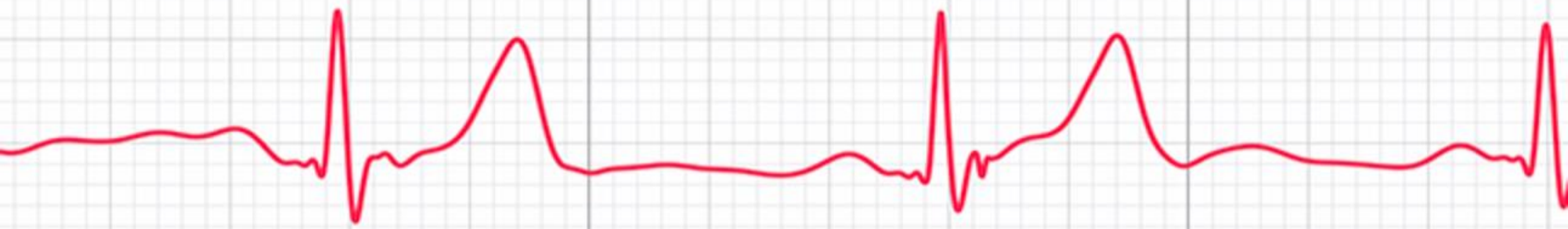
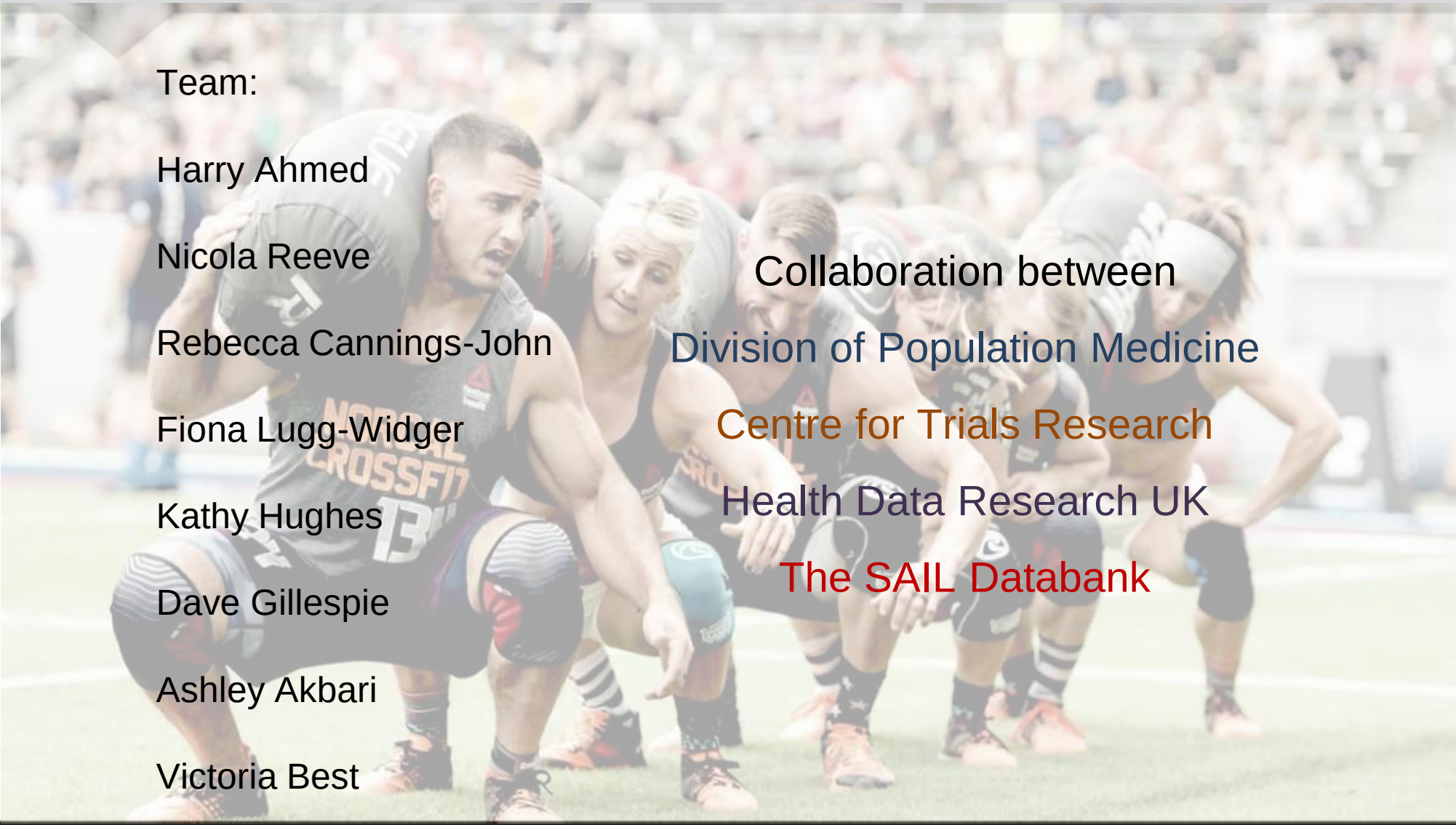
CARDIFF UNIVERSITY
PRIFYSGOL CAERDYDD

School of Medicine
Yr Ysgol Meddygaeth

Myocardial Infarction and Stroke Subsequent tO URInary tract infection (MISSOURI)



Funded by the BHF
May 2021 – April 2024



Team:

Harry Ahmed

Nicola Reeve

Rebecca Cannings-John

Fiona Lugg-Widger

Kathy Hughes

Dave Gillespie

Ashley Akbari

Victoria Best

Collaboration between

Division of Population Medicine

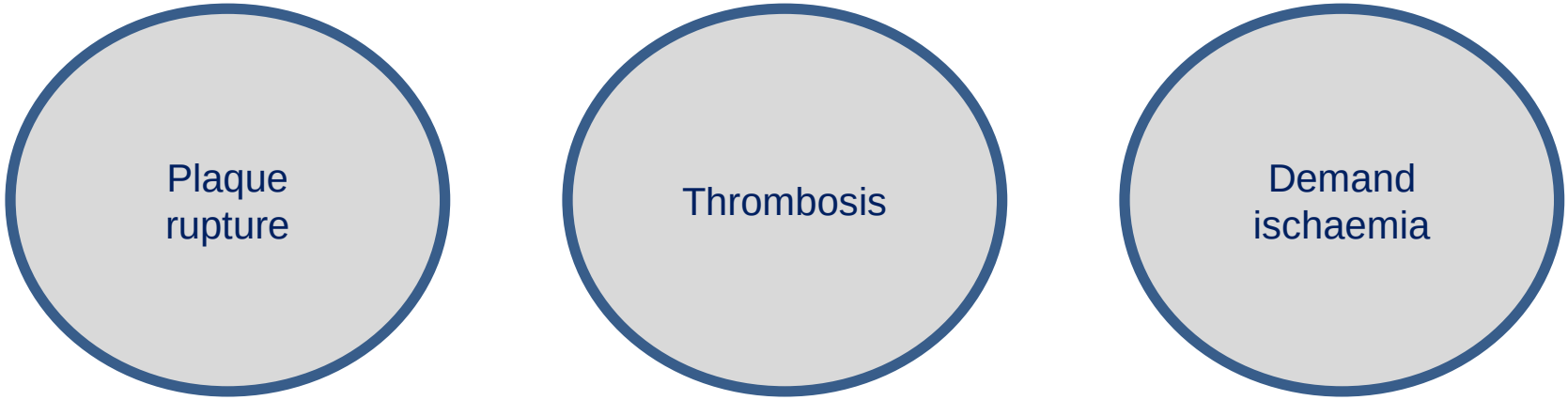
Centre for Trials Research

Health Data Research UK

The SAIL Databank

Research question:

Does urinary tract infection increase your risk of a heart attack or stroke?



What do we know?

Observational Study > Euro Surveill. 2020 Apr;25(17):1900199. doi: 10.2807/1560-7917.ES.2020.25.17.1900199.

Acute myocardial infarctions and stroke triggered by laboratory-confirmed respiratory infections in Denmark, 2010 to 2016

Jessica Ohland [1], Charlotte Warren-Gash [2], Ruth Blackburn [3], Kåre Mølbak [4] [1], Palle Valentiner-Branth [1], Jens Nielsen [1], Hanne-Dorthe Emborg [1]

> J Infect Dis. 2012 Dec 1;206(11):1652-9. doi: 10.1093/infdis/jis597. Epub 2012 Oct 9.

Influenza infection and risk of acute myocardial infarction in England and Wales: a CALIBER self-controlled case series study

Charlotte Warren-Gash [1], Andrew C Hayward, Harry Hemingway, Spiros Denaxas, Sara L Thomas, Adam D Timmis, Heather Whitaker, Liam Smeeth

Review > Lancet Infect Dis. 2009 Oct;9(10):601-10. doi: 10.1016/S1473-3099(09)70233-6.

Influenza as a trigger for acute myocardial infarction or death from cardiovascular disease: a systematic review

Charlotte Warren-Gash [1], Liam Smeeth, Andrew C Hayward

Affiliations + expand

PMID: 19778762 DOI: 10.1016/S1473-3099(09)70233-6

> N Engl J Med. 2018 Jan 25;378(4):345-353. doi: 10.1056/NEJMoa1702090.

Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection

Jeffrey C Kwong [1], Kevin L Schwartz [1], Michael A Campitelli [1], Hannah Chung [1], Natasha S Crowcroft [1], Timothy Karnauchow [1], Kevin Katz [1], Dennis T Ko [1], Allison J McGeer [1], Dayre McNally [1], David C Richardson [1], Laura C Rosella [1], Andrew Simor [1], Marek Smieja [1], George Zahariadis [1], Jonathan B Gubbay [1]

What do we know?

ORIGINAL ARTICLE

Risk of Myocardial Infarction and Stroke after Acute Infection or Vaccination

Liam Smeeth, Ph.D., Sara L. Thomas, Ph.D., Andrew J. Hall, Ph.D., Richard Hubbard, D.M., Paddy Farrington, Ph.D., and Patrick Vallance, M.D.

Article Figures/Media

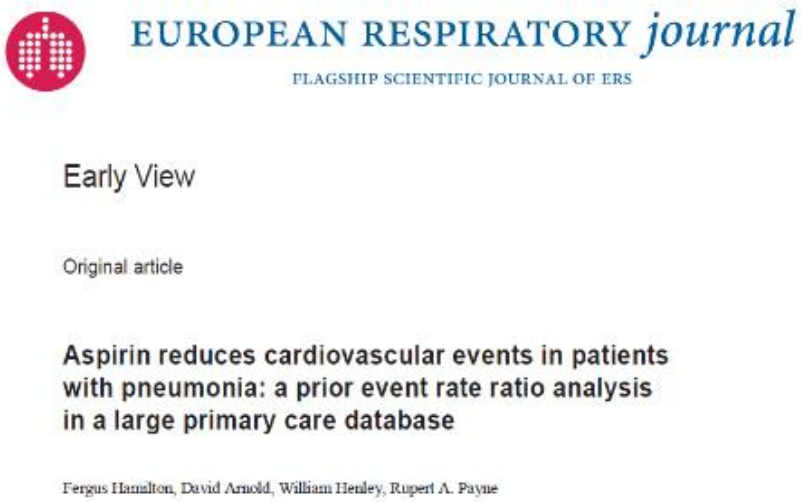
29 References 796 Citing Articles Letters

December 16, 2004
N Engl J Med 2004; 351:2611-2618
DOI: 10.1056/NEJMoa041747

Table 1. Age-Adjusted Incidence Ratios of a First Myocardial Infarction and a First Stroke in Risk Periods after Exposure to Vaccination or Infection.*

Outcome and Risk Period	Influenza Vaccination (N=20,486)		Tetanus Vaccination (N=7966)		Pneumococcal Vaccination (N=5925)		Systemic Respiratory Tract Infection (N=20,921)		Urinary Tract Infection (N=10,448)	
	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)
Myocardial infarction										
1–3 days	77	0.75 (0.60–0.94)	12	1.10 (0.62–1.92)	4	0.49 (0.19–1.32)	322	4.95 (4.43–5.53)	58	1.66 (1.28–2.14)
4–7 days	94	0.68 (0.56–0.84)	17	1.16 (0.72–1.87)	12	1.11 (0.63–1.96)	276	3.20 (2.84–3.60)	75	1.61 (1.28–2.02)
8–14 days	176	0.73 (0.63–0.85)	25	0.97 (0.66–1.44)	23	1.22 (0.81–1.84)	422	2.81 (2.54–3.09)	100	1.22 (1.00–1.49)
15–28 days	417	0.87 (0.79–0.96)	46	0.89 (0.66–1.19)	43	1.15 (0.85–1.55)	576	1.95 (1.79–2.12)	217	1.32 (1.16–1.52)
29–91 days	2,154	1.03 (0.98–1.08)	253	1.07 (0.94–1.21)	177	1.10 (0.95–1.28)	1,658	1.40 (1.33–1.48)	820	1.23 (1.14–1.33)
Baseline period	17,533	1.00	7605	1.00	5662	1.00	17,099	1.00	9079	1.00
	Influenza Vaccination (N=19,063)		Tetanus Vaccination (N=6155)		Pneumococcal Vaccination (N=4416)		Systemic Respiratory Tract Infection (N=22,400)		Urinary Tract Infection (N=14,603)	
	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)	No. of Cases	IR (95% CI)
Stroke										
1–3 days	76	0.77 (0.61–0.96)	11	1.33 (0.74–2.41)	9	1.29 (0.67–2.49)	244	3.19 (2.81–3.62)	152	2.72 (2.32–3.20)
4–7 days	95	0.72 (0.59–0.88)	15	1.36 (0.82–2.26)	10	1.08 (0.58–2.01)	237	2.34 (2.05–2.66)	158	2.12 (1.81–2.48)
8–14 days	194	0.84 (0.73–0.96)	15	0.77 (0.46–1.28)	19	1.18 (0.75–1.85)	368	2.09 (1.89–2.32)	245	1.89 (1.65–2.13)
15–28 days	409	0.88 (0.80–0.97)	40	1.02 (0.74–1.39)	29	0.90 (0.63–1.30)	561	1.68 (1.54–1.82)	445	1.71 (1.55–1.88)
29–91 days	2,051	1.01 (0.96–1.06)	209	1.15 (1.00–1.32)	160	1.15 (0.98–1.35)	1,650	1.33 (1.26–1.40)	1,250	1.22 (1.15–1.30)
Baseline period	16,188	1.00	5853	1.00	4184	1.00	18,056	1.00	12,164	1.00

If we find a relationship between UTI and MI/Stroke, what might we do next to benefit Patients and the NHS?



EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Original article

Aspirin reduces cardiovascular events in patients with pneumonia: a prior event rate ratio analysis in a large primary care database

Fergus Hamilton, David Arnold, William Henley, Rupert A. Payne

ASPECT RCT

Aspirin after hospitalisation with pneumonia to prevent CV events

NIHR

£2.3Million

September 2021

Led by Bristol

Key strengths:

Study design

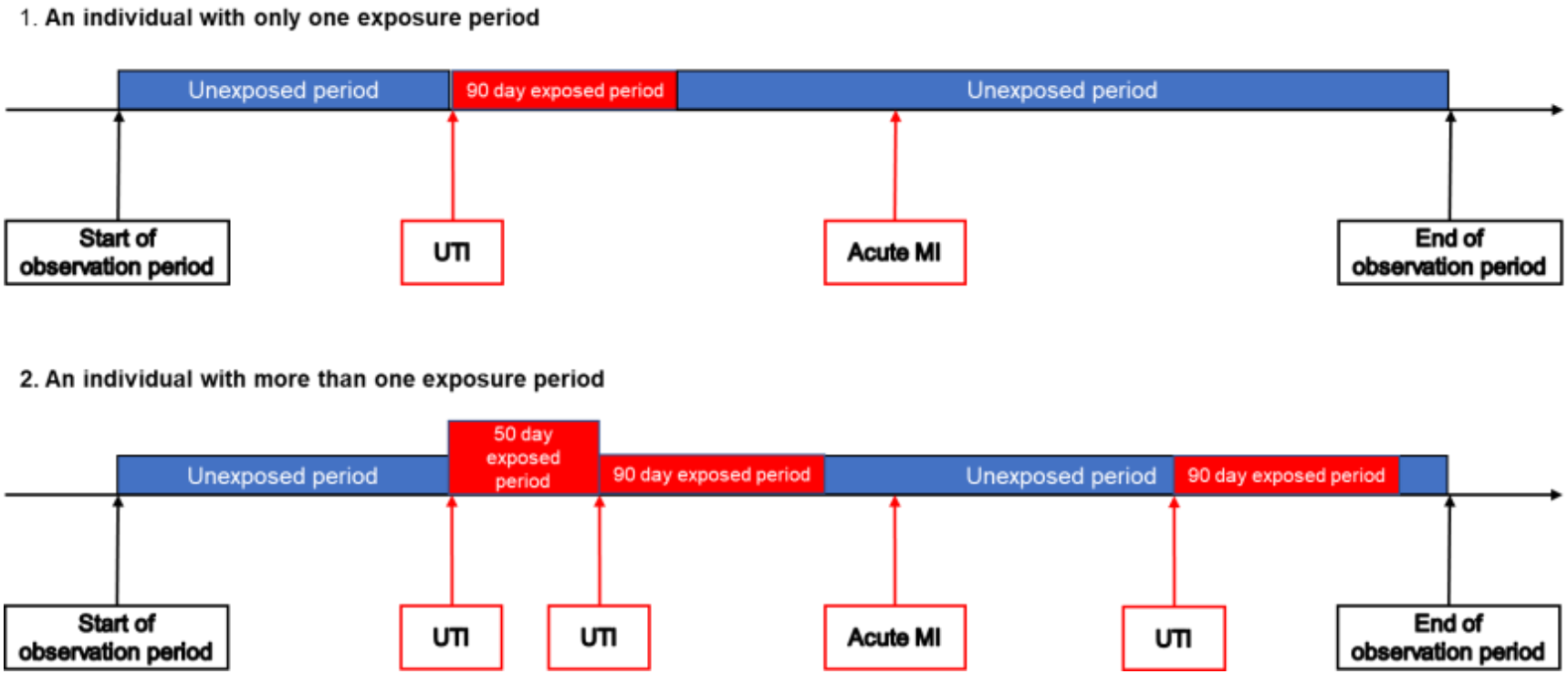
- Self-controlled case series
- Linkage of microbiology data

Self-Controlled Case Series (SCCS)

- MISSOURI uses a self-controlled case series (SCCS) design.
- A study design for which individuals act as their own control.
- Only individuals who have experienced an MI or stroke are included.
- Exposure period: period of time after UTI when risk of MI or stroke is considered greater.
- An appropriate method to estimate the risk of an MI or stroke when there are important differences between individuals that do and do not experience UTI that might introduce bias if assessed using a traditional method.

Self-Controlled Case Series (SCCS)

Comparisons are made within individuals, comparing the rate of MI or stroke during exposed and unexposed periods. This eliminates bias caused by individual characteristics which do not change over time, such as sex.



Investigating causal relationships between UTI and MI or stroke

Cases of MI or stroke

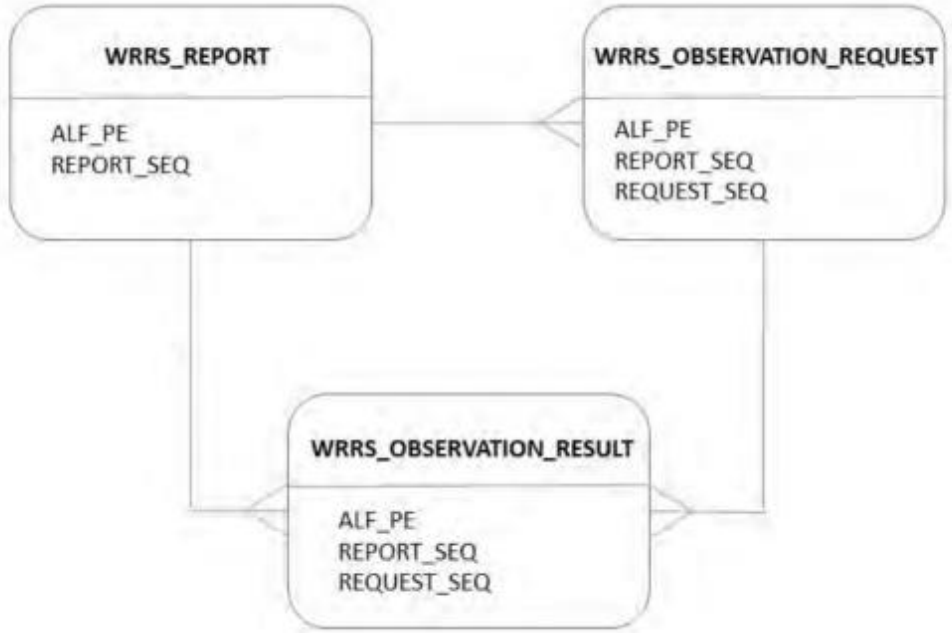
- 2010 - 2020
- Welsh residents
- Aged 30 - 100
- UTI diagnosis
- Using microbiology, general practice, and inpatient hospital data using the Secure Anonymised Information Linkage (SAIL) Databank

Defining UTI

	UTI-related Read code in GP data	Antibiotic prescription in GP data	UTI-related ICD-10 code in PEDW	Urine culture results in WRRS	Time frame	Clinical scenario
Primary analysis	Yes	Yes	No	Yes, showing bacterial growth of >=10^8 cfu/L and WBC>= 10^8/L	Three codes occur within a 7-day window	GP clinically suspected and microbiologically confirmed UTI
Secondary analysis 1	Yes	Yes	No	Yes, showing mixed bacterial growth (any descriptor for 'mixed growth' or >3 organisms).	Three codes occur within a 7-day window	GP clinically suspected UTI with mixed growth
Secondary analysis 2	Yes	Yes	No	No	Same day	GP clinically diagnosed and treated UTI. It is important to consider this group as not all individuals with suspected UTI have urine culture, and limiting to those with culture is subject to selection bias.
Secondary analysis 3	Yes	Yes	No	Yes, showing bacterial growth of < 10^7 cfu per litre	Three codes occur within a 7-day window	UTI is clinically suspected but not supported by microbiology. This group is important to understand if early symptoms and signs of acute MI or stroke are attributed to UTI.
Secondary analysis 4	No	No	Yes	Yes, showing bacterial growth of >=10^8 cfu/L and WBC>= 10^8/L	Two codes occur within a 7-day window	UTI diagnosed and/or treated in hospital
Secondary analysis 5	Yes, OR ICD-10 code	Yes, OR ICD-10 code	Yes, OR: UTI Read code AND antibiotic Read code	Yes, showing bacterial growth of >=10^8 cfu/L and WBC>= 10^8/L	Two/three codes occur within a 7-day window	GP clinically suspected and microbiologically confirmed UTI or UTI diagnosed and/or treated in hospital

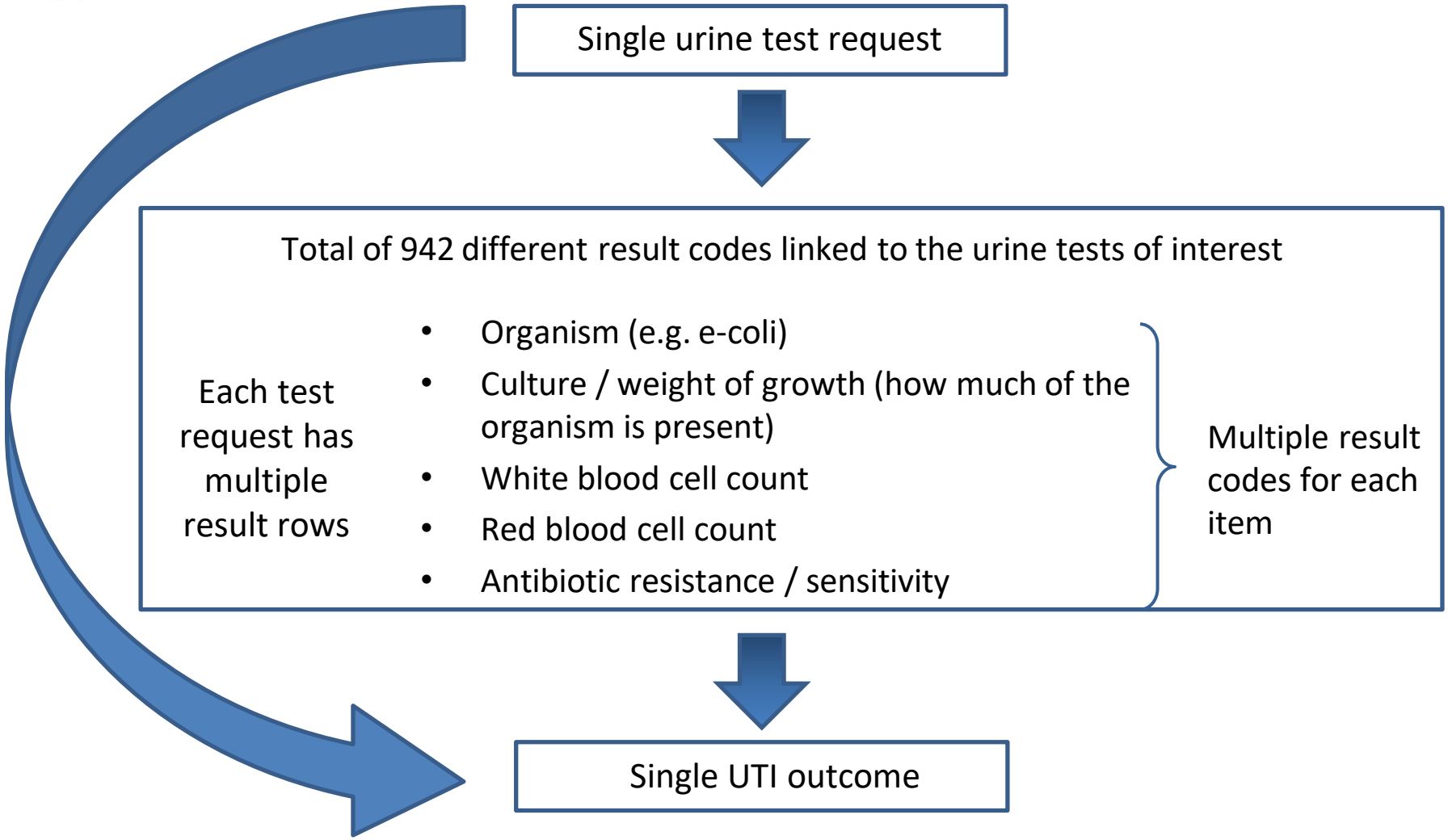
Welsh Results Reports Service (WRRS) Data

The WRRS “allows health care professionals (HCPs) across Wales to access, enter and view laboratory results for pathology requests and any other associated results across all health boards in Wales, from both primary and secondary care, regardless of where they were requested, tested or provided back to patients in Wales.” (Davies et al, 2022)

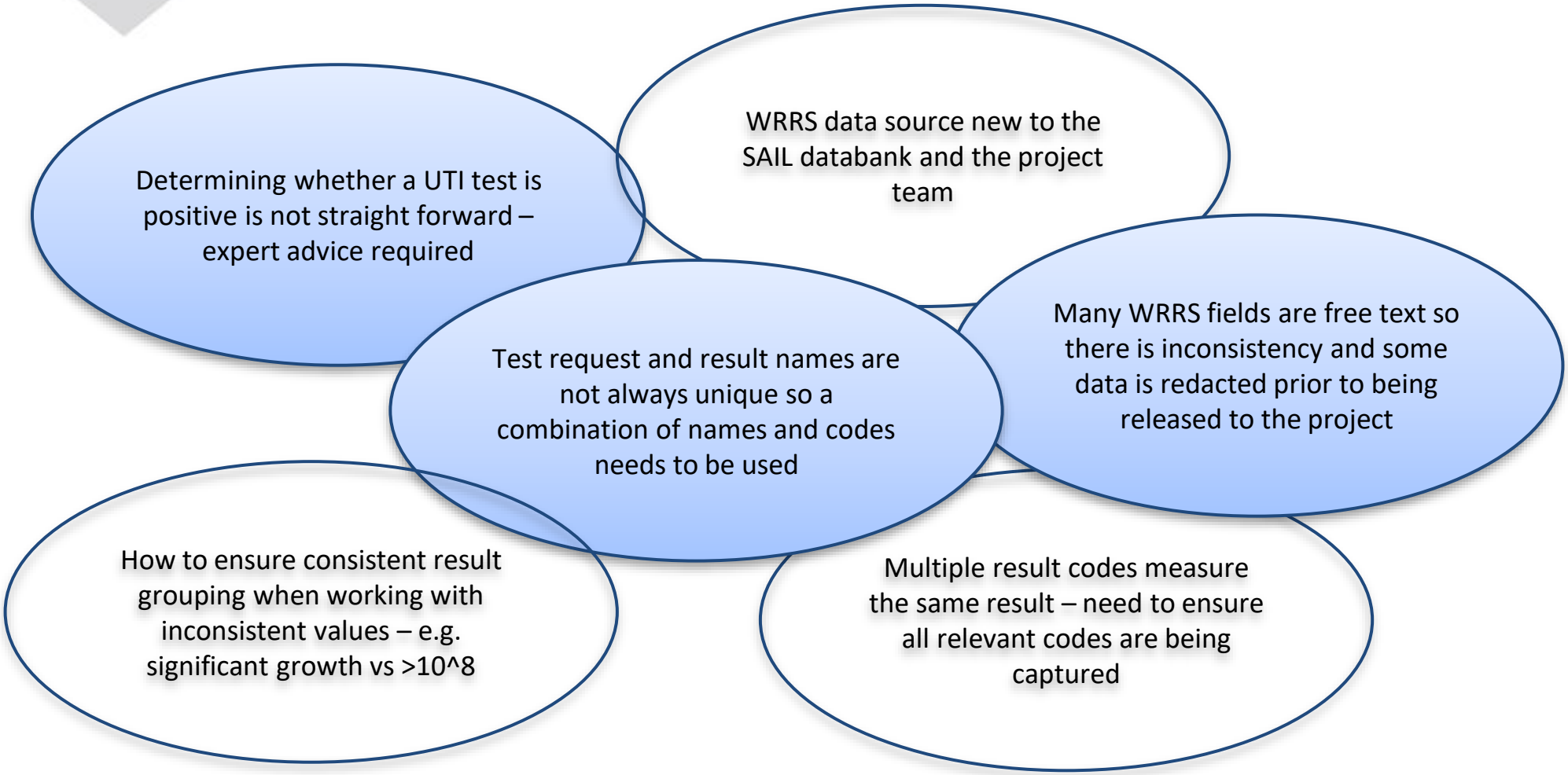


Davies G, et al. (2022) The Welsh Results Reports Service (WRRS) Data: Wales Population-Scale Pathology Data, A National Data Asset. Available at: https://popdatasci.swan.ac.uk/wp-content/uploads/2022/04/Data-Explained-The-Welsh-Results-Reports-Service-WRRS-Data.pdf

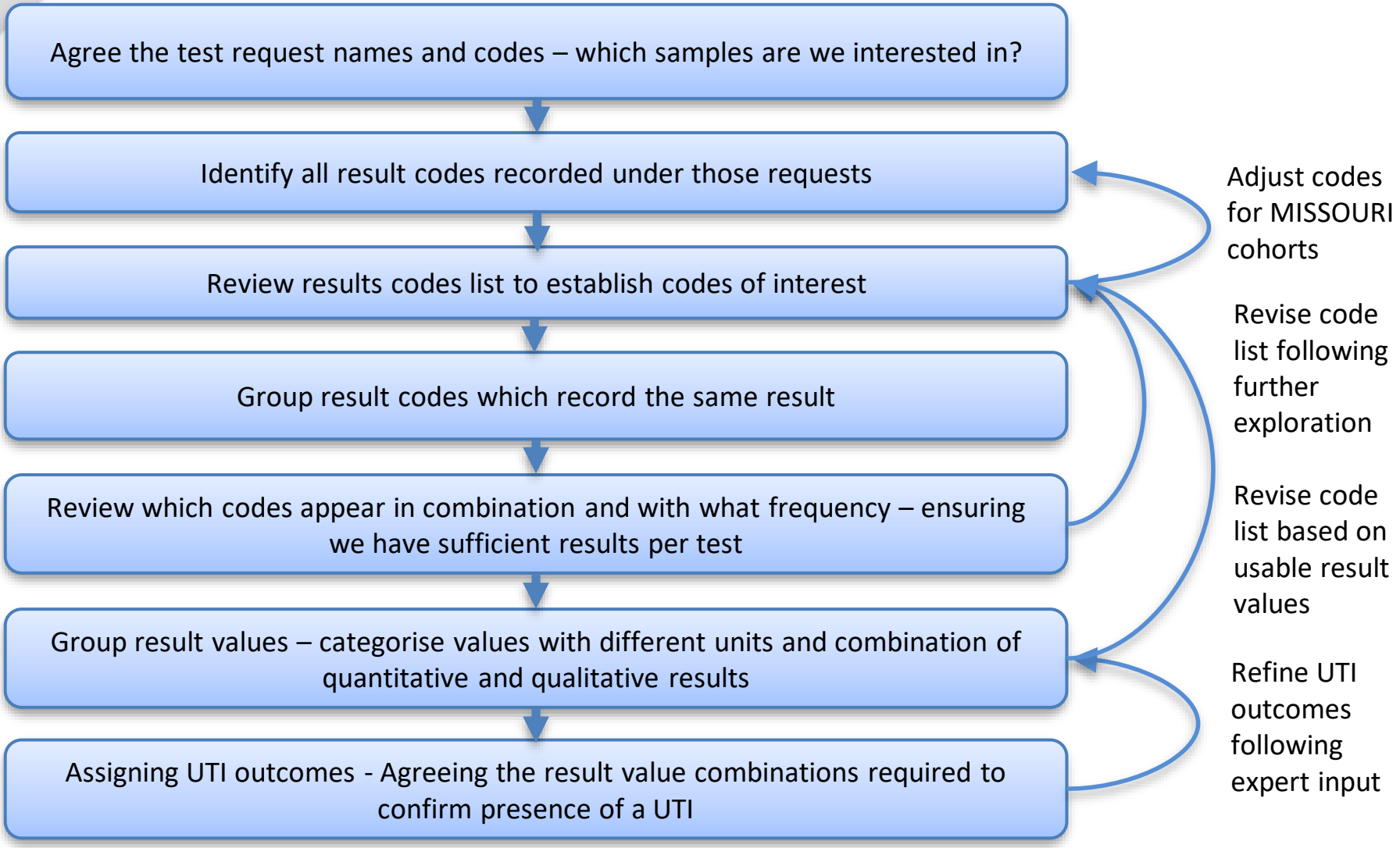
Task – Identify UTIs



Challenges


Determining whether a UTI test is positive is not straight forward – expert advice required
WRRS data source new to the SAIL databank and the project team
Test request and result names are not always unique so a combination of names and codes needs to be used
Many WRRS fields are free text so there is inconsistency and some data is redacted prior to being released to the project
How to ensure consistent result grouping when working with inconsistent values – e.g. significant growth vs >10^8
Multiple result codes measure the same result – need to ensure all relevant codes are being captured

Process


Agree the test request names and codes – which samples are we interested in?
Identify all result codes recorded under those requests
Review results codes list to establish codes of interest
Group result codes which record the same result
Review which codes appear in combination and with what frequency – ensuring we have sufficient results per test
Group result values – categorise values with different units and combination of quantitative and qualitative results
Assigning UTI outcomes - Agreeing the result value combinations required to confirm presence of a UTI
Adjust codes for MISSOURI cohorts
Revise code list following further exploration
Revise code list based on usable result values
Refine UTI outcomes following expert input

Agreed UTI Outcomes

Culture Result	Organism Result	White Blood Cell Result	Outcome
Growth>=10^8	Is not null and is not candida 2 organisms (exc. candida)	>10^8	Confirmed UTI
Growth>=10^7	Is not null and is not candida 2 organisms (exc. candida)	All values	Possible UTI
Mixed Growth	All values	All values	Mixed growth
Mixed growth >=10^8 cfu/L	All values	All values	Heavy mixed growth
No Growth or growth <10^7	All values	All values	No microbiological evidence of UTI
NULL	All values	All values	Exclude NULL Culture

Output

- A method for extracting UTI results from the WRRS and identifying the UTI outcome
- This method is already being adopted by another project investigating UTIs
- UTI outcomes can be linked to other data within SAIL, enabling MISSOURI to investigate the link between UTIs and subsequent MIs and Strokes from hospital (PEDW) and primary care (WLGP) data