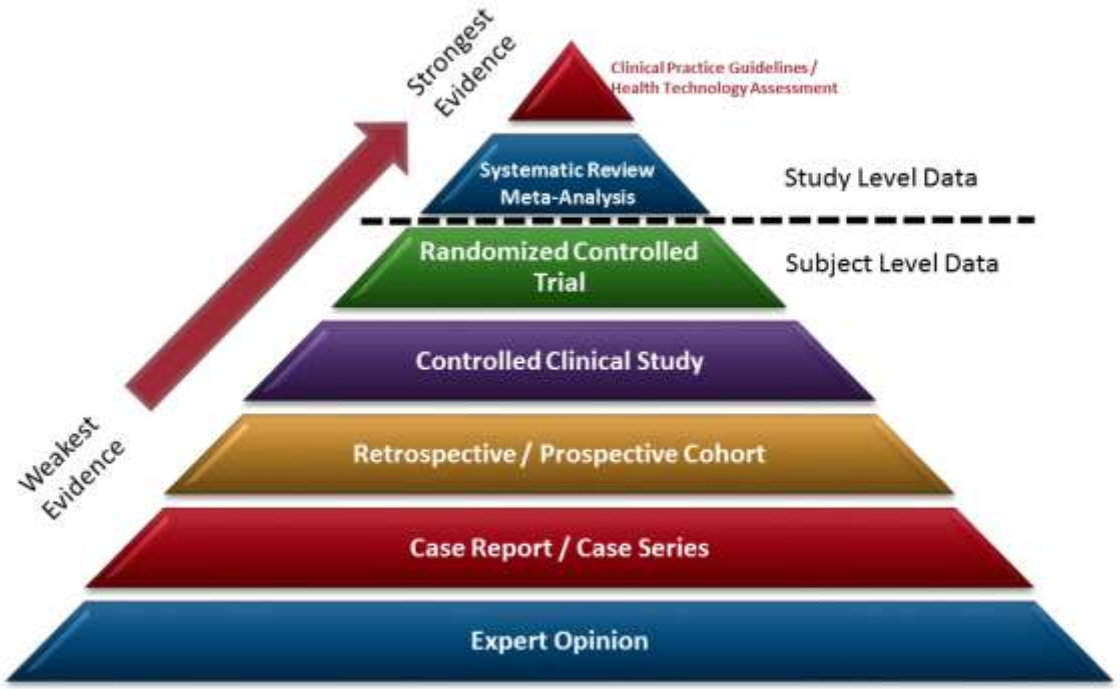
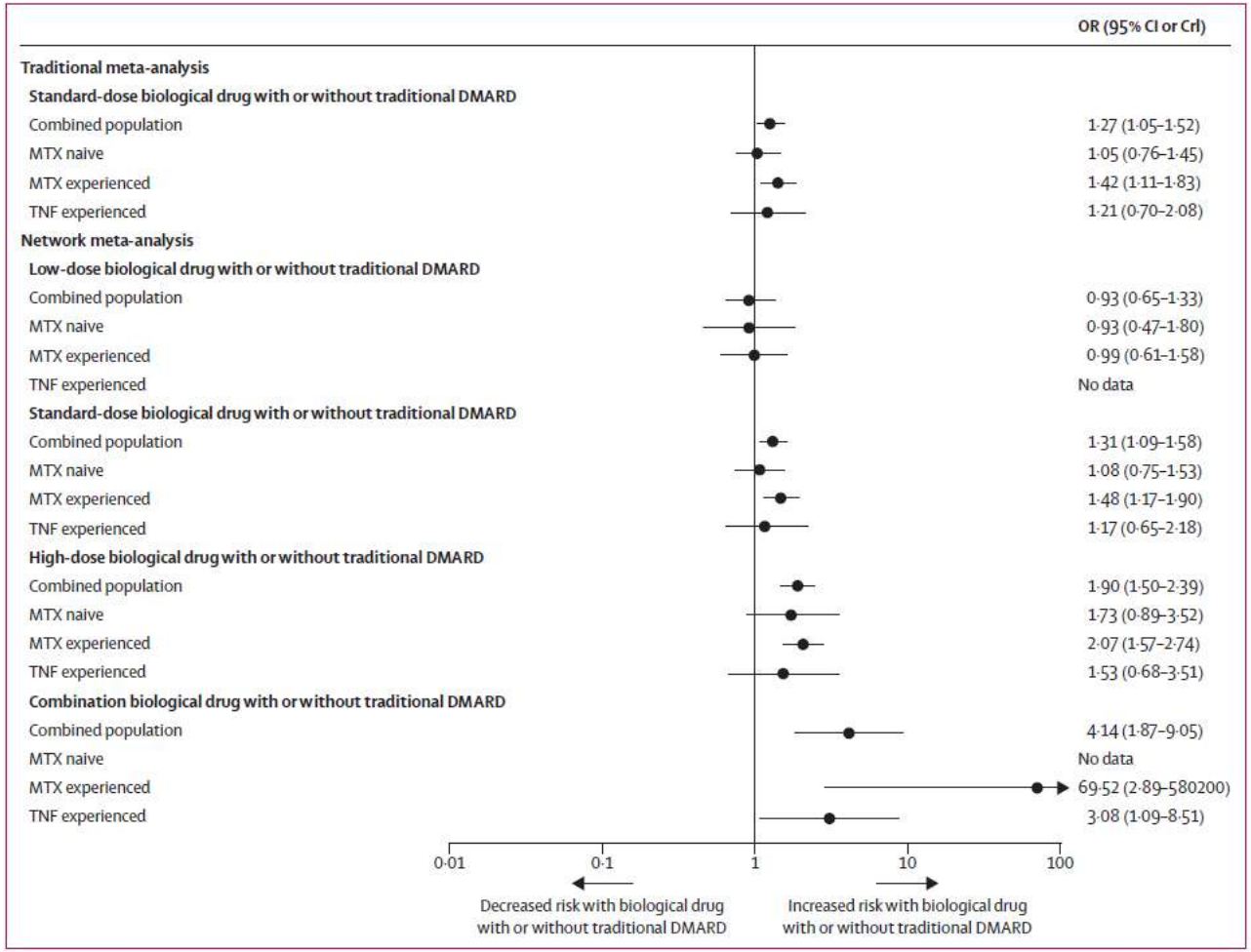
CLINICAL QUESTION AND LEVEL OF EVIDENCE

- Risk of serious infection in biological treatment of patients with rheumatoid arthritis

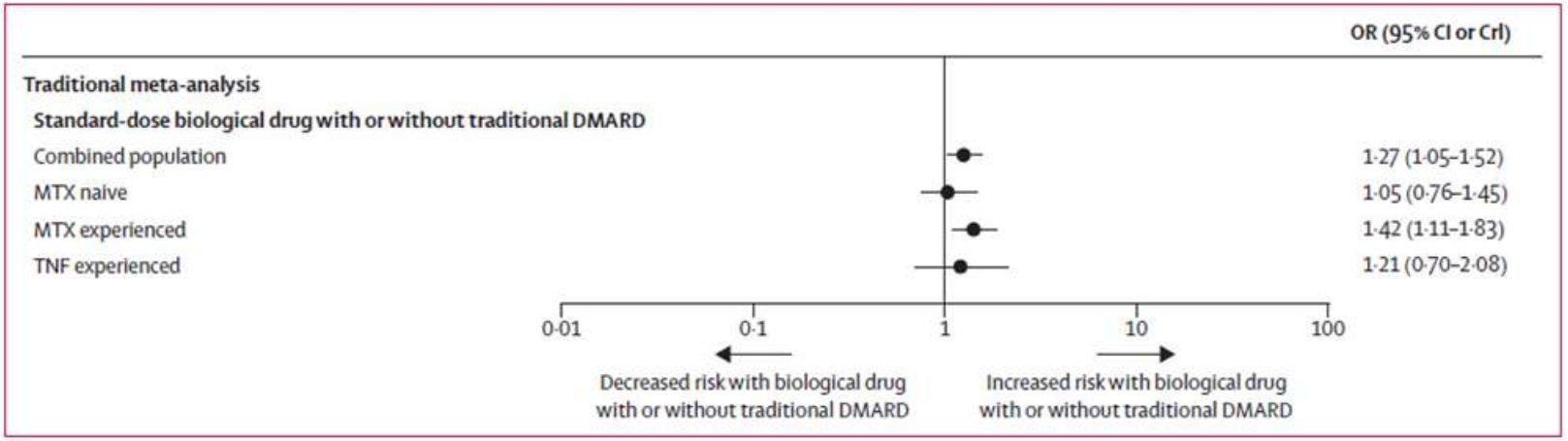


TRADITIONAL AND NETWORK META-ANALYSIS OF RCT



Singh J et al. (Lancet 2015) - Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis

HETEROGENEITY IN RA POPULATIONS



Singh J et al. (Lancet 2015) - Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis

"If the study was not randomised we'd suggest that your stop reading it and go on to the next article in your search"

EVIDENCE BASED MEDICINE

Sackett DW., Richardson W., Rosenberg W., Haynes RB., (1996), Evidence Based Medicine.London: Churchill-Livingstone, pp. 108

RCT AND OBSERVATIONAL STUDIES

- RCT are the gold standard for defining the efficacy
- RCT recruit highly selected populations for short durations and in very controlled settings
- Selection and duration impact on
  - benefits
  - adverse events

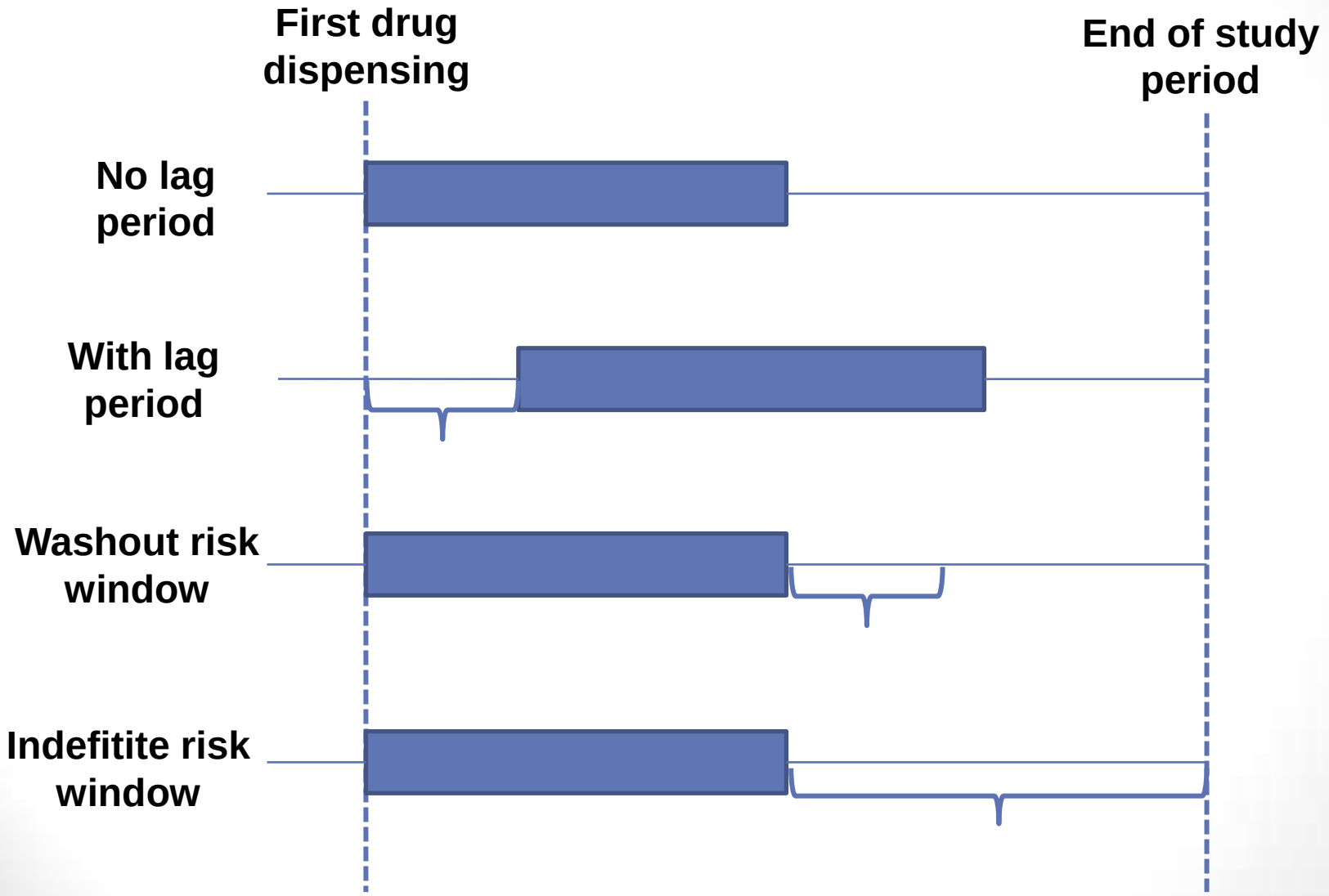
SUMMARY OF MAJOR EPIDEMIOLOGIC COHORT STUDIES OF THE RISK OF INFECTION ASSOCIATED WITH TNFI IN RA

First author, year	Study population	No. of patients	End point	Comparator group	Drug-specific adjusted relative risk (95% CI)
Listing, 2005	German Biologics Registry	1,529	Hospitalized with infection	Nonbiologic DMARD	etan. 2.16 (0.9–5.4); inflix. 2.13 (0.8–5.5)
Wolfe, 2006	National Data Bank for Rheumatic Diseases	16,788	Hospitalized with pneumonia	Absence of drug of interest	ada. 1.1 (0.6–1.9); etan. 0.8 (0.6–1.1); inflix. 1.1 (0.9–1.4)
Dixon, 2006	British Society of Rheumatology Biologics Register	8,973	Hospitalized with infection, death, or requiring IV antibiotics	Nonbiologic DMARD	ada. 1.07 (0.67–1.72); etan. 0.97 (0.63–1.50); inflix. 1.04 (0.68–1.61)
Curtis, 2007	Commercial insurance beneficiaries	5,326	Hospitalized with infection or requiring IV antibiotics	Methotrexate	TNFα 1.94 (1.32–2.83)
Schneeweiss, 2007	Medicare beneficiaries 65 years and older	15,597	Hospitalized with infection	Methotrexate	TNFα 1.0 (0.60–1.67)
Dixon, 2007	British Society of Rheumatology Biologics Register	10,829	Hospitalized with infection, death, or requiring IV antibiotics	Nonbiologic DMARD	TNFα 1.30 (0.93–1.78); TNFα 4.6 (1.8–11.9)*
Curtis, 2007	Commercial insurance beneficiaries	5,195	Hospitalized with infection or requiring IV antibiotics	Methotrexate	etan. 1.55 (0.73–3.34); inflix. 2.41 (1.23–4.70)

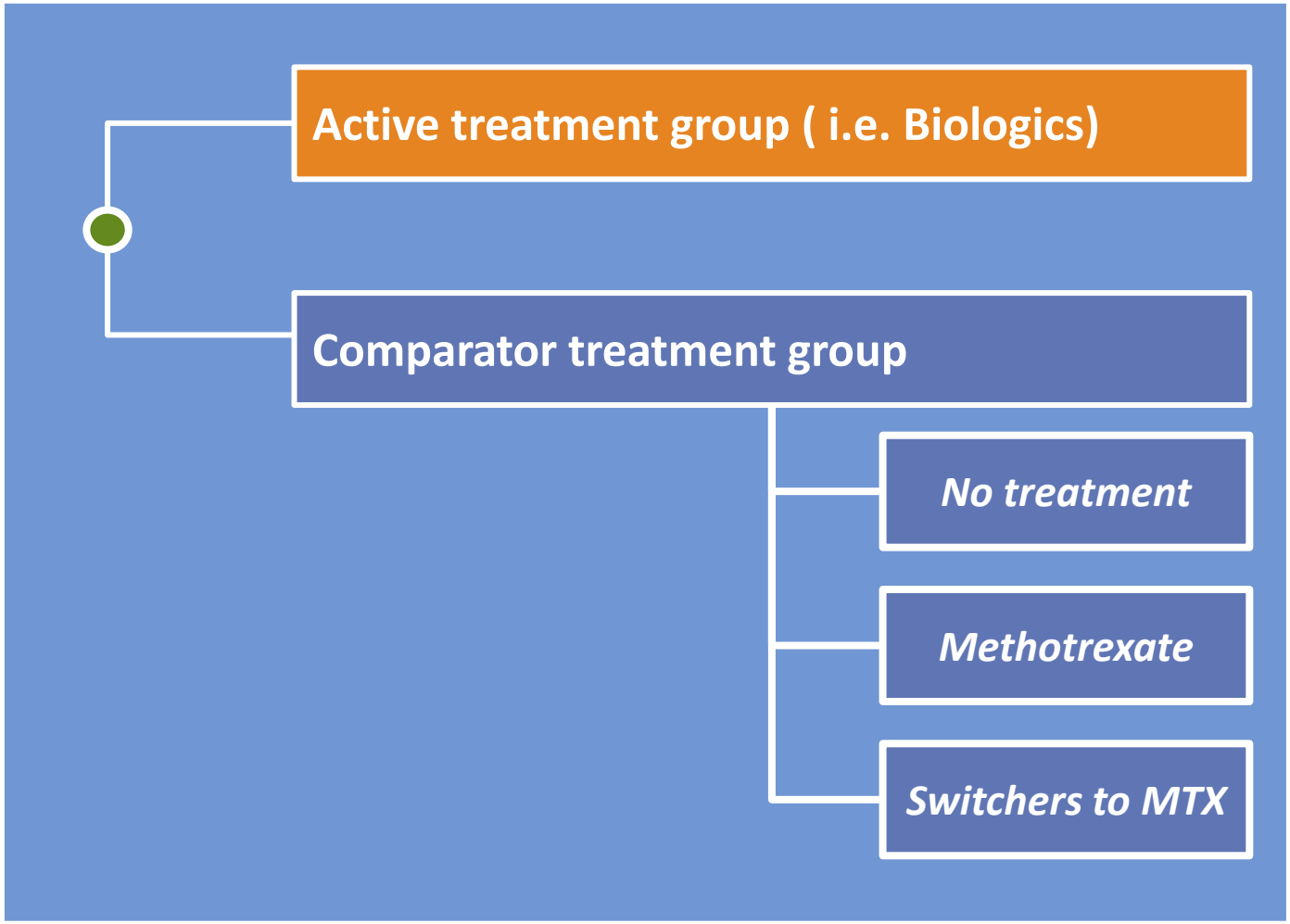
Key methodological aspects to consider

- Exposure risk windows
- Comparator Drug
- Drug initiator and ongoing user designs
- Combination therapy
- Potential confounders
- Definition of the end point
- Time-varying variables
- Data sources

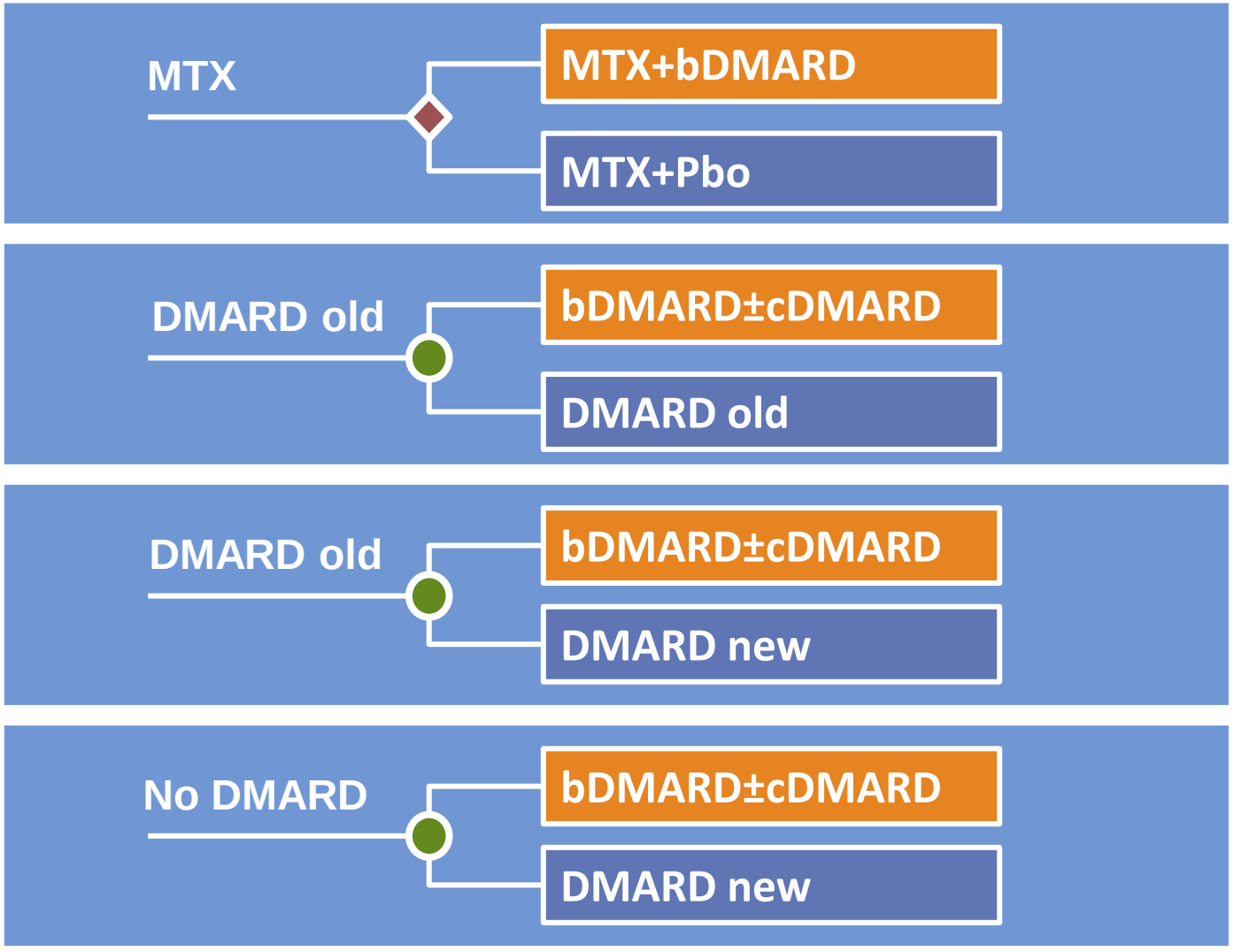
EXPOSURE RISK WINDOWS



COMPARATOR DRUG



DRUG INITIATOR AND ONGOING USER DESIGNS



COMBINATION THERAPY

simple

bDMARD	cDMARD	GC
0	0	0
1	1	1

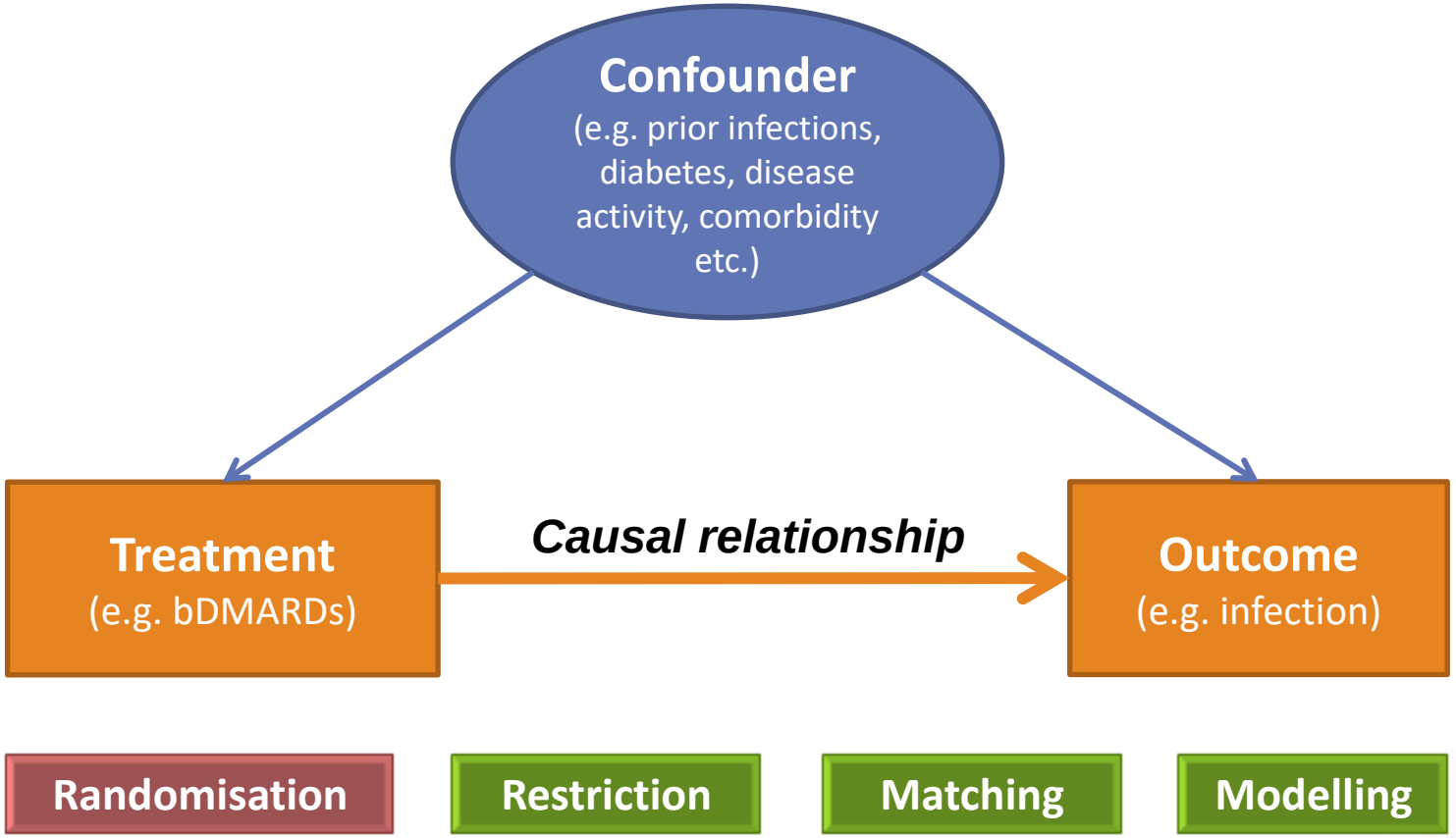
hierarchical

bDMARD	cDMARD	GC
0	0	0
1	X	X
0	1	X
0	0	1

pattern

bDMARD	cDMARD	GC
0	0	0
1	0	0
1	1	0
1	1	1
1	0	1
0	1	0
0	1	1
0	0	1

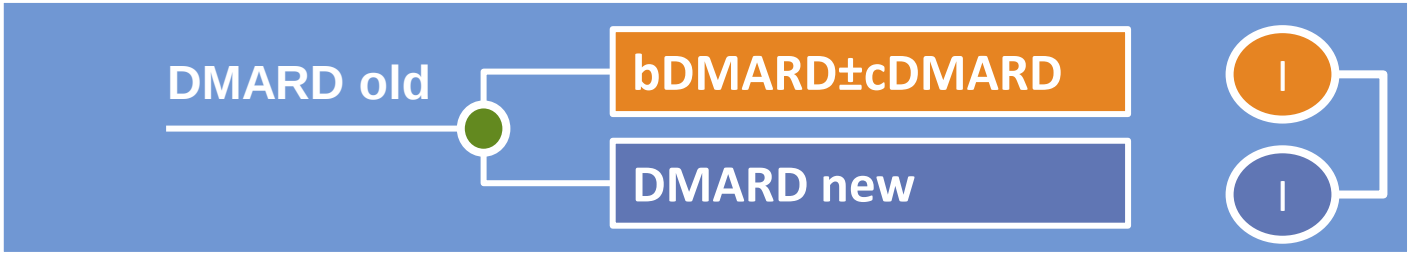
POTENTIAL CONFOUNDERS IN THE RELATIONSHIP BETWEEN BDMARDS AND INFECTION



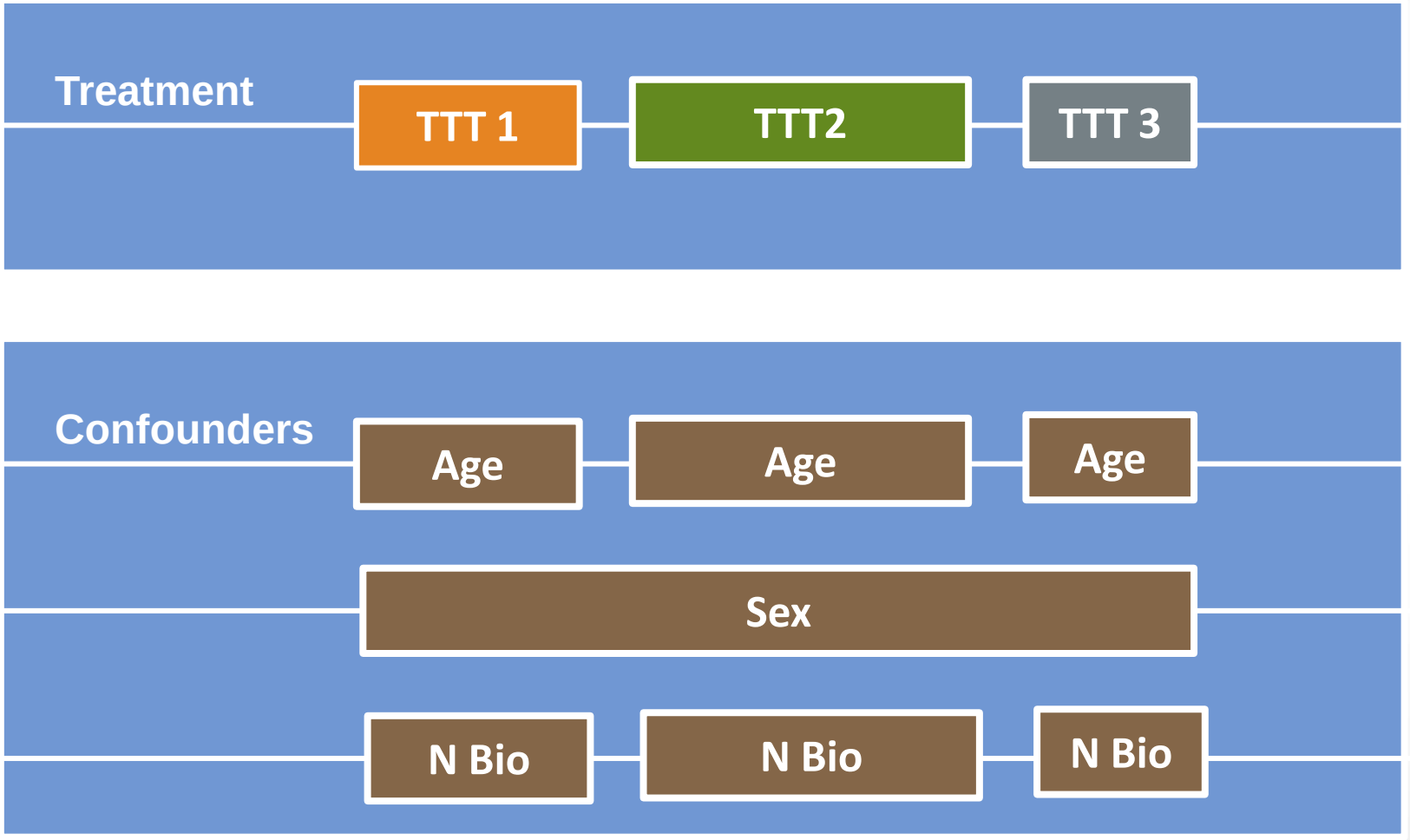
DEFINITION OF THE END POINT

- Self reported
- Physician reported (confirmed in medical records)
- Events requiring hospitalisation

- Major issue: *surveillance bias* (observation bias - type of differential misclassification)



TIME-VARYING VARIABLES



DIFFERENT DATA SOURCES

Cohort type	Strengths	Weaknesses
Disease-based registry	Diagnosis is usually very accurate; disease-specific information is very rich; medical records are often available	Patients may not represent "typical" cases
Drug-based registry	Diagnosis is usually very accurate; disease-specific information is very rich; medical records are often available	"Unexposed" patients may not be similar
Practice-based or population-based registries	Medical records are often available; patients represent those in routine care; often allows for linkage to pharmacy data; often allows for linkage to other registries	Diagnosis may not be accurate; outcome assessment may not be accurate; disease-specific information may be lacking
Health care utilization data	Patients represent those in routine care; includes linkage to pharmacy data; often very large cohorts can be assembled	Diagnosis may not be accurate; outcome assessment may not be accurate; disease-specific information may be lacking

First author, year	Exposure risk window	Comparator drug	Drug initiated	Control for confounding	Duration of followup	End point assessment
Listing, 2005	No lag, fixed duration of 365 days	Nonbiologic DMARD	DMARD, TNFα	Propensity score with disease severity measures, prednisone use, no comorbidities	12 months maximum, 74% completed the full 12 months	Reported by study investigators
Wolfe, 2006	No lag, duration not reported	No prednisone	No DMARD, no TNFα	HAQ scores, disease duration, prednisone use, comorbidities	Median 30 months	Patient self-report, with some confirmation
Dixon, 2006	No lag, duration according to supply	Nonbiologic DMARD	No DMARD, TNFα	HAQ score, DAS, prednisone use, comorbidities	Median 15 months with TNFα, median 11 months with nonbiologic DMARD	Hospitalized with infections, death, or IV antibiotics
Curtis, 2007	No lag, duration according to supply plus 90 days	MTX	No MTX, TNFα	Comorbidities, prednisone use, health system factors	Median 17 months	Hospitalized with infections defined by diagnosis codes with primary record confirmation
Schneeweiss, 2007	No lag, duration according to supply plus 3 half lives	MTX	MTX, TNFα	Propensity score, comorbidities, prednisone use, health system factors	Mean 15 months with TNFα, mean 7 months with nonbiologic DMARD	Hospitalized with infections defined by validated primary diagnosis code
Dixon, 2007	No lag, varied duration	Nonbiologic DMARD	No DMARD, TNFα	HAQ score, DAS, prednisone use, comorbidities	Varied	Hospitalized with infections, death, or IV antibiotics
Curtis ,2007	No lag, duration according to supply plus 90 days	MTX	No MTX, TNFα	Comorbidities, prednisone use, health system factors	Median 17 months	Hospitalized with infections defined by diagnosis codes with primary record confirmation

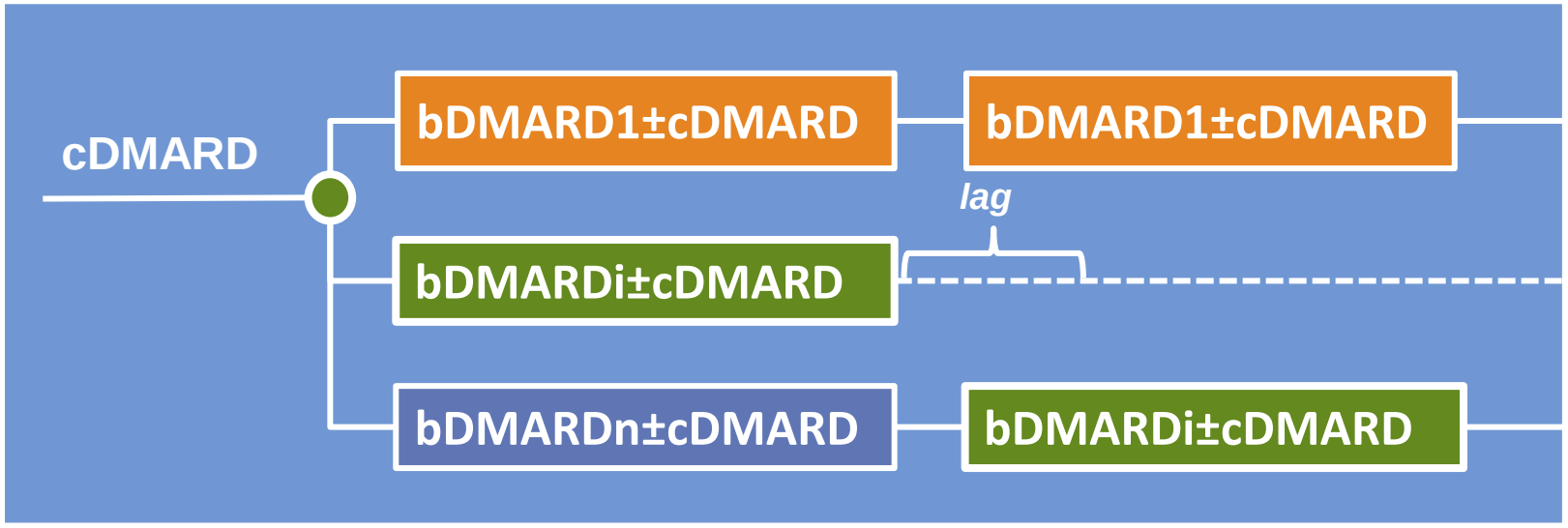
RECORD DATASET

- Record linkage of the administrative data base of the Regional Health System of the Lombardy Region (>10.000.000 benificiaries)
- Cohort 2004-2014
- RA patients* and JCA
- 4:1 age- sex- matched control cohort from the general population

* Carrara, G., et al. *BMJ Open* (2015).

ANALYSIS OF THE RECORD STUDY

- ***Pharmacoepidemiology work package***
- Aim of the analysis: to compare the risk of hospitalised bacterial infections in RA patients starting biologics



INCLUSION CRITERIA

RECORD algorithm for pharmacoepidemology studies

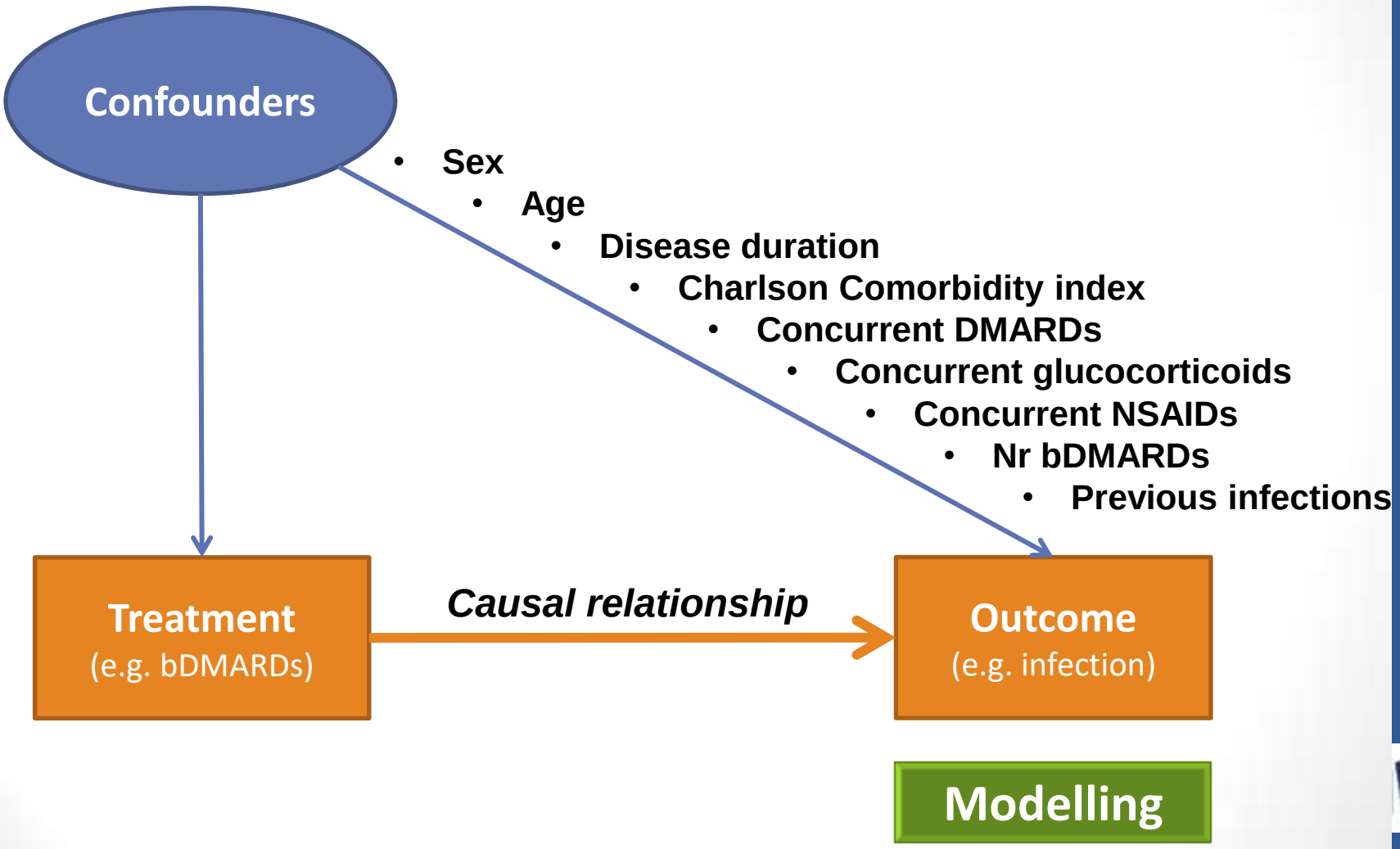
At least one administration of:

- **ABATACEPT or**
- **ADALIMUMAB or**
- **CERTOLIZUMAB or**
- **ETANERCEPT or**
- **GOLIMUMAB or**
- **INFLIXIMAB or**
- **RITUXIMAB or**
- **TOCILIZUMAB**

DEFINITION OF THE END POINT

Bacterial infection	ICD-9CM (any position)
Pneumonia	481*-482*
Septicaemia	038*, 790.7
Cellulitis	681*-682*
Septic arthritis	711*
Osteomyelitis	730.0*-730.2*
Urinary tract Infections	590*
Meningitis	049*, 320*
Encephalitis	054.3, 323*
Endocarditis	421*

PRE-SPECIFIED CONFOUNDERS



CHARLSON COMORBIDITY SCORE

Diagnostic category	Number (%) of patients in study dataset	ICD-9-CM codes
Myocardial infarction	892 (3.3)	410–410.9 412*
Congestive heart failure	595 (2.2)	428–428.9
Peripheral vascular disease	698 (2.6)	443.9* 441.441.9* 785.4* V43.4* procedure 38.48
Cerebrovascular disease	940 (3.5)	430–438†
Dementia	59 (0.2)	290–290.9*
Chronic pulmonary disease	2466 (9.1)	490–496* 500–505* 506.4*
Rheumatologic disease	440 (1.6)	710.0* 710.1* 710.4* 714.0–714.2* 714.81* 725*

Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992 Jun;45(6):613-9.

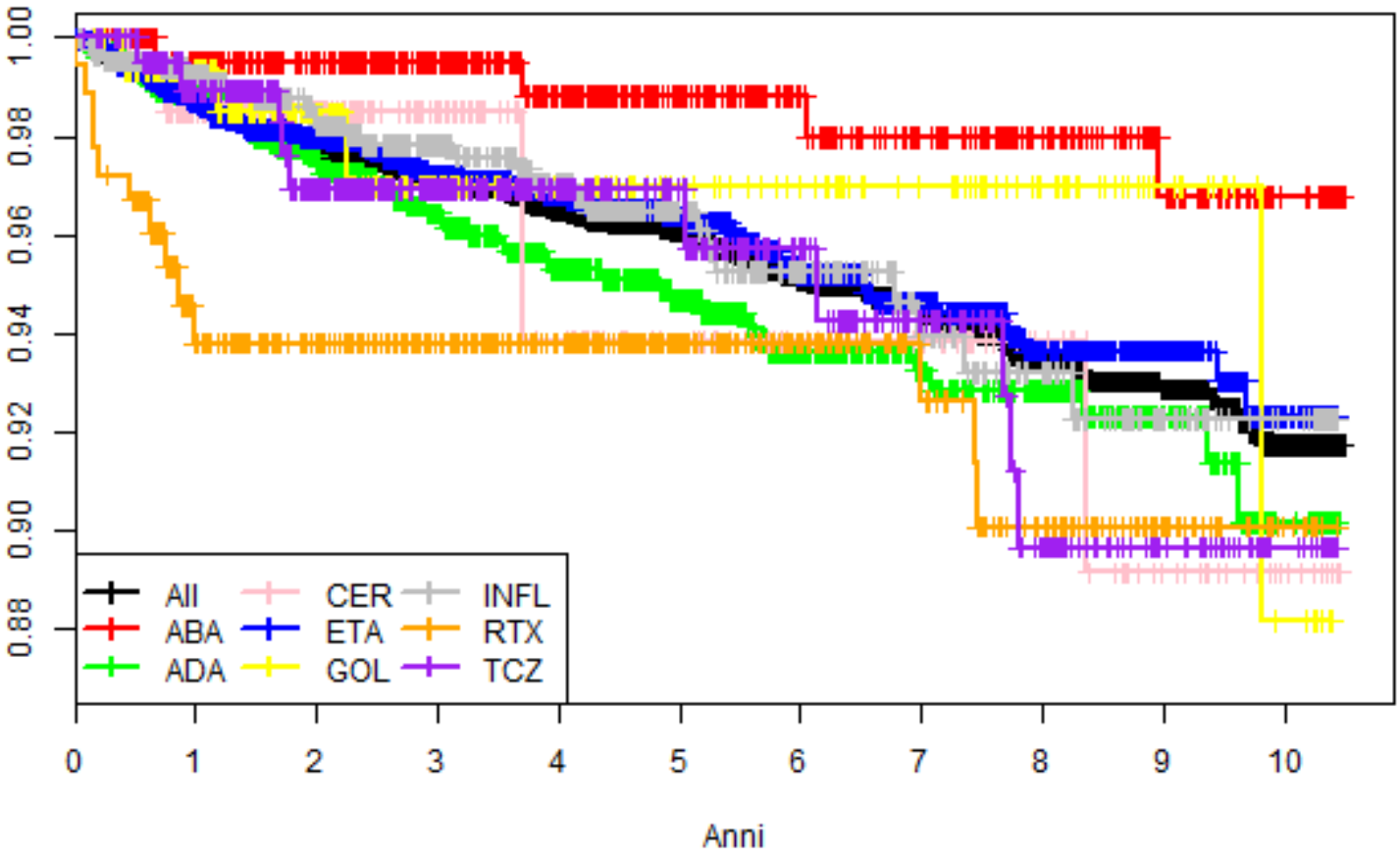
DESCRIPTIVE RESULTS. STUDY SAMPLE

Mean age (SD, years)	55.7 (12.7)
Female, n (%)	3603 (77.4)
Disease duration N (%)	
< 1 years	1052 (22.6)
> 1 to ≤ 2 years	1137 (24.4)
≥ 3 1 to ≤ 5 years	1090 (23.4)
> 5 years	1377 (29.6)
Charlson Index, Mean (SD)	1.23 (0.75)
Serious infections in the previous year N (%)	24 (0.5)
Antibiotic prescription in the previous year N (%)	877 (18.8)

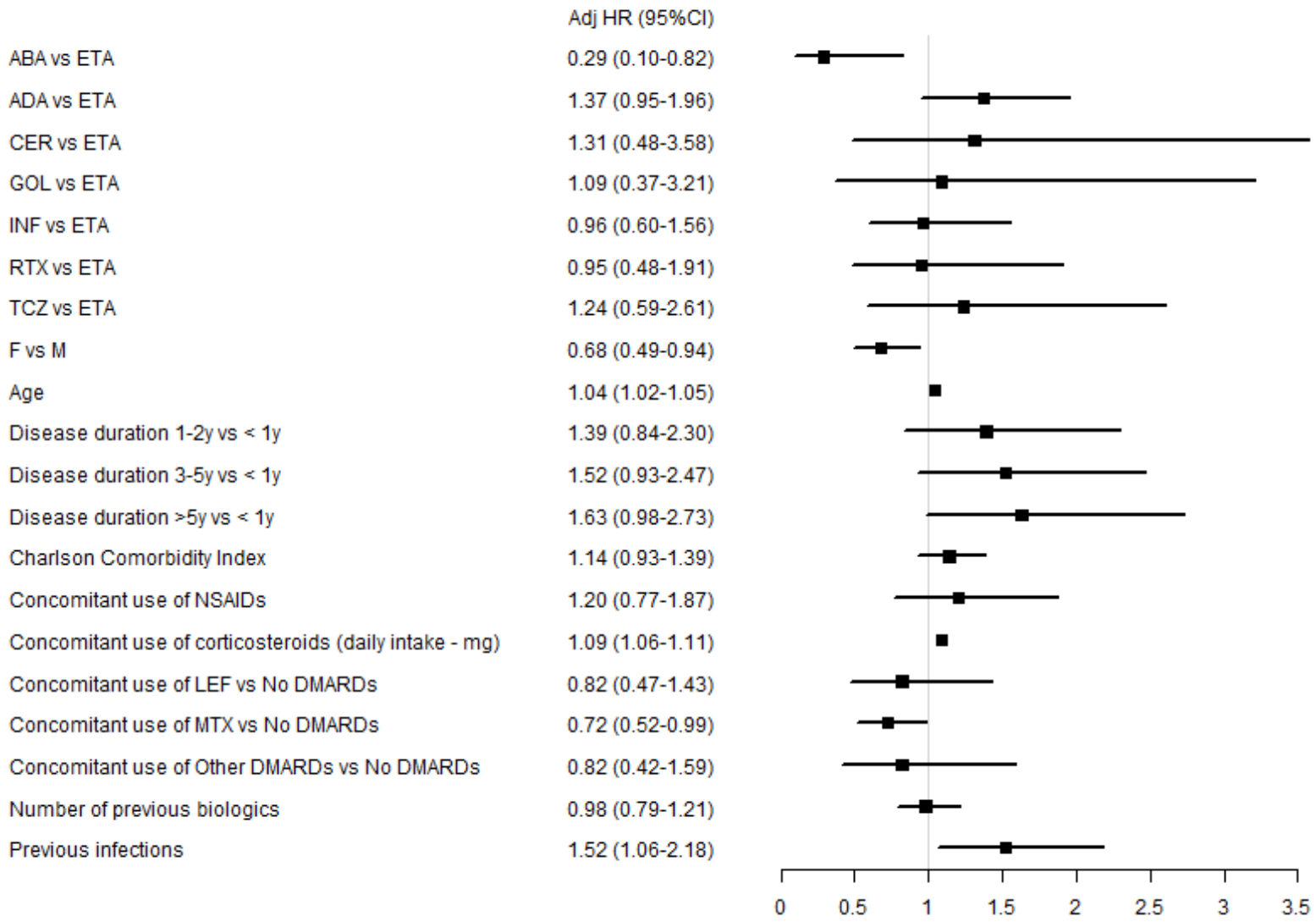
DESCRIPTIVE RESULTS. INFECTION RATE

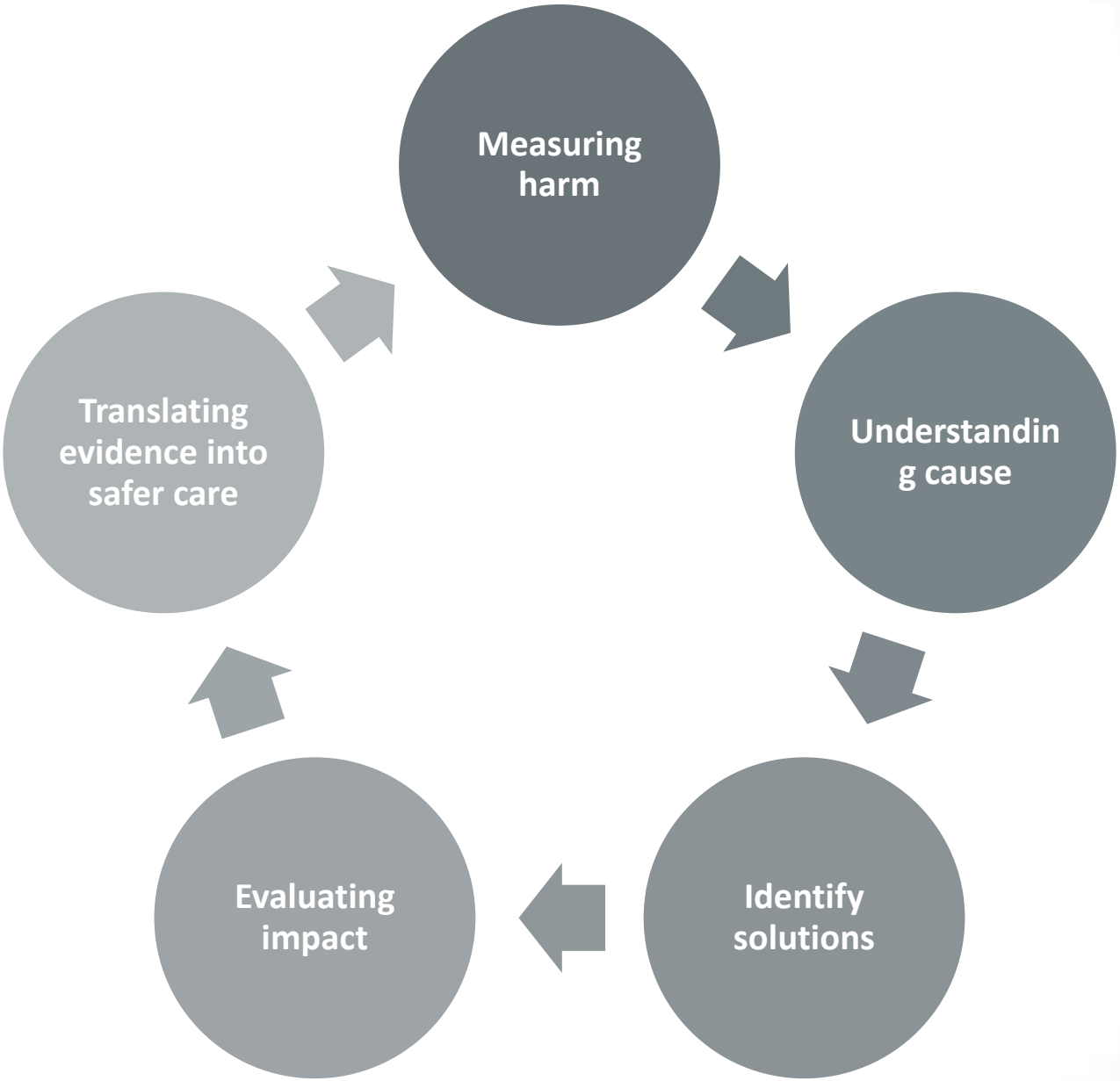
Type of infection	N events/person years	Incidence rate (x 1000)
Meningitis	8/20762	0.39 (0.17,0.76)
Encephalitis	3/20763	0.14 (0.03,0.42)
Cellulitis	27/20721	1.30 (0.86,1.90)
Endocarditis	3/20764	0.14 (0.03,0.42)
Pneumonia	61/20660	2.95 (2.26, 3.79)
Pyelonephritis	10/20740	0.48 (0.23, 0.89)
Septic arthritis	22/20746	1.06 (0.66, 1.61)
Osteomyelitis	13/20764	0.63 (0.33, 1.07)
Bacteraemia	52/20711	2.51 (1.88, 3.29)

SURVIVAL CURVE

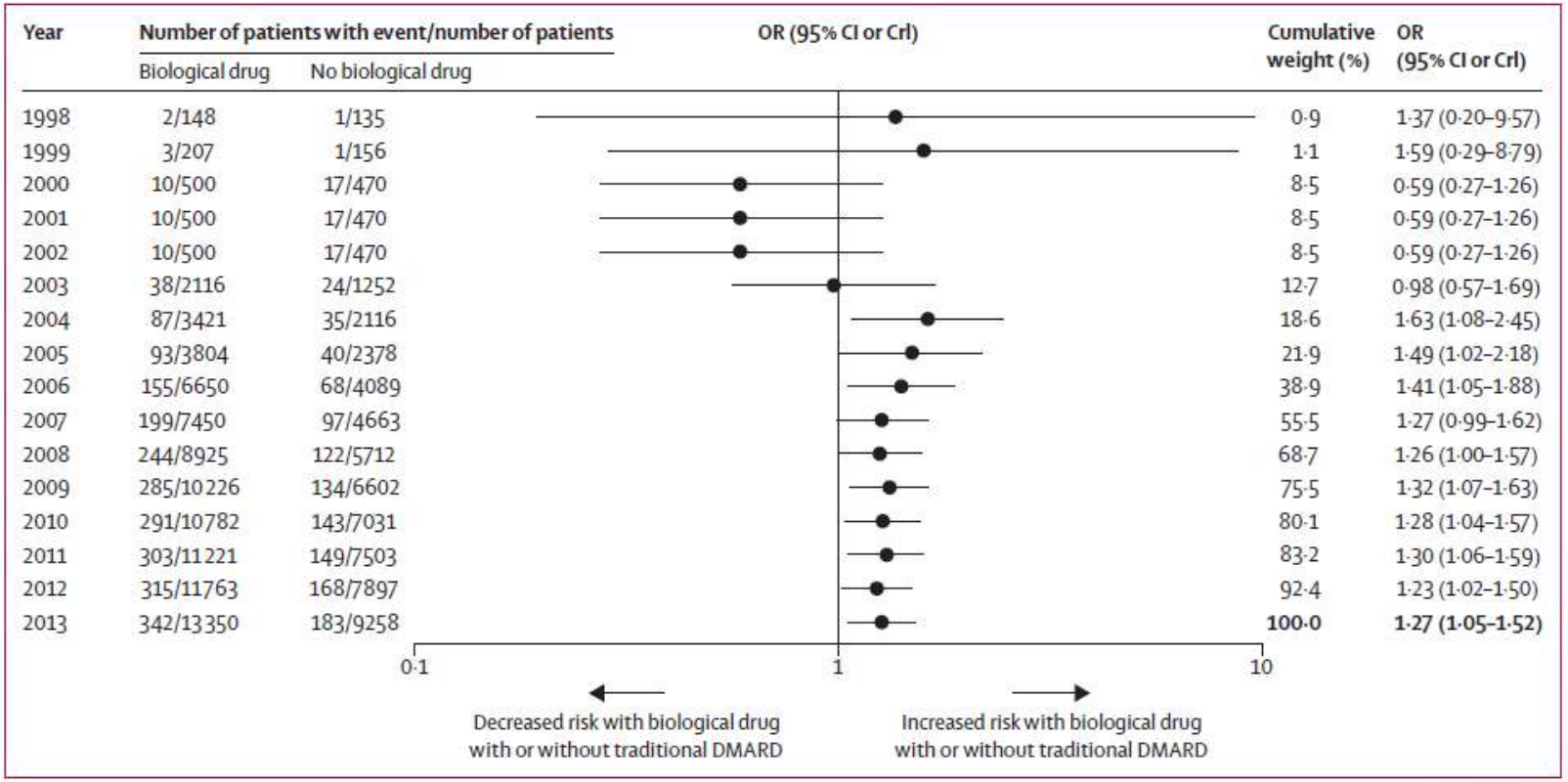


Risk of hospitalized infections



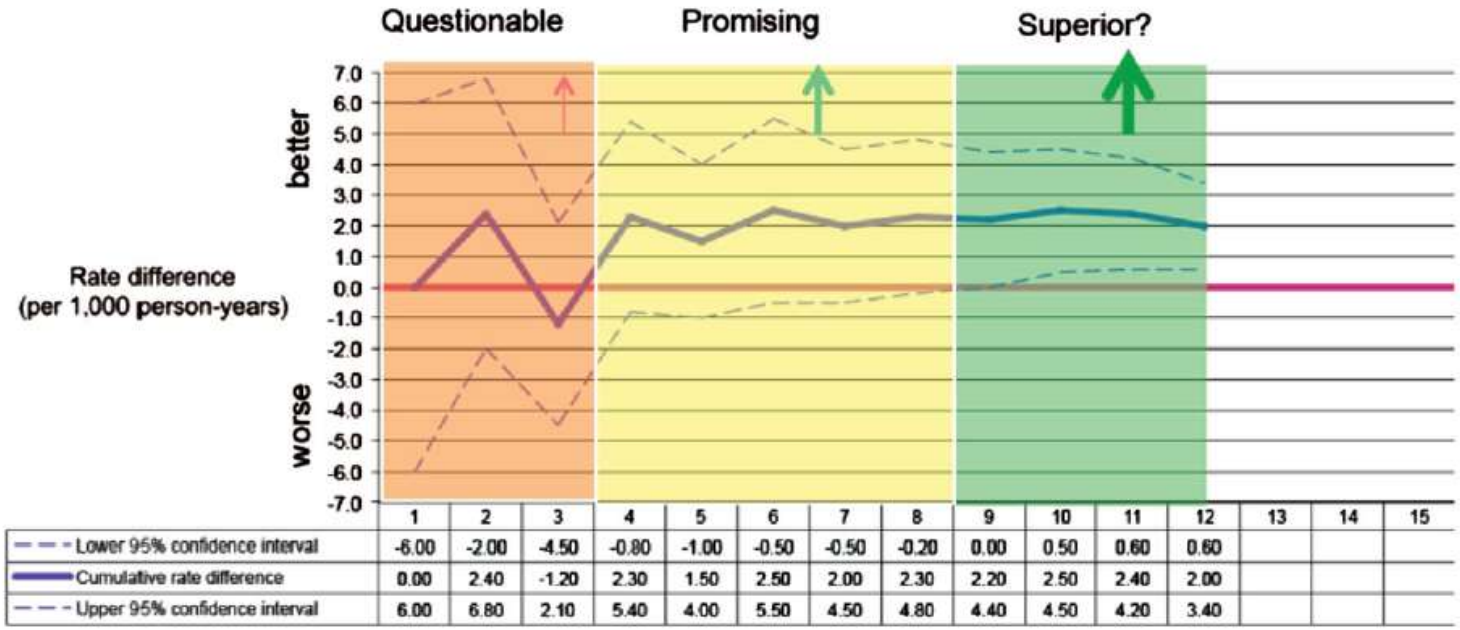

Measuring harm
Understandin g cause
Identify solutions
Evaluating impact
Translating evidence into safer care

CUMULATIVE META-ANALYSIS OF RCT



Singh J et al. (Lancet 2015) - Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis

REAL-TIME EVALUATION OF REAL LIFE-EVIDENCE



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Lower 95% confidence interval	-6.00	-2.00	-4.50	-0.80	-1.00	-0.50	-0.50	-0.20	0.00	0.50	0.60	0.60			
Cumulative rate difference	0.00	2.40	-1.20	2.30	1.50	2.50	2.00	2.30	2.20	2.50	2.40	2.00			
Upper 95% confidence interval	6.00	6.80	2.10	5.40	4.00	5.50	4.50	4.80	4.40	4.50	4.20	3.40			

Questionable:

- Investigate subgroup effects
- Continue evaluation

Promising:

- Continue program
- Continue evaluation
- Moderately expand program

Superior:

- Widely disseminate

Schneeweiss S. Int J Technology Assessment in Health Care (2015)

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