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Chronic kidney disease as a risk factor for acute community-acquired infections: a systematic review and meta-analysis

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Title: Chronic kidney disease as a risk factor for acute community-acquired infections: a systematic review and meta-analysis

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ABSTRACT:

Objectives: A systematic review of the association of pre-dialysis chronic kidney disease (CKD) with the incidence of acute, community-acquired infections.

Design: We searched Medline, Embase and Cochrane databases (inception to 29/03/2012) for studies analysing the association of pre-dialysis kidney disease with the incidence of acute, community-acquired urinary tract infection (UTI), lower respiratory tract or central nervous system infections, or sepsis. Studies were required to include at least 30 participants with and without kidney disease.

Setting & participants: Community-based populations of adults in high income countries.

Outcome measures: Acute, community-acquired urinary tract infection (UTI), lower respiratory tract or central nervous system infections, or sepsis.

Results: We identified eleven eligible studies. Estimates from two studies lacked 95% confidence intervals and standard errors. The remaining nine studies yielded 12 independent effect estimates. Most studies identified only severe infections resulting in hospitalisation. Quality assessment revealed that probable misclassification of kidney disease status and poor adjustment for confounding were common. There was evidence from a few large high quality studies of a graded association between pre-dialysis CKD stage and hospitalisation for infection. One study found an interaction with age, with a declining effect of CKD on infection risk as age increased. There was evidence of between-studies heterogeneity (outcomes: UTI I^2=55.2%, p=0.135; other infections I^2 =98.0%, p<0.001;) and thus meta-analysis was not performed.

Conclusions: Pre-dialysis kidney disease appears to be associated with increased risk of severe infection. Whether pre-dialysis kidney disease increases the susceptibility to infections and whether age modifies this association remains unclear.

ARTICLE SUMMARY

Article focus:

- This review sought to assess systematically whether pre-dialysis chronic kidney disease (CKD) is a risk factor for the incidence of acute, community-acquired urinary tract infection (UTI), lower respiratory tract infection (LRTI) central nervous system (CNS) infection, or sepsis, among community-based adults in high income countries.
- Any increased risk of infection incidence at early stages of CKD would affect a large and growing number of patients. Awareness and quantification of this risk could have benefits for patient management, more effective vaccination strategies and healthcare planning.

Key messages:

- We identified major gaps in the literature including: a scarcity of high-quality studies on this research topic; a lack of studies using less severe outcome measures than hospitalisation, to allow any association of CKD with susceptibility to infection to be distinguished from an association with severity of infection; and a lack of data on the relationship between proteinuria and infection incidence independently of glomerular filtration rate.
- All studies were consistent with a positive association between CKD and infection risk.

Strengths and limitations of this study:

- This study used a sensitive search strategy, with a broad definition of kidney disease, for a thorough and inclusive search.

- Between-study heterogeneity, and the low quality of many of the studies, limit interpretation of results of the studies currently available.

INTRODUCTION

Chronic kidney disease (CKD) is common, and its prevalence is increasing.[1] Infection is a major cause of mortality in end-stage renal disease (ESRD) and hospitalisation at all stages of CKD. The second commonest cause of death among ESRD patients in the US is septicaemia, and patients with ESRD are at increased risk of death from infection compared to the general population.[2-4] Both ESRD and pre-dialysis patients with CKD in the US are at higher risk of hospitalisation for infection than the general population.[2, 5-6] Pre-dialysis CKD has been found to increase mortality among patients hospitalised with infections.[7]

Increased mortality and hospitalisation from infection could be driven by increased severity of infection, i.e. once an infection is present, the course of the associated illness is more severe, or increased incidence, i.e. CKD may make people more susceptible to develop an infection. Patients with CKD display impaired host immunity: reduced vaccination responsiveness is observed at all stages of CKD.[8]

Among ESRD patients, aspects of dialysis, such as vascular and peritoneal access for dialysis, may be a risk factor for infection incidence and severity. However, this does not tell the whole story, and only 23% of infection-related hospitalisations among haemodialysis patients in the US were identified as related to vascular access in the HEMO study.[9] Risk factors for infection identified among ESRD patients which are not related to renal replacement therapy, and could apply at all stages of pre-dialysis CKD, include: the causes and treatment of kidney disease; co-morbidities; reduced vaccine effectiveness; and high levels of exposure to health care facilities.[10]

If there is an increased risk of infection incidence at early stages of CKD, this would affect a large and growing number of patients. Awareness and quantification of this risk could have

benefits for patient management, more effective vaccination strategies and healthcare planning.

Narrative reviews have concluded that it is likely that CKD in itself increases infection incidence, but reported a lack of evidence.[10-12] We are not aware of any relevant systematic literature reviews of the effect of CKD on infection incidence.

This review sought to assess systematically whether pre-dialysis CKD is a risk factor for the incidence of acute, community-acquired urinary tract infection (UTI), lower respiratory tract infection (LRTI) central nervous system (CNS) infection, or sepsis, among community-based adults in high income countries.

METHODS

Data Sources and Searches

One reviewer (HM) searched the Medline and Embase databases, and the Cochrane library, from inception to 29 March 2012. The search strategies combined text words and MeSH terms for three concepts: acute community-acquired infection (either sepsis, UTI, LRTI or CNS infection); kidney disease; and relative risk. We used search terms to identify studies among adult humans in high-income countries (according to the World Bank classification),[13] and limited the search to articles in English, French or German. The full strategies are available in **Supplementary Tables 1-3**.

We searched the reference lists of all included studies and any pertinent review articles to identify further eligible studies.

Study Selection

One reviewer (HM) screened titles and abstracts, reviewed the full-text of identified studies and made initial decisions on eligibility according to pre-specified inclusion criteria (**Supplementary Table 4)**. Any borderline cases were discussed between HM, DN and ST. A second reviewer (DN) checked a sample of 100 abstracts, selected randomly after de-duplication of records, and a kappa statistic was calculated to describe agreement in selection of studies.

Eligible studies analysed the effect of pre-dialysis kidney disease on the relative risk of at least one of the four specified acute, community-acquired infections among community-based adults in high-income countries. We excluded study populations routinely treated with

specialist medication in secondary care (unless these were for kidney disease) which often has potential immunosuppressive effects, and study populations exclusively of pregnant women, as both groups have a raised risk of infection, and the relationship of CKD to infection risk may be different among these groups compared to that in the general adult population.

To maximise the sensitivity of our search strategy, we accepted a wide range of definitions of kidney disease, including: medical diagnosis of kidney disease, reduced estimated glomerular filtration rate, elevated creatinine or creatinine clearance, proteinuria, micro- or macro-albuminuria, and renal structural abnormalities. We also accepted definitions which included some patients with ESRD among the patients with CKD, but excluded definitions which were exclusively patients receiving renal replacement therapy.

Outcomes of interest were relative risk estimates of acute community-acquired LRTIs, UTIs, CNS infections or sepsis. We accepted outcomes describing incidence of severe infections (such as hospitalisation with pneumonia).

We restricted our search to published studies which were sufficiently large to include at least 30 participants with and without kidney disease, to allow reasonable precision of the study estimate. Detailed eligibility criteria are listed in **Supplementary Table 4.**

Data Extraction and Quality Assessment

Data were extracted from relevant studies using a pre-specified collection form. Study characteristics extracted included study design, data source, any participant exclusion criteria, number of participants, age, gender, baseline renal function, definition of renal impairment, definition of the outcome infection. An estimate of relative risk (rate ratio, risk ratio or odds ratio) with any measures taken to address confounding was extracted from each eligible

independent analysis in each study. Studies with no confidence intervals and for which the standard error was not calculable from the data presented were included in the review but not considered for meta-analysis.

When multiple estimates were available from a study but were not independent, a single estimate was identified for potential meta-analysis by selecting the estimate best adjusted for confounding, using the most recent data, comparing the level of CKD most common in the general population with no CKD.

Study quality was assessed using a pre-specified tool adapted from Higgins *et al*. for observational studies.[14] Studies were assigned a high, low or uncertain risk of each of: selection bias, non-differential measurement error for exposure and outcome, information bias in exposure and outcome, confounding and reverse causation. The minimum requirement for a low risk of bias from confounding was appropriate management of confounding by age, sex and diabetes. Specific criteria used are detailed in **Supplementary Table 5**.

Data Synthesis and Analysis

The relationship between CKD and UTIs was considered likely to differ from that of CKD to other infections, due to potential reverse causality. For example, repeat UTIs may cause kidney disease, or structural kidney disease may be identified though investigation of repeat UTIs. Therefore in all quantitative analysis, UTIs were analysed separately from other infections.

Estimates were examined for heterogeneity using Cochran's Q statistic and the I^2 statistic as described by Higgins *et al*.[15] If I^2 was less than 50% and Cochran's Q statistic $p \geq 0.1$, fixed-effects meta-analysis was considered for each of the two categories (UTI, and other

infections). Funnel plots were constructed to look for publication bias. All analysis was conducted using STATA version 12.0.

RESULTS

The database searches identified 8,363 citations, of which 1,001 were duplicates (**Figure 1**). Both reviewers had 100% agreement on which studies to extract for full-text analysis from screening a random sample of 100 abstracts (Cohen's K= 1).

We identified 11 eligible studies, with varying study characteristics (**Table 1**). Three studies were case-control studies,[16-18] and eight were cohort studies.[5, 19-25] Five studies investigated a range of risk factors for infection,[16-18, 24-25] two studies reported the effect of CKD on infection as a confounder of the effect of interest,[20-21] and only four studies investigated the effect of CKD on infection risk as their primary research question.[5, 19, 22-23, 26]

Four studies were based among the general population.[5, 16, 24-25] Other study populations included: attendants at a specialist renal clinic,[19] patients with diabetes mellitus,[21] patients admitted to hospital for an acute cardiovascular event or an arterial revascularisation procedure, [20] and the Navajo Nation – a population which experiences 3–5 times higher rates of invasive pneumococcal disease than the general US population.[17] The population of the cohort studies in Calgary, Canada were adults with a serum creatinine test result available in their medical records.[22-23] There is some overlap in the study populations of these two cohort studies: residents aged over 65 years with a serum creatinine measurement between 1 July 2001 and 31 December 2001 and also between 1 July 2003 and 30 June 2004 would have been included in both studies for the period from the second creatinine measurement until 31 December 2004.[22-23]

Definitions of kidney disease included medical diagnoses of chronic renal disease, elevated creatinine levels, impaired creatinine clearance, and structural abnormalities of the kidney. Four studies excluded patients with ESRD, and one specified the number included, but for the

remaining six studies it was unclear how many of the included patients received renal replacement therapy.

Two studies recorded infections diagnosed in primary care,[16, 24] two recorded infections identified from a positive culture result,[17, 22] one included infections diagnosed in the emergency department,[18] five required hospital admission for infection,[5, 20-21, 23, 25] and for one study the definition and severity of infection was unclear.[19]

For two studies, the results extracted had no confidence interval or standard error and these could not be calculated from the reported data. From the remaining nine studies, 12 independent effect estimates with standard errors were available for meta-analysis, among which UTI was the outcome in two estimates.

For infections other than UTIs, there was strong evidence of considerable heterogeneity (Cochran's Q statistic $p<0.001$, $I^2=98.0\%$) and among the two studies of UTIs, there was some evidence of heterogeneity ($p=0.135$, $I^2=55.2\%$). This remained after considering LRTIs alone ($p<0.001$, $I^2=98.6\%$). For this reason, meta-analysis was not performed. There were only two studies excluding patients with ESRD for which standard errors were available, and so these estimates were not analysed separately.

The results available for quantitative analysis are displayed in the Forest plot (**Figure 2**). Despite the quantitative heterogeneity, the results were qualitatively similar: all estimates were compatible with a positive association between kidney disease and infection. The four studies which compared different stages of CKD found a graded association of increased risk of infection with more severe CKD.[5, 19, 22-23] One study found that the effect of CKD on infection risk was modified by age, with a declining effect of CKD on infection risk as age increased.[23] This effect was consistent with the lower effect of CKD on UTI incidence

found among 86–90 year olds (0.90, 95% CI 0.50–1.77) compared with an adult study population with a mean age of 66 years (1.50, 95% CI 1.10–1.90).[21, 24]

The funnel plot was sparsely populated, with widely scattered effect estimates, and provides no clear evidence for or against publication bias (**Supplementary Figure 1**).

Study quality was variable. Relying on routine medical diagnosis introduced a potential source of misclassification of kidney disease status for six studies.[5, 16-18, 20, 25] There was variable adjustment for confounding, from unadjusted crude estimates to estimates adjusted for a range of comorbidities, demographic and socio-economic factors. Four studies did not meet this review's minimal requirements.[19, 21, 24-25] The summarised results are displayed in **Table 2**, and the full quality assessment is in **Supplementary Table 5**.

Table 1: Characteristics of eligible studies (n=11)

Case-control studies												
	Study			Kidney disease			Infection			Kidney disease prevalence		Odds ratio (95% CI)
	Date	Setting	Population Age % Female	Defined	ESRD included	Ascertained	Type	Defined	Ascertained	Cases	Controls	
Vinogradova 2009[16]	1996 - 2005	UK	General population Any age Median age band 45-64 years Cases 49.3%, controls 49.1%	Chronic renal disease	Unclear	Primary care medical record diagnosis code in previous 5 years	Pneumonia	Medical diagnosis recorded in primary care records	READ code in primary care medical records	203/ 17,172 (1.2%)	386/ 71,299 (0.5%)	1.72 (1.3 – 2.07)[1]
Watt 2007[17]	1999 - 2002	The Navajo Nation USA	Navajo adults ≥18 years Summary age and sex n/r	Chronic renal failure	17 participants receiving dialysis	Medical record abstraction	Invasive pneumococcal disease	S.pneumoniae isolated from a normally sterile body fluid during illness	Active laboratory surveillance system[2]	20/118 (16.9%)	12/353 (3.4%)	2.6 (0.87 – 7.7)[3] P=0.087
Loeb 2009[18]	2002 - 2005	Ontario & Alberta Canada	General population ≥ 65 years Mean age: cases 79.1, controls 74.4 years. Cases 39.6%, controls 68.5%	Renal disease	Unclear	Cases: hospital interview. Controls: telephone interview at home.	Pneumonia	Consistent chest X-ray and ≥2 of: chest pain, shortness of breath, productive cough, temperature >38°C, crackles on auscultation.	Recruited patients attending emergency departments	127/690 (18.4%)	38/82 (4.4%)	4.06 (1.98–8.35) P<0.001[4]

Cohort studies											
	Study			Kidney disease			Comparison group	Infection			Risk or rate ratio (95% CI)
	Date	Setting Follow up time	Population Number Age Sex	Defined Number with kidney disease	ESRD	Ascertained	Defined	Type	Defined	Ascertained	
Higgins 1989[19]	1985	Oxford UK 1 year	Patients attending a Renal Unit with chronic renal failure n=211 17-77 years Mean 50.5 years % female n/r	Creatinine ≥250 µmol/l Number n/r	Excluded	Serum creatinine	Creatinine <250 µmol/l n/r	UTI	>10[5] organism/ml and ≥10 leucocytes /hpf in clean catch urine specimen	Medical record review	Creatinine µmol/l <250: 1 250-500: 1.5[5] >500: 2[5]
Hackam 2006[20]	1997 - 2002	Ontario Canada Mean 2.2 years	Patients with cardiovascular disease n=69,168 >65 years Mean 74.1 years 44% female	Chronic renal insufficiency n=7,169	Unclear	Health record databases[6]	No chronic renal insufficiency	Sepsis	Hospital admission with a diagnosis of sepsis[7]	Health record database[8]	1.47 (1.27–1.72)[9]
Karunajeewa 2005[21]	1999 - 2000	Western Australia Mean 2.9 years	Patients with diabetes n=496 >10 years Mean 66.1 years[10]	Albuminuria; serum urea; serum creatinine	Unclear	Baseline urinary albumin: creatinine ratio (ACR), serum urea, serum creatinine	Hazard ratio per 2.72-fold increase in ACR or serum urea	Urinary sepsis and non-urinary sepsis	Hospitalisation diagnosis codes (principal diagnosis, or principal or secondary diagnosis)[11]	Health record database[12]	Urinary sepsis (principal code) Ln(ACR): 1.5 (1.1 – 1.9)[13] p=0.004 Urinary sepsis (principal or secondary code) Ln(ACR): 1.3 (1.1 – 1.6)[14] p=0.005 Non-urinary sepsis (principal) Ln(ACR): 1.4(1.1-1.9)[13]

			46.2% female								Non-urinary sepsis (principal or secondary code)	
											Ln(urea)	4.6 (2.3-9.4) [13] p<0.001
James 2008[22]	2001 - 2004	Calgary Canada Mean 3.2 years	General population n=25,675 >65 years Mean by eGFR [15] 55.9% female	Baseline eGFR<60 mL/min/1.73 m^2 [16] n=6,941	Excluded	Calgary Laboratory Services records	Baseline eGFR ≥60 mL/min/1.73 m^2 [16]	Bloodstream infection	Any pathogenic organism isolated from ≥1 blood cultures submitted from the community or ≤2 days of hospital admission	Calgary Laboratory Services records	eGFR mL/min/1.73m^2	
											≥60	1
											45-59	1.17 (0.92–1.49) [17]
											30-44	1.60 (1.20–2.13) [17]
											<30	2.95 (2.11–4.14) [17]
James 2009[23]	2003 - 2006	Calgary Canada Median 2.5 years	General population n=252,516 ≥18 years Mean by eGFR[18] 42.3% female	Time updated eGFR<60 mL/min/1.73 m^2 [19] n=35,948	Excluded	Calgary Laboratory Services records	eGFR 60-104 mL/min/1.73 m^2 [19]	Pneumonia	ICD-10 code for pneumonia any position in hospital discharge report	Hospital discharge reports	eGFR mL/min/1.73m^2	
											18-54 years	
											60-104	1
											45-59	3.23 (2.40–4.36) [20]
											30-44	9.67 (6.36–14.69) [20]
											<30	15.04 (9.64–23.47) [20]
											Age 55 – 64 years	
											60-104	1
											45-59	1.43 (1.11–1.84) [20]
											30-44	1.94 (1.32–2.87) [20]
											<30	5.50 (3.83–7.92) [20]
											Age 65 – 74 years	
											60-104	1
											45-59	1.18 (0.99–1.40) [20]
											30-44	2.24 (1.84–2.73) [20]
											<30	3.23 (2.52–4.13) [20]
											Age ≥75 years	
											60-104	1
											45-59	0.95 (0.85–1.05) [20]
											30-44	1.03 (0.92–1.16) [20]
											<30	1.79 (1.55–2.06) [20]

Caljouw 2011[24]	1998 - 2004	Leiden The Netherlands Mean 2.6 years	General population n= 479 86-90 years All aged 86 years at entry 67.2% female	Creatinine clearance <30mL/min[21] n=43	Unclear	Baseline serum creatinine	Creatinine clearance ≥30mL/min[21]	UTI	Diagnosed by treating physician based on signs, symptoms and urine analysis; or death records[22]	Physician interview and medical record review. Statistics Netherlands for cause of death data.	0.9 (0.5–1.7) p=0.794
Campbell 2011[25]	2009 - 2010	England UK 9 months	General population n=43.9 million 6 months - 64 years Summary age and sex n/r	Chronic kidney disease n=182,000	Unclear	Cases: consultant microbiologist report. Denominator: primary care population estimate.[23]	No pre-existing conditions [23]	Pandemic influenza A(H1N1)	Polymerase chain reaction (PCR) test confirmation of pandemic influenza A (H1N1) from a hospital inpatient.	Consultant microbiologist report to national surveillance system.	17.5 (13.4 – 22.9)
USRDS 2010[26]	2008	USA 1 year [24]	Medicare patients 66+ years	Chronic kidney disease	Excluded	Insurance database ICD-9_CM codes [25]	No CKD	Pneumonia	Principal cause of hospital admission using hospital insurance claim records	ICD-9-CM codes 480-486	2.76 (unadjusted)
								UTI		ICD-9-CM codes [26]	3.15 (unadjusted)
								Bacteraemia/ septicaemia		ICD-9-CM codes 038.0 – 038.9	3.90 (unadjusted)
USRDS 2012[5]	2010	USA 1 year [24]	Medicare 66+ years	Chronic kidney disease	Excluded	Insurance database ICD-9_CM codes [25]	No CKD	All infection	Principal cause of hospital admission using hospital insurance claim records	ICD-9-CM codes [27]	1.46 [28]
			MarketScan 50-64 years								1.40 [28]
			Ingenix i3 50-64 years								1.42 [28]

95% CI = 95% confidence interval; n/r = not reported; CKD= chronic kidney disease; UTI = urinary tract infection

1. Controls matched to cases on age at index data (within 1 year), sex, general practice, and calendar time. Estimate adjusted for smoking status, Townsend deprivation score, use of influenza vaccine in previous 12 months, use of pneumococcal vaccine in previous 5 years, number of years of medical records data available in database, and

comorbidities including: diabetes, chronic heart disease, chronic respiratory disease, asplenia, cerebrospinal shunt, chronic liver disease, sickle cell disease or coeliac disease, cochlear implant, HIV/AIDS, immunosuppression, stroke or transient ischaemic attack, rheumatoid arthritis, Parkinson's disease, multiple sclerosis, dementia, osteoporosis, and any cancer.

2. Center for American Indian Health surveillance system.

3. Cases and controls matched by gender and age group. Adjusted for age, receipt of pneumococcal polysaccharide vaccine, congestive heart failure, alcohol use, body mass index and unemployment.

4. Adjusted for age, non-English language spoken most at home, living in detached house, living alone, congestive heart failure, chronic obstructive pulmonary disease, dysphagia, functional status using Barthel Index, immunosuppressive medications, nutritional score, tobacco use (lifetime history and secondhand smoke), alcohol consumption and history of regular exposure to gases, fumes or chemicals at home, or at work.

5. Approximate numbers, read from bar graph in publication. No confidence intervals available.

6. Canadian Institute for Health Information Discharge Abstract database or Ontario Health Insurance Plan database

7. ICD-9 codes 003 1, 036 2 and 038 0 – 038 9.

8. Canadian Institute for Health Information Discharge Abstract database.

9. Adjusted for statins, age, sex, nature of index event, charlson index, healthcare use, malignant disease, chemotherapy, neutropaenia, diabetes mellitus, oral steroids, antineoplastics, other immunosuppressants, history of aspiration, structural lung disease, previous infection (respiratory, GI, skin/soft tissue or other), recent trauma, transplant recipient, heart failure, stroke, chronic liver disease, chronic obstructive pulmonary disease, alcoholism, dementia, Parkinson's disease. Statin and non-statin users matched using propensity scoring for the above factors.

10. Mean age among the 460 participants without asymptomatic bacteriuria, 66.1years (SD11.0): mean age among the 36 participants with asymptomatic bacteriuria, 67.7 years (SD 10.5).

11. ICD-9 or ICD-10 codes for urinary sepsis were those encoding UTI, cystitis, pyelonephritis, orchitis, epididymitis and prostatitis; codes for non-urinary sepsis were those for sepsis, septicaemia and/or abscess.

12. Western Australia Data Linkage System.

13.Adjusted for presence of asymptomatic bacteriuria.

14. Adjusted for presence of asymptomatic bacteriuria and age.

15. Mean age ±SD by eGFR. >=60: 74.4±6.5years. 45-59: 77.5±7.2 years. 30-44: 79.3±7.4years. <30: 78.6±7.4 years.

16. eGFR calculated using abbreviated Modification of Diet in Renal Disease Study equation (omitting ethnicity) from single outpatient serum creatinine result.

17. Adjusted for age, sex, diabetes mellitus, comorbidity score and care in a CKD clinic.

18. Mean age ±SD by eGFR. >=105: 38.7±14.6. 60-104: 50.9±15.4. 45-59: 67.0± 14.1. 30-44: 74.5±12.9. <30: 73.3±15.2.

19. eGFR calculated using abbreviated Modification of Diet in Renal Disease Study equation (omitting ethnicity) from most recent outpatient serum creatinine result.

20. Adjusted for age, sex, socio-economic status, ethnicity, diabetes mellitus, Charlson comorbidity score.

21. Creatinine clearance calculated from serum creatinine concentration and weight using Cockcroft-Gault formula.

22. Cause of death recorded as UTI (ICD-10 code N39.0)/

23. Department of Health-Health Protection Agency influenza vaccine uptake primary care monitoring system data.

24. Smoothed estimate: Models include data from the stated year and the two years proceeding it, applying weights of 1, ¼ and 1/8 with increasing distance in time.

25. ICD-9-CM diagnosis codes recorded in insurance claims during the preceding year: 585.1 – 585.5 (chronic kidney disease stages 1-5); or 585.6 with no ESRD 2728 form or other indication of ESRD.
26. Principal hospital admission ICD-9-CM codes: 590-590.9, 595-595.4, 597-597.89, 598, 599.0, 601-601.9, 604-604.9, 607.1-2, 608.0, 608.4, 616.1, 616.3-4, and 616.8.
27. Principal hospital admission ICD-9-CM codes: 001–139, 254.1, 320–326, 331.81, 372–372.39, 373.0–373.2, 382–382.4, 383.0, 386.33, 386.35, 388.60, 390–393, 421–421.1, 422.0, 422.91–422.93, 460–466, 472–474.0, 475–476.1, 478.21–478.24, 478.29, 480–490, 491.1, 494, 510–511, 513.0, 518.6, 519.01, 522.5, 522.7, 527.3, 528.3, 540–542, 566–567.9, 569.5, 572–572.1, 573.1–573.3, 575–575.12, 590–590.9, 595–595.4, 597–597.89, 598, 599.0, 601–601.9, 604–604.9, 607.1, 607.2, 608.0, 608.4, 611.0, 614–616.1, 616.3–616.4, 616.8, 670, 680–686.9, 706.0, 711–711.9, 730–730.3, 730.8–730.9, 790.7–790.8, 996.60–996.69, 997.62, 998.5, and 999.3.
28. Rate ratios calculated as the ratio of the rate among participants with CKD, compared with no CKD, each rate having been adjusted for gender, prior hospitalisation, ASHD, CHF, CVA, PVD, dysrhythmia, other cardiac disease, diabetes, COPD, hypertension, liver disease, gastrointestinal disease, cancer, and anemia.

Table 2: Summary of risk of bias within studies (quality assessment tool adapted from Higgins *et al.*)[14]

	Selection bias: control selection	Selection bias: participation	Selection bias: loss to follow up	Non-differential misclassification: Exposure	Information bias: Exposure	Non-differential misclassification: Outcome	Information bias: Outcome	Confounding	Reverse causation
Case-control studies									
Vinogradova 2009[16]			N/A						
Watt 2007[17]			N/A						
Loeb 2009[18]			N/A						
Cohort studies									
Higgins 1989[19]	N/A	N/A							
Hackam 2006[20]	N/A	N/A							
Karunajeewa 2005[21]	N/A	N/A							
James 2008[22]	N/A	N/A							
James 2009[23]	N/A	N/A							
Caljouw 2011[24]	N/A	N/A							
Campbell 2011[25]	N/A	N/A							
USRDS 2010[26]	N/A	N/A							
USRDS 2012[5]	N/A	N/A							

Key to table 2

Low risk of bias

Uncertain risk of bias

High risk of bias

DISCUSSION

Our comprehensive search strategy identified 11 studies describing an association between kidney disease and acute community-acquired infection. Although between-study heterogeneity precluded meta-analysis, all were consistent with a positive direction of association. The four studies which reported estimates on more than one category of kidney disease all found a graded association in which risk of infection increased with greater severity of CKD.[5, 19, 22-23]

To our knowledge, this is the first review to address this research question systematically. We used a sensitive search strategy, with a broad definition of kidney disease, for a thorough and inclusive search. The results are consistent with the conclusion of previous narrative reviews: that an association between CKD and infection incidence is likely, but that there is a paucity of evidence.[10-12]

Since our literature search, a subsequently published US prospective cohort study of 5,142 adults over 65 years old found an association between worse kidney function and higher risk of hospitalisation for infection.[27] Identification of CKD status was proactive and based on baseline blood measurements. The association was linear when kidney function was calculated using serum cystatin C, and U-shaped when kidney function was calculated using serum creatinine.

Heterogeneity between the studies precluded meta-analysis of results. Variable study designs and biases may have contributed to heterogeneity: for example, the three case-control studies calculated odds ratios, which may differ from equivalent rate ratios for common infections.[16-18] Failure to control the confounding effects of age, sex and diabetes would be likely to result in overestimation of the effect of CKD on infection. Non-differential

misclassification of kidney disease status in studies which relied on routine medical diagnosis would be expected to underestimate the effect of CKD on infection risk.

The heterogeneity may reflect true differences in effect size between the studies.

Firstly, the studies considered a range of outcomes. CKD may have a different effect on the incidence of different infections. We analysed the effect of CKD on UTIs separately. For all but three studies, detection of infection required either hospital attendance for the infection or a positive blood culture. CKD may affect severity of infection, as an alternative or in addition to any effect on infection incidence. CKD may also increase the probability of hospital admission for management of a moderately severe infection. Either would result in a larger effect of CKD on the risk of severe infectious outcomes (such as hospitalisation for sepsis) than on less severe infections (such as community-diagnosed LRTI), and could result in the graded association we observed, with increasing hospitalisation for patients with more severe stages of CKD.

Secondly, the studies included a variety of definitions of kidney disease. For example, proteinuria (and renal loss of complement) may represent a separate mechanism for risk of infection than uraemia. For the seven studies which did not exclude patients with ESRD it is unclear to what extent the results reflect the effect of treatments associated with dialysis, such as vascular or peritoneal access for dialysis, on infection incidence.

Thirdly, the association of CKD with infection may be modified by age. James *et al.* observed a weaker association of CKD with hospitalisation for pneumonia as age increased. They suggested that such an observation could be explained by a lower baseline rate of hospitalisation for pneumonia among younger adults, the natural decline in renal function by age, and inaccuracy in the estimation of renal function using the Modification of Diet in Renal Disease (MDRD) Study equation in older populations.[23] As their study population

included only adults who had had a creatinine test result, reasons for testing creatinine could also be relevant confounders. As age-increases, more comorbidities accrue which require creatinine tests to guide therapy. Hence, younger people who receive a creatinine test may be at an unusually high risk for both infections and CKD due to the reasons associated with getting a creatinine test. A real age-dependency of the CKD-infection association would be consistent with the lower effect of CKD on UTI incidence found among 86–90 year olds (0.90, 95% CI 0.50–1.77) compared with an adult study population with a mean age of 66 years (1.50, 95% CI 1.10–1.90). However, it may be that the study among the older adults measured a less severe outcome, and CKD may be associated with other factors that eventually lead to hospitalisation for UTI.[21, 24]

CKD was not a component of the primary study question for 7 of the 11 studies, thus there is a risk that this association may have been reported and published only when CKD was found to be a risk factor for infection or an important confounder of another relationship. This would result in selective reporting bias, with a subsequent overestimation of the association of CKD with infection risk. This bias would be expected to affect smaller studies to a greater extent, and a funnel plot might show an asymmetry of relative risk estimates about the central pooled estimate among smaller studies. The sparsely populated funnel plot (**Fig S1**) provides no clear evidence for or against selective reporting bias, but some evidence of selective reporting bias comes from within the individual studies. For example, the crude hazard ratio for the association of creatinine clearance with UTI incidence is reported in Caljouw *et al.* (0.9, 95% CI 0.5–1.7) but as creatinine clearance was not found to be significant in the multivariable model the adjusted association is not reported.[24]

The overlap in the study populations of the two large cohort studies based in Calgary, Canada could result in more similar estimates than if the study populations were independent.[22-23]

Outcomes in the two studies are likely to be correlated with each other: hospitalisation with pneumonia could cause a positive blood culture, which would result in one infection being included as an outcome in both studies. This is unlikely to have a large effect, particularly in qualitative assessment of the combined evidence, as the potential overlap of person-time is limited.

Although we excluded study populations routinely treated with specialist medication (unless for kidney disease), some study populations may have been at higher risk of infection than the general population, and this may have affected the relationship of CKD to infection. For example, the cohort of patients admitted for an acute cardiovascular event or an arterial revascularisation procedure will have had a higher prevalence of co-morbidities (such as diabetes) than the general population and excluded patients with severe co-morbidities who did not survive an acute cardiovascular event, or who were not fit enough to undergo the procedure.[20] Each of the selected study populations limits the generalisability of the individual study result, but the qualitatively similar findings across the variety of study populations, and their qualitative consistency with the four studies based among the general population,[5, 16, 24-25] support a positive association between CKD and infection risk in a variety of study populations.

A few large, high quality studies have found a graded association between CKD and risk of hospitalisation with infection. All studies identified in this review were compatible with a positive association of CKD with increased infection risk. There are little data available on the association of CKD with infection incidence using less severe outcome measures than hospitalisation, and it is not possible in most studies to distinguish an effect on susceptibility to infection from an effect on the severity of infection.

The potential age-dependency of the relationship between CKD and infection is intriguing and needs further research. There is also currently no evidence on the relationship between proteinuria and infection incidence independently of glomerular filtration rate. Future studies should identify infections in the community in addition to hospitalisations for infection, characterise the association of proteinuria adjusted for glomerular filtration rate, explore the age-dependency of the association, and assess vaccine efficacy among older people with CKD.

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FIGURE LEGENDS

Figure 1: Flow chart of study selection

Figure 2: Forest plot of estimates of the association of CKD with infection(n=12) from the nine studies included in quantitative analysis

LRTI: lower respiratory tract infection
UTI: urinary tract infection
* Outcome selected was urinary sepsis as the principal diagnosis for the hospitalisation
** Estimated glomerular filtration rate (eGFR) 45-59 compared with eGFR≥60 mL/min/1.73m^2
*** eGFR 45-59 compared with eGFR 60-104 mL/min/1.73m^2

Contributor statement:

All authors designed the study strategy including the search terms, inclusion and exclusion criteria. HM performed the search, study selection and data extraction. DN screened the randomly selected sample of 100 abstracts. All authors agreed quality assessment of included papers and interpretation of results by discussion. HM drafted the article, which DN and ST revised. All authors approved the final version of the manuscript.

Competing interests statement:

H I McDonald: None. S L Thomas: None. D Nitsch: None to declare.

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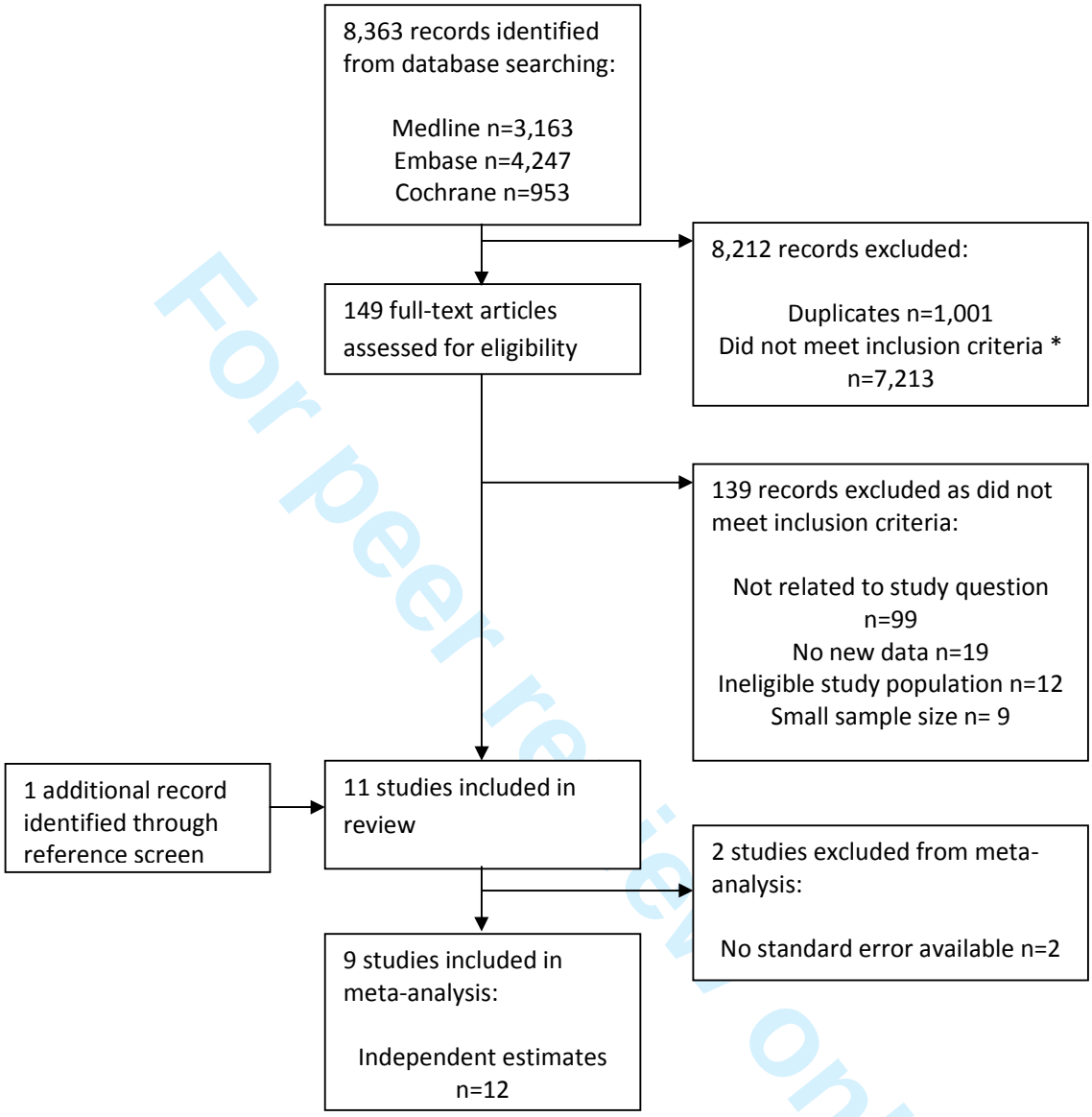
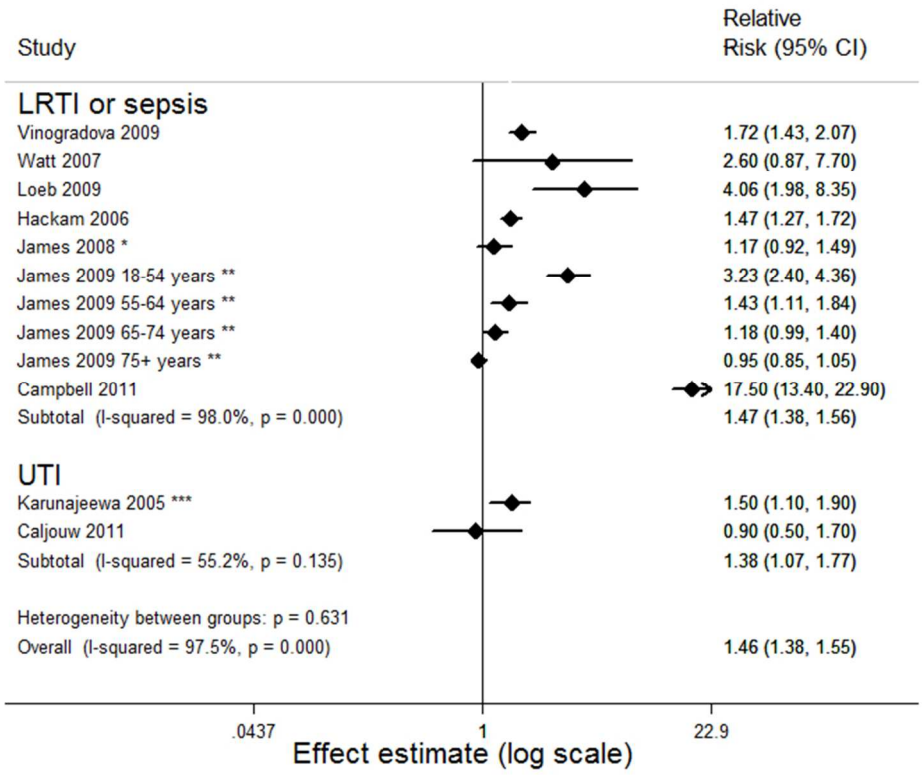
Data sharing statement:

All data, including full search terms and eligibility criteria, are available either in the article or as online supplementary material submitted with this manuscript.

Figure1: Flow chart of study selection



* Common examples of ineligible studies returned by the database searches included: studies in which renal failure and infection were both outcomes, studies in which renal failure and infection were both exclusion criteria, studies of acute renal failure resulting from sepsis or antibiotic use, studies of chronic infections (e.g. hepatitis C, BK viraemia, tuberculosis) following organ transplantation, descriptive studies of UTIs, descriptive studies of CKD, studies of predictors of prognosis among patients with infections, and review articles without any original data.



253x215mm (72 x 72 DPI)

Supplementary Table 1: Medline search strategy

	Search	Results
1	(sepsis* or septic?emia or bacter?emia or fung?emia or pneumonia* or bronchopneumonia* or pleuropneumonia* or LRTI or empy?ema or influenza* or legionell* or bacteriuri* or pyelonephriti* or cystitis* or pyelocystitis* or pyelitis* or urethriti* or UTI or meningiti* or meningococc* or encephaliti* or poliomyeliti* or septic shock).tw.	343181
2	(CNS adj4 infection*).tw.	2545
3	(central nervous adj4 infection*).tw.	3805
4	exp cerebral phaeohyphomycosis/ or central nervous system infections/ or exp brain abscess/ or exp toxoplasmosis, cerebral/ or central nervous system bacterial infections/ or exp empyema, subdural/ or exp epidural abscess/ or exp lyme neuroborreliosis/ or exp meningitis, bacterial/ or exp meningitis, escherichia coli/ or exp meningitis, haemophilus/ or exp meningitis, listeria/ or exp meningitis, meningococcal/ or exp meningitis, pneumococcal/ or exp central nervous system fungal infections/ or exp meningitis, fungal/ or exp meningitis, cryptococcal/ or exp neuroaspergillosis/ or central nervous system viral diseases/ or exp encephalitis/ or exp encephalitis, viral/ or exp encephalitis, arbovirus/ or exp encephalitis, california/ or exp encephalitis, japanese/ or exp "encephalitis, st. louis"/ or exp encephalitis, tick-borne/ or exp west nile fever/ or exp encephalitis, herpes simplex/ or exp encephalitis, varicella zoster/ or exp encephalomyelitis, equine/ or exp meningitis, viral/ or exp lymphocytic choriomeningitis/ or exp meningitis, aseptic/ or exp paraparesis, tropical spastic/ or poliomyelitis/ or exp poliomyelitis, bulbar/ or exp encephalomyelitis/ or exp meningitis/	102876
5	exp endocarditis, bacterial/ or exp endocarditis, subacute bacterial/ or exp pneumococcal infections/ or catheter-related infections/ or exp coinfection/ or communicable diseases/ or exp community-acquired infections/ or exp sepsis/ or exp bacteremia/ or exp hemorrhagic septicemia/ or exp fungemia/ or exp shock, septic/ or exp empyema/ or exp viremia/ or exp parasitemia/	139752
6	((renal or kidney) adj4 chronic adj4 failure*).tw.	21053
7	((renal or kidney) adj4 chronic adj4 disease*).tw.	15978
8	((renal or kidney) adj4 chronic adj4 insufficienc*).tw.	4448
9	((renal or kidney) adj4 chronic adj4 injury).tw.	454
10	((renal or kidney) adj4 chronic adj4 impairment*).tw.	336
11	(creatinine* or GFR or eGFR or albuminuri* or proteinuri* or microalbuminuri* or	194742

	nephropath* or glomerulo* or nephr#ti* or nephrosi* or ur?emia or ESRD or CKD or cardio-renal or Kimmelstiel-Wilson).tw.	
12	Creatinine/bl [Blood]	25724
13	Kidney Diseases/co, ep [Complications, Epidemiology]	11809
14	exp diabetic nephropathies/ or exp hypertension, renal/ or exp nephritis/ or exp anti-glomerular basement membrane disease/ or exp glomerulonephritis, iga/ or exp glomerulonephritis, membranoproliferative/ or exp glomerulonephritis, membranous/ or exp lupus nephritis/ or exp nephrosclerosis/ or exp nephrosis/ or exp renal insufficiency/ or exp cardio-renal syndrome/ or exp uremia/ or exp azotemia/ or exp proteinuria/	234481
15	kidney function tests/ or exp glomerular filtration rate/	44837
16	Animals/	4889105
17	Humans/	12139628
18	16 not (16 and 17)	3594930
19	Adult/	3567838
20	exp child/ or exp child, preschool/ or exp infant/	1849722
21	20 not (19 and 20)	1265383
22	Case reports/	1557478
23	developing countries/ or exp africa/ or cuba/ or dominica/ or dominican republic/ or grenada/ or guadeloupe/ or haiti/ or jamaica/ or exp central america/ or "gulf of mexico"/ or latin america/ or exp south america/ or exp asia, central/ or borneo/ or cambodia/ or east timor/ or indonesia/ or laos/ or malaysia/ or mekong valley/ or myanmar/ or philippines/ or thailand/ or vietnam/ or bangladesh/ or india/ or afghanistan/ or iran/ or iraq/ or jordan/ or lebanon/ or syria/ or turkey/ or yemen/ or nepal/ or pakistan/ or sri lanka/ or exp china/ or "democratic people's republic of korea"/ or mongolia/ or albania/ or latvia/ or lithuania/ or bosnia-herzegovina/ or bulgaria/ or "republic of belarus"/ or romania/ or exp russia/ or serbia/ or ukraine/ or yugoslavia/ or exp transcaucasia/ or exp indian ocean islands/ or fiji/ or papua new guinea/ or vanuatu/ or palau/ or hawaii/	620630
24	developed countries/ or bahamas/ or barbados/ or netherlands antilles/ or puerto rico/ or "trinidad and tobago"/ or "virgin islands of the united states"/ or canada/ or greenland/ or united states/ or brunei/ or singapore/ or bahrain/ or israel/ or kuwait/ or oman/ or qatar/ or saudi arabia/ or united arab emirates/ or hong kong/ or macau/ or exp japan/ or "republic of korea"/ or bermuda/ or exp australia/ or andorra/ or austria/ or belgium/ or estonia/ or croatia/ or czech republic/ or hungary/ or poland/ or	1800832

	slovakia/ or slovenia/ or finland/ or exp france/ or exp germany/ or gibraltar/ or exp great britain/ or greece/ or iceland/ or ireland/ or exp italy/ or liechtenstein/ or luxembourg/ or cyprus/ or malta/ or monaco/ or netherlands/ or portugal/ or san marino/ or exp scandinavia/ or spain/ or switzerland/ or new zealand/ or new caledonia/ or guam/	
25	23 not (23 and 24)	556094
26	Postoperative complications.sh.	263650
27	(incidence* or odds ratio or risk ratio or risk factor or relative risk).tw.	608698
28	(respiratory adj3 infection*).tw.	28563
29	(lower respiratory adj3 infection*).tw.	4633
30	(urinary adj3 infection*).tw.	28333
31	(upper urinary adj3 infection*).tw.	312
32	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	366856
33	(exp incidence/ or exp multivariate analysis/ or exp odds ratio/ or exp logistic models/ or exp risk factors/ or exp epidemiologic studies/).sh.	1799348
34	(exp pyelitis/ or exp pyelocystitis/ or exp pyelonephritis/ or exp urethritis/ or cystitis or urinary tract infections or exp pyuria/).sh.	50526
35	(respiratory tract infections or exp bronchiolitis/ or exp bronchiolitis, viral/ or empyema, pleural or exp influenza, human/ or exp legionellosis/ or exp legionnaires' disease/ or exp lung abscess/ or exp lung diseases, fungal/ or exp lung diseases, parasitic/ or exp pneumonia/ or exp bronchopneumonia/ or exp pleuropneumonia/ or exp pneumonia, bacterial/ or exp chlamydial pneumonia/ or exp pneumonia, mycoplasma/ or exp pneumonia, pneumococcal/ or exp pneumonia, rickettsial/ or exp pneumonia, staphylococcal/ or exp pneumonia, pneumocystis/ or exp pneumonia, viral/ or exp severe acute respiratory syndrome/ or exp tracheitis/ or exp whooping cough/).sh.	155035
36	1 or 2 or 3 or 4 or 5 or 28 or 29 or 30 or 31 or 34 or 35	585963
37	27 or 33	2098986
38	32 and 36 and 37	5940
39	38 not 18 not 21 not 22 not 25 not 26	3514
40	limit 39 to (english or french or german)	3163

Supplementary Table 2: Embase search strategy

	Search	Results
1	kidney failure/co, ep [Complication, Epidemiology]	13218
2	chronic kidney failure/co, ep [Complication, Epidemiology]	10827
3	exp proteinuria/co, ep [Complication, Epidemiology]	5456
4	uremia/co, ep [Complication, Epidemiology]	3030
5	glomerulus filtration rate/	43185
6	creatinine clearance/	17973
7	glomerulosclerosis/co, ep [Complication, Epidemiology]	450
8	kidney disease/co, ep [Complication, Epidemiology]	10406
9	analgesic nephropathy/co, ep [Complication, Epidemiology]	39
10	chronic kidney disease/co, ep [Complication, Epidemiology]	1733
11	diabetic nephropathy/co, ep [Complication, Epidemiology]	9683
12	allergic glomerulonephritis/co, ep [Complication, Epidemiology]	109
13	immune complex nephritis/co, ep [Complication, Epidemiology]	77
14	immunoglobulin A nephropathy/co, ep [Complication, Epidemiology]	678
15	kidney amyloidosis/co, ep [Complication, Epidemiology]	228
16	nephritis/co, ep [Complication, Epidemiology]	1053
17	glomerulitis/	456
18	Goodpasture syndrome/co, ep [Complication, Epidemiology]	31
19	immune complex nephritis/co, ep [Complication, Epidemiology]	77
20	interstitial nephritis/co, ep [Complication, Epidemiology]	901
21	lupus erythematosus nephritis/co, ep [Complication, Epidemiology]	850
22	nephrosis/co, ep [Complication, Epidemiology]	189
23	nephrotic syndrome/co, ep [Complication, Epidemiology]	2133
24	exp glomerulopathy/co, ep [Complication, Epidemiology]	5475
25	exp glomerulonephritis/co, ep [Complication, Epidemiology]	4296
26	exp kidney dysfunction/co, ep [Complication, Epidemiology]	1322
27	(creatinine* or GFR or eGFR or albuminuri* or proteinuri* or microalbuminuri* or nephropath* or glomerulo* or nephr#ti* or nephrosi* or ur?emia or ESRD or CKD or	282722

	cardio-renal or Kimmelstiel-Wilson).tw.	
28	((renal or kidney) adj4 chronic adj4 failure*).tw.	28639
29	((renal or kidney) adj4 chronic adj4 disease*).tw.	23893
30	((renal or kidney) adj4 chronic adj4 insufficienc*).tw.	6425
31	((renal or kidney) adj4 chronic adj4 injury).tw.	631
32	((renal or kidney) adj4 chronic adj4 impairment*).tw.	501
33	exp infectious pneumonia/ or bacterial pneumonia/ or chlamydial pneumonia/ or group b streptococcal pneumonia/ or legionnaire disease/ or mycoplasma pneumonia/ or pneumocystis pneumonia/ or pulmonary candidiasis/ or severe acute respiratory syndrome/ or staphylococcal pneumonia/ or virus pneumonia/	50671
34	respiratory tract infection/ or exp influenza/ or laryngotracheobronchitis/ or lower respiratory tract infection/ or parainfluenza virus infection/ or respiratory syncytial virus infection/ or viral respiratory tract infection/	106624
35	avian influenza/	5081
36	chest infection/ or pertussis/	13997
37	bronchiolitis/ or laryngotracheobronchitis/ or tracheobronchitis/	10003
38	pleura empyema/	3703
39	pyuria/ or urinary tract infection/	66023
40	candiduria/ or kidney infection/	1502
41	kidney abscess/ or pyonephrosis/	1666
42	cystitis/	11865
43	pyelonephritis/ or acute pyelonephritis/	22138
44	brain infection/ or brain abscess/ or herpes simplex encephalitis/ or herpes zoster encephalitis/ or subdural empyema/ or tick borne encephalitis/ or virus encephalitis/	24862
45	central nervous system infection/ or epidural abscess/ or poliomyelitis/	38386
46	meningitis/ or bacterial meningitis/ or exp fungal meningitis/ or haemophilus meningitis/ or lymphocytic choriomeningitis/ or subdural empyema/ or virus meningitis/	57864
47	encephalitis/ or brain ventriculitis/ or eastern equine encephalitis/ or encephalomyelitis/ or epidemic encephalitis/ or meningoencephalitis/ or panencephalitis/ or primary amebic meningoencephalitis/	47288
48	exp meningococcosis/	11231
49	exp pneumococcal infection/	5729

50	exp group b streptococcal infection/ or group b streptococcal pneumonia/	405
51	exp bacteremia/ or staphylococcal bacteremia/	29638
52	bloodstream infection/	2518
53	candidemia/	1358
54	systemic mycosis/ or fungemia/ or invasive aspergillosis/ or invasive candidiasis/	5182
55	sepsis/ or bacteremia/ or septic shock/ or septicemia/ or urosepsis/	140091
56	viremia/	12287
57	parasitemia/	6918
58	(sepsis* or septic?emia or bacter?emia or fung?emia or pneumonia* or bronchopneumonia* or pleuropneumonia* or LRTI or empy?ema or influenza* or legionell* or bacteriuri* or pyelonephritis or cystitis or pyelocystitis or pyelitis or urethriti* or meningiti* or meningococc* or encephaliti* or poliomyeliti* or septic shock).tw.	497436
59	(CNS adj4 infection*).tw.	3591
60	(central nervous adj4 infection*).tw.	4861
61	UTI.tw.	6684
62	bronchopneumonia/	8394
63	arachnoiditis/ or aseptic meningitis/ or epidemic meningitis/ or group b streptococcal meningitis/ or meningoencephalitis/ or pneumococcal meningitis/	21305
64	exp epidemiology/ or exp incidence/	1705072
65	exp risk factor/	513022
66	exp attributable risk/	1487
67	exp hazard ratio/	11362
68	statistical model/	87903
69	(odds adj1 ratio).tw.	101865
70	(relative adj2 ratio).tw.	2736
71	case report/	1892302
72	developing country/	71459
73	developed country/	25618
74	postoperative complication/ or postoperative infection/ or surgical infection/	272218
75	exp Africa/	196804

76	argentina/ or bolivia/ or brazil/ or chile/ or colombia/ or ecuador/ or french guiana/ or guyana/ or paraguay/ or peru/ or suriname/ or uruguay/ or venezuela/	98392
77	exp Central America/	15618
78	china/ or mongolia/ or philippines/	82530
79	borneo/ or cambodia/ or indonesia/ or laos/ or malaysia/ or myanmar/ or papua new guinea/ or thailand/ or timor-leste/ or viet nam/	53670
80	North Korea/	237
81	latvia/ or lithuania/	3316
82	albania/ or armenia/ or azerbaijan/ or belarus/ or "bosnia and herzegovina"/ or bulgaria/ or "georgia (republic)"/ or "macedonia (republic)"/ or romania/ or russian federation/ or serbia/ or ukraine/	83374
83	USSR/	50149
84	iran/ or iraq/ or jordan/ or lebanon/ or "turkey (republic)"/ or yemen/	49920
85	kazakhstan/ or kyrgyzstan/ or tajikistan/ or turkmenistan/ or uzbekistan/	5682
86	afghanistan/ or bangladesh/ or india/ or nepal/ or pakistan/ or sikkim/ or sri lanka/	105351
87	cuba/ or dominica/ or dominican republic/ or grenada/ or guadeloupe/ or haiti/ or jamaica/	11346
88	fiji/ or philippines/ or polynesia/	8607
89	exp Indian Ocean/	2505
90	Mexico/	28748
91	72 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90	789122
92	exp Western Europe/	911511
93	croatia/ or czech republic/ or hungary/ or poland/ or slovakia/ or slovenia/	73494
94	Estonia/	2056
95	canada/ or united states/	1031054
96	japan/ or macao/	115065
97	South Korea/	4982
98	bahrain/ or cyprus/ or israel/ or kuwait/ or oman/ or qatar/ or saudi arabia/ or united arab emirates/	37707
99	exp "Australia and New Zealand"/	129186

100	brunei darussalam/ or hong kong/ or singapore/	21427
101	73 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100	2259038
102	91 not (91 and 101)	710496
103	treatment outcome/	579285
104	editorial/	438527
105	embryo/	177038
106	infant/	533322
107	child/	1295310
108	preschool child/	469034
109	school child/	217344
110	adolescent/	1180705
111	adult/	4186945
112	105 or 106 or 107 or 108 or 109 or 110	2546570
113	112 not (112 and 111)	1658687
114	animal model/	630310
115	animal experiment/	1606715
116	nonhuman/	3807183
117	animal/	1773703
118	human/	13422168
119	114 or 115 or 116 or 117	5921124
120	119 not (119 and 118)	4747089
121	pneumonia/	97950
122	lung infection/ or hantavirus pulmonary syndrome/ or lung abscess/ or viral bronchiolitis/	21795
123	(respiratory adj3 infection*).tw.	43371
124	(lower respiratory adj3 infection*).tw.	6553
125	(urinary adj3 infection*).tw.	44177
126	(upper urinary adj3 infection*).tw.	444
127	(epidemiolog$ or incidence).tw.	878025
128	(relative adj risk*).tw.	55195
129	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	364340

	or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	
130	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 121 or 122 or 123 or 124 or 125 or 126	851259
131	64 or 65 or 66 or 67 or 68 or 69 or 70 or 127 or 128	2659100
132	129 and 130 and 131	7357
133	132 not 120 not 113 not 104 not 71 not 74 not 102	4970
134	limit 133 to (english or french or german)	4602
135	limit 134 to embase	4247

Supplementary Table 3: Cochrane library search strategy

	Search	Results
1	sepsis* or septic*mia or bacter*mia or fung*mia or pneumonia* or bronchopneumonia* or pleuropneumonia* or LRTI or empy*ma or influenza* or legionell* or bacteriuri* or pyelonephriti* or cystitis* or pyelocystitis* or pyelitis* or urethriti* or UTI or meningiti* or meningococc* or encephaliti* or poliomyeliti* or "septic shock"	19098
2	CNS near/4 infection*	47
3	"central nervous" near/4 infection*	92
4	[mh "cerebral phaeohyphomycosis"] or [mh ^"central nervous system infections"] or [mh "brain abscess"] or [mh "toxoplasmosis, cerebral"] or [mh ^"central nervous system bacterial infections"] or [mh "empyema, subdural"] or [mh "epidural abscess"] or [mh "lyme neuroborreliosis"] or [mh "meningitis, bacterial"] or [mh "meningitis, escherichia coli"] or [mh "meningitis, haemophilus"] or [mh "meningitis, listeria"] or [mh "meningitis, meningococcal"] or [mh "meningitis, pneumococcal"] or [mh "central nervous system fungal infections"] or [mh "meningitis, fungal"] or [mh "meningitis, cryptococcal"] or [mh neuroaspergillosis] or [mh ^"central nervous system viral diseases"] or [mh encephalitis] or [mh "encephalitis, viral"] or [mh "encephalitis, arbovirus"] or [mh "encephalitis, california"] or [mh "encephalitis, japanese"] or [mh "encephalitis, st. louis"] or [mh "encephalitis, tick-borne"] or [mh "west nile fever"] or [mh "encephalitis, herpes simplex"] or [mh "encephalitis, varicella zoster"] or [mh "encephalomyelitis, equine"] or [mh "meningitis, viral"] or [mh "lymphocytic choriomeningitis"] or [mh "meningitis, aseptic"] or [mh "paraparesis, tropical spastic"] or [mh ^poliomyelitis] or [mh "poliomyelitis, bulbar"] or [mh encephalomyelitis] or [mh meningitis]	1015
5	[mh "endocarditis, bacterial"] or [mh "endocarditis, subacute bacterial"] or [mh "pneumococcal infections"] or [mh ^"catheter-related infections"] or [mh coinfection] or [mh ^"communicable diseases"] or [mh "community-acquired infections"] or [mh sepsis] or [mh bacteremia] or [mh "hemorrhagic septicemia"] or [mh fungemia] or [mh "shock, septic"] or [mh empyema] or [mh viremia] or [mh parasitemia]	4033
6	respiratory near/3 infection*	4398
7	urinary near/3 infection*	3732
8	[mh pyelitis] or [mh pyelocystitis] or [mh pyelonephritis] or [mh urethritis] or [mh ^cystitis] or [mh ^"urinary tract infections"] or [mh pyuria]	2143
9	[mh ^"respiratory tract infections"] or [mh bronchiolitis] or [mh "bronchiolitis, viral"] or [mh ^"empyema, pleural"] or [mh "influenza, human"] or [mh legionellosis] or [mh	5402

	"legionnaires' disease"] or [mh "lung abscess"] or [mh "lung diseases, fungal"] or exp [mh "lung diseases, parasitic"] or [mh pneumonia] or [mh bronchopneumonia] or [mh pleuropneumonia] or [mh "pneumonia, bacterial"] or [mh "chlamydial pneumonia"] or [mh "pneumonia, mycoplasma"] or [mh "pneumonia, pneumococcal"] or [mh "pneumonia, rickettsial"] or [mh "pneumonia, staphylococcal"] or [mh "pneumonia, pneumocystis"] or [mh "pneumonia, viral"] or [mh "severe acute respiratory syndrome"] or [mh tracheitis] or [mh "whooping cough"]	
10	(renal or kidney) near/4 chronic near/4 failure*	4476
11	(renal or kidney) near/4 chronic near/4 disease*	1647
12	(renal or kidney) near/4 chronic near/4 insufficienc*	510
13	(renal or kidney) near/4 chronic near/4 injury	29
14	(renal or kidney) near/4 chronic near/4 impairment*	34
15	creatinine* or GFR or eGFR or albuminuri* or proteinuri* or microalbuminuri* or nephropath* or glomerulo* or nephr?ti* or nephrosi* or ur*mia or ESRD or CKD or cardio-renal or Kimmelstiel-Wilson	16810
16	[mh ^creatinine/BL]	2042
17	[mh ^"kidney diseases"/CO,EP]	341
18	[mh "diabetic nephropathies"] or [mh "hypertension, renal"] or [mh nephritis] or [mh "anti-glomerular basement membrane disease"] or [mh "glomerulonephritis, iga"] or [mh "glomerulonephritis, membranoproliferative"] or [mh "glomerulonephritis, membranous"] or [mh "lupus nephritis"] or [mh nephrosclerosis] or [mh nephrosis] or [mh "renal insufficiency"] or [mh "cardio-renal syndrome"] or [mh uremia] or [mh azotemia] or [mh proteinuria]	7117
19	[mh ^"kidney function tests"] or [mh "glomerular filtration rate"]	2417
20	{or #1-#9}	25511
21	{or #10-#19}	21120
22	{and #20-#21}	1422
23	incidence* or "odds ratio" or "risk ratio" or "risk factor" or "relative risk"	69239
24	[mh incidence] or [mh "multivariate analysis"] or [mh "odds ratio"] or [mh "logistic models"] or [mh "risk factors"] or [mh "epidemiologic studies"]	122866
25	{or #23-#24}	165844
26	{and #22, #25}	953

Supplementary Table 4: Inclusion and exclusion criteria for determining study eligibility

	Included	Excluded
Participants	Adult human participants.	Populations exclusively of: - pregnant women; - kidney transplant recipients or patients receiving renal replacement therapy; - patient groups usually managed in secondary care unless this was for chronic kidney disease, or routinely treated with immunosuppressive medication.
Study settings	High income countries (World Bank classification).(13) Community settings, including adults living in institutional care.	
Exposure of interest	Chronic acquired kidney disease, indicated by any of the following: - medical diagnosis; - reduced estimated glomerular filtration rate; - elevated creatinine clearance; - elevated creatinine; - proteinuria, micro- or macro-albuminuria; - renal structural abnormalities. Where there was no 'unexposed' group without kidney disease, comparison between stages 1-2 and stages 3-5 CKD was accepted.	
Outcomes of interest	Incidence rate ratio, risk ratio or odds ratio estimates of the effect of kidney disease on any of the following community-acquired acute infections: - lower respiratory tract infections; - urinary tract infections (UTIs); - central nervous system infections; - sepsis. Urinary catheter-associated UTIs from community settings, and incidence of severe disease (such as hospitalisation for infection) were accepted.	Outcomes not accepted: - infection prevalence; - hospital-associated infection rates; - post-operative follow up outcomes; - incidence of infection-related mortality; - prognosis among infected patients.
Study methodology	Trials, case-control studies, cohort studies or other observational study designs containing original data. Relevant review articles without original data were identified for reference list screening.	Case reports. Descriptive studies without a comparison group. Studies with fewer than 30 participants in either the exposed or unexposed categories.
Publication details	Any publication date. Languages: English, German, French.	

Supplementary Table 5: Quality assessment of studies including rationale (n=11)

	Case-control studies			Cohort studies							
	Vinogradova 2009 (16)	Watt 2007 (17)	Loeb 2009 (18)	Higgins 1989 (19)	Hackam 2006 (20)	Karunajeewa 2005 (21)	James 2008 (22)	James 2009 (23)	Caljouw 2011 (24)	Campbell 2011 * (25)	USRDS 2010 (26)
Selection bias											
Selection of controls [1]	Low: matched selection of primary care registered patients	Low: neighbourhood controls selected systematically by proximity	Low: random digit dialling of hospital catchment area residents	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study
Participation bias [2]	Low: automatic participation	Low: participation 83% of cases, 84% of controls	Uncertain: participation rate not reported	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study
Loss to follow up [3]	N/A: case-control study	N/A: case-control study	N/A: case-control study	Uncertain: not reported and clinically determined. May be differential, but study period only one year.	Low: automated follow up	Low: automated follow up	Low: automated follow up	Low: automated follow up	Low: followed up 479 of 551 participants alive aged 86 years: 86% follow up	Low: active case-finding applied to national census figure (no follow up required)	Low: automated follow up
Non-differential misclassification of exposure [4]	High: relies on medical diagnosis of chronic renal disease in medical records.	High: relied on medical diagnosis of chronic renal disease in medical records.	High: ascertained medical diagnosis of chronic renal disease in participant interview.	Uncertain: not reported when creatinine measured.	High: relies on medical diagnosis of chronic renal disease in medical records.	Low: determined prospectively from test results	Low: determined prospectively from blood results	Low: determined prospectively from blood results	Low: determined prospectively from blood results	High: relies on medical diagnosis of chronic renal disease in medical records.	High: relies on medical diagnosis of chronic renal disease in insurance claims
Information bias: exposure											
Recall bias [5]	Low:	Low: kidney	High:	Low: determined	Low: kidney	Low:	Low:	Low:	Low:	Low: kidney	Low:

	kidney disease diagnosis ascertained from pre-existing medical records	disease diagnosis ascertained from pre-existing medical records	ascertained medical diagnosis of kidney disease in participant interview in hospital for cases and at home for controls	from serum creatinine with clear cut-off (objective measure)	disease diagnosis ascertained from pre-existing medical records	determined prospectively from test results.	determined prospectively from blood results.	determined prospectively from blood results.	determined prospectively from blood results.	disease diagnosis ascertained from pre-existing medical records	kidney disease diagnosis ascertained from pre-existing insurance records
Observer bias [6]	Low: used pre-specified codes to define kidney disease status	Uncertain: Medical record abstractors not blinded to case-control status and criteria for assigning kidney disease status not reported	High: interviewers aware of case status (interviewed in hospital) or control status (telephone interview at home)	Low: determined from serum creatinine with clear cut-off (objective measure)	Uncertain: source of kidney disease status data not reported. If hospital records are used, decision to list diagnosis in discharge record made in context of illness for cases.	Low: determined from blood and urine test results (objective measure)	Low: determined from serum creatinine (objective measure)	Low: determined from serum creatinine (objective measure)	Low: determined from serum creatinine (objective measure)	High: decision to list diagnosis of kidney disease in case report made in context of illness for cases	Low: used pre-specified codes to define kidney disease status
Ascertainment [7]	Low: chronic kidney disease diagnosis would have to predate current acute infection	Low: chronic kidney disease diagnosis would have to predate current acute infection	Low: chronic kidney disease diagnosis would have to predate current acute infection	Uncertain: not reported when creatinine measured, or whether this is recurrent/ prompted by illness	Uncertain: source of kidney disease status data not reported. If hospital records used, patients with infection-related hospitalisatio	Low: participants monitored annually.	Low: baseline measure used (that only patients with a result were eligible was considered a limitation to generalisability)	Low: sensitivity analysis using only the baseline creatinine test found similar results to the last-carried	Low: all participants tested at baseline.	High: ascertainment entirely different for cases than non-cases	Low: kidney disease status ascertained in year prior to study

					ns more likely to have CKD status recorded.			forward method			
Non-differential misclassification of outcome [8]	Low: medical diagnosis of severe outcome	Low: active surveillance with clear criteria	Low: severe outcome with clear criteria	Uncertain: methods for ascertaining infection not reported	Low: severe outcome with widely accepted clinical criteria	Low: severe outcome with widely accepted clinical criteria	Low: severe outcome with clear criteria	Low: severe outcome with widely accepted clinical criteria	Uncertain: kidney disease status may affect healthcare attendance for minor illness such as UTI	Uncertain: sending of PCR test during influenza pandemic vulnerable to be influenced by kidney disease status	Low: severe outcome unlikely to be missed
Information bias: outcome											
Recall bias [9]	Low: cases identified from medical records based on GP diagnosis	Low: cases identified by laboratory surveillance	Low: cases determined by medical diagnosis in hospital	Uncertain: methods for ascertaining infection not reported	Low: monitoring of all hospital discharge reports	Low: monitoring of all hospital discharge reports	Low: monitoring of all biochemistry results	Low: monitoring of all hospital discharge reports	Low: annual clinician interviews supplemented with medical record review	Low: realtime case finding system through laboratory results	Low: monitoring of all hospital insurance claims
Observer bias [10]	Low: clinical diagnosis of severe outcome unlikely to be severely affected by kidney disease comorbidity	Low: Laboratory based surveillance system with clear criteria for cases	Low: CKD status unlikely to severely affect physician application of clear criteria	Uncertain: standard definition of APN is vague and not reported whether any observer blinded to renal status	Low: kidney disease status unlikely to affect choice of hospital diagnosis code for severe outcome	Low: kidney disease status unlikely to affect choice of hospital diagnosis code for severe outcome	Low: objective definition of outcome independent of exposure status	Low: kidney disease status unlikely to affect choice of hospital diagnosis code for severe outcome	Low: kidney disease status unlikely to strongly influence diagnosis of UTI at age 86-89 years, given case criteria include symptoms and urinary	Low: objective criteria for cases once tested	Low: kidney disease status unlikely to affect choice of hospital diagnosis code for severe outcome

									analysis		
Ascertainment [11]	Low: kidney disease status unlikely to affect primary care attendance with severe outcome	Low: active surveillance with clear criteria, testing for IPD unlikely to be markedly influenced by CKD status in context of known high incidence among the Navajo Nation	Low: kidney disease status unlikely to affect hospital attendance with severe outcome	Uncertain: methods for ascertaining infection not reported	Low: kidney disease status unlikely to affect diagnosis of severe outcome with widely accepted clinical criteria	Low: kidney disease status unlikely to affect hospital attendance with severe outcome	Low: sending of blood culture unlikely to be influenced by kidney disease in context of severe illness	Low: kidney disease status unlikely to affect diagnosis of severe outcome with widely accepted clinical	Uncertain: kidney disease status may affect healthcare attendance for minor illness such as UTI	Uncertain: sending of PCR test during influenza pandemic vulnerable to be influenced by comorbiditie s	Low: kidney disease status unlikely to affect hospital attendanc e with severe outcome
Confounding [12]	Low: controls matched to cases on age and sex, estimate adjusted for wide range of confounde rs including diabetes [13]	Low: controls matched for age and sex. Diabetes eligible for inclusion in final model [14]	Low. Age, sex and diabetes eligible for inclusion in final model [15]	High: unadjusted estimate. In particular, high immunosuppress ant use among the study population	Low: adjusted for age, sex, nature of index event, charlson index, healthcare use, and other comorbidities	High: no adjustment for sex [16]	Low: adjusted for age, sex, diabetes, comorbidity score, care in a dedicated renal clinic	Low: adjusted for age, sex, socio-economic status, ethnicity, diabetes mellitus, Charlson comorbidit y score	High: no adjustment for sex or diabetes [17]	High: adjusted for age only	High: unadjuste d [19]
Reverse causation [18]	Low: pre-existing kidney disease reported at time of infection	Low: pre-existing kidney disease reported at time of infection	Low: pre-existing kidney disease reported at time of infection	Uncertain: Timing of creatinine measurement relative to infections not specified	Low: chronic renal failure should not be diagnosed within one hospital episode for infection	Low: serum biochemistr y tested at screening	Low: baseline creatinine used	Low: only followed to first outcome event, creatinine result predates qualifying	Low: baseline creatinine used	Low: pre-existing kidney disease reported at time of infection	Low: kidney disease status establishe d in year prior to study

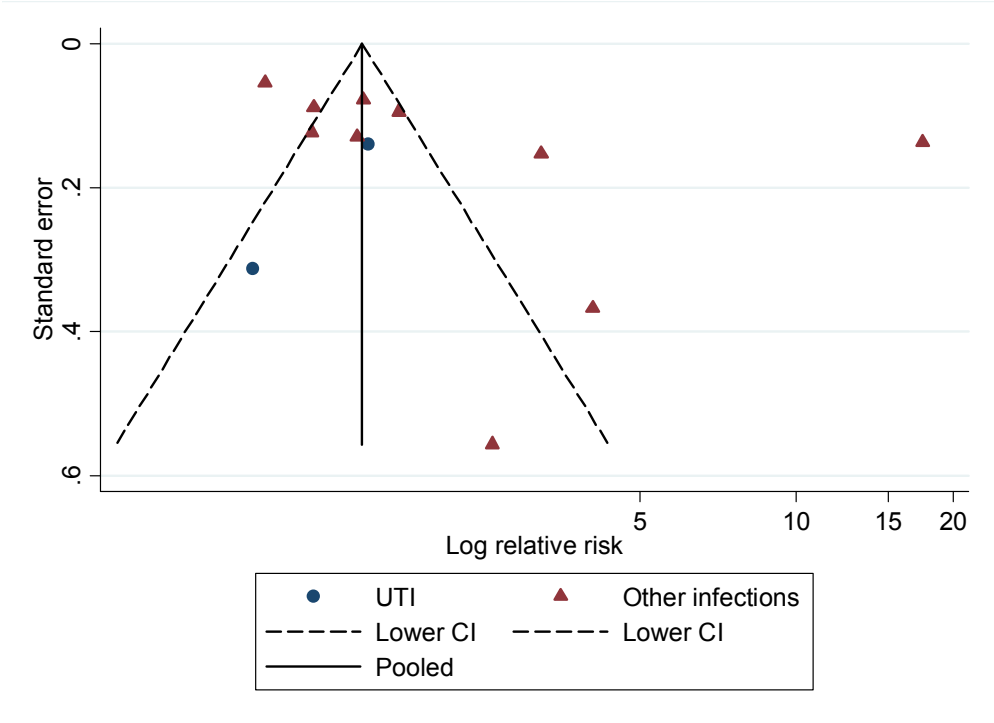
								infection			

*The unusual design of the artificial cohort study by Campbell *et al*. is worth clarification. During the 2009–2010 influenza pandemic, hospitalised cases of laboratory confirmed pandemic influenza A (H1N1) were reported by a laboratory-based national surveillance system. The surveillance report, completed by the microbiologist, asked whether the case had a diagnosis of CKD. Denominators for infection rates were obtained from primary care registers of patients eligible for pandemic influenza vaccination by virtue of a CKD diagnosis (for CKD): and from the national census (for non-CKD).(29) The effect of CKD on influenza may be overestimated in this study, because CKD was advertised as a possible risk factor for pandemic influenza to encourage vaccine uptake among this group, and patients with flu-like symptoms could have been more likely to attend hospital or be tested for pandemic influenza A (H1N1) if they had a diagnosis of CKD.

1. High risk: probability of selection as a control likely to be affected by kidney disease status (known or unknown).
Low risk: controls selected using random sampling (or other system unlikely to be biased by kidney disease status) from the population from which the cases arose.
2. Low risk: (1) automated participation (e.g. medical record review), or (2) ≥80% participation, or (3) 70-80% participation with a comparison (min age, sex, death/morbidity) showing similar characteristics between those included and those not included in the study.
3. Low risk: (1) automated follow up (e.g. through record linkage), or (2) ≥80% follow up, or (3) 70-80% follow up with a comparison (min age, sex, death/morbidity) showing similar characteristics between those included and those not included in the study.
4. High risk: allocation of kidney disease status relies on existing kidney disease having been diagnosed as part of routine medical care.
Low risk: All members of study assessed for kidney disease at baseline.
5. High risk: kidney disease status defined by patient recall of CKD diagnosis in context of recent infection.
6. High risk: kidney disease status defined by observer unblinded to case status, without clear objective criteria to apply.
7. High risk: participants with infections are more or less likely to be tested for kidney disease.
8. Low risk: Active screening for infection, or severe outcome unlikely to be missed or presents validation results of >70% sensitivity and specificity
9. High risk: infection status defined by patient recall of infection in context of kidney disease e.g. participants with kidney disease asked to recall infections while at renal clinic.
10. High risk: infection status defined by observer in context likely to be influenced by kidney disease status (assumed that clinical diagnosis of severe infections was unlikely to be strongly influenced by awareness of CKD as a comorbidity but that less severe infections may be influenced by this in the absence of clear diagnostic criteria).
11. High risk: ascertainment of infections likely to be influenced by kidney disease status (assumed that attendance to healthcare facility for severe infections was unlikely to be strongly influenced by awareness of CKD as a comorbidity but that attendance for less severe infections may be influenced by this in the absence of active surveillance).

12. Low risk: At least age, sex and diabetes must have been eligible and considered for the final model.
13. Controls matched to cases on age at index data (within 1 year), sex, general practice, and calendar time. Estimate adjusted for smoking status, Townsend deprivation score, use of influenza vaccine in previous 12 months, use of pneumococcal vaccine in previous 5 years, number of years of medical records data available in database, and comorbidities including: diabetes, chronic heart disease, chronic respiratory disease, asplenia, cerebrospinal shunt, chronic liver disease, sickle cell disease or coeliac disease, cochlear implant, HIV/AIDS, immunosuppression, stroke or transient ischaemic attack, rheumatoid arthritis, Parkinson's disease, multiple sclerosis, dementia, osteoporosis, and any cancer.
14. Controls matched for age and sex. Diabetes eligible for inclusion in final model, which was adjusted for age, pneumococcal vaccine, congestive heart failure, alcohol use, BMI and unemployment.
15. Age, sex and diabetes eligible for inclusion in final model. Final model adjusted for age, non-English language at home, living in a detached house, living alone, congestive heart failure, chronic obstructive pulmonary disease, dysphagia, Barthel index of functional status, immunosuppressive medications, nutritional score, tobacco use, alcohol use, and exposure to fumes.
16. The best adjusted estimate for urinary sepsis is adjusted for asymptomatic bacteriuria and age, and restricted to diabetics, but not adjusted for sex.
17. High risk: age-restricted and stratified by long term care facility (LCTF) residency, but no management of confounding by sex or co-morbidities.
18. High risk: exposure defined after the infection defined as the study outcome.
19. Rate ratios for hospitalisation with UTI, pneumonia and bacteraemia/ sepsis unadjusted. Rate ratios for hospitalisation with any infection calculated as the ratio of the rate among participants with CKD, compared with no CKD, each rate having been adjusted for gender, prior hospitalisation, ASHD, CHF, CVA, PVD, dysrhythmia, other cardiac disease, diabetes, COPD, hypertension, liver disease, gastrointestinal disease, cancer, and anemia.

Supplementary Figure 1: Funnel plot showing the relationship between relative risk and standard error for the 12 estimates from all nine studies included in meta-analysis (all infections combined)



UTI = urinary tract infection

Other infections comprised lower respiratory tract infections and sepsis.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8 and Appendix Table 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix Tables 1-3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (I^2) for each meta-analysis.	10

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12 and figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12 and Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14 and Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13 and Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13 and Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14 and Appendix Figure 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	22,24
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	25-26
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	31

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Chronic kidney disease as a risk factor for acute community-acquired infections: a systematic review

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Secondary Subject Heading:	Public health, Infectious diseases, General practice / Family practice, Renal medicine
Keywords:	Epidemiology < INFECTIOUS DISEASES, Nephrology < INTERNAL MEDICINE, Chronic renal failure < NEPHROLOGY, PRIMARY CARE

Title: Chronic kidney disease as a risk factor for acute community-acquired infections: a systematic review

Authors: Helen I McDonald,[1] Sara L Thomas,[2] Dorothea Nitsch.[1]

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Keywords: Community-acquired infections, Chronic Renal Insufficiency, Systematic review, Risk factors.

Word counts:

Abstract: 246 words

Body: 3,134 words

ABSTRACT:

Objectives: A systematic review of the association of pre-dialysis chronic kidney disease (CKD) with the incidence of acute, community-acquired infections.

Design: We searched Medline, Embase and Cochrane databases (inception to 16/01/2014) for studies analysing the association of pre-dialysis kidney disease with the incidence of acute, community-acquired urinary tract infection (UTI), lower respiratory tract or central nervous system infections, or sepsis. Studies were required to include at least 30 participants with and without kidney disease.

Setting & participants: Community-based populations of adults in high income countries.

Outcome measures: Acute, community-acquired urinary tract infection (UTI), lower respiratory tract or central nervous system infections, or sepsis.

Results: We identified 14 eligible studies. Estimates from two studies lacked 95% confidence intervals and standard errors. The remaining 12 studies yielded 17 independent effect estimates. Only three studies included infections managed in the community. Quality assessment revealed that probable misclassification of kidney disease status and poor adjustment for confounding were common. There was evidence from a few large high quality studies of a graded association between pre-dialysis CKD stage and hospitalisation for infection. One study found an interaction with age, with a declining effect of CKD on infection risk as age increased. There was evidence of between-studies heterogeneity (I^2=96.5%, p<0.001) which persisted in subgroup analysis, and thus meta-analysis was not performed.

Conclusions: Pre-dialysis kidney disease appears to be associated with increased risk of severe infection. Whether pre-dialysis kidney disease increases the susceptibility to infections and whether age modifies this association remains unclear.

ARTICLE SUMMARY

Article focus:

- This review sought to assess systematically whether pre-dialysis chronic kidney disease (CKD) is a risk factor for the incidence of acute, community-acquired urinary tract infection (UTI), lower respiratory tract infection (LRTI) central nervous system (CNS) infection, or sepsis, among community-based adults in high income countries.
- Any increased risk of infection incidence at early stages of CKD would affect a large and growing number of patients. Awareness and quantification of this risk could have benefits for patient management, more effective vaccination strategies and healthcare planning.

Key messages:

- We identified major gaps in the literature including: a scarcity of high-quality studies on this research topic; a lack of studies using less severe outcome measures than hospitalisation, to allow any association of CKD with susceptibility to infection to be distinguished from an association with severity of infection; and a lack of data on the relationship between proteinuria and infection incidence independently of glomerular filtration rate.
- All studies were consistent with a positive association between CKD and infection risk.

Strengths and limitations of this study:

- This study used a sensitive search strategy, with a broad definition of kidney disease, for a thorough and inclusive search.

- Between-study heterogeneity, and the low quality of many of the studies, limit interpretation of results of the studies currently available.

INTRODUCTION

Chronic kidney disease (CKD) is common, and its prevalence is increasing.[1] Infection is a major cause of mortality in end-stage renal disease (ESRD) and hospitalisation at all stages of CKD. The second commonest cause of death among ESRD patients in the US is septicaemia, and patients with ESRD are at increased risk of death from infection compared to the general population.[2-4] Both ESRD and pre-dialysis patients with CKD in the US are at higher risk of hospitalisation for infection than the general population.[2, 5-6] Pre-dialysis CKD has been found to increase mortality among patients hospitalised with infections.[7]

Increased mortality and hospitalisation from infection could be driven by increased severity of infection, i.e. once an infection is present, the course of the associated illness is more severe, or increased incidence, i.e. CKD may make people more susceptible to develop an infection. Patients with CKD display impaired host immunity: reduced vaccination responsiveness is observed at all stages of CKD.[8]

Among ESRD patients, aspects of dialysis, such as vascular and peritoneal access for dialysis, may be a risk factor for infection incidence and severity. However, this does not tell the whole story, and only 23% of infection-related hospitalisations among haemodialysis patients in the US were identified as related to vascular access in the HEMO study.[9] Risk factors for infection identified among ESRD patients which are not related to renal replacement therapy, and could apply at all stages of pre-dialysis CKD, include: the causes and treatment of kidney disease; co-morbidities; reduced vaccine effectiveness; and high levels of exposure to health care facilities.[10]

If there is an increased risk of infection incidence at early stages of CKD, this would affect a large and growing number of patients. Awareness and quantification of this risk could have

benefits for patient management, more effective vaccination strategies and healthcare planning.

Narrative reviews have concluded that it is likely that CKD in itself increases infection incidence, but reported a lack of evidence.[10-12] We are not aware of any relevant systematic literature reviews of the effect of CKD on infection incidence.

This review sought to assess systematically whether pre-dialysis CKD is a risk factor for the incidence of acute, community-acquired urinary tract infection (UTI), lower respiratory tract infection (LRTI) central nervous system (CNS) infection, or sepsis, among community-based adults in high income countries.

METHODS

Data Sources and Searches

One reviewer (HM) searched the Medline and Embase databases, and the Cochrane library, from inception to 16 January 2014. The search strategies combined text words and MeSH terms for three concepts: acute community-acquired infection (either sepsis, UTI, LRTI or CNS infection); kidney disease; and relative risk. We used search terms to identify studies among adult humans in high-income countries (according to the World Bank classification),[13] and limited the search to articles in English, French or German. The full strategies are available in **Supplementary Tables 1-3**.

We searched the reference lists of all included studies and any pertinent review articles to identify further eligible studies.

Study Selection

One reviewer (HM) screened titles and abstracts, reviewed the full-text of identified studies and made initial decisions on eligibility according to pre-specified inclusion criteria (**Supplementary Table 4**). Any borderline cases were discussed between HM, DN and ST. A second reviewer (DN) checked a sample of 100 abstracts, selected randomly after de-duplication of records, and a kappa statistic was calculated to describe agreement in selection of studies.

Eligible studies analysed the effect of pre-dialysis kidney disease on the relative risk of at least one of the four specified acute, community-acquired infections among community-based adults in high-income countries. We excluded study populations managed in secondary

care (unless for kidney disease), routinely treated with immunosuppressants, or exclusively of pregnant women, as these groups have a raised risk of infection, and the relationship of CKD to infection risk may be different among these groups compared to that in the general adult population in primary care.

To maximise the sensitivity of our search strategy, we accepted a wide range of definitions of kidney disease, including: medical diagnosis of kidney disease, reduced estimated glomerular filtration rate or creatinine clearance, elevated creatinine, proteinuria, micro- or macro-albuminuria, and renal structural abnormalities. We also accepted definitions which included some patients with ESRD among the patients with CKD, but excluded definitions which were exclusively patients receiving renal replacement therapy.

Outcomes of interest were relative risk estimates of acute community-acquired LRTIs, UTIs, CNS infections or sepsis. We accepted outcomes describing incidence of severe infections (such as hospitalisation with pneumonia).

We restricted our search to published studies which were sufficiently large to include at least 30 participants with and without kidney disease, to allow reasonable precision of the study estimate. Detailed eligibility criteria are listed in **Supplementary Table 4.**

Data Extraction and Quality Assessment

Data were extracted from relevant studies using a pre-specified collection form. Study characteristics extracted included study design, data source, any participant exclusion criteria, number of participants, age, gender, baseline renal function, definition of renal impairment, definition of the outcome infection. An estimate of relative risk (rate ratio, risk ratio or odds ratio) with any measures taken to address confounding was extracted from each eligible independent analysis in each study. Studies with no confidence intervals and for which the

standard error was not calculable from the data presented were included in the review but not considered for meta-analysis.

When multiple estimates were available from a study but were not independent, a single estimate was identified for potential meta-analysis by selecting the estimate best adjusted for confounding, using the most recent data, comparing the level of CKD most common in the general population with no CKD.

Study quality was assessed using a pre-specified tool adapted from Higgins *et al*. for observational studies.[14] Studies were assigned a high, low or uncertain risk of each of: selection bias, non-differential measurement error for exposure and outcome, information bias in exposure and outcome, confounding and reverse causation. The minimum requirement for a low risk of bias from confounding was appropriate management of confounding by age, sex and diabetes. Specific criteria used are detailed in **Supplementary Table 5**.

Data Synthesis and Analysis

The relationship between CKD and UTIs was considered likely to differ from that of CKD to other infections, due to potential reverse causality. For example, repeat UTIs may cause kidney disease, or structural kidney disease may be identified though investigation of repeat UTIs. Therefore in all quantitative analysis, UTIs were analysed separately from other infections.

Estimates were examined for heterogeneity using Cochran's Q statistic and the I^2 statistic as described by Higgins *et al*.[15] If I^2 was less than 50% and Cochran's Q statistic $p \geq 0.1$, fixed-effects meta-analysis was considered for each of the two categories (UTI, and other infections). Funnel plots were constructed to look for publication bias. All analysis was conducted using STATA version 12.0.

RESULTS

The database searches identified 10,380 citations, of which 1,204 were duplicates (**Figure 1**). Both reviewers had 100% agreement on which studies to extract for full-text analysis from screening a random sample of 100 abstracts (Cohen's K= 1).

We identified 14 eligible studies, with varying study characteristics (**Table 1**). Four studies were case-control studies,[16-19] and ten were cohort studies.[20-29] Seven studies investigated a range of risk factors for infection,[16-19, 21, 28-29] two studies reported the effect of CKD on infection as a confounder of the effect of interest,[24-25] and five studies investigated the effect of CKD on infection risk as their primary research question.[5, 20, 22, 26-27]

Seven studies were based among the general population.[5, 16, 19, 21, 23, 28-29] Other study populations included: attendants at a specialist renal clinic,[22] patients with diabetes mellitus,[25] patients admitted to hospital for an acute cardiovascular event or an arterial revascularisation procedure, [24] and the Navajo Nation – a population which experiences 3–5 times higher rates of invasive pneumococcal disease than the general US population.[17] The population of the cohort studies in Calgary, Canada were adults with a serum creatinine test result available in their medical records.[26-27] There is some overlap in the study populations of these two cohort studies: residents aged over 65 years with a serum creatinine measurement between 1 July 2001 and 31 December 2001 and also between 1 July 2003 and 30 June 2004 would have been included in both studies for the period from the second creatinine measurement until 31 December 2004.[26-27]

Definitions of kidney disease included medical diagnoses of chronic renal disease, elevated creatinine levels, impaired creatinine clearance, and structural abnormalities of the kidney. Five studies excluded patients with ESRD, and one specified the number included, but for the

remaining eight studies it was unclear how many of the included patients received renal replacement therapy (**Table 1**).

Three studies recorded infections diagnosed in primary care or outpatients,[16, 19, 29] two recorded infections identified from a positive culture result,[17, 26] one included infections diagnosed in the emergency department,[18] seven required hospital admission for infection,[5, 21, 23-25, 27-28] and for one study the definition and severity of infection was unclear.[22]

For two studies, the results extracted had no confidence interval or standard error and these could not be calculated from the reported data. From the remaining 12 studies, 17 independent effect estimates with standard errors were available for meta-analysis, among which UTI was the outcome in three estimates.

For all infections there was strong evidence of considerable heterogeneity (Cochran's Q statistic p<0.001, I^2=96.5%). This persisted when estimates for UTIs were excluded (p<0.001, I^2=97.2%), when considering LRTIs alone (p<0.001, I^2=98.2%), when limited to cohort studies (p<0.001, I^2=97.3%), and when stratified by exclusion of patients with ESRD (ESRD excluded, p<0.001, I^2=88.9%: ESRD not excluded p<0.001, I^2=97.2%). Due to this heterogeneity, meta-analysis was not performed.

All results are displayed in the Forest plot (**Figure 2**). Despite the quantitative heterogeneity, the results were qualitatively similar: all estimates were compatible with a positive association between kidney disease and infection. The four studies which compared different stages of CKD found a graded association of increased risk of infection with more severe CKD. These studies all excluded patients with end-stage renal disease.[22-23, 26-27] One study found that the effect of CKD on infection risk was modified by age, with a declining effect of CKD on infection risk as age increased.[27] This effect was consistent with the

lower effect of CKD on UTI incidence found among 86–90 year olds (0.90, 95% CI 0.50–1.77) compared with an adult study population with a mean age of 66 years (1.50, 95% CI 1.10–1.90).[25, 29]

The funnel plot was sparsely populated, with widely scattered effect estimates, and provides no clear evidence for or against publication bias (**Supplementary Figure 1**).

Study quality was variable. Relying on routine medical diagnosis introduced a potential source of misclassification of kidney disease status for seven studies.[5, 16-19, 21, 24] There was variable adjustment for confounding, from unadjusted crude estimates to estimates adjusted for a range of comorbidities, demographic and socio-economic factors. Six studies did not meet this review's minimal requirements.[19, 21-22, 25, 28-29] The summarised results are displayed in **Table 2**, and the full quality assessment is in **Supplementary Table 5**.

Table 1: Characteristics of eligible studies (n=14)

Case-control studies												
	Study			Kidney disease			Infection			Kidney disease prevalence		Odds ratio (95% CI)
	Date	Setting	Population Age % Female	Defined	ESRD included	Ascertained	Type	Defined	Ascertained	Cases	Controls	
Vinogradova 2009[16]	1996 - 2005	UK	General population Any age Median age band 45-64 years Cases 49.3%, controls 49.1%	Chronic renal disease	Unclear	Primary care medical record diagnosis code in previous 5 years	Pneumonia	Medical diagnosis recorded in primary care records	READ code in primary care medical records	203/ 17,172 (1.2%)	386/ 71,299 (0.5%)	1.72 (1.3 – 2.07)[1]
Watt 2007[17]	1999 - 2002	The Navajo Nation USA	Navajo adults ≥18 years Summary age and sex n/r	Chronic renal failure	17 participants receiving dialysis	Medical record abstraction	Invasive pneumococcal disease	S.pneumoniae isolated from a normally sterile body fluid during illness	Active laboratory surveillance system[2]	20/118 (16.9%)	12/353 (3.4%)	2.6 (0.87 – 7.7)[3] P=0.087
Loeb 2009[18]	2002 - 2005	Ontario & Alberta Canada	General population ≥ 65 years Mean age: cases 79.1, controls 74.4 years. Cases 39.6%, controls 68.5%	Renal disease	Unclear	Cases: hospital interview. Controls: telephone interview at home.	Pneumonia	Consistent chest X-ray and ≥2 of: chest pain, shortness of breath, productive cough, temperature >38°C, crackles on auscultation.	Recruited patients attending emergency departments	127/690 (18.4%)	38/82 (4.4%)	4.06 (1.98–8.35)[4] P<0.001
Schnoor	2002	Germany	General	Chronic	Unclear	Cases:	Pneumonia	(1) Infiltrate on chest	Community-	49/1128	27/1044	1.7 (1.1–2.8)

2007[19]	– 2005		population >18 years Mean age: cases 57, controls 57.5 years Cases 44.8%, controls 54.7%	renal disease		reporting physician. Controls: self-reported questionnaire.		X-ray or (2) temperature ≥38.3°C with any of: cough, purulent sputum, positive auscultation. Excluded if hospitalised within prior 4 weeks, or immunodeficient.	acquired pneumonia network registry reports (primary and secondary care)	(4.3%)	(2.6%)	(unadjusted) P<0.05	

Cohort studies

	Study			**Kidney disease**			**Comparison group**	**Infection**			**Risk or rate ratio (95% CI)**	
	Date	**Setting** **Follow up time**	**Population** **Number** **Age** **Sex**	**Defined** **Number with kidney disease**	**ESRD**	**Ascertained**	**Defined**	**Type**	**Defined**	**Ascertained**		
Higgins 1989[22]	1985	Oxford UK 1 year	Patients attending a Renal Unit with chronic renal failure n=211 17-77 years Mean 50.5 years % female n/r	Creatinine ≥250 µmol/l Number n/r	Excluded	Serum creatinine	Creatinine <250 µmol/l	UTI	>10[5] organism/ml and ≥10 leucocytes /hpf in clean catch urine specimen	Medical record review	Creatinine µmol/l	
											<250	1
											250-500	1.5 [5]
											>500	2[5]
Dalrymple 2012[23]	1989 – 2007	United States Mean 11.5 years	General community-dwelling population[6] n=5,142 >65 years Mean 72 years	Baseline eGFR<90 mL/min/1.73 m^{2} [7] n=3,863	Excluded	Baseline cystatin C	Baseline eGFR ≥90 mL/min/1.73 m^{2} [7]	Pulmonary	Hospital admission with a principal discharge diagnosis of the relevant infection (ICD-9-CM codes)	Medical record review following patient report of hospital admission in cohort study	eGFR mL/min/1.73m^{2}	
											≥90	1
											60–89	1.22 (0.99–1.54)[8]
											45–59	1.27 (0.94–1.71) [8]
											15–44	1.81 (1.25–2.63) [8]
								Genitourinary			≥90	1
											60–89	1.08 (0.75–1.56) [8]
											45–59	1.17 (0.67–2.05) [8]
											15–44	2.63 (1.40–4.96) [8]

			61% female					Bacteremia and sepsis			≥90	1
											60–89	1.10 (0.77–1.58) [8]
											45–59	1.55 (0.93–2.57) [8]
											15–44	0.77 (0.29–2.03) [8]
Hackam 2006[24]	1997 - 2002	Ontario Canada Mean 2.2 years	Patients with cardiovascular disease n=69,168 >65 years Mean 74.1 years 44% female	Chronic renal insufficiency n=7,169	Unclear	Health record databases[9]	No chronic renal insufficiency	Sepsis	Hospital admission with a diagnosis of sepsis[10]	Health record database[11]	1.47 (1.27–1.72)[12]	
Karunajeewa 2005[25]	1999 - 2000	Western Australia Mean 2.9 years	Patients with diabetes n=496 >10 years Mean 66.1 years[13] 46.2% female	Albuminuria; serum urea; serum creatinine	Unclear	Baseline urinary albumin: creatinine ratio (ACR), serum urea, serum creatinine	Hazard ratio per 2.72-fold increase in ACR or serum urea	Urinary sepsis and non-urinary sepsis	Hospitalisation diagnosis codes (principal diagnosis, or principal or secondary diagnosis)[14]	Health record database[15]	Urinary sepsis (principal code)	
											Ln(ACR)	1.5 (1.1 – 1.9) [16] p=0.004
											Urinary sepsis (principal or secondary code)	
											Ln(ACR)	1.3 (1.1 – 1.6) [17] p=0.005
											Non-urinary sepsis (principal)	
											Ln(ACR)	1.4(1.1-1.9) [16]
											Non-urinary sepsis (principal or secondary code)	
											Ln(urea)	4.6 (2.3-9.4) [16] p<0.001
James 2008[26]	2001 - 2004	Calgary Canada Mean 3.2 years	General population n=25,675 >65 years Mean by eGFR [18] 55.9% female	Baseline eGFR<60 mL/min/1.73 m^2 [19] n=6,941	Excluded	Calgary Laboratory Services records	Baseline eGFR ≥60 mL/min/1.73 m^2 [19]	Bloodstream infection	Any pathogenic organism isolated from ≥1 blood cultures submitted from the community or ≤2 days of hospital admission	Calgary Laboratory Services records	eGFR mL/min/1.73m^2	
											≥60	1
											45-59	1.17 (0.92–1.49)[20]
											30-44	1.60 (1.20–2.13) [20]
											<30	2.95 (2.11–4.14) [20]
James 2009[27]	2003 -	Calgary Canada	General population	Time updated	Excluded	Calgary Laboratory	eGFR 60-104 mL/min/1.73	Pneumonia	ICD-10 code for pneumonia any	Hospital discharge	eGFR mL/min/1.73m^2	
											18-54 years	

	2006	Median 2.5 years	n=252,516 ≥18 years Mean by eGFR[21] 42.3% female	eGFR<60 mL/min/1.73 m^2 [22] n=35,948		Services records	m^2 [22]		position in hospital discharge report	reports	60-104	1
											45-59	3.23 (2.40–4.36) [23]
											30-44	9.67 (6.36–14.69) [23]
											<30	15.04 (9.64–23.47) [23]
											Age 55 – 64 years	
											60-104	1
											45-59	1.43 (1.11–1.84) [23]
											30-44	1.94 (1.32–2.87) [23]
											<30	5.50 (3.83–7.92) [23]
											Age 65 – 74 years	
											60-104	1
											45-59	1.18 (0.99–1.40) [23]
											30-44	2.24 (1.84–2.73) [23]
											<30	3.23 (2.52–4.13) [23]
											Age ≥75 years	
											60-104	1
											45-59	0.95 (0.85–1.05) [23]
											30-44	1.03 (0.92–1.16) [23]
											<30	1.79 (1.55–2.06) [23]
Wang 2012[28]	2003 – 2011	United States Mean .7 years	General population sample (weighted by age, geography and ethnicity) [24] n=30,239 ≥45 years 69%>60 years 55% female	Baseline eGFR<60 mL/min/1.73 m^2 [25]	Unclear	Baseline serum creatinine	Baseline eGFR ≥60 mL/min/1.73 m^2 [25]	Sepsis	Among hospitalisations attributed by participants to serious infection, medical record review [26]	Initially reported by study participants, confirmed with medical record review	1.99 (1.73–2.29) [27]	

Caljouw 2011[29]	1998 - 2004	Leiden The Netherlands Mean 2.6 years	General population n= 479 86-90 years All aged 86 years at entry 67.2% female	Creatinine clearance <30mL/min[28] n=43	Unclear	Baseline serum creatinine	Creatinine clearance ≥30mL/min[28]	UTI	Diagnosed by treating physician based on signs, symptoms and urine analysis; or death records[29]	Physician interview and medical record review. Statistics Netherlands for cause of death data.	0.9 (0.5–1.7) (unadjusted) p=0.794
Campbell 2011[21]	2009 - 2010	England UK 9 months	General population n=43.9 million 6 months - 64 years Summary age and sex n/r	Chronic kidney disease n=182,000	Unclear	Cases: consultant microbiologist report. Denominator: primary care population estimate.[30]	No pre-existing conditions [30]	Pandemic influenza A(H1N1)	Polymerase chain reaction (PCR) test confirmation of pandemic influenza A (H1N1) from a hospital inpatient.	Consultant microbiologist report to national surveillance system.	17.5 (13.4 – 22.9) [31]
USRDS 2010[20]	2008	USA 1 year [32]	Medicare patients 66+ years	Chronic kidney disease	Excluded	Insurance database ICD-9_CM codes [33]	No CKD	Pneumonia	Principal cause of hospital admission using hospital insurance claim records	ICD-9-CM codes 480-486	2.76 (unadjusted)
								UTI		ICD-9-CM codes [34]	3.15 (unadjusted)
								Bacteraemia/ septicaemia		ICD-9-CM codes 038.0 – 038.9	3.90 (unadjusted)

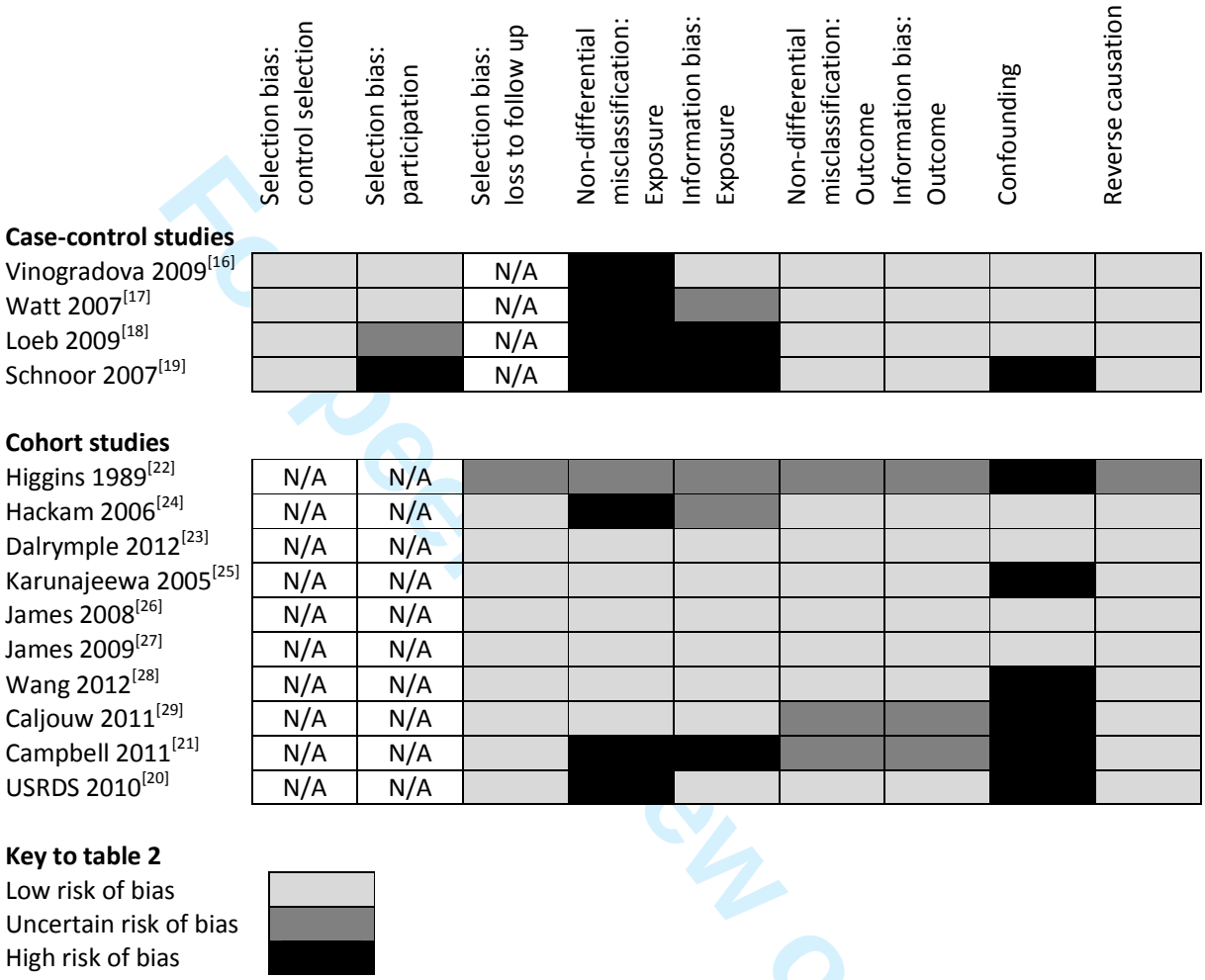
95% CI = 95% confidence interval; n/r = not reported; CKD= chronic kidney disease; UTI = urinary tract infection

1. Controls matched to cases on age at index data (within 1 year), sex, general practice, and calendar time. Estimate adjusted for smoking status, Townsend deprivation score, use of influenza vaccine in previous 12 months, use of pneumococcal vaccine in previous 5 years, number of years of medical records data available in database, and comorbidities including: diabetes, chronic heart disease, chronic respiratory disease, asplenia, cerebrospinal shunt, chronic liver disease, sickle cell disease or coeliac disease, cochlear implant, HIV/AIDS, immunosuppression, stroke or transient ischaemic attack, rheumatoid arthritis, Parkinson's disease, multiple sclerosis, dementia, osteoporosis, and any cancer.
2. Center for American Indian Health surveillance system.

3. Cases and controls matched by gender and age group. Adjusted for age, receipt of pneumococcal polysaccharide vaccine, congestive heart failure, alcohol use, body mass index and unemployment.
4. Adjusted for age, non-English language spoken most at home, living in detached house, living alone, congestive heart failure, chronic obstructive pulmonary disease, dysphagia, functional status using Barthel Index, immunosuppressive medications, nutritional score, tobacco use (lifetime history and secondhand smoke), alcohol consumption and history of regular exposure to gases, fumes or chemicals at home, or at work.
5. Approximate numbers, read from bar graph in publication. No confidence intervals available.
6. Cohort selected for the Cardiovascular Health Study. Exclusion criteria included: inability to provide informed consent or communicate with the interviewer, institutionalisation, being homebound, receipt of hospice care, treatment with radiation or chemotherapy for cancer, or plans to move out of the community within 3 years.
7. Serum cystatin C measured by particle-enhanced immunonephelometic assay, and eGFR calculated using: $eGFR=6.7xCysC^{-1.19}$.
8. Adjusted for age, sex, race, tobacco use, body mass index, diabetes mellitus, coronary heart disease, stroke, heart failure, cancer, chronic obstructive pulmonary disease, serum albumin, C-reactive protein, interleukin-6.
9. Canadian Institute for Health Information Discharge Abstract database or Ontario Health Insurance Plan database
10. ICD-9 codes 003 1, 036 2 and 038 0 – 038 9.
11. Canadian Institute for Health Information Discharge Abstract database.
12. Adjusted for statins, age, sex, nature of index event, charlson index, healthcare use, malignant disease, chemotherapy, neutropaenia, diabetes mellitus, oral steroids, antineoplastics, other immunosuppressants, history of aspiration, structural lung disease, previous infection (respiratory, GI, skin/soft tissue or other), recent trauma, transplant recipient, heart failure, stroke, chronic liver disease, chronic obstructive pulmonary disease, alcoholism, dementia, Parkinson's disease. Statin and non-statin users matched using propensity scoring for the above factors.
13. Mean age among the 460 participants without asymptomatic bacteriuria, 66.1years (SD11.0): mean age among the 36 participants with asymptomatic bacteriuria, 67.7 years (SD 10.5).
14. ICD-9 or ICD-10 codes for urinary sepsis were those encoding UTI, cystitis, pyelonephritis, orchitis, epididymitis and prostatitis; codes for non-urinary sepsis were those for sepsis, septicaemia and/or abscess.
15. Western Australia Data Linkage System.
16.Adjusted for presence of asymptomatic bacteriuria.
17. Adjusted for presence of asymptomatic bacteriuria and age.
18. Mean age ±SD by eGFR. >=60: 74.4±6.5years. 45-59: 77.5±7.2 years. 30-44: 79.3±7.4years. <30: 78.6±7.4 years.
19. eGFR calculated using abbreviated Modification of Diet in Renal Disease Study equation (omitting ethnicity) from single outpatient serum creatinine result.
20. Adjusted for age, sex, diabetes mellitus, comorbidity score and care in a CKD clinic.
21. Mean age ±SD by eGFR. >=105: 38.7±14.6. 60-104: 50.9±15.4. 45-59: 67.0± 14.1. 30-44: 74.5±12.9. <30: 73.3±15.2.
22. eGFR calculated using abbreviated Modification of Diet in Renal Disease Study equation (omitting ethnicity) from most recent outpatient serum creatinine result.
23. Adjusted for age, sex, socio-economic status, ethnicity, diabetes mellitus, Charlson comorbidity score.
24. Cohort selected for the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. Population weighted by age, ethnicity and geography according to local stroke incidence rates.
25. eGFR calculated using CKD-EPI equation.

26. Medical record review confirming (1) serious infection as major reason for admission and (2) ≥2 of heart rate >90 beats/minute, temperative>383°C or <36°C, tachypnoea >20 breaths/minute or leucocytosis.
27. Adjusted for age, sex, race, education, income, geographic region, alcohol use and smoking status.28. Creatinine clearance calculated from serum creatinine concentration and weight using Cockcroft-Gault formula.
29. Cause of death recorded as UTI (ICD-10 code N39.0)/
30. Department of Health-Health Protection Agency influenza vaccine uptake primary care monitoring system data.
31. Adjusted for age.
32. Smoothed estimate: Models include data from the stated year and the two years proceeding it, applying weights of 1, ¼ and 1/8 with increasing distance in time.
33. ICD-9-CM diagnosis codes recorded in insurance claims during the preceding year: 585.1 – 585.5 (chronic kidney disease stages 1-5); or 585.6 with no ESRD 2728 form or other indication of ESRD.
34. Principal hospital admission ICD-9-CM codes: 590-590.9, 595-595.4, 597-597.89, 598, 599.0, 601-601.9, 604-604.9, 607.1-2, 608.0, 608.4, 616.1, 616.3-4, and 616.8.

Table 2: Summary of risk of bias within studies (quality assessment tool adapted from Higgins *et al.*)[14]



DISCUSSION

Our comprehensive search strategy identified 14 studies describing an association between kidney disease and acute community-acquired infection. Although between-study heterogeneity precluded meta-analysis, all were consistent with a positive direction of association. The four studies which reported estimates on more than one category of kidney disease all found a graded association in which risk of infection increased with greater severity of CKD. These four studies all excluded patients with end-stage renal disease, and three were at low risk of bias in all categories of quality assessment.[22-23, 26-27]

To our knowledge, this is the first review to address this research question systematically. We used a sensitive search strategy, with a broad definition of kidney disease, for a thorough and inclusive search. The results are consistent with the conclusion of previous narrative reviews: that an association between CKD and infection incidence is likely, but that there is a paucity of evidence.[10-12]

Heterogeneity between the studies precluded meta-analysis of results. Variable study designs and biases may have contributed to heterogeneity: for example, the three case-control studies calculated odds ratios, which may differ from equivalent rate ratios for common infections.[16-18] Failure to control the confounding effects of age, sex and diabetes would be likely to result in overestimation of the effect of CKD on infection. Non-differential misclassification of kidney disease status in studies which relied on routine medical diagnosis would be expected to underestimate the effect of CKD on infection risk. In general the risk of ascertainment bias from increased monitoring for infection among patients with CKD is probably low, although one study assessed risk factors for hospitalisation with influenza during an influenza pandemic, in which context patients with influenza-like symptoms may have been more likely to be tested for influenza A(H1N1) if they also had CKD.[21]

The heterogeneity may reflect true differences in effect size between the studies.

Firstly, the studies considered a range of outcomes. CKD may have a different effect on the incidence of different infections. For all but three studies, detection of infection required either hospital attendance for the infection or a positive blood culture. CKD may affect severity of infection, as an alternative or in addition to any effect on infection incidence. CKD may also increase the probability of hospital admission for management of a moderately severe infection. Either would result in a larger effect of CKD on the risk of severe infectious outcomes (such as hospitalisation for sepsis) than on less severe infections (such as community-diagnosed LRTI), and could result in the graded association we observed, with increasing hospitalisation for patients with more severe stages of CKD.

Secondly, the studies included a variety of definitions of kidney disease. For example, proteinuria (and renal loss of complement) may represent a separate mechanism for risk of infection than uraemia. For the nine studies which did not exclude patients with ESRD it is unclear to what extent the results reflect the effect of treatments associated with dialysis, such as vascular or peritoneal access for dialysis, on infection incidence.

Thirdly, the association of CKD with infection may be modified by age. James *et al.* observed a weaker association of CKD with hospitalisation for pneumonia as age increased. They suggested that such an observation could be explained by a lower baseline rate of hospitalisation for pneumonia among younger adults, the natural decline in renal function by age, and inaccuracy in the estimation of renal function using the Modification of Diet in Renal Disease (MDRD) Study equation in older populations.[27] As their study population included only adults who had had a creatinine test result, reasons for testing creatinine could also be relevant confounders. As age-increases, more comorbidities accrue which require creatinine tests to guide therapy. Hence, younger people who receive a creatinine test may be

at an unusually high risk for both infections and CKD due to the reasons associated with getting a creatinine test. A real age-dependency of the CKD-infection association would be consistent with the lower effect of CKD on UTI incidence found among 86–90 year olds (0.90, 95% CI 0.50–1.77) compared with an adult study population with a mean age of 66 years (1.50, 95% CI 1.10–1.90). However, it may be that the study among the older adults measured a less severe outcome, and CKD may be associated with other factors that eventually lead to hospitalisation for UTI.[25, 29]

CKD was not a component of the primary study question for nine of the 14 studies, thus there is a risk that this association may have been reported and published only when CKD was found to be a risk factor for infection or an important confounder of another relationship. This would result in selective reporting bias, with a subsequent overestimation of the association of CKD with infection risk. This bias would be expected to affect smaller studies to a greater extent, and a funnel plot might show an asymmetry of relative risk estimates about the central pooled estimate among smaller studies. The sparsely populated funnel plot (**Fig S1**) provides no clear evidence for or against selective reporting bias, but some evidence of selective reporting bias comes from within the individual studies. For example, the crude hazard ratio for the association of creatinine clearance with UTI incidence is reported in Caljouw *et al.* (0.9, 95% CI 0.5–1.7) but as creatinine clearance was not found to be significant in the multivariable model the adjusted association is not reported.[29]

The overlap in the study populations of the two large cohort studies based in Calgary, Canada could result in more similar estimates than if the study populations were independent.[26-27] Outcomes in the two studies are likely to be correlated with each other: hospitalisation with pneumonia could cause a positive blood culture, which would result in one infection being included as an outcome in both studies. This is unlikely to have a large effect, particularly in

qualitative assessment of the combined evidence, as the potential overlap of person-time is limited.

Although we excluded study populations routinely treated with specialist medication (unless for kidney disease), some study populations may have been at higher risk of infection than the general population, and this may have affected the relationship of CKD to infection. For example, the cohort of patients admitted for an acute cardiovascular event or an arterial revascularisation procedure will have had a higher prevalence of co-morbidities (such as diabetes) than the general population and excluded patients with severe co-morbidities who did not survive an acute cardiovascular event, or who were not fit enough to undergo the procedure.[24] Each of the selected study populations limits the generalisability of the individual study result, but the qualitatively similar findings across the variety of study populations, and their qualitative consistency with the four studies based among the general population,[5, 16, 21, 29] support a positive association between CKD and infection risk in a variety of study populations.

A few large, high quality studies which excluded patients with ESRD have found a graded association between pre-dialysis CKD and risk of hospitalisation with infection. All studies identified in this review were compatible with a positive association of CKD with increased infection risk. There are little data available on the association of CKD with infection incidence using less severe outcome measures than hospitalisation, and it is not possible in most studies to distinguish an effect on susceptibility to infection from an effect on the severity of infection.

The potential age-dependency of the relationship between CKD and infection is intriguing and needs further research. There is also currently no evidence on the relationship between proteinuria and infection incidence independently of glomerular filtration rate. Future studies

should identify infections in the community in addition to hospitalisations for infection, characterise the association of proteinuria adjusted for glomerular filtration rate, explore the age-dependency of the association, and assess vaccine efficacy among older people with CKD.

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Contributor statement:

All authors designed the study strategy including the search terms, inclusion and exclusion criteria. HM performed the search, study selection and data extraction. DN screened the randomly selected sample of 100 abstracts. All authors agreed quality assessment of included papers and interpretation of results by discussion. HM drafted the article, which DN and ST revised. All authors approved the final version of the manuscript.

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Data sharing statement:

All data, including full search terms and eligibility criteria, are available either in the article or as online supplementary material submitted with this manuscript.

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FIGURE LEGENDS

Figure 1: Flow chart of study selection

Figure 2: Forest plot of all estimates of the association of CKD with infection(n=17) from all 14 studies identified

UTI: urinary tract infection
The estimates from Higgin 1985 and USRDS 2010 did not include standard errors.
Dalrymple 2012: Presented estimates compare eGFR 45-59 with eGFR ≥90 mL/min/1.73m^2
James 2009: Presented estimates compare eGFR 45-59 with eGFR 60-104 mL/min/1.73m^2
James 2008: Presented estimates compare estimated glomerular filtration rate (eGFR) 45-59 with eGFR ≥60 mL/min/1.73m^2

Title: Chronic kidney disease as a risk factor for acute community-acquired infections: a systematic review ~~and meta-analysis~~

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Body: ~~3,346~~ 3,134 words

ABSTRACT:

Objectives: A systematic review of the association of pre-dialysis chronic kidney disease (CKD) with the incidence of acute, community-acquired infections.

Design: We searched Medline, Embase and Cochrane databases (inception to ~~29/03/2012~~16/01/2014) for studies analysing the association of pre-dialysis kidney disease with the incidence of acute, community-acquired urinary tract infection (UTI), lower respiratory tract or central nervous system infections, or sepsis. Studies were required to include at least 30 participants with and without kidney disease.

Setting & participants: Community-based populations of adults in high income countries.

Outcome measures: Acute, community-acquired urinary tract infection (UTI), lower respiratory tract or central nervous system infections, or sepsis.

Results: We identified ~~eleven~~ 14 eligible studies. Estimates from two studies lacked 95% confidence intervals and standard errors. The remaining 12 ~~nine~~ studies yielded 17~~12~~ independent effect estimates. ~~Most studies identified only severe infections resulting in hospitalisation~~Only three studies included infections managed in the community. Quality assessment revealed that probable misclassification of kidney disease status and poor adjustment for confounding were common. There was evidence from a few large high quality studies of a graded association between pre-dialysis CKD stage and hospitalisation for infection. One study found an interaction with age, with a declining effect of CKD on infection risk as age increased. There was evidence of between-studies heterogeneity (I^2=96.5%, p<0.001) which persisted in subgroup analysis.~~outcomes: UTI I^2=55.2%, p=0.135; other infections I^2=98.0%, p<0.001;)~~ and thus meta-analysis was not performed.

Conclusions: Pre-dialysis kidney disease appears to be associated with increased risk of severe infection. Whether pre-dialysis kidney disease increases the susceptibility to infections and whether age modifies this association remains unclear.

ARTICLE SUMMARY

Article focus:

- This review sought to assess systematically whether pre-dialysis chronic kidney disease (CKD) is a risk factor for the incidence of acute, community-acquired urinary tract infection (UTI), lower respiratory tract infection (LRTI) central nervous system (CNS) infection, or sepsis, among community-based adults in high income countries.
- Any increased risk of infection incidence at early stages of CKD would affect a large and growing number of patients. Awareness and quantification of this risk could have benefits for patient management, more effective vaccination strategies and healthcare planning.

Key messages:

- We identified major gaps in the literature including: a scarcity of high-quality studies on this research topic; a lack of studies using less severe outcome measures than hospitalisation, to allow any association of CKD with susceptibility to infection to be distinguished from an association with severity of infection; and a lack of data on the relationship between proteinuria and infection incidence independently of glomerular filtration rate.
- All studies were consistent with a positive association between CKD and infection risk.

Strengths and limitations of this study:

- This study used a sensitive search strategy, with a broad definition of kidney disease, for a thorough and inclusive search.

- Between-study heterogeneity, and the low quality of many of the studies, limit interpretation of results of the studies currently available.

INTRODUCTION

Chronic kidney disease (CKD) is common, and its prevalence is increasing.[1] Infection is a major cause of mortality in end-stage renal disease (ESRD) and hospitalisation at all stages of CKD. The second commonest cause of death among ESRD patients in the US is septicaemia, and patients with ESRD are at increased risk of death from infection compared to the general population.[2-4] Both ESRD and pre-dialysis patients with CKD in the US are at higher risk of hospitalisation for infection than the general population.[2, 5-6] Pre-dialysis CKD has been found to increase mortality among patients hospitalised with infections.[7]

Increased mortality and hospitalisation from infection could be driven by increased severity of infection, i.e. once an infection is present, the course of the associated illness is more severe, or increased incidence, i.e. CKD may make people more susceptible to develop an infection. Patients with CKD display impaired host immunity: reduced vaccination responsiveness is observed at all stages of CKD.[8]

Among ESRD patients, aspects of dialysis, such as vascular and peritoneal access for dialysis, may be a risk factor for infection incidence and severity. However, this does not tell the whole story, and only 23% of infection-related hospitalisations among haemodialysis patients in the US were identified as related to vascular access in the HEMO study.[9] Risk factors for infection identified among ESRD patients which are not related to renal replacement therapy, and could apply at all stages of pre-dialysis CKD, include: the causes and treatment of kidney disease; co-morbidities; reduced vaccine effectiveness; and high levels of exposure to health care facilities.[10]

If there is an increased risk of infection incidence at early stages of CKD, this would affect a large and growing number of patients. Awareness and quantification of this risk could have

benefits for patient management, more effective vaccination strategies and healthcare planning.

Narrative reviews have concluded that it is likely that CKD in itself increases infection incidence, but reported a lack of evidence.[10-12] We are not aware of any relevant systematic literature reviews of the effect of CKD on infection incidence.

This review sought to assess systematically whether pre-dialysis CKD is a risk factor for the incidence of acute, community-acquired urinary tract infection (UTI), lower respiratory tract infection (LRTI) central nervous system (CNS) infection, or sepsis, among community-based adults in high income countries.

METHODS

Data Sources and Searches

One reviewer (HM) searched the Medline and Embase databases, and the Cochrane library, from inception to ~~29 March 2012~~16 January 2014. The search strategies combined text words and MeSH terms for three concepts: acute community-acquired infection (either sepsis, UTI, LRTI or CNS infection); kidney disease; and relative risk. We used search terms to identify studies among adult humans in high-income countries (according to the World Bank classification),[13] and limited the search to articles in English, French or German. The full strategies are available in **Supplementary Tables 1-3**.

We searched the reference lists of all included studies and any pertinent review articles to identify further eligible studies.

Study Selection

One reviewer (HM) screened titles and abstracts, reviewed the full-text of identified studies and made initial decisions on eligibility according to pre-specified inclusion criteria (**Supplementary Table 4)**. Any borderline cases were discussed between HM, DN and ST. A second reviewer (DN) checked a sample of 100 abstracts, selected randomly after de-duplication of records, and a kappa statistic was calculated to describe agreement in selection of studies.

Eligible studies analysed the effect of pre-dialysis kidney disease on the relative risk of at least one of the four specified acute, community-acquired infections among community-based adults in high-income countries. We excluded study populations ~~routinely treated with~~

~~specialist medication~~managed in secondary care (unless ~~these were~~ for kidney disease), ~~which often has potential immunosuppressive effects~~ routinely treated with immunosuppressants, ~~and study populations~~ or exclusively of pregnant women, as ~~both~~ these groups have a raised risk of infection, and the relationship of CKD to infection risk may be different among these groups compared to that in the general adult population in primary care.

To maximise the sensitivity of our search strategy, we accepted a wide range of definitions of kidney disease, including: medical diagnosis of kidney disease, reduced estimated glomerular filtration rate or creatinine clearance, elevated creatinine, ~~or creatinine clearance,~~ proteinuria, micro- or macro-albuminuria, and renal structural abnormalities. We also accepted definitions which included some patients with ESRD among the patients with CKD, but excluded definitions which were exclusively patients receiving renal replacement therapy.

Outcomes of interest were relative risk estimates of acute community-acquired LRTIs, UTIs, CNS infections or sepsis. We accepted outcomes describing incidence of severe infections (such as hospitalisation with pneumonia).

We restricted our search to published studies which were sufficiently large to include at least 30 participants with and without kidney disease, to allow reasonable precision of the study estimate. Detailed eligibility criteria are listed in **Supplementary Table 4.**

Data Extraction and Quality Assessment

Data were extracted from relevant studies using a pre-specified collection form. Study characteristics extracted included study design, data source, any participant exclusion criteria, number of participants, age, gender, baseline renal function, definition of renal impairment, definition of the outcome infection. An estimate of relative risk (rate ratio, risk ratio or odds

ratio) with any measures taken to address confounding was extracted from each eligible independent analysis in each study. Studies with no confidence intervals and for which the standard error was not calculable from the data presented were included in the review but not considered for meta-analysis.

When multiple estimates were available from a study but were not independent, a single estimate was identified for potential meta-analysis by selecting the estimate best adjusted for confounding, using the most recent data, comparing the level of CKD most common in the general population with no CKD.

Study quality was assessed using a pre-specified tool adapted from Higgins *et al*. for observational studies.[14] Studies were assigned a high, low or uncertain risk of each of: selection bias, non-differential measurement error for exposure and outcome, information bias in exposure and outcome, confounding and reverse causation. The minimum requirement for a low risk of bias from confounding was appropriate management of confounding by age, sex and diabetes. Specific criteria used are detailed in **Supplementary Table 5**.

Data Synthesis and Analysis

The relationship between CKD and UTIs was considered likely to differ from that of CKD to other infections, due to potential reverse causality. For example, repeat UTIs may cause kidney disease, or structural kidney disease may be identified though investigation of repeat UTIs. Therefore in all quantitative analysis, UTIs were analysed separately from other infections.

Estimates were examined for heterogeneity using Cochran's Q statistic and the I^2 statistic as described by Higgins *et al*.[15] If I^2 was less than 50% and Cochran's Q statistic $p \geq 0.1$, fixed-effects meta-analysis was considered for each of the two categories (UTI, and other

infections). Funnel plots were constructed to look for publication bias. All analysis was conducted using STATA version 12.0.

RESULTS

The database searches identified ~~8,363~~10,380 citations, of which ~~1,001~~1,204 were duplicates (**Figure 1**). Both reviewers had 100% agreement on which studies to extract for full-text analysis from screening a random sample of 100 abstracts (Cohen's K= 1).

We identified ~~11~~ 14 eligible studies, with varying study characteristics (**Table 1**). ~~Three~~ Four studies were case-control studies,[16-19] and ~~eight~~ ten were cohort studies.[20-29] ~~Five~~ Seven studies investigated a range of risk factors for infection,[16-19, 21, 28-29] two studies reported the effect of CKD on infection as a confounder of the effect of interest,[24-25] and ~~only four~~ five studies investigated the effect of CKD on infection risk as their primary research question.[5, 20, 22, 26-27]

~~Four~~ Seven studies were based among the general population.[5, 16, 19, 21, 23, 28-29] Other study populations included: attendants at a specialist renal clinic,[22] patients with diabetes mellitus,[25] patients admitted to hospital for an acute cardiovascular event or an arterial revascularisation procedure, [24] and the Navajo Nation – a population which experiences 3–5 times higher rates of invasive pneumococcal disease than the general US population.[17] The population of the cohort studies in Calgary, Canada were adults with a serum creatinine test result available in their medical records.[26-27] There is some overlap in the study populations of these two cohort studies: residents aged over 65 years with a serum creatinine measurement between 1 July 2001 and 31 December 2001 and also between 1 July 2003 and 30 June 2004 would have been included in both studies for the period from the second creatinine measurement until 31 December 2004.[26-27]

Definitions of kidney disease included medical diagnoses of chronic renal disease, elevated creatinine levels, impaired creatinine clearance, and structural abnormalities of the kidney. ~~Four~~ Five studies excluded patients with ESRD, and one specified the number included, but

for the remaining ~~six~~ eight studies it was unclear how many of the included patients received renal replacement therapy **(Table 1)**.

~~Two~~Three studies recorded infections diagnosed in primary care or outpatients,[16, 19, 29] two recorded infections identified from a positive culture result,[17, 26] one included infections diagnosed in the emergency department,[18] ~~five~~ seven required hospital admission for infection,[5, 21, 23-25, 27-28] and for one study the definition and severity of infection was unclear.[22]

For two studies, the results extracted had no confidence interval or standard error and these could not be calculated from the reported data. From the remaining ~~nine~~ 12 studies, ~~12~~ 17 independent effect estimates with standard errors were available for meta-analysis, among which UTI was the outcome in ~~two~~ three estimates.

For all infections there was strong evidence of considerable heterogeneity (Cochran's Q statistic p<0.001, I^2=96.5%). This persisted when estimates for UTIs were excluded (p<0.001, I^2=97.2%), when considering LRTIs alone (p<0.001, I^2=98.2%), when limited to cohort studies (p<0.001, I^2=97.3%), and when stratified by exclusion of patients with ESRD (ESRD excluded, p<0.001, I^2=88.9%: ESRD not excluded p<0.001, I^2=97.2%). Due to this heterogeneity, meta-analysis was not performed. ~~For infections other than UTIs, there was strong evidence of considerable heterogeneity (Cochran's Q statistic p<0.001, I^2=98.0%) and among the two studies of UTIs, there was some evidence of heterogeneity (p=0.135, I^2=55.2%). This remained after considering LRTIs alone (p<0.001, I^2=98.6%). For this reason, meta-analysis was not performed. There were only two studies excluding patients with ESRD for which standard errors were available, and so these estimates were not analysed separately.~~

All results ~~The results available for quantitative analysis~~ are displayed in the Forest plot (**Figure 2**). Despite the quantitative heterogeneity, the results were qualitatively similar: all estimates were compatible with a positive association between kidney disease and infection. The four studies which compared different stages of CKD found a graded association of increased risk of infection with more severe CKD. These studies all excluded patients with end-stage renal disease.[22-23, 26-27] One study found that the effect of CKD on infection risk was modified by age, with a declining effect of CKD on infection risk as age increased.[27] This effect was consistent with the lower effect of CKD on UTI incidence found among 86–90 year olds (0.90, 95% CI 0.50–1.77) compared with an adult study population with a mean age of 66 years (1.50, 95% CI 1.10–1.90).[25, 29]

The funnel plot was sparsely populated, with widely scattered effect estimates, and provides no clear evidence for or against publication bias (**Supplementary Figure 1**).

Study quality was variable. Relying on routine medical diagnosis introduced a potential source of misclassification of kidney disease status for ~~six~~seven- studies.[5, 16-19, 21, 24] There was variable adjustment for confounding, from unadjusted crude estimates to estimates adjusted for a range of comorbidities, demographic and socio-economic factors. ~~Four~~ Six studies did not meet this review's minimal requirements.[19, 21-22, 25, 28-29] The summarised results are displayed in **Table 2**, and the full quality assessment is in **Supplementary Table 5**.

Table 1: Characteristics of eligible studies (n=~~11~~14)

Case-control studies												
	Study			Kidney disease			Infection			Kidney disease prevalence		Odds ratio (95% CI)
	Date	Setting	Population Age % Female	Defined	ESRD included	Ascertained	Type	Defined	Ascertained	Cases	Controls	
Vinogradova 2009[16]	1996 - 2005	UK	General population Any age Median age band 45-64 years Cases 49.3%, controls 49.1%	Chronic renal disease	Unclear	Primary care medical record diagnosis code in previous 5 years	Pneumonia	Medical diagnosis recorded in primary care records	READ code in primary care medical records	203/ 17,172 (1.2%)	386/ 71,299 (0.5%)	1.72 (1.3 – 2.07)[1]
Watt 2007[17]	1999 - 2002	The Navajo Nation USA	Navajo adults ≥18 years Summary age and sex n/r	Chronic renal failure	17 participants receiving dialysis	Medical record abstraction	Invasive pneumococcal disease	S.pneumoniae isolated from a normally sterile body fluid during illness	Active laboratory surveillance system[2]	20/118 (16.9%)	12/353 (3.4%)	2.6 (0.87 – 7.7)[3] P=0.087
Loeb 2009[18]	2002 - 2005	Ontario & Alberta Canada	General population ≥ 65 years Mean age: cases 79.1, controls 74.4 years. Cases 39.6%, controls 68.5%	Renal disease	Unclear	Cases: hospital interview. Controls: telephone interview at home.	Pneumonia	Consistent chest X-ray and ≥2 of: chest pain, shortness of breath, productive cough, temperature >38°C, crackles on auscultation.	Recruited patients attending emergency departments	127/690 (18.4%)	38/82 (4.4%)	4.06 (1.98–8.35)[4] P<0.001
Schnoor	2002	Germany	General	Chronic	Unclear	Cases:	Pneumonia	(1) Infiltrate on chest	Community-	49/1128	27/1044	1.7 (1.1–2.8)

2007[19]	– 2005		population >18 years Mean age: cases 57, controls 57.5 years Cases 44.8%, controls 54.7%	renal disease		reporting physician. Controls: self-reported questionnaire.		X-ray or (2) temperature ≥38.3°C with any of: cough, purulent sputum, positive auscultation. Excluded if hospitalised within prior 4 weeks, or immunodeficient.	acquired pneumonia network registry reports (primary and secondary care)	(4.3%)	(2.6%)	(unadjusted) P<0.05	

Cohort studies

	Study			Kidney disease			Comparison group	Infection			Risk or rate ratio (95% CI)	
	Date	Setting Follow up time	Population Number Age Sex	Defined Number with kidney disease	ESRD	Ascertained	Defined	Type	Defined	Ascertained		
Higgins 1989[22]	1985	Oxford UK 1 year	Patients attending a Renal Unit with chronic renal failure n=211 17-77 years Mean 50.5 years % female n/r	Creatinine ≥250 µmol/l Number n/r	Excluded	Serum creatinine	Creatinine <250 µmol/l ~~n/r~~	UTI	>10[5] organism/ml and ≥10 leucocytes /hpf in clean catch urine specimen	Medical record review	Creatinine µmol/l	
											<250	1
											250-500	1.5 [5]
											>500	2[5]
Dalrymple 2012[23]	1989 – 2007	United States Mean 11.5 years	General community-dwelling population[6] n=5,142 >65 years Mean 72 years	Baseline eGFR<90 mL/min/1.73 m^{2} [7] n=3,863	Excluded	Baseline cystatin C	Baseline eGFR ≥90 mL/min/1.73 m^{2} [7]	Pulmonary	Hospital admission with a principal discharge diagnosis of the relevant infection (ICD-9-CM codes)	Medical record review following patient report of hospital admission in cohort study	eGFR mL/min/1.73m^{2}	
											≥90	1
											60–89	1.22 (0.99–1.54)[8]
											45–59	1.27 (0.94–1.71)[8]
											15–44	1.81 (1.25–2.63)[8]
								Genitourinary			≥90	1
											60–89	1.08 (0.75–1.56)[8]
											45–59	1.17 (0.67–2.05)[8]
											15–44	2.63 (1.40–4.96)[8]

			61% female					Bacteremia and sepsis			≥90	1
											60–89	1.10 (0.77–1.58) [8]
											45–59	1.55 (0.93–2.57) [8]
											15–44	0.77 (0.29–2.03) [8]
Hackam 2006[24]	1997 - 2002	Ontario Canada Mean 2.2 years	Patients with cardiovascular disease n=69,168 >65 years Mean 74.1 years 44% female	Chronic renal insufficiency n=7,169	Unclear	Health record databases[9]	No chronic renal insufficiency	Sepsis	Hospital admission with a diagnosis of sepsis[10]	Health record database[11]	1.47 (1.27–1.72)[12]	
Karunajeewa 2005[25]	1999 - 2000	Western Australia Mean 2.9 years	Patients with diabetes n=496 >10 years Mean 66.1 years[13] 46.2% female	Albuminuria; serum urea; serum creatinine	Unclear	Baseline urinary albumin: creatinine ratio (ACR), serum urea, serum creatinine	Hazard ratio per 2.72-fold increase in ACR or serum urea	Urinary sepsis and non-urinary sepsis	Hospitalisation diagnosis codes (principal diagnosis, or principal or secondary diagnosis)[14]	Health record database[15]	Urinary sepsis (principal code)	
											Ln(ACR)	1.5 (1.1 – 1.9) [16] p=0.004
											Urinary sepsis (principal or secondary code)	
											Ln(ACR)	1.3 (1.1 – 1.6) [17] p=0.005
											Non-urinary sepsis (principal)	
											Ln(ACR)	1.4(1.1-1.9) [16]
											Non-urinary sepsis (principal or secondary code)	
											Ln(urea)	4.6 (2.3-9.4) [16] p<0.001
James 2008[26]	2001 - 2004	Calgary Canada Mean 3.2 years	General population n=25,675 >65 years Mean by eGFR [18] 55.9% female	Baseline eGFR<60 mL/min/1.73 m^2 [19] n=6,941	Excluded	Calgary Laboratory Services records	Baseline eGFR ≥60 mL/min/1.73 m^2 [19]	Bloodstream infection	Any pathogenic organism isolated from ≥1 blood cultures submitted from the community or ≤2 days of hospital admission	Calgary Laboratory Services records	eGFR mL/min/1.73m^2	
											≥60	1
											45-59	1.17 (0.92–1.49)[20]
											30-44	1.60 (1.20–2.13) [20]
											<30	2.95 (2.11–4.14) [20]
James 2009[27]	2003 -	Calgary Canada	General population	Time updated	Excluded	Calgary Laboratory	eGFR 60-104 mL/min/1.73	Pneumonia	ICD-10 code for pneumonia any	Hospital discharge	eGFR mL/min/1.73m^2	
											18-54 years	

	2006	Median 2.5 years	n=252,516 ≥18 years Mean by eGFR[21] 42.3% female	eGFR<60 mL/min/1.73 m^2 [22] n=35,948		Services records	m^2 [22]		position in hospital discharge report	reports	60-104	1
											45-59	3.23 (2.40–4.36) [23]
											30-44	9.67 (6.36–14.69) [23]
											<30	15.04 (9.64–23.47) [23]
											Age 55 – 64 years	
											60-104	1
											45-59	1.43 (1.11–1.84) [23]
											30-44	1.94 (1.32–2.87) [23]
											<30	5.50 (3.83–7.92) [23]
											Age 65 – 74 years	
											60-104	1
											45-59	1.18 (0.99–1.40) [23]
											30-44	2.24 (1.84–2.73) [23]
											<30	3.23 (2.52–4.13) [23]
											Age ≥75 years	
											60-104	1
											45-59	0.95 (0.85–1.05) [23]
											30-44	1.03 (0.92–1.16) [23]
											<30	1.79 (1.55–2.06) [23]
Wang 2012[28]	2003 – 2011	United States Mean .7 years	General population sample (weighted by age, geography and ethnicity) [24] n=30,239 ≥45 years 69%>60 years 55% female	Baseline eGFR<60 mL/min/1.73 m^2 [25]	Unclear	Baseline serum creatinine	Baseline eGFR ≥60 mL/min/1.73 m^2 [25]	Sepsis	Among hospitalisations attributed by participants to serious infection, medical record review [26]	Initially reported by study participants, confirmed with medical record review	1.99 (1.73–2.29) [27]	

Caljouw 2011[29]	1998 - 2004	Leiden The Netherlands Mean 2.6 years	General population n= 479 86-90 years All aged 86 years at entry 67.2% female	Creatinine clearance <30mL/min[28] n=43	Unclear	Baseline serum creatinine	Creatinine clearance ≥30mL/min[28]	UTI	Diagnosed by treating physician based on signs, symptoms and urine analysis; or death records[29]	Physician interview and medical record review. Statistics Netherlands for cause of death data.	0.9 (0.5–1.7) (unadjusted) p=0.794
Campbell 2011[21]	2009 - 2010	England UK 9 months	General population n=43.9 million 6 months - 64 years Summary age and sex n/r	Chronic kidney disease n=182,000	Unclear	Cases: consultant microbiologist report. Denominator: primary care population estimate.[30]	No pre-existing conditions [30]	Pandemic influenza A(H1N1)	Polymerase chain reaction (PCR) test confirmation of pandemic influenza A (H1N1) from a hospital inpatient.	Consultant microbiologist report to national surveillance system.	17.5 (13.4 – 22.9) [31]
USRDS 2010[20]	2008	USA 1 year [32]	Medicare patients 66+ years	Chronic kidney disease	Excluded	Insurance database ICD-9_CM codes [33]	No CKD	Pneumonia	Principal cause of hospital admission using hospital insurance claim records	ICD-9-CM codes 480-486	2.76 (unadjusted)
								UTI		ICD-9-CM codes [34]	3.15 (unadjusted)
								Bacteraemia/ septicaemia		ICD-9-CM codes 038.0 – 038.9	3.90 (unadjusted)

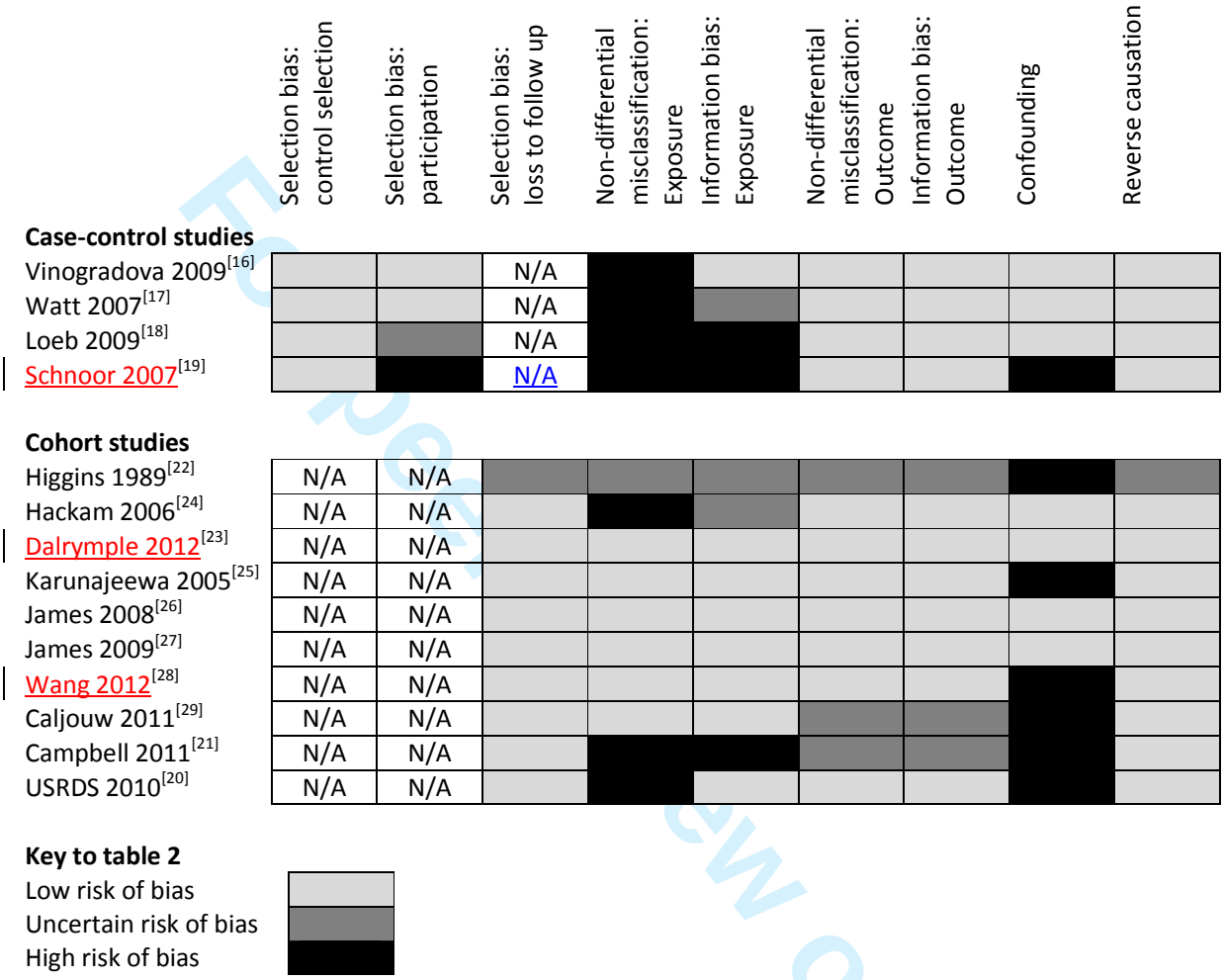
95% CI = 95% confidence interval; n/r = not reported; CKD= chronic kidney disease; UTI = urinary tract infection

1. Controls matched to cases on age at index data (within 1 year), sex, general practice, and calendar time. Estimate adjusted for smoking status, Townsend deprivation score, use of influenza vaccine in previous 12 months, use of pneumococcal vaccine in previous 5 years, number of years of medical records data available in database, and comorbidities including: diabetes, chronic heart disease, chronic respiratory disease, asplenia, cerebrospinal shunt, chronic liver disease, sickle cell disease or coeliac disease, cochlear implant, HIV/AIDS, immunosuppression, stroke or transient ischaemic attack, rheumatoid arthritis, Parkinson's disease, multiple sclerosis, dementia, osteoporosis, and any cancer.
2. Center for American Indian Health surveillance system.

3. Cases and controls matched by gender and age group. Adjusted for age, receipt of pneumococcal polysaccharide vaccine, congestive heart failure, alcohol use, body mass index and unemployment.
4. Adjusted for age, non-English language spoken most at home, living in detached house, living alone, congestive heart failure, chronic obstructive pulmonary disease, dysphagia, functional status using Barthel Index, immunosuppressive medications, nutritional score, tobacco use (lifetime history and secondhand smoke), alcohol consumption and history of regular exposure to gases, fumes or chemicals at home, or at work.
5. Approximate numbers, read from bar graph in publication. No confidence intervals available.
6. Cohort selected for the Cardiovascular Health Study. Exclusion criteria included: inability to provide informed consent or communicate with the interviewer, institutionalisation, being homebound, receipt of hospice care, treatment with radiation or chemotherapy for cancer, or plans to move out of the community within 3 years.
7. Serum cystatin C measured by particle-enhanced immunonephelometic assay, and eGFR calculated using: $eGFR=6.7xCysC^{-1.19}$.
8. Adjusted for age, sex, race, tobacco use, body mass index, diabetes mellitus, coronary heart disease, stroke, heart failure, cancer, chronic obstructive pulmonary disease, serum albumin, C-reactive protein, interleukin-6.
9. Canadian Institute for Health Information Discharge Abstract database or Ontario Health Insurance Plan database
10. ICD-9 codes 003 1, 036 2 and 038 0 – 038 9.
11. Canadian Institute for Health Information Discharge Abstract database.
12. Adjusted for statins, age, sex, nature of index event, charlson index, healthcare use, malignant disease, chemotherapy, neutropaenia, diabetes mellitus, oral steroids, antineoplastics, other immunosuppressants, history of aspiration, structural lung disease, previous infection (respiratory, GI, skin/soft tissue or other), recent trauma, transplant recipient, heart failure, stroke, chronic liver disease, chronic obstructive pulmonary disease, alcoholism, dementia, Parkinson's disease. Statin and non-statin users matched using propensity scoring for the above factors.
13. Mean age among the 460 participants without asymptomatic bacteriuria, 66.1years (SD11.0): mean age among the 36 participants with asymptomatic bacteriuria, 67.7 years (SD 10.5).
14. ICD-9 or ICD-10 codes for urinary sepsis were those encoding UTI, cystitis, pyelonephritis, orchitis, epididymitis and prostatitis; codes for non-urinary sepsis were those for sepsis, septicaemia and/or abscess.
15. Western Australia Data Linkage System.
16.Adjusted for presence of asymptomatic bacteriuria.
17. Adjusted for presence of asymptomatic bacteriuria and age.
18. Mean age ±SD by eGFR. >=60: 74.4±6.5years. 45-59: 77.5±7.2 years. 30-44: 79.3±7.4years. <30: 78.6±7.4 years.
19. eGFR calculated using abbreviated Modification of Diet in Renal Disease Study equation (omitting ethnicity) from single outpatient serum creatinine result.
20. Adjusted for age, sex, diabetes mellitus, comorbidity score and care in a CKD clinic.
21. Mean age ±SD by eGFR. >=105: 38.7±14.6. 60-104: 50.9±15.4. 45-59: 67.0± 14.1. 30-44: 74.5±12.9. <30: 73.3±15.2.
22. eGFR calculated using abbreviated Modification of Diet in Renal Disease Study equation (omitting ethnicity) from most recent outpatient serum creatinine result.
23. Adjusted for age, sex, socio-economic status, ethnicity, diabetes mellitus, Charlson comorbidity score.
24. Cohort selected for the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. Population weighted by age, ethnicity and geography according to local stroke incidence rates.
25. eGFR calculated using CKD-EPI equation.

26. Medical record review confirming (1) serious infection as major reason for admission and (2) ≥2 of heart rate >90 beats/minute, temperative>383°C or <36°C, tachypnoea >20 breaths/minute or leucocytosis.
27. Adjusted for age, sex, race, education, income, geographic region, alcohol use and smoking status.
28. Creatinine clearance calculated from serum creatinine concentration and weight using Cockcroft-Gault formula.
29. Cause of death recorded as UTI (ICD-10 code N39.0)/
30. Department of Health-Health Protection Agency influenza vaccine uptake primary care monitoring system data.
31. Adjusted for age.
32. Smoothed estimate: Models include data from the stated year and the two years proceeding it, applying weights of 1, ¼ and 1/8 with increasing distance in time.
33. ICD-9-CM diagnosis codes recorded in insurance claims during the preceding year: 585.1 – 585.5 (chronic kidney disease stages 1-5); or 585.6 with no ESRD 2728 form or other indication of ESRD.
34. Principal hospital admission ICD-9-CM codes: 590-590.9, 595-595.4, 597-597.89, 598, 599.0, 601-601.9, 604-604.9, 607.1-2, 608.0, 608.4, 616.1, 616.3-4, and 616.8.

Table 2: Summary of risk of bias within studies (quality assessment tool adapted from Higgins *et al.*)[14]



DISCUSSION

Our comprehensive search strategy identified ~~11~~ 14 studies describing an association between kidney disease and acute community-acquired infection. Although between-study heterogeneity precluded meta-analysis, all were consistent with a positive direction of association. The four studies which reported estimates on more than one category of kidney disease all found a graded association in which risk of infection increased with greater severity of CKD. ~~.~~ These four studies all excluded patients with end-stage renal disease, and three were at low risk of bias in all categories of quality assessment.[22-23, 26-27]

To our knowledge, this is the first review to address this research question systematically. We used a sensitive search strategy, with a broad definition of kidney disease, for a thorough and inclusive search. The results are consistent with the conclusion of previous narrative reviews: that an association between CKD and infection incidence is likely, but that there is a paucity of evidence.[10-12]

~~Since our literature search, a subsequently published US prospective cohort study of 5,142 adults over 65 years old found an association between worse kidney function and higher risk of hospitalisation for infection.[21] Identification of CKD status was proactive and based on baseline blood measurements. The association was linear when kidney function was calculated using serum cystatin C, and U-shaped when kidney function was calculated using serum creatinine.~~

Heterogeneity between the studies precluded meta-analysis of results. Variable study designs and biases may have contributed to heterogeneity: for example, the three case-control studies calculated odds ratios, which may differ from equivalent rate ratios for common infections.[16-18] Failure to control the confounding effects of age, sex and diabetes would be likely to result in overestimation of the effect of CKD on infection. Non-differential

misclassification of kidney disease status in studies which relied on routine medical diagnosis would be expected to underestimate the effect of CKD on infection risk. In general the risk of ascertainment bias from increased monitoring for infection among patients with CKD is probably low, although one study assessed risk factors for hospitalisation with influenza during an influenza pandemic, in which context patients with influenza-like symptoms may have been more likely to be tested for influenza A(H1N1) if they also had CKD.[21]

The heterogeneity may reflect true differences in effect size between the studies.

Firstly, the studies considered a range of outcomes. CKD may have a different effect on the incidence of different infections. ~~We analysed the effect of CKD on UTIs separately.~~ For all but three studies, detection of infection required either hospital attendance for the infection or a positive blood culture. CKD may affect severity of infection, as an alternative or in addition to any effect on infection incidence. CKD may also increase the probability of hospital admission for management of a moderately severe infection. Either would result in a larger effect of CKD on the risk of severe infectious outcomes (such as hospitalisation for sepsis) than on less severe infections (such as community-diagnosed LRTI), and could result in the graded association we observed, with increasing hospitalisation for patients with more severe stages of CKD.

Secondly, the studies included a variety of definitions of kidney disease. For example, proteinuria (and renal loss of complement) may represent a separate mechanism for risk of infection than uraemia. For the ~~seven~~ nine studies which did not exclude patients with ESRD it is unclear to what extent the results reflect the effect of treatments associated with dialysis, such as vascular or peritoneal access for dialysis, on infection incidence.

Thirdly, the association of CKD with infection may be modified by age. James *et al.* observed a weaker association of CKD with hospitalisation for pneumonia as age increased.

They suggested that such an observation could be explained by a lower baseline rate of hospitalisation for pneumonia among younger adults, the natural decline in renal function by age, and inaccuracy in the estimation of renal function using the Modification of Diet in Renal Disease (MDRD) Study equation in older populations.[27] As their study population included only adults who had had a creatinine test result, reasons for testing creatinine could also be relevant confounders. As age-increases, more comorbidities accrue which require creatinine tests to guide therapy. Hence, younger people who receive a creatinine test may be at an unusually high risk for both infections and CKD due to the reasons associated with getting a creatinine test. A real age-dependency of the CKD-infection association would be consistent with the lower effect of CKD on UTI incidence found among 86–90 year olds (0.90, 95% CI 0.50–1.77) compared with an adult study population with a mean age of 66 years (1.50, 95% CI 1.10–1.90). However, it may be that the study among the older adults measured a less severe outcome, and CKD may be associated with other factors that eventually lead to hospitalisation for UTI.[25, 29]

CKD was not a component of the primary study question for ~~7~~ nine of the ~~11~~ 14 studies, thus there is a risk that this association may have been reported and published only when CKD was found to be a risk factor for infection or an important confounder of another relationship. This would result in selective reporting bias, with a subsequent overestimation of the association of CKD with infection risk. This bias would be expected to affect smaller studies to a greater extent, and a funnel plot might show an asymmetry of relative risk estimates about the central pooled estimate among smaller studies. The sparsely populated funnel plot (**Fig S1**) provides no clear evidence for or against selective reporting bias, but some evidence of selective reporting bias comes from within the individual studies. For example, the crude hazard ratio for the association of creatinine clearance with UTI incidence is reported in

Caljouw *et al.* (0.9, 95% CI 0.5–1.7) but as creatinine clearance was not found to be significant in the multivariable model the adjusted association is not reported.[29]

The overlap in the study populations of the two large cohort studies based in Calgary, Canada could result in more similar estimates than if the study populations were independent.[26-27] Outcomes in the two studies are likely to be correlated with each other: hospitalisation with pneumonia could cause a positive blood culture, which would result in one infection being included as an outcome in both studies. This is unlikely to have a large effect, particularly in qualitative assessment of the combined evidence, as the potential overlap of person-time is limited.

Although we excluded study populations routinely treated with specialist medication (unless for kidney disease), some study populations may have been at higher risk of infection than the general population, and this may have affected the relationship of CKD to infection. For example, the cohort of patients admitted for an acute cardiovascular event or an arterial revascularisation procedure will have had a higher prevalence of co-morbidities (such as diabetes) than the general population and excluded patients with severe co-morbidities who did not survive an acute cardiovascular event, or who were not fit enough to undergo the procedure.[24] Each of the selected study populations limits the generalisability of the individual study result, but the qualitatively similar findings across the variety of study populations, and their qualitative consistency with the four studies based among the general population,[5, 16, 21, 29] support a positive association between CKD and infection risk in a variety of study populations.

A few large, high quality studies which excluded patients with ESRD have found a graded association between pre-dialysis CKD and risk of hospitalisation with infection. All studies identified in this review were compatible with a positive association of CKD with increased

infection risk. There are little data available on the association of CKD with infection incidence using less severe outcome measures than hospitalisation, and it is not possible in most studies to distinguish an effect on susceptibility to infection from an effect on the severity of infection.

The potential age-dependency of the relationship between CKD and infection is intriguing and needs further research. There is also currently no evidence on the relationship between proteinuria and infection incidence independently of glomerular filtration rate. Future studies should identify infections in the community in addition to hospitalisations for infection, characterise the association of proteinuria adjusted for glomerular filtration rate, explore the age-dependency of the association, and assess vaccine efficacy among older people with CKD.

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FIGURE LEGENDS

Figure 1: Flow chart of study selection

Figure 2: Forest plot of all estimates of the association of CKD with infection(n=~~12~~17)

~~from the nine studies included in quantitative analysis~~ from all 14 studies identified

UTI: urinary tract infection
The estimates from Higgin 1985 and USRDS 2010 did not include standard errors.
Dalrymple 2012: Presented estimates compare eGFR 45-59 with eGFR ≥90 mL/min/1.73m^2
James 2009: Presented estimates compare eGFR 45-59 with eGFR 60-104 mL/min/1.73m^2
James 2008: Presented estimates compare estimated glomerular filtration rate (eGFR) 45-59 with eGFR ≥60 mL/min/1.73m^2

Contributor statement:

All authors designed the study strategy including the search terms, inclusion and exclusion criteria. HM performed the search, study selection and data extraction. DN screened the randomly selected sample of 100 abstracts. All authors agreed quality assessment of included papers and interpretation of results by discussion. HM drafted the article, which DN and ST revised. All authors approved the final version of the manuscript.

Competing interests statement:

H I McDonald: None. S L Thomas: None. D Nitsch: None to declare.

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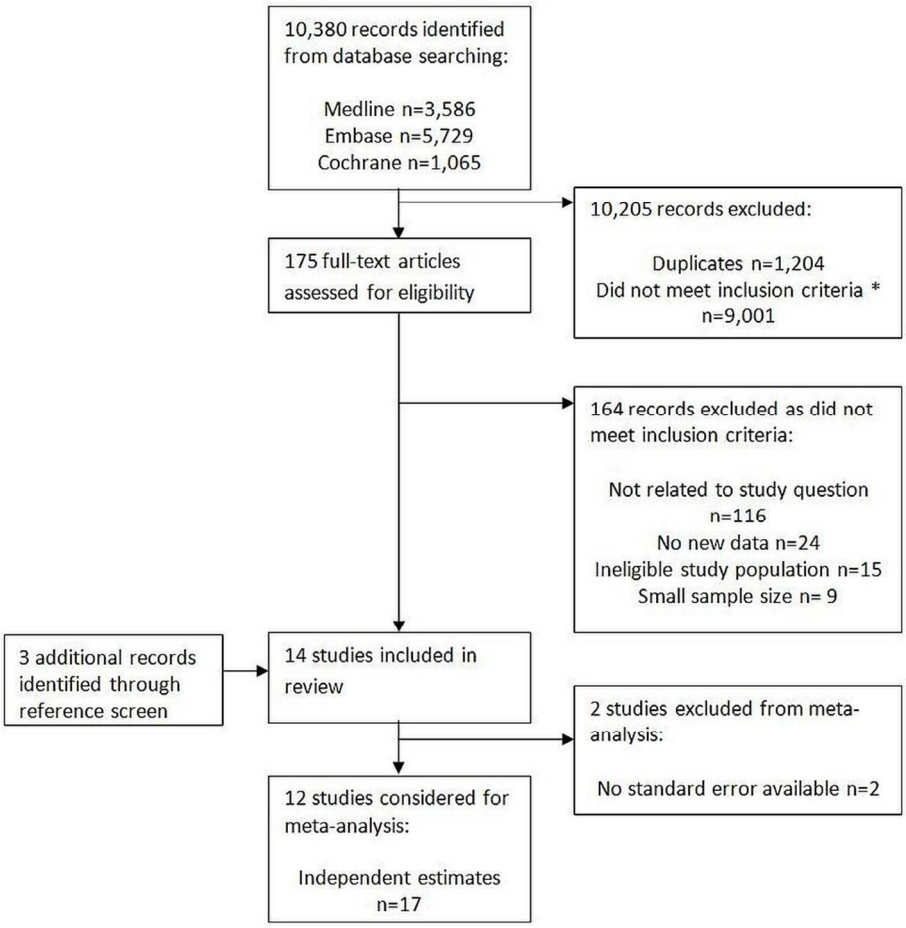
Data sharing statement:

All data, including full search terms and eligibility criteria, are available either in the article or as online supplementary material submitted with this manuscript.



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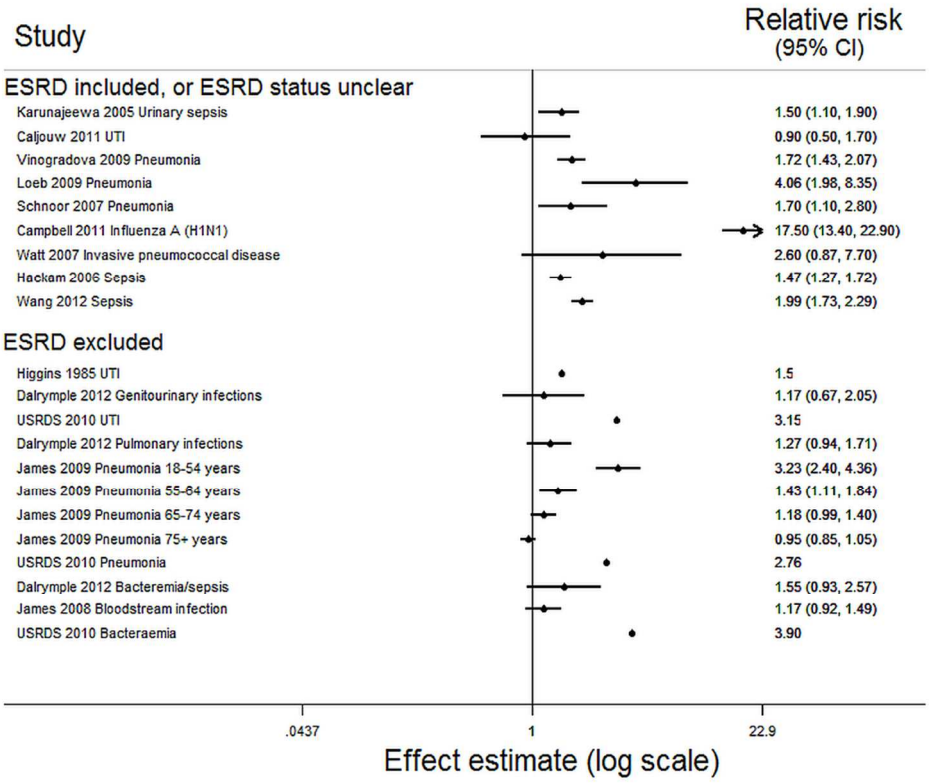

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Supplementary Table 1: Medline search strategy

	Search	Results
1	(sepsis* or septic?emia or bacter?emia or fung?emia or pneumonia* or bronchopneumonia* or pleuropneumonia* or LRTI or empy?ema or influenza* or legionell* or bacteriuri* or pyelonephriti* or cystitis* or pyelocystitis* or pyelitis* or urethriti* or UTI or meningiti* or meningococc* or encephaliti* or poliomyeliti* or septic shock).tw.	343181
2	(CNS adj4 infection*).tw.	2545
3	(central nervous adj4 infection*).tw.	3805
4	exp cerebral phaeohyphomycosis/ or central nervous system infections/ or exp brain abscess/ or exp toxoplasmosis, cerebral/ or central nervous system bacterial infections/ or exp empyema, subdural/ or exp epidural abscess/ or exp lyme neuroborreliosis/ or exp meningitis, bacterial/ or exp meningitis, escherichia coli/ or exp meningitis, haemophilus/ or exp meningitis, listeria/ or exp meningitis, meningococcal/ or exp meningitis, pneumococcal/ or exp central nervous system fungal infections/ or exp meningitis, fungal/ or exp meningitis, cryptococcal/ or exp neuroaspergillosis/ or central nervous system viral diseases/ or exp encephalitis/ or exp encephalitis, viral/ or exp encephalitis, arbovirus/ or exp encephalitis, california/ or exp encephalitis, japanese/ or exp "encephalitis, st. louis"/ or exp encephalitis, tick-borne/ or exp west nile fever/ or exp encephalitis, herpes simplex/ or exp encephalitis, varicella zoster/ or exp encephalomyelitis, equine/ or exp meningitis, viral/ or exp lymphocytic choriomeningitis/ or exp meningitis, aseptic/ or exp paraparesis, tropical spastic/ or poliomyelitis/ or exp poliomyelitis, bulbar/ or exp encephalomyelitis/ or exp meningitis/	102876
5	exp endocarditis, bacterial/ or exp endocarditis, subacute bacterial/ or exp pneumococcal infections/ or catheter-related infections/ or exp coinfection/ or communicable diseases/ or exp community-acquired infections/ or exp sepsis/ or exp bacteremia/ or exp hemorrhagic septicemia/ or exp fungemia/ or exp shock, septic/ or exp empyema/ or exp viremia/ or exp parasitemia/	139752
6	((renal or kidney) adj4 chronic adj4 failure*).tw.	21053
7	((renal or kidney) adj4 chronic adj4 disease*).tw.	15978
8	((renal or kidney) adj4 chronic adj4 insufficienc*).tw.	4448
9	((renal or kidney) adj4 chronic adj4 injury).tw.	454
10	((renal or kidney) adj4 chronic adj4 impairment*).tw.	336
11	(creatinine* or GFR or eGFR or albuminuri* or proteinuri* or microalbuminuri* or	194742

	nephropath* or glomerulo* or nephr#ti* or nephrosi* or ur?emia or ESRD or CKD or cardio-renal or Kimmelstiel-Wilson).tw.	
12	Creatinine/bl [Blood]	25724
13	Kidney Diseases/co, ep [Complications, Epidemiology]	11809
14	exp diabetic nephropathies/ or exp hypertension, renal/ or exp nephritis/ or exp anti-glomerular basement membrane disease/ or exp glomerulonephritis, iga/ or exp glomerulonephritis, membranoproliferative/ or exp glomerulonephritis, membranous/ or exp lupus nephritis/ or exp nephrosclerosis/ or exp nephrosis/ or exp renal insufficiency/ or exp cardio-renal syndrome/ or exp uremia/ or exp azotemia/ or exp proteinuria/	234481
15	kidney function tests/ or exp glomerular filtration rate/	44837
16	Animals/	4889105
17	Humans/	12139628
18	16 not (16 and 17)	3594930
19	Adult/	3567838
20	exp child/ or exp child, preschool/ or exp infant/	1849722
21	20 not (19 and 20)	1265383
22	Case reports/	1557478
23	developing countries/ or exp africa/ or cuba/ or dominica/ or dominican republic/ or grenada/ or guadeloupe/ or haiti/ or jamaica/ or exp central america/ or "gulf of mexico"/ or latin america/ or exp south america/ or exp asia, central/ or borneo/ or cambodia/ or east timor/ or indonesia/ or laos/ or malaysia/ or mekong valley/ or myanmar/ or philippines/ or thailand/ or vietnam/ or bangladesh/ or india/ or afghanistan/ or iran/ or iraq/ or jordan/ or lebanon/ or syria/ or turkey/ or yemen/ or nepal/ or pakistan/ or sri lanka/ or exp china/ or "democratic people's republic of korea"/ or mongolia/ or albania/ or latvia/ or lithuania/ or bosnia-herzegovina/ or bulgaria/ or "republic of belarus"/ or romania/ or exp russia/ or serbia/ or ukraine/ or yugoslavia/ or exp transcaucasia/ or exp indian ocean islands/ or fiji/ or papua new guinea/ or vanuatu/ or palau/ or hawaii/	620630
24	developed countries/ or bahamas/ or barbados/ or netherlands antilles/ or puerto rico/ or "trinidad and tobago"/ or "virgin islands of the united states"/ or canada/ or greenland/ or united states/ or brunei/ or singapore/ or bahrain/ or israel/ or kuwait/ or oman/ or qatar/ or saudi arabia/ or united arab emirates/ or hong kong/ or macau/ or exp japan/ or "republic of korea"/ or bermuda/ or exp australia/ or andorra/ or austria/ or belgium/ or estonia/ or croatia/ or czech republic/ or hungary/ or poland/ or	1800832

	slovakia/ or slovenia/ or finland/ or exp france/ or exp germany/ or gibraltar/ or exp great britain/ or greece/ or iceland/ or ireland/ or exp italy/ or liechtenstein/ or luxembourg/ or cyprus/ or malta/ or monaco/ or netherlands/ or portugal/ or san marino/ or exp scandinavia/ or spain/ or switzerland/ or new zealand/ or new caledonia/ or guam/	
25	23 not (23 and 24)	556094
26	Postoperative complications.sh.	263650
27	(incidence* or odds ratio or risk ratio or risk factor or relative risk).tw.	608698
28	(respiratory adj3 infection*).tw.	28563
29	(lower respiratory adj3 infection*).tw.	4633
30	(urinary adj3 infection*).tw.	28333
31	(upper urinary adj3 infection*).tw.	312
32	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	366856
33	(exp incidence/ or exp multivariate analysis/ or exp odds ratio/ or exp logistic models/ or exp risk factors/ or exp epidemiologic studies/).sh.	1799348
34	(exp pyelitis/ or exp pyelocystitis/ or exp pyelonephritis/ or exp urethritis/ or cystitis or urinary tract infections or exp pyuria/).sh.	50526
35	(respiratory tract infections or exp bronchiolitis/ or exp bronchiolitis, viral/ or empyema, pleural or exp influenza, human/ or exp legionellosis/ or exp legionnaires' disease/ or exp lung abscess/ or exp lung diseases, fungal/ or exp lung diseases, parasitic/ or exp pneumonia/ or exp bronchopneumonia/ or exp pleuropneumonia/ or exp pneumonia, bacterial/ or exp chlamydial pneumonia/ or exp pneumonia, mycoplasma/ or exp pneumonia, pneumococcal/ or exp pneumonia, rickettsial/ or exp pneumonia, staphylococcal/ or exp pneumonia, pneumocystis/ or exp pneumonia, viral/ or exp severe acute respiratory syndrome/ or exp tracheitis/ or exp whooping cough/).sh.	155035
36	1 or 2 or 3 or 4 or 5 or 28 or 29 or 30 or 31 or 34 or 35	585963
37	27 or 33	2098986
38	32 and 36 and 37	5940
39	38 not 18 not 21 not 22 not 25 not 26	3514
40	limit 39 to (english or french or german)	3163

Supplementary Table 2: Embase search strategy

	Search	Results
1	kidney failure/co, ep [Complication, Epidemiology]	13218
2	chronic kidney failure/co, ep [Complication, Epidemiology]	10827
3	exp proteinuria/co, ep [Complication, Epidemiology]	5456
4	uremia/co, ep [Complication, Epidemiology]	3030
5	glomerulus filtration rate/	43185
6	creatinine clearance/	17973
7	glomerulosclerosis/co, ep [Complication, Epidemiology]	450
8	kidney disease/co, ep [Complication, Epidemiology]	10406
9	analgesic nephropathy/co, ep [Complication, Epidemiology]	39
10	chronic kidney disease/co, ep [Complication, Epidemiology]	1733
11	diabetic nephropathy/co, ep [Complication, Epidemiology]	9683
12	allergic glomerulonephritis/co, ep [Complication, Epidemiology]	109
13	immune complex nephritis/co, ep [Complication, Epidemiology]	77
14	immunoglobulin A nephropathy/co, ep [Complication, Epidemiology]	678
15	kidney amyloidosis/co, ep [Complication, Epidemiology]	228
16	nephritis/co, ep [Complication, Epidemiology]	1053
17	glomerulitis/	456
18	Goodpasture syndrome/co, ep [Complication, Epidemiology]	31
19	immune complex nephritis/co, ep [Complication, Epidemiology]	77
20	interstitial nephritis/co, ep [Complication, Epidemiology]	901
21	lupus erythematosus nephritis/co, ep [Complication, Epidemiology]	850
22	nephrosis/co, ep [Complication, Epidemiology]	189
23	nephrotic syndrome/co, ep [Complication, Epidemiology]	2133
24	exp glomerulopathy/co, ep [Complication, Epidemiology]	5475
25	exp glomerulonephritis/co, ep [Complication, Epidemiology]	4296
26	exp kidney dysfunction/co, ep [Complication, Epidemiology]	1322
27	(creatinine* or GFR or eGFR or albuminuri* or proteinuri* or microalbuminuri* or nephropath* or glomerulo* or nephr#ti* or nephrosi* or ur?emia or ESRD or CKD or	282722

	cardio-renal or Kimmelstiel-Wilson).tw.	
28	((renal or kidney) adj4 chronic adj4 failure*).tw.	28639
29	((renal or kidney) adj4 chronic adj4 disease*).tw.	23893
30	((renal or kidney) adj4 chronic adj4 insufficienc*).tw.	6425
31	((renal or kidney) adj4 chronic adj4 injury).tw.	631
32	((renal or kidney) adj4 chronic adj4 impairment*).tw.	501
33	exp infectious pneumonia/ or bacterial pneumonia/ or chlamydial pneumonia/ or group b streptococcal pneumonia/ or legionnaire disease/ or mycoplasma pneumonia/ or pneumocystis pneumonia/ or pulmonary candidiasis/ or severe acute respiratory syndrome/ or staphylococcal pneumonia/ or virus pneumonia/	50671
34	respiratory tract infection/ or exp influenza/ or laryngotracheobronchitis/ or lower respiratory tract infection/ or parainfluenza virus infection/ or respiratory syncytial virus infection/ or viral respiratory tract infection/	106624
35	avian influenza/	5081
36	chest infection/ or pertussis/	13997
37	bronchiolitis/ or laryngotracheobronchitis/ or tracheobronchitis/	10003
38	pleura empyema/	3703
39	pyuria/ or urinary tract infection/	66023
40	candiduria/ or kidney infection/	1502
41	kidney abscess/ or pyonephrosis/	1666
42	cystitis/	11865
43	pyelonephritis/ or acute pyelonephritis/	22138
44	brain infection/ or brain abscess/ or herpes simplex encephalitis/ or herpes zoster encephalitis/ or subdural empyema/ or tick borne encephalitis/ or virus encephalitis/	24862
45	central nervous system infection/ or epidural abscess/ or poliomyelitis/	38386
46	meningitis/ or bacterial meningitis/ or exp fungal meningitis/ or haemophilus meningitis/ or lymphocytic choriomeningitis/ or subdural empyema/ or virus meningitis/	57864
47	encephalitis/ or brain ventriculitis/ or eastern equine encephalitis/ or encephalomyelitis/ or epidemic encephalitis/ or meningoencephalitis/ or panencephalitis/ or primary amebic meningoencephalitis/	47288
48	exp meningococcosis/	11231
49	exp pneumococcal infection/	5729

50	exp group b streptococcal infection/ or group b streptococcal pneumonia/	405
51	exp bacteremia/ or staphylococcal bacteremia/	29638
52	bloodstream infection/	2518
53	candidemia/	1358
54	systemic mycosis/ or fungemia/ or invasive aspergillosis/ or invasive candidiasis/	5182
55	sepsis/ or bacteremia/ or septic shock/ or septicemia/ or urosepsis/	140091
56	viremia/	12287
57	parasitemia/	6918
58	(sepsis* or septic?emia or bacter?emia or fung?emia or pneumonia* or bronchopneumonia* or pleuropneumonia* or LRTI or empy?ema or influenza* or legionell* or bacteriuri* or pyelonephritis or cystitis or pyelocystitis or pyelitis or urethriti* or meningiti* or meningococc* or encephaliti* or poliomyeliti* or septic shock).tw.	497436
59	(CNS adj4 infection*).tw.	3591
60	(central nervous adj4 infection*).tw.	4861
61	UTI.tw.	6684
62	bronchopneumonia/	8394
63	arachnoiditis/ or aseptic meningitis/ or epidemic meningitis/ or group b streptococcal meningitis/ or meningoencephalitis/ or pneumococcal meningitis/	21305
64	exp epidemiology/ or exp incidence/	1705072
65	exp risk factor/	513022
66	exp attributable risk/	1487
67	exp hazard ratio/	11362
68	statistical model/	87903
69	(odds adj1 ratio).tw.	101865
70	(relative adj2 ratio).tw.	2736
71	case report/	1892302
72	developing country/	71459
73	developed country/	25618
74	postoperative complication/ or postoperative infection/ or surgical infection/	272218
75	exp Africa/	196804

76	argentina/ or bolivia/ or brazil/ or chile/ or colombia/ or ecuador/ or french guiana/ or guyana/ or paraguay/ or peru/ or suriname/ or uruguay/ or venezuela/	98392
77	exp Central America/	15618
78	china/ or mongolia/ or philippines/	82530
79	borneo/ or cambodia/ or indonesia/ or laos/ or malaysia/ or myanmar/ or papua new guinea/ or thailand/ or timor-leste/ or viet nam/	53670
80	North Korea/	237
81	latvia/ or lithuania/	3316
82	albania/ or armenia/ or azerbaijan/ or belarus/ or "bosnia and herzegovina"/ or bulgaria/ or "georgia (republic)"/ or "macedonia (republic)"/ or romania/ or russian federation/ or serbia/ or ukraine/	83374
83	USSR/	50149
84	iran/ or iraq/ or jordan/ or lebanon/ or "turkey (republic)"/ or yemen/	49920
85	kazakhstan/ or kyrgyzstan/ or tajikistan/ or turkmenistan/ or uzbekistan/	5682
86	afghanistan/ or bangladesh/ or india/ or nepal/ or pakistan/ or sikkim/ or sri lanka/	105351
87	cuba/ or dominica/ or dominican republic/ or grenada/ or guadeloupe/ or haiti/ or jamaica/	11346
88	fiji/ or philippines/ or polynesia/	8607
89	exp Indian Ocean/	2505
90	Mexico/	28748
91	72 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90	789122
92	exp Western Europe/	911511
93	croatia/ or czech republic/ or hungary/ or poland/ or slovakia/ or slovenia/	73494
94	Estonia/	2056
95	canada/ or united states/	1031054
96	japan/ or macao/	115065
97	South Korea/	4982
98	bahrain/ or cyprus/ or israel/ or kuwait/ or oman/ or qatar/ or saudi arabia/ or united arab emirates/	37707
99	exp "Australia and New Zealand"/	129186

100	brunei darussalam/ or hong kong/ or singapore/	21427
101	73 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100	2259038
102	91 not (91 and 101)	710496
103	treatment outcome/	579285
104	editorial/	438527
105	embryo/	177038
106	infant/	533322
107	child/	1295310
108	preschool child/	469034
109	school child/	217344
110	adolescent/	1180705
111	adult/	4186945
112	105 or 106 or 107 or 108 or 109 or 110	2546570
113	112 not (112 and 111)	1658687
114	animal model/	630310
115	animal experiment/	1606715
116	nonhuman/	3807183
117	animal/	1773703
118	human/	13422168
119	114 or 115 or 116 or 117	5921124
120	119 not (119 and 118)	4747089
121	pneumonia/	97950
122	lung infection/ or hantavirus pulmonary syndrome/ or lung abscess/ or viral bronchiolitis/	21795
123	(respiratory adj3 infection*).tw.	43371
124	(lower respiratory adj3 infection*).tw.	6553
125	(urinary adj3 infection*).tw.	44177
126	(upper urinary adj3 infection*).tw.	444
127	(epidemiolog$ or incidence).tw.	878025
128	(relative adj risk*).tw.	55195
129	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	364340

	or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	
130	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 121 or 122 or 123 or 124 or 125 or 126	851259
131	64 or 65 or 66 or 67 or 68 or 69 or 70 or 127 or 128	2659100
132	129 and 130 and 131	7357
133	132 not 120 not 113 not 104 not 71 not 74 not 102	4970
134	limit 133 to (english or french or german)	4602
135	limit 134 to embase	4247

Supplementary Table 3: Cochrane library search strategy

	Search	Results
1	sepsis* or septic*mia or bacter*mia or fung*mia or pneumonia* or bronchopneumonia* or pleuropneumonia* or LRTI or empy*ma or influenza* or legionell* or bacteriuri* or pyelonephriti* or cystitis* or pyelocystitis* or pyelitis* or urethriti* or UTI or meningiti* or meningococc* or encephaliti* or poliomyeliti* or "septic shock"	19098
2	CNS near/4 infection*	47
3	"central nervous" near/4 infection*	92
4	[mh "cerebral phaeohyphomycosis"] or [mh ^"central nervous system infections"] or [mh "brain abscess"] or [mh "toxoplasmosis, cerebral"] or [mh ^"central nervous system bacterial infections"] or [mh "empyema, subdural"] or [mh "epidural abscess"] or [mh "lyme neuroborreliosis"] or [mh "meningitis, bacterial"] or [mh "meningitis, escherichia coli"] or [mh "meningitis, haemophilus"] or [mh "meningitis, listeria"] or [mh "meningitis, meningococcal"] or [mh "meningitis, pneumococcal"] or [mh "central nervous system fungal infections"] or [mh "meningitis, fungal"] or [mh "meningitis, cryptococcal"] or [mh neuroaspergillosis] or [mh ^"central nervous system viral diseases"] or [mh encephalitis] or [mh "encephalitis, viral"] or [mh "encephalitis, arbovirus"] or [mh "encephalitis, california"] or [mh "encephalitis, japanese"] or [mh "encephalitis, st. louis"] or [mh "encephalitis, tick-borne"] or [mh "west nile fever"] or [mh "encephalitis, herpes simplex"] or [mh "encephalitis, varicella zoster"] or [mh "encephalomyelitis, equine"] or [mh "meningitis, viral"] or [mh "lymphocytic choriomeningitis"] or [mh "meningitis, aseptic"] or [mh "paraparesis, tropical spastic"] or [mh ^poliomyelitis] or [mh "poliomyelitis, bulbar"] or [mh encephalomyelitis] or [mh meningitis]	1015
5	[mh "endocarditis, bacterial"] or [mh "endocarditis, subacute bacterial"] or [mh "pneumococcal infections"] or [mh ^"catheter-related infections"] or [mh coinfection] or [mh ^"communicable diseases"] or [mh "community-acquired infections"] or [mh sepsis] or [mh bacteremia] or [mh "hemorrhagic septicemia"] or [mh fungemia] or [mh "shock, septic"] or [mh empyema] or [mh viremia] or [mh parasitemia]	4033
6	respiratory near/3 infection*	4398
7	urinary near/3 infection*	3732
8	[mh pyelitis] or [mh pyelocystitis] or [mh pyelonephritis] or [mh urethritis] or [mh ^cystitis] or [mh ^"urinary tract infections"] or [mh pyuria]	2143
9	[mh ^"respiratory tract infections"] or [mh bronchiolitis] or [mh "bronchiolitis, viral"] or [mh ^"empyema, pleural"] or [mh "influenza, human"] or [mh legionellosis] or [mh	5402

	"legionnaires' disease"] or [mh "lung abscess"] or [mh "lung diseases, fungal"] or exp [mh "lung diseases, parasitic"] or [mh pneumonia] or [mh bronchopneumonia] or [mh pleuropneumonia] or [mh "pneumonia, bacterial"] or [mh "chlamydial pneumonia"] or [mh "pneumonia, mycoplasma"] or [mh "pneumonia, pneumococcal"] or [mh "pneumonia, rickettsial"] or [mh "pneumonia, staphylococcal"] or [mh "pneumonia, pneumocystis"] or [mh "pneumonia, viral"] or [mh "severe acute respiratory syndrome"] or [mh tracheitis] or [mh "whooping cough"]	
10	(renal or kidney) near/4 chronic near/4 failure*	4476
11	(renal or kidney) near/4 chronic near/4 disease*	1647
12	(renal or kidney) near/4 chronic near/4 insufficienc*	510
13	(renal or kidney) near/4 chronic near/4 injury	29
14	(renal or kidney) near/4 chronic near/4 impairment*	34
15	creatinine* or GFR or eGFR or albuminuri* or proteinuri* or microalbuminuri* or nephropath* or glomerulo* or nephr?ti* or nephrosi* or ur*mia or ESRD or CKD or cardio-renal or Kimmelstiel-Wilson	16810
16	[mh ^creatinine/BL]	2042
17	[mh ^"kidney diseases"/CO,EP]	341
18	[mh "diabetic nephropathies"] or [mh "hypertension, renal"] or [mh nephritis] or [mh "anti-glomerular basement membrane disease"] or [mh "glomerulonephritis, iga"] or [mh "glomerulonephritis, membranoproliferative"] or [mh "glomerulonephritis, membranous"] or [mh "lupus nephritis"] or [mh nephrosclerosis] or [mh nephrosis] or [mh "renal insufficiency"] or [mh "cardio-renal syndrome"] or [mh uremia] or [mh azotemia] or [mh proteinuria]	7117
19	[mh ^"kidney function tests"] or [mh "glomerular filtration rate"]	2417
20	{or #1-#9}	25511
21	{or #10-#19}	21120
22	{and #20-#21}	1422
23	incidence* or "odds ratio" or "risk ratio" or "risk factor" or "relative risk"	69239
24	[mh incidence] or [mh "multivariate analysis"] or [mh "odds ratio"] or [mh "logistic models"] or [mh "risk factors"] or [mh "epidemiologic studies"]	122866
25	{or #23-#24}	165844
26	{and #22, #25}	953

Supplementary Table 4: Inclusion and exclusion criteria for determining study eligibility

	Included	Excluded
Participants	Adult human participants.	Populations exclusively of: - pregnant women; - kidney transplant recipients or patients receiving renal replacement therapy; - patient groups usually managed in secondary care unless this was for chronic kidney disease, or routinely treated with immunosuppressive medication.
Study settings	High income countries (World Bank classification).(13) Community settings, including adults living in institutional care.	
Exposure of interest	Chronic acquired kidney disease, indicated by any of the following: - medical diagnosis; - reduced estimated glomerular filtration rate; - reduced creatinine clearance; - elevated creatinine; - proteinuria, micro- or macro-albuminuria; - renal structural abnormalities. Where there was no 'unexposed' group without kidney disease, comparison between stages 1-2 and stages 3-5 CKD was accepted.	
Outcomes of interest	Incidence rate ratio, risk ratio or odds ratio estimates of the effect of kidney disease on any of the following community-acquired acute infections: - lower respiratory tract infections; - urinary tract infections (UTIs); - central nervous system infections; - sepsis. Urinary catheter-associated UTIs from community settings, and incidence of severe disease (such as hospitalisation for infection) were accepted.	Outcomes not accepted: - infection prevalence; - hospital-associated infection rates; - post-operative follow up outcomes; - incidence of infection-related mortality; - prognosis among infected patients.
Study methodology	Trials, case-control studies, cohort studies or other observational study designs containing original data. Relevant review articles without original data were identified for reference list screening.	Case reports. Descriptive studies without a comparison group. Studies with fewer than 30 participants in either the exposed or unexposed categories.
Publication details	Any publication date. Languages: English, German, French.	

Supplementary Table 5: Quality assessment of studies including rationale (n=14)

	Case-control studies				Cohort studies									
	Vinogradova 2009 (16)	Watt 2007 (17)	Loeb 2009 (18)	Schnoor 2007 (19)	Higgins 1989 (22)	Hackam 2006 (24)	Dalrymple 2012 (23)	Karunajeewa 2005 (25)	James 2008 (26)	James 2009 (27)	Wang 2012 (28)	Caljouw 2011 (29)	Campbell 2011 * (21)	USRDS 2010(20)
Selection bias														
Selection of controls [1]	Low: matched selection of primary care registered patients	Low: neighbourhood controls selected systematically by proximity	Low: random digit dialling of hospital catchment area residents	Low: random selection from population register	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study
Participation bias [2]	Low: automatic participation	Low: participation 83% of cases, 84% of controls	Uncertain: participation rate not reported	High: Participation <60% overall	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study
Loss to follow up [3]	N/A: case-control study	N/A: case-control study	N/A: case-control study	N/A: case-control study	Uncertain: not reported and clinically determined. May be differential, but study period only one year.	Low: automated follow up	Low: >80% follow up	Low: automated follow up	Low: automated follow up	Low: automated follow up	Low: >80% follow-up	Low: followed up 479 of 551 participants alive aged 86 years: 86% follow up	Low: active case-finding applied to national census figure (no follow up required)	Low: automated follow up
Non-differential misclassification of exposure [4]	High: relies on medical diagnosis of chronic renal disease in medical records.	High: relied on medical diagnosis of chronic renal disease in medical records.	High: ascertained medical diagnosis of chronic renal disease in participant interview.	High: ascertained medical diagnosis of chronic renal disease in questionnaire for controls	Uncertain: not reported when creatinine measured.	High: relies on medical diagnosis of chronic renal disease in medical records.	Low: determined prospectively from blood results	Low: determined prospectively from test results	Low: determined prospectively from blood results	Low: determined prospectively from blood results	Low: determined prospectively from blood results	Low: determined prospectively from blood results	High: relies on medical diagnosis of chronic renal disease in medical records.	High: relies on medical diagnosis of chronic renal disease in insurance claims
Information bias: exposure														
Recall bias [5]	Low: kidney disease diagnosis ascertained from pre-	Low: kidney disease diagnosis ascertained from pre-	High: ascertained medical diagnosis of kidney	High: ascertained medical diagnosis of kidney	Low: determined from serum creatinine with clear	Low: kidney disease diagnosis ascertained from pre-	Low: determined prospectively from blood results.	Low: determined prospectively from test results.	Low: determined prospectively from blood results.	Low: determined prospectively from blood results.	Low: determined prospectively from blood results.	Low: determined prospectively from blood results.	Low: kidney disease diagnosis ascertained from pre-	Low: kidney disease diagnosis ascertained from pre-

	existing medical records	existing medical records	disease in participant interview in hospital for cases and at home for controls	disease at home for controls	cut-off (objective measure)	existing medical records							existing medical records	existing insurance records
Observer bias [6]	Low: used pre-specified codes to define kidney disease status	Uncertain: Medical record abstractors not blinded to case-control status and criteria for assigning kidney disease status not reported	High: interviewers aware of case status (interviewed in hospital) or control status (telephone interview at home)	High: decision to list diagnosis of kidney disease in case report made in context of illness for cases	Low: determined from serum creatinine with clear cut-off (objective measure)	Uncertain: source of kidney disease status data not reported. If hospital records are used, decision to list diagnosis in discharge record made in context of illness for cases.	Low: determined from serum cystatin C (objective measure)	Low: determined from blood and urine test results (objective measure)	Low: determined from serum creatinine (objective measure)	Low: determined from serum creatinine (objective measure)	Low: determined from serum creatinine (objective measure)	Low: determined from serum creatinine (objective measure)	High: decision to list diagnosis of kidney disease in case report made in context of illness for cases	Low: used pre-specified codes to define kidney disease status
Ascertainment [7]	Low: chronic kidney disease diagnosis would have to predate current acute infection	Low: chronic kidney disease diagnosis would have to predate current acute infection	Low: chronic kidney disease diagnosis would have to predate current acute infection	High: ascertainment entirely different for cases than controls	Uncertain: not reported when creatinine measured, or whether this is recurrent/ prompted by illness	Uncertain: source of kidney disease status data not reported. If hospital records used, patients with infection-related hospitalisations more likely to have CKD status recorded.	Low: all participants tested at baseline.	Low: participants monitored annually.	Low: baseline measure used (that only patients with a result were eligible was considered a limitation to generalisability)	Low: sensitivity analysis using only the baseline creatinine test found similar results to the last-carried forward method	Low: all participants tested at baseline.	Low: all participants tested at baseline.	High: ascertainment entirely different for cases than non-cases	Low: kidney disease status ascertained in year prior to study
Non-differential misclassifica	Low: medical diagnosis of severe	Low: active surveillance with clear	Low: severe outcome with clear	Low: severe outcome with clear	Uncertain: methods for ascertaining	Low: severe outcome with widely	Low: severe outcome with clear	Low: severe outcome with widely	Low: severe outcome with clear	Low: severe outcome with widely	Low: severe outcome with clear	Uncertain: kidney disease	Uncertain: sending of PCR test	Low: severe outcome unlikely to

tion of outcome [8]	outcome	criteria	criteria	criteria	infection not reported	accepted clinical criteria	criteria	accepted clinical criteria	criteria	accepted clinical criteria	criteria	status may affect healthcare attendance for minor illness such as UTI	during influenza pandemic vulnerable to be influenced by kidney disease status	be missed
nformation bias: outcome														
Recall bias [9]	Low: cases identified from medical records based on GP diagnosis	Low: cases identified by laboratory surveillance	Low: cases determined by medical diagnosis in hospital	Low: Low: realtime reporting system through established surveillance network	Uncertain: methods for ascertaining infection not reported	Low: monitoring of all hospital discharge reports	Low: semi-annual cohort monitoring	Low: monitoring of all hospital discharge reports	Low: monitoring of all biochemistry results	Low: monitoring of all hospital discharge reports	Low: semi-annual cohort monitoring	Low: annual clinician interviews supplemented with medical record review	Low: realtime case finding system through laboratory results	Low: monitoring of all hospital insurance claims
Observer bias [10]	Low: clinical diagnosis of severe outcome unlikely to be severely affected by kidney disease comorbidity	Low: Laboratory based surveillance system with clear criteria for cases	Low: CKD status unlikely to severely affect physician application of clear criteria	Low: surveillance system with clear criteria for cases	Uncertain: standard definition of APN is vague and not reported whether any observer blinded to renal status	Low: kidney disease status unlikely to affect choice of hospital diagnosis code for severe outcome	Low: kidney disease status unlikely to affect choice of hospital diagnosis code for severe outcome	Low: kidney disease status unlikely to affect choice of hospital diagnosis code for severe outcome	Low: objective definition of outcome independent of exposure status	Low: kidney disease status unlikely to affect choice of hospital diagnosis code for severe outcome	Low: CKD status unlikely to severely affect application of clear criteria	Low: kidney disease status unlikely to strongly influence diagnosis of UTI at age 86-89 years, given case criteria include symptoms and urinary analysis	Low: objective criteria for cases once tested	Low: kidney disease status unlikely to affect choice of hospital diagnosis code for severe outcome
Ascertainment [11]	Low: kidney disease status unlikely to affect primary care attendance with severe outcome	Low: active surveillance with clear criteria, testing for IPD unlikely to be markedly influenced by CKD	Low: kidney disease status unlikely to affect hospital attendance with severe outcome	Low: kidney disease status unlikely to affect primary care or hospital attendance with severe outcome	Uncertain: methods for ascertaining infection not reported	Low: kidney disease status unlikely to affect diagnosis of severe outcome with widely accepted	Low: kidney disease status unlikely to affect hospital attendance with severe outcome	Low: kidney disease status unlikely to affect hospital attendance with severe outcome	Low: sending of blood culture unlikely to be influenced by kidney disease in context of severe	Low: kidney disease status unlikely to affect diagnosis of severe outcome with widely accepted	Low: kidney disease status unlikely to affect hospital attendance with severe outcome	Uncertain: kidney disease status may affect healthcare attendance for minor illness such as UTI	Uncertain: sending of PCR test during influenza pandemic vulnerable to be influenced by	Low: kidney disease status unlikely to affect hospital attendance with severe outcome

		status in context of known high incidence among the Navajo Nation				clinical criteria			illness	clinical			comorbiditie s	
Confounding [2]	Low: controls matched to cases on age and sex, estimate adjusted for wide range of confounders including diabetes[13]	Low: controls matched for age and sex. Diabetes eligible for inclusion in final model [14]	Low. Age, sex and diabetes eligible for inclusion in final model [15]	High: unadjusted	High: unadjusted estimate. In particular, high immunosupp ressant use among the study population	Low: adjusted for age, sex, nature of index event, charlson index, healthcare use, and other comorbiditie s	Low: adjusted for age, sex, race, smoking, BMI, diabetes mellitus, and multiple co-morbidities.	High: no adjustment for sex [16]	Low: adjusted for age, sex, diabetes, comorbidity score, care in a dedicated renal clinic	Low: adjusted for age, sex, socio-economic status, ethnicity, diabetes mellitus, Charlson comorbidity score	High: adjusted for age, sex, alcohol, smoking and demographic factors but no comorbitidie s.	High: no adjustment for sex or diabetes [17]	High: adjusted for age only	High: unadjusted [19]
Reverse causation [18]	Low: pre-existing kidney disease reported at time of infection	Low: pre-existing kidney disease reported at time of infection	Low: pre-existing kidney disease reported at time of infection	Low: pre-existing kidney disease reported at time of infection	Uncertain: Timing of creatinine measuremen t relative to infections not specified	Low: chronic renal failure should not be diagnosed within one hospital episode for infection	Low: baseline serum cystatin C used	Low: serum biochemistry tested at screening	Low: baseline creatinine used	Low: only followed to first outcome event, creatinine result predates qualifying infection	Low: baseline creatinine used	Low: baseline creatinine used	Low: pre-existing kidney disease reported at time of infection	Low: kidney disease status established in year prior to study

*The unusual design of the artificial cohort study by Campbell *et al*. is worth clarification. During the 2009–2010 influenza pandemic, hospitalised cases of laboratory confirmed pandemic influenza A (H1N1) were reported by a laboratory-based national surveillance system. The surveillance report, completed by the microbiologist, asked whether the case had a diagnosis of CKD. Denominators for infection rates were obtained from primary care registers of patients eligible for pandemic influenza vaccination by virtue of a CKD diagnosis (for CKD): and from the national census (for non-CKD).(29) The effect of CKD on influenza may be overestimated in this study, because CKD was advertised as a possible risk factor for pandemic influenza to encourage vaccine uptake among this group, and patients with flu-like symptoms could have been more likely to attend hospital or be tested for pandemic influenza A (H1N1) if they had a diagnosis of CKD.

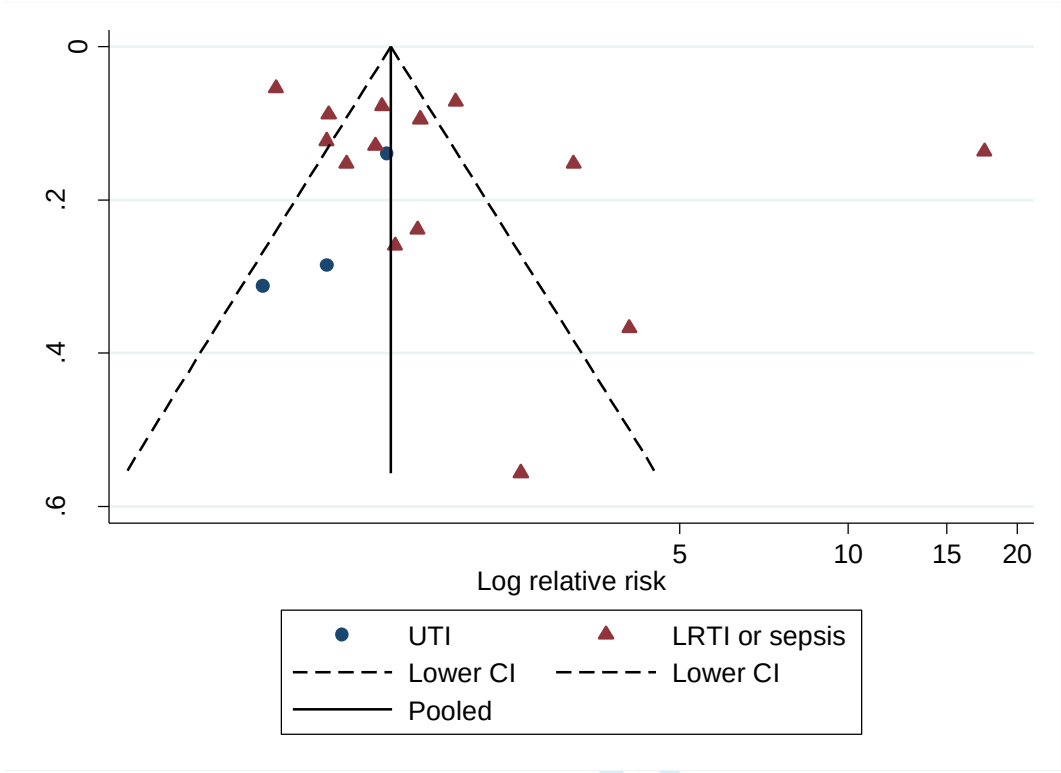
1. High risk: probability of selection as a control likely to be affected by kidney disease status (known or unknown).

Low risk: controls selected using random sampling (or other system unlikely to be biased by kidney disease status) from the population from which the cases arose.

2. Low risk: (1) automated participation (e.g. medical record review), or (2) ≥80% participation, or (3) 70-80% participation with a comparison (min age, sex, death/morbidity) showing similar characteristics between those included and those not included in the study.
3. Low risk: (1) automated follow up (e.g. through record linkage), or (2) ≥80% follow up, or (3) 70-80% follow up with a comparison (min age, sex, death/morbidity) showing similar characteristics between those included and those not included in the study.
4. High risk: allocation of kidney disease status relies on existing kidney disease having been diagnosed as part of routine medical care.
Low risk: All members of study assessed for kidney disease at baseline.
5. High risk: kidney disease status defined by patient recall of CKD diagnosis in context of recent infection.
6. High risk: kidney disease status defined by observer unblinded to case status, without clear objective criteria to apply.
7. High risk: participants with infections are more or less likely to be tested for kidney disease.
8. Low risk: Active screening for infection, or severe outcome unlikely to be missed or presents validation results of >70% sensitivity and specificity
9. High risk: infection status defined by patient recall of infection in context of kidney disease e.g. participants with kidney disease asked to recall infections while at renal clinic.
10. High risk: infection status defined by observer in context likely to be influenced by kidney disease status (assumed that clinical diagnosis of severe infections was unlikely to be strongly influenced by awareness of CKD as a comorbidity but that less severe infections may be influenced by this in the absence of clear diagnostic criteria).
11. High risk: ascertainment of infections likely to be influenced by kidney disease status (assumed that attendance to healthcare facility for severe infections was unlikely to be strongly influenced by awareness of CKD as a comorbidity but that attendance for less severe infections may be influenced by this in the absence of active surveillance).
12. Low risk: At least age, sex and diabetes must have been eligible and considered for the final model.
13. Controls matched to cases on age at index data (within 1 year), sex, general practice, and calendar time. Estimate adjusted for smoking status, Townsend deprivation score, use of influenza vaccine in previous 12 months, use of pneumococcal vaccine in previous 5 years, number of years of medical records data available in database, and comorbidities including: diabetes, chronic heart disease, chronic respiratory disease, asplenia, cerebrospinal shunt, chronic liver disease, sickle cell disease or coeliac disease, cochlear implant, HIV/AIDS, immunosuppression, stroke or transient ischaemic attack, rheumatoid arthritis, Parkinson's disease, multiple sclerosis, dementia, osteoporosis, and any cancer.
14. Controls matched for age and sex. Diabetes eligible for inclusion in final model, which was adjusted for age, pneumococcal vaccine, congestive heart failure, alcohol use, BMI and unemployment.
15. Age, sex and diabetes eligible for inclusion in final model. Final model adjusted for age, non-English language at home, living in a detached house, living alone, congestive heart failure, chronic obstructive pulmonary disease, dysphagia, Barthel index of functional status, immunosuppressive medications, nutritional score, tobacco use, alcohol use, and exposure to fumes.

16. The best adjusted estimate for urinary sepsis is adjusted for asymptomatic bacteriuria and age, and restricted to diabetics, but not adjusted for sex.
17. High risk: age-restricted and stratified by long term care facility (LCTF) residency, but no management of confounding by sex or co-morbidities.
18. High risk: exposure defined after the infection defined as the study outcome.
19. Rate ratios for hospitalisation with UTI, pneumonia and bacteraemia/ sepsis unadjusted. Rate ratios for hospitalisation with any infection calculated as the ratio of the rate among participants with CKD, compared with no CKD, each rate having been adjusted for gender, prior hospitalisation, ASHD, CHF, CVA, PVD, dysrhythmia, other cardiac disease, diabetes, COPD, hypertension, liver disease, gastrointestinal disease, cancer, and anemia.

Supplementary Figure 1: Funnel plot showing the relationship between relative risk and standard error for the 17 estimates from all 12 studies considered for meta-analysis (all infections combined)



UTI = urinary tract infection

Other infections comprised lower respiratory tract infections and sepsis.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8 and Appendix Table 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix Tables 1-3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (I^2) for each meta-analysis.	10

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12 and figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12 and Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14 and Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13 and Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13 and Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14 and Appendix Figure 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	22,24
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	25-26
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	31

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Chronic kidney disease as a risk factor for acute community-acquired infections in high income countries: a systematic review

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Title: Chronic kidney disease as a risk factor for acute community-acquired infections in high-income countries: a systematic review

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Body: 3,206 words

ABSTRACT:

Objectives: A systematic review of the association of pre-dialysis chronic kidney disease (CKD) with the incidence of acute, community-acquired infections.

Design: We searched Medline, Embase and Cochrane databases (inception to 16/01/2014) for studies analysing the association of pre-dialysis kidney disease with the incidence of acute, community-acquired urinary tract infection (UTI), lower respiratory tract or central nervous system infections, or sepsis. Studies were required to include at least 30 participants with and without kidney disease.

Setting & participants: Community-based populations of adults in high income countries.

Outcome measures: Acute, community-acquired urinary tract infection (UTI), lower respiratory tract or central nervous system infections, or sepsis.

Results: We identified 14 eligible studies. Estimates from two studies lacked 95% confidence intervals and standard errors. The remaining 12 studies yielded 17 independent effect estimates. Only three studies included infections managed in the community. Quality assessment revealed that probable misclassification of kidney disease status and poor adjustment for confounding were common. There was evidence from a few large high quality studies of a graded association between pre-dialysis CKD stage and hospitalisation for infection. One study found an interaction with age, with a declining effect of CKD on infection risk as age increased. There was evidence of between-studies heterogeneity (I^2=96.5%, p<0.001) which persisted in subgroup analysis, and thus meta-analysis was not performed.

Conclusions: Pre-dialysis kidney disease appears to be associated with increased risk of severe infection. Whether pre-dialysis kidney disease increases the susceptibility to infections and whether age modifies this association remains unclear.

ARTICLE SUMMARY

Article focus:

- This review sought to assess systematically whether pre-dialysis chronic kidney disease (CKD) is a risk factor for the incidence of acute, community-acquired urinary tract infection (UTI), lower respiratory tract infection (LRTI) central nervous system (CNS) infection, or sepsis, among community-based adults in high income countries.
- Any increased risk of infection incidence at early stages of CKD would affect a large and growing number of patients. Awareness and quantification of this risk could have benefits for patient management, more effective vaccination strategies and healthcare planning.

Key messages:

- We identified major gaps in the literature including: a scarcity of high-quality studies on this research topic; a lack of studies using less severe outcome measures than hospitalisation, to allow any association of CKD with susceptibility to infection to be distinguished from an association with severity of infection; and a lack of data on the relationship between proteinuria and infection incidence independently of glomerular filtration rate.
- All studies were consistent with a positive association between CKD and infection risk.

Strengths and limitations of this study:

- This study used a sensitive search strategy, with a broad definition of kidney disease, for a thorough and inclusive search.

- Between-study heterogeneity, and the low quality of many of the studies, limit interpretation of results of the studies currently available.

INTRODUCTION

Chronic kidney disease (CKD) is common, and its prevalence is increasing.[1] Infection is a major cause of mortality in end-stage renal disease (ESRD) and hospitalisation at all stages of CKD. The second commonest cause of death among ESRD patients in the US is septicaemia, and patients with ESRD are at increased risk of death from infection compared to the general population.[2-4] Both ESRD and pre-dialysis patients with CKD in the US are at higher risk of hospitalisation for infection than the general population.[2, 5-6] Pre-dialysis CKD has been found to increase mortality among patients hospitalised with infections.[7]

Increased mortality and hospitalisation from infection could be driven by increased severity of infection, i.e. once an infection is present, the course of the associated illness is more severe, or increased incidence, i.e. CKD may make people more susceptible to develop an infection. Patients with CKD display impaired host immunity: reduced vaccination responsiveness is observed at all stages of CKD.[8]

Among ESRD patients, aspects of dialysis, such as vascular and peritoneal access for dialysis, may be a risk factor for infection incidence and severity. However, this does not tell the whole story, and only 23% of infection-related hospitalisations among haemodialysis patients in the US were identified as related to vascular access in the HEMO study.[9] Risk factors for infection identified among ESRD patients which are not related to renal replacement therapy, and could apply at all stages of pre-dialysis CKD, include: the causes and treatment of kidney disease; co-morbidities; reduced vaccine effectiveness; and high levels of exposure to health care facilities.[10]

If there is an increased risk of infection incidence at early stages of CKD, this would affect a large and growing number of patients. Awareness and quantification of this risk could have

benefits for patient management, more effective vaccination strategies and healthcare planning.

Narrative reviews have concluded that it is likely that CKD in itself increases infection incidence, but reported a lack of evidence.[10-12] We are not aware of any relevant systematic literature reviews of the effect of CKD on infection incidence.

This review sought to assess systematically whether pre-dialysis CKD is a risk factor for the incidence of acute, community-acquired urinary tract infection (UTI), lower respiratory tract infection (LRTI) central nervous system (CNS) infection, or sepsis, among community-based adults in high income countries.

METHODS

Data Sources and Searches

One reviewer (HM) searched the Medline and Embase databases, and the Cochrane library, from inception to 16 January 2014. The search strategies combined text words and MeSH terms for three concepts: acute community-acquired infection (either sepsis, UTI, LRTI or CNS infection); kidney disease; and relative risk. We used search terms to identify studies among adult humans in high-income countries (according to the World Bank classification),[13] and limited the search to articles in English, French or German. The full strategies are available in **Supplementary Tables 1-3**.

We searched the reference lists of all included studies and any pertinent review articles to identify further eligible studies.

Study Selection

One reviewer (HM) screened titles and abstracts, reviewed the full-text of identified studies and made initial decisions on eligibility according to pre-specified inclusion criteria (**Supplementary Table 4)**. Any borderline cases were discussed between HM, DN and ST. A second reviewer (DN) checked a sample of 100 abstracts, selected randomly after de-duplication of records, and a kappa statistic was calculated to describe agreement in selection of studies.

Eligible studies analysed the effect of pre-dialysis kidney disease on the relative risk of at least one of the four specified acute, community-acquired infections among community-based adults in high-income countries. We excluded study populations managed in secondary

care (unless for kidney disease), routinely treated with immunosuppressants, or exclusively of pregnant women, as these groups have a raised risk of infection, and the relationship of CKD to infection risk may be different among these groups compared to that in the general adult population in primary care. Ascertainment of CKD, as a silent disease, and, to a certain extent, ascertainment of acute community-acquired infections, are dependent on high levels of monitoring and good access to healthcare, so we restricted our search to high-income countries. Chronic infections such as tuberculosis were not included, as the relationship between CKD and chronic infection is very likely to differ from that between CKD and acute infections, which was our focus in this review.

To maximise the sensitivity of our search strategy, we accepted a wide range of definitions of kidney disease, including: medical diagnosis of kidney disease, reduced estimated glomerular filtration rate or creatinine clearance, elevated creatinine, proteinuria, micro- or macro-albuminuria, and renal structural abnormalities. We also accepted definitions which included some patients with ESRD among the patients with CKD, but excluded definitions which were exclusively patients receiving renal replacement therapy.

Outcomes of interest were relative risk estimates of acute community-acquired LRTIs, UTIs, CNS infections or sepsis. We accepted outcomes describing incidence of severe infections (such as hospitalisation with pneumonia).

We restricted our search to published studies which were sufficiently large to include at least 30 participants with and without kidney disease, to allow reasonable precision of the study estimate. Detailed eligibility criteria are listed in **Supplementary Table 4.**

Data Extraction and Quality Assessment

Data were extracted from relevant studies using a pre-specified collection form. Study characteristics extracted included study design, data source, any participant exclusion criteria, number of participants, age, gender, baseline renal function, definition of renal impairment, definition of the outcome infection. An estimate of relative risk (rate ratio, risk ratio or odds ratio) with any measures taken to address confounding was extracted from each eligible independent analysis in each study. Studies with no confidence intervals and for which the standard error was not calculable from the data presented were included in the review but not considered for meta-analysis.

When multiple estimates were available from a study but were not independent, a single estimate was identified for potential meta-analysis by selecting the estimate best adjusted for confounding, using the most recent data, comparing the level of CKD most common in the general population with no CKD.

Study quality was assessed using a pre-specified tool adapted from Higgins *et al*. for observational studies.[14] Studies were assigned a high, low or uncertain risk of each of: selection bias, non-differential measurement error for exposure and outcome, information bias in exposure and outcome, confounding and reverse causation. The minimum requirement for a low risk of bias from confounding was appropriate management of confounding by age, sex and diabetes. Specific criteria used are detailed in **Supplementary Table 5**.

Data Synthesis and Analysis

The relationship between CKD and UTIs was considered likely to differ from that of CKD to other infections, due to potential reverse causality. For example, repeat UTIs may cause kidney disease, or structural kidney disease may be identified though investigation of repeat UTIs. Therefore in all quantitative analysis, UTIs were analysed separately from other infections.

Estimates were examined for heterogeneity using Cochran's Q statistic and the I^2 statistic as described by Higgins *et al*.[15] If I^2 was less than 50% and Cochran's Q statistic $p \geq 0.1$, fixed-effects meta-analysis was considered for each of the two categories (UTI, and other infections). Funnel plots were constructed to look for publication bias. All analysis was conducted using STATA version 12.0.

RESULTS

The database searches identified 10,380 citations, of which 1,204 were duplicates (**Figure 1**). Both reviewers had 100% agreement on which studies to extract for full-text analysis from screening a random sample of 100 abstracts (Cohen's K= 1).

We identified 14 eligible studies, with varying study characteristics (**Table 1**). Four studies were case-control studies,[16-19] and ten were cohort studies.[20-29] Seven studies investigated a range of risk factors for infection,[16-19, 21, 28-29] two studies reported the effect of CKD on infection as a confounder of the effect of interest,[24-25] and five studies investigated the effect of CKD on infection risk as their primary research question.[5, 20, 22, 26-27]

Seven studies were based among the general population.[5, 16, 19, 21, 23, 28-29] Other study populations included: attendants at a specialist renal clinic,[22] patients with diabetes mellitus,[25] patients admitted to hospital for an acute cardiovascular event or an arterial revascularisation procedure, [24] and the Navajo Nation – a population which experiences 3–5 times higher rates of invasive pneumococcal disease than the general US population.[17] The population of the cohort studies in Calgary, Canada were adults with a serum creatinine test result available in their medical records.[26-27] There is some overlap in the study populations of these two cohort studies: residents aged over 65 years with a serum creatinine measurement between 1 July 2001 and 31 December 2001 and also between 1 July 2003 and 30 June 2004 would have been included in both studies for the period from the second creatinine measurement until 31 December 2004.[26-27]

Definitions of kidney disease included medical diagnoses of chronic renal disease, elevated creatinine levels, impaired creatinine clearance, and structural abnormalities of the kidney. Five studies excluded patients with ESRD, and one specified the number included, but for the

remaining eight studies it was unclear how many of the included patients received renal replacement therapy **(Table 1)**.

Three studies recorded infections diagnosed in primary care or outpatients,[16, 19, 29] two recorded infections identified from a positive culture result,[17, 26] one included infections diagnosed in the emergency department,[18] seven required hospital admission for infection,[5, 21, 23-25, 27-28] and for one study the definition and severity of infection was unclear.[22]

For two studies, the results extracted had no confidence interval or standard error and these could not be calculated from the reported data. From the remaining 12 studies, 17 independent effect estimates with standard errors were available for meta-analysis, among which UTI was the outcome in three estimates.

For all infections there was strong evidence of considerable heterogeneity (Cochran's Q statistic p<0.001, I^2=96.5%). This persisted when estimates for UTIs were excluded (p<0.001, I^2=97.2%), when considering LRTIs alone (p<0.001, I^2=98.2%), when limited to cohort studies (p<0.001, I^2=97.3%), and when stratified by exclusion of patients with ESRD (ESRD excluded, p<0.001, I^2=88.9%: ESRD not excluded p<0.001, I^2=97.2%). Due to this heterogeneity, meta-analysis was not performed.

All results are displayed in the Forest plot (**Figure 2**). Despite the quantitative heterogeneity, the results were qualitatively similar: all estimates were compatible with a positive association between kidney disease and infection. The four studies which compared different stages of CKD found a graded association of increased risk of infection with more severe CKD. These studies all excluded patients with end-stage renal disease.[22-23, 26-27] One study found that the effect of CKD on infection risk was modified by age, with a declining effect of CKD on infection risk as age increased.[27] This effect was consistent with the

lower effect of CKD on UTI incidence found among 86–90 year olds (0.90, 95% CI 0.50–1.77) compared with an adult study population with a mean age of 66 years (1.50, 95% CI 1.10–1.90).[25, 29]

The funnel plot was sparsely populated, with widely scattered effect estimates, and provides no clear evidence for or against publication bias (**Supplementary Figure 1**).

Study quality was variable. Relying on routine medical diagnosis introduced a potential source of misclassification of kidney disease status for seven studies.[5, 16-19, 21, 24] There was variable adjustment for confounding, from unadjusted crude estimates to estimates adjusted for a range of comorbidities, demographic and socio-economic factors. Six studies did not meet this review's minimal requirements.[19, 21-22, 25, 28-29] The summarised results are displayed in **Table 2**, and the full quality assessment is in **Supplementary Table 5**.

Table 1: Characteristics of eligible studies (n=14)

Case-control studies												
	Study			Kidney disease			Infection			Kidney disease prevalence		Odds ratio (95% CI)
	Date	Setting	Population Age % Female	Defined	ESRD included	Ascertained	Type	Defined	Ascertained	Cases	Controls	
Vinogradova 2009[16]	1996 - 2005	UK	General population Any age Median age band 45-64 years Cases 49.3%, controls 49.1%	Chronic renal disease	Unclear	Primary care medical record diagnosis code in previous 5 years	Pneumonia	Medical diagnosis recorded in primary care records	READ code in primary care medical records	203/ 17,172 (1.2%)	386/ 71,299 (0.5%)	1.72 (1.3 – 2.07)[1]
Watt 2007[17]	1999 - 2002	The Navajo Nation USA	Navajo adults ≥18 years Summary age and sex n/r	Chronic renal failure	17 participants receiving dialysis	Medical record abstraction	Invasive pneumococcal disease	S.pneumoniae isolated from a normally sterile body fluid during illness	Active laboratory surveillance system[2]	20/118 (16.9%)	12/353 (3.4%)	2.6 (0.87 – 7.7)[3] P=0.087
Loeb 2009[18]	2002 - 2005	Ontario & Alberta Canada	General population ≥ 65 years Mean age: cases 79.1, controls 74.4 years. Cases 39.6%, controls 68.5%	Renal disease	Unclear	Cases: hospital interview. Controls: telephone interview at home.	Pneumonia	Consistent chest X-ray and ≥2 of: chest pain, shortness of breath, productive cough, temperature >38°C, crackles on auscultation.	Recruited patients attending emergency departments	127/690 (18.4%)	38/82 (4.4%)	4.06 (1.98–8.35)[4] P<0.001
Schnoor	2002	Germany	General	Chronic	Unclear	Cases:	Pneumonia	(1) Infiltrate on chest	Community-	49/1128	27/1044	1.7 (1.1–2.8)

2007[19]	– 2005		population >18 years Mean age: cases 57, controls 57.5 years Cases 44.8%, controls 54.7%	renal disease		reporting physician. Controls: self-reported questionnaire.		X-ray or (2) temperature ≥38.3°C with any of: cough, purulent sputum, positive auscultation. Excluded if hospitalised within prior 4 weeks, or immunodeficient.	acquired pneumonia network registry reports (primary and secondary care)	(4.3%)	(2.6%)	(unadjusted) P<0.05	

Cohort studies

	Study			**Kidney disease**			**Comparison group**	**Infection**			**Risk or rate ratio (95% CI)**	
	Date	**Setting** **Follow up time**	**Population** **Number** **Age** **Sex**	**Defined** **Number with kidney disease**	**ESRD**	**Ascertained**	**Defined**	**Type**	**Defined**	**Ascertained**		
Higgins 1989[22]	1985	Oxford UK 1 year	Patients attending a Renal Unit with chronic renal failure n=211 17-77 years Mean 50.5 years % female n/r	Creatinine ≥250 µmol/l Number n/r	Excluded	Serum creatinine	Creatinine <250 µmol/l	UTI	>10[5] organism/ml and ≥10 leucocytes /hpf in clean catch urine specimen	Medical record review	Creatinine µmol/l	
											<250	1
											250-500	1.5 [5]
											>500	2[5]
Dalrymple 2012[23]	1989 – 2007	United States Mean 11.5 years	General community-dwelling population[6] n=5,142 >65 years Mean 72 years	Baseline eGFR<90 mL/min/1.73 m^{2} [7] n=3,863	Excluded	Baseline cystatin C	Baseline eGFR ≥90 mL/min/1.73 m^{2} [7]	Pulmonary	Hospital admission with a principal discharge diagnosis of the relevant infection (ICD-9-CM codes)	Medical record review following patient report of hospital admission in cohort study	eGFR mL/min/1.73m^{2}	
											≥90	1
											60–89	1.22 (0.99–1.54)[8]
											45–59	1.27 (0.94–1.71)[8]
											15–44	1.81 (1.25–2.63)[8]
								Genitourinary			≥90	1
											60–89	1.08 (0.75–1.56)[8]
											45–59	1.17 (0.67–2.05)[8]
											15–44	2.63 (1.40–4.96)[8]

			61% female					Bacteremia and sepsis			≥90	1
											60–89	1.10 (0.77–1.58) [8]
											45–59	1.55 (0.93–2.57) [8]
											15–44	0.77 (0.29–2.03) [8]
Hackam 2006[24]	1997 - 2002	Ontario Canada Mean 2.2 years	Patients with cardiovascular disease n=69,168 >65 years Mean 74.1 years 44% female	Chronic renal insufficiency n=7,169	Unclear	Health record databases[9]	No chronic renal insufficiency	Sepsis	Hospital admission with a diagnosis of sepsis[10]	Health record database[11]	1.47 (1.27–1.72)[12]	
Karunajeewa 2005[25]	1999 - 2000	Western Australia Mean 2.9 years	Patients with diabetes n=496 >10 years Mean 66.1 years[13] 46.2% female	Albuminuria; serum urea; serum creatinine	Unclear	Baseline urinary albumin: creatinine ratio (ACR), serum urea, serum creatinine	Hazard ratio per 2.72-fold increase in ACR or serum urea	Urinary sepsis and non-urinary sepsis	Hospitalisation diagnosis codes (principal diagnosis, or principal or secondary diagnosis)[14]	Health record database[15]	Urinary sepsis (principal code)	
											Ln(ACR)	1.5 (1.1 – 1.9) [16] p=0.004
											Urinary sepsis (principal or secondary code)	
											Ln(ACR)	1.3 (1.1 – 1.6) [17] p=0.005
											Non-urinary sepsis (principal)	
											Ln(ACR)	1.4(1.1-1.9) [16]
											Non-urinary sepsis (principal or secondary code)	
											Ln(urea)	4.6 (2.3-9.4) [16] p<0.001
James 2008[26]	2001 - 2004	Calgary Canada Mean 3.2 years	General population n=25,675 >65 years Mean by eGFR [18] 55.9% female	Baseline eGFR<60 mL/min/1.73 m^2 [19] n=6,941	Excluded	Calgary Laboratory Services records	Baseline eGFR ≥60 mL/min/1.73 m^2 [19]	Bloodstream infection	Any pathogenic organism isolated from ≥1 blood cultures submitted from the community or ≤2 days of hospital admission	Calgary Laboratory Services records	eGFR mL/min/1.73m^2	
											≥60	1
											45-59	1.17 (0.92–1.49)[20]
											30-44	1.60 (1.20–2.13) [20]
											<30	2.95 (2.11–4.14) [20]
James 2009[27]	2003 -	Calgary Canada	General population	Time updated	Excluded	Calgary Laboratory	eGFR 60-104 mL/min/1.73	Pneumonia	ICD-10 code for pneumonia any	Hospital discharge	eGFR mL/min/1.73m^2	
											18-54 years	

	2006	Median 2.5 years	n=252,516 ≥18 years Mean by eGFR[21] 42.3% female	eGFR<60 mL/min/1.73 m^2 [22] n=35,948		Services records	m^2 [22]		position in hospital discharge report	reports	60-104	1
											45-59	3.23 (2.40–4.36) [23]
											30-44	9.67 (6.36–14.69) [23]
											<30	15.04 (9.64–23.47) [23]
											Age 55 – 64 years	
											60-104	1
											45-59	1.43 (1.11–1.84) [23]
											30-44	1.94 (1.32–2.87) [23]
											<30	5.50 (3.83–7.92) [23]
											Age 65 – 74 years	
											60-104	1
											45-59	1.18 (0.99–1.40) [23]
											30-44	2.24 (1.84–2.73) [23]
											<30	3.23 (2.52–4.13) [23]
											Age ≥75 years	
											60-104	1
											45-59	0.95 (0.85–1.05) [23]
											30-44	1.03 (0.92–1.16) [23]
											<30	1.79 (1.55–2.06) [23]
Wang 2012[28]	2003 – 2011	United States Mean .7 years	General population sample (weighted by age, geography and ethnicity) [24] n=30,239 ≥45 years 69%>60 years 55% female	Baseline eGFR<60 mL/min/1.73 m^2 [25]	Unclear	Baseline serum creatinine	Baseline eGFR ≥60 mL/min/1.73 m^2 [25]	Sepsis	Among hospitalisations attributed by participants to serious infection, medical record review [26]	Initially reported by study participants, confirmed with medical record review	1.99 (1.73–2.29) [27]	

Caljouw 2011[29]	1998 - 2004	Leiden The Netherlands Mean 2.6 years	General population n= 479 86-90 years All aged 86 years at entry 67.2% female	Creatinine clearance <30mL/min[28] n=43	Unclear	Baseline serum creatinine	Creatinine clearance ≥30mL/min[28]	UTI	Diagnosed by treating physician based on signs, symptoms and urine analysis; or death records[29]	Physician interview and medical record review. Statistics Netherlands for cause of death data.	0.9 (0.5–1.7) (unadjusted) p=0.794
Campbell 2011[21]	2009 - 2010	England UK 9 months	General population n=43.9 million 6 months - 64 years Summary age and sex n/r	Chronic kidney disease n=182,000	Unclear	Cases: consultant microbiologist report. Denominator: primary care population estimate.[30]	No pre-existing conditions [30]	Pandemic influenza A(H1N1)	Polymerase chain reaction (PCR) test confirmation of pandemic influenza A (H1N1) from a hospital inpatient.	Consultant microbiologist report to national surveillance system.	17.5 (13.4 – 22.9) [31]
USRDS 2010[20]	2008	USA 1 year [32]	Medicare patients 66+ years	Chronic kidney disease	Excluded	Insurance database ICD-9_CM codes [33]	No CKD	Pneumonia	Principal cause of hospital admission using hospital insurance claim records	ICD-9-CM codes 480-486	2.76 (unadjusted)
								UTI		ICD-9-CM codes [34]	3.15 (unadjusted)
								Bacteraemia/ septicaemia		ICD-9-CM codes 038.0 – 038.9	3.90 (unadjusted)

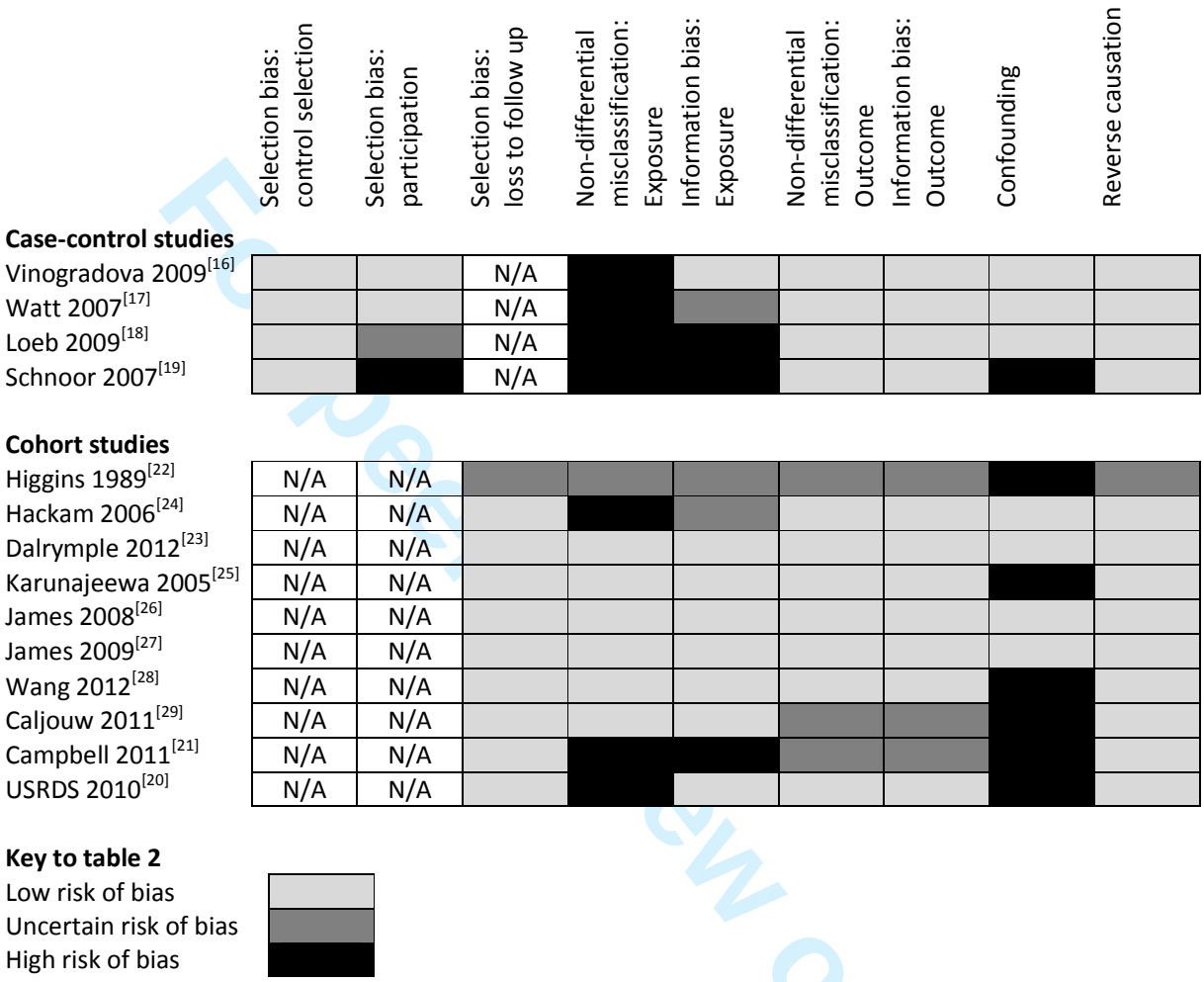
95% CI = 95% confidence interval; n/r = not reported; CKD= chronic kidney disease; UTI = urinary tract infection

1. Controls matched to cases on age at index data (within 1 year), sex, general practice, and calendar time. Estimate adjusted for smoking status, Townsend deprivation score, use of influenza vaccine in previous 12 months, use of pneumococcal vaccine in previous 5 years, number of years of medical records data available in database, and comorbidities including: diabetes, chronic heart disease, chronic respiratory disease, asplenia, cerebrospinal shunt, chronic liver disease, sickle cell disease or coeliac disease, cochlear implant, HIV/AIDS, immunosuppression, stroke or transient ischaemic attack, rheumatoid arthritis, Parkinson's disease, multiple sclerosis, dementia, osteoporosis, and any cancer.
2. Center for American Indian Health surveillance system.

3. Cases and controls matched by gender and age group. Adjusted for age, receipt of pneumococcal polysaccharide vaccine, congestive heart failure, alcohol use, body mass index and unemployment.
4. Adjusted for age, non-English language spoken most at home, living in detached house, living alone, congestive heart failure, chronic obstructive pulmonary disease, dysphagia, functional status using Barthel Index, immunosuppressive medications, nutritional score, tobacco use (lifetime history and secondhand smoke), alcohol consumption and history of regular exposure to gases, fumes or chemicals at home, or at work.
5. Approximate numbers, read from bar graph in publication. No confidence intervals available.
6. Cohort selected for the Cardiovascular Health Study. Exclusion criteria included: inability to provide informed consent or communicate with the interviewer, institutionalisation, being homebound, receipt of hospice care, treatment with radiation or chemotherapy for cancer, or plans to move out of the community within 3 years.
7. Serum cystatin C measured by particle-enhanced immunonephelometic assay, and eGFR calculated using: $eGFR=6.7xCysC^{-1.19}$.
8. Adjusted for age, sex, race, tobacco use, body mass index, diabetes mellitus, coronary heart disease, stroke, heart failure, cancer, chronic obstructive pulmonary disease, serum albumin, C-reactive protein, interleukin-6.
9. Canadian Institute for Health Information Discharge Abstract database or Ontario Health Insurance Plan database
10. ICD-9 codes 003 1, 036 2 and 038 0 – 038 9.
11. Canadian Institute for Health Information Discharge Abstract database.
12. Adjusted for statins, age, sex, nature of index event, charlson index, healthcare use, malignant disease, chemotherapy, neutropaenia, diabetes mellitus, oral steroids, antineoplastics, other immunosuppressants, history of aspiration, structural lung disease, previous infection (respiratory, GI, skin/soft tissue or other), recent trauma, transplant recipient, heart failure, stroke, chronic liver disease, chronic obstructive pulmonary disease, alcoholism, dementia, Parkinson's disease. Statin and non-statin users matched using propensity scoring for the above factors.
13. Mean age among the 460 participants without asymptomatic bacteriuria, 66.1years (SD11.0): mean age among the 36 participants with asymptomatic bacteriuria, 67.7 years (SD 10.5).
14. ICD-9 or ICD-10 codes for urinary sepsis were those encoding UTI, cystitis, pyelonephritis, orchitis, epididymitis and prostatitis; codes for non-urinary sepsis were those for sepsis, septicaemia and/or abscess.
15. Western Australia Data Linkage System.
16.Adjusted for presence of asymptomatic bacteriuria.
17. Adjusted for presence of asymptomatic bacteriuria and age.
18. Mean age ±SD by eGFR. >=60: 74.4±6.5years. 45-59: 77.5±7.2 years. 30-44: 79.3±7.4years. <30: 78.6±7.4 years.
19. eGFR calculated using abbreviated Modification of Diet in Renal Disease Study equation (omitting ethnicity) from single outpatient serum creatinine result.
20. Adjusted for age, sex, diabetes mellitus, comorbidity score and care in a CKD clinic.
21. Mean age ±SD by eGFR. >=105: 38.7±14.6. 60-104: 50.9±15.4. 45-59: 67.0± 14.1. 30-44: 74.5±12.9. <30: 73.3±15.2.
22. eGFR calculated using abbreviated Modification of Diet in Renal Disease Study equation (omitting ethnicity) from most recent outpatient serum creatinine result.
23. Adjusted for age, sex, socio-economic status, ethnicity, diabetes mellitus, Charlson comorbidity score.
24. Cohort selected for the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. Population weighted by age, ethnicity and geography according to local stroke incidence rates.
25. eGFR calculated using CKD-EPI equation.

26. Medical record review confirming (1) serious infection as major reason for admission and (2) ≥2 of heart rate >90 beats/minute, temperative>383°C or <36°C, tachypnoea >20 breaths/minute or leucocytosis.
27. Adjusted for age, sex, race, education, income, geographic region, alcohol use and smoking status.28. Creatinine clearance calculated from serum creatinine concentration and weight using Cockcroft-Gault formula.
29. Cause of death recorded as UTI (ICD-10 code N39.0)/
30. Department of Health-Health Protection Agency influenza vaccine uptake primary care monitoring system data.
31. Adjusted for age.
32. Smoothed estimate: Models include data from the stated year and the two years proceeding it, applying weights of 1, ¼ and 1/8 with increasing distance in time.
33. ICD-9-CM diagnosis codes recorded in insurance claims during the preceding year: 585.1 – 585.5 (chronic kidney disease stages 1-5); or 585.6 with no ESRD 2728 form or other indication of ESRD.
34. Principal hospital admission ICD-9-CM codes: 590-590.9, 595-595.4, 597-597.89, 598, 599.0, 601-601.9, 604-604.9, 607.1-2, 608.0, 608.4, 616.1, 616.3-4, and 616.8.

Table 2: Summary of risk of bias within studies (quality assessment tool adapted from Higgins *et al.*)[14]



DISCUSSION

Our comprehensive search strategy identified 14 studies describing an association between kidney disease and acute community-acquired infection. Although between-study heterogeneity precluded meta-analysis, all were consistent with a positive direction of association. The four studies which reported estimates on more than one category of kidney disease all found a graded association in which risk of infection increased with greater severity of CKD. These four studies all excluded patients with end-stage renal disease, and three were at low risk of bias in all categories of quality assessment.[22-23, 26-27]

To our knowledge, this is the first review to address this research question systematically. We used a sensitive search strategy, with a broad definition of kidney disease, for a thorough and inclusive search. The results are consistent with the conclusion of previous narrative reviews: that an association between CKD and infection incidence is likely, but that there is a paucity of evidence.[10-12]

Heterogeneity between the studies precluded meta-analysis of results. Variable study designs and biases may have contributed to heterogeneity: for example, the three case-control studies calculated odds ratios, which may differ from equivalent rate ratios for common infections.[16-18] Failure to control the confounding effects of age, sex and diabetes would be likely to result in overestimation of the effect of CKD on infection. Non-differential misclassification of kidney disease status in studies which relied on routine medical diagnosis would be expected to underestimate the effect of CKD on infection risk. In general the risk of ascertainment bias from increased monitoring for infection among patients with CKD is probably low, although one study assessed risk factors for hospitalisation with influenza during an influenza pandemic, in which context patients with influenza-like symptoms may have been more likely to be tested for influenza A(H1N1) if they also had CKD.[21]

The heterogeneity may reflect true differences in effect size between the studies.

Firstly, the studies considered a range of outcomes. CKD may have a different effect on the incidence of different infections. For all but three studies, detection of infection required either hospital attendance for the infection or a positive blood culture. CKD may affect severity of infection, as an alternative or in addition to any effect on infection incidence. CKD may also increase the probability of hospital admission for management of a moderately severe infection. Either would result in a larger effect of CKD on the risk of severe infectious outcomes (such as hospitalisation for sepsis) than on less severe infections (such as community-diagnosed LRTI), and could result in the graded association we observed, with increasing hospitalisation for patients with more severe stages of CKD.

Secondly, the studies included a variety of definitions of kidney disease. For example, proteinuria (and renal loss of complement) may represent a separate mechanism for risk of infection than uraemia. For the nine studies which did not exclude patients with ESRD it is unclear to what extent the results reflect the effect of treatments associated with dialysis, such as vascular or peritoneal access for dialysis, on infection incidence.

Thirdly, the association of CKD with infection may be modified by age. James *et al.* observed a weaker association of CKD with hospitalisation for pneumonia as age increased. They suggested that such an observation could be explained by a lower baseline rate of hospitalisation for pneumonia among younger adults, the natural decline in renal function by age, and inaccuracy in the estimation of renal function using the Modification of Diet in Renal Disease (MDRD) Study equation in older populations.[27] As their study population included only adults who had had a creatinine test result, reasons for testing creatinine could also be relevant confounders. As age-increases, more comorbidities accrue which require creatinine tests to guide therapy. Hence, younger people who receive a creatinine test may be

at an unusually high risk for both infections and CKD due to the reasons associated with getting a creatinine test. A real age-dependency of the CKD-infection association would be consistent with the lower effect of CKD on UTI incidence found among 86–90 year olds (0.90, 95% CI 0.50–1.77) compared with an adult study population with a mean age of 66 years (1.50, 95% CI 1.10–1.90). However, it may be that the study among the older adults measured a less severe outcome, and CKD may be associated with other factors that eventually lead to hospitalisation for UTI.[25, 29]

CKD was not a component of the primary study question for nine of the 14 studies, thus there is a risk that this association may have been reported and published only when CKD was found to be a risk factor for infection or an important confounder of another relationship. This would result in selective reporting bias, with a subsequent overestimation of the association of CKD with infection risk. This bias would be expected to affect smaller studies to a greater extent, and a funnel plot might show an asymmetry of relative risk estimates about the central pooled estimate among smaller studies. The sparsely populated funnel plot (**Fig S1**) provides no clear evidence for or against selective reporting bias, but some evidence of selective reporting bias comes from within the individual studies. For example, the crude hazard ratio for the association of creatinine clearance with UTI incidence is reported in Caljouw *et al.* (0.9, 95% CI 0.5–1.7) but as creatinine clearance was not found to be significant in the multivariable model the adjusted association is not reported.[29]

The overlap in the study populations of the two large cohort studies based in Calgary, Canada could result in more similar estimates than if the study populations were independent.[26-27] Outcomes in the two studies are likely to be correlated with each other: hospitalisation with pneumonia could cause a positive blood culture, which would result in one infection being included as an outcome in both studies. This is unlikely to have a large effect, particularly in

qualitative assessment of the combined evidence, as the potential overlap of person-time is limited.

Although we excluded study populations routinely treated with specialist medication (unless for kidney disease), some study populations may have been at higher risk of infection than the general population, and this may have affected the relationship of CKD to infection. For example, the cohort of patients admitted for an acute cardiovascular event or an arterial revascularisation procedure will have had a higher prevalence of co-morbidities (such as diabetes) than the general population and excluded patients with severe co-morbidities who did not survive an acute cardiovascular event, or who were not fit enough to undergo the procedure.[24] Each of the selected study populations limits the generalisability of the individual study result, but the qualitatively similar findings across the variety of study populations, and their qualitative consistency with the four studies based among the general population,[5, 16, 21, 29] support a positive association between CKD and infection risk in a variety of study populations.

A few large, high quality studies which excluded patients with ESRD have found a graded association between pre-dialysis CKD and risk of hospitalisation with infection. All studies identified in this review were compatible with a positive association of CKD with increased infection risk. There are little data available on the association of CKD with infection incidence using less severe outcome measures than hospitalisation, and it is not possible in most studies to distinguish an effect on susceptibility to infection from an effect on the severity of infection.

The potential age-dependency of the relationship between CKD and infection is intriguing and needs further research. There is also currently no evidence on the relationship between proteinuria and infection incidence independently of glomerular filtration rate. Future studies

should identify infections in the community in addition to hospitalisations for infection, characterise the association of proteinuria adjusted for glomerular filtration rate, explore the age-dependency of the association, and assess vaccine efficacy among older people with CKD.

Contributor statement:

All authors designed the study strategy including the search terms, inclusion and exclusion criteria. HM performed the search, study selection and data extraction. DN screened the randomly selected sample of 100 abstracts. All authors agreed quality assessment of included papers and interpretation of results by discussion. HM drafted the article, which DN and ST revised. All authors approved the final version of the manuscript.

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Competing interests statement:

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Data sharing statement:

All data, including full search terms and eligibility criteria, are available either in the article or as online supplementary material submitted with this manuscript.

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FIGURE LEGENDS

Figure 1: Flow chart of study selection

Figure 2: Forest plot of all estimates of the association of CKD with infection(n=17) from all 14 studies identified

UTI: urinary tract infection
The estimates from Higgin 1985 and USRDS 2010 did not include standard errors.
Dalrymple 2012: Presented estimates compare eGFR 45-59 with eGFR ≥90 mL/min/1.73m^2
James 2009: Presented estimates compare eGFR 45-59 with eGFR 60-104 mL/min/1.73m^2
James 2008: Presented estimates compare estimated glomerular filtration rate (eGFR) 45-59 with eGFR ≥60 mL/min/1.73m^2

Title: Chronic kidney disease as a risk factor for acute community-acquired infections in high-income countries: a systematic review

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ABSTRACT:

Objectives: A systematic review of the association of pre-dialysis chronic kidney disease (CKD) with the incidence of acute, community-acquired infections.

Design: We searched Medline, Embase and Cochrane databases (inception to 16/01/2014) for studies analysing the association of pre-dialysis kidney disease with the incidence of acute, community-acquired urinary tract infection (UTI), lower respiratory tract or central nervous system infections, or sepsis. Studies were required to include at least 30 participants with and without kidney disease.

Setting & participants: Community-based populations of adults in high income countries.

Outcome measures: Acute, community-acquired urinary tract infection (UTI), lower respiratory tract or central nervous system infections, or sepsis.

Results: We identified 14 eligible studies. Estimates from two studies lacked 95% confidence intervals and standard errors. The remaining 12 studies yielded 17 independent effect estimates. Only three studies included infections managed in the community. Quality assessment revealed that probable misclassification of kidney disease status and poor adjustment for confounding were common. There was evidence from a few large high quality studies of a graded association between pre-dialysis CKD stage and hospitalisation for infection. One study found an interaction with age, with a declining effect of CKD on infection risk as age increased. There was evidence of between-studies heterogeneity (I^2=96.5%, p<0.001) which persisted in subgroup analysis, and thus meta-analysis was not performed.

Conclusions: Pre-dialysis kidney disease appears to be associated with increased risk of severe infection. Whether pre-dialysis kidney disease increases the susceptibility to infections and whether age modifies this association remains unclear.

ARTICLE SUMMARY

Article focus:

- This review sought to assess systematically whether pre-dialysis chronic kidney disease (CKD) is a risk factor for the incidence of acute, community-acquired urinary tract infection (UTI), lower respiratory tract infection (LRTI) central nervous system (CNS) infection, or sepsis, among community-based adults in high income countries.
- Any increased risk of infection incidence at early stages of CKD would affect a large and growing number of patients. Awareness and quantification of this risk could have benefits for patient management, more effective vaccination strategies and healthcare planning.

Key messages:

- We identified major gaps in the literature including: a scarcity of high-quality studies on this research topic; a lack of studies using less severe outcome measures than hospitalisation, to allow any association of CKD with susceptibility to infection to be distinguished from an association with severity of infection; and a lack of data on the relationship between proteinuria and infection incidence independently of glomerular filtration rate.
- All studies were consistent with a positive association between CKD and infection risk.

Strengths and limitations of this study:

- This study used a sensitive search strategy, with a broad definition of kidney disease, for a thorough and inclusive search.

- Between-study heterogeneity, and the low quality of many of the studies, limit interpretation of results of the studies currently available.

INTRODUCTION

Chronic kidney disease (CKD) is common, and its prevalence is increasing.[1] Infection is a major cause of mortality in end-stage renal disease (ESRD) and hospitalisation at all stages of CKD. The second commonest cause of death among ESRD patients in the US is septicaemia, and patients with ESRD are at increased risk of death from infection compared to the general population.[2-4] Both ESRD and pre-dialysis patients with CKD in the US are at higher risk of hospitalisation for infection than the general population.[2, 5-6] Pre-dialysis CKD has been found to increase mortality among patients hospitalised with infections.[7]

Increased mortality and hospitalisation from infection could be driven by increased severity of infection, i.e. once an infection is present, the course of the associated illness is more severe, or increased incidence, i.e. CKD may make people more susceptible to develop an infection. Patients with CKD display impaired host immunity: reduced vaccination responsiveness is observed at all stages of CKD.[8]

Among ESRD patients, aspects of dialysis, such as vascular and peritoneal access for dialysis, may be a risk factor for infection incidence and severity. However, this does not tell the whole story, and only 23% of infection-related hospitalisations among haemodialysis patients in the US were identified as related to vascular access in the HEMO study.[9] Risk factors for infection identified among ESRD patients which are not related to renal replacement therapy, and could apply at all stages of pre-dialysis CKD, include: the causes and treatment of kidney disease; co-morbidities; reduced vaccine effectiveness; and high levels of exposure to health care facilities.[10]

If there is an increased risk of infection incidence at early stages of CKD, this would affect a large and growing number of patients. Awareness and quantification of this risk could have

benefits for patient management, more effective vaccination strategies and healthcare planning.

Narrative reviews have concluded that it is likely that CKD in itself increases infection incidence, but reported a lack of evidence.[10-12] We are not aware of any relevant systematic literature reviews of the effect of CKD on infection incidence.

This review sought to assess systematically whether pre-dialysis CKD is a risk factor for the incidence of acute, community-acquired urinary tract infection (UTI), lower respiratory tract infection (LRTI) central nervous system (CNS) infection, or sepsis, among community-based adults in high income countries.

METHODS

Data Sources and Searches

One reviewer (HM) searched the Medline and Embase databases, and the Cochrane library, from inception to 16 January 2014. The search strategies combined text words and MeSH terms for three concepts: acute community-acquired infection (either sepsis, UTI, LRTI or CNS infection); kidney disease; and relative risk. We used search terms to identify studies among adult humans in high-income countries (according to the World Bank classification),[13] and limited the search to articles in English, French or German. The full strategies are available in **Supplementary Tables 1-3**.

We searched the reference lists of all included studies and any pertinent review articles to identify further eligible studies.

Study Selection

One reviewer (HM) screened titles and abstracts, reviewed the full-text of identified studies and made initial decisions on eligibility according to pre-specified inclusion criteria (**Supplementary Table 4)**. Any borderline cases were discussed between HM, DN and ST. A second reviewer (DN) checked a sample of 100 abstracts, selected randomly after de-duplication of records, and a kappa statistic was calculated to describe agreement in selection of studies.

Eligible studies analysed the effect of pre-dialysis kidney disease on the relative risk of at least one of the four specified acute, community-acquired infections among community-based adults in high-income countries. We excluded study populations managed in secondary

care (unless for kidney disease), routinely treated with immunosuppressants, or exclusively of pregnant women, as these groups have a raised risk of infection, and the relationship of CKD to infection risk may be different among these groups compared to that in the general adult population in primary care. Ascertainment of CKD, as a silent disease, and, to a certain extent, ascertainment of acute community-acquired infections, are dependent on high levels of monitoring and good access to healthcare, so we restricted our search to high-income countries. Chronic infections such as tuberculosis were not included, as the relationship between CKD and chronic infection is very likely to differ from that between CKD and acute infections, which was our focus in this review.

To maximise the sensitivity of our search strategy, we accepted a wide range of definitions of kidney disease, including: medical diagnosis of kidney disease, reduced estimated glomerular filtration rate or creatinine clearance, elevated creatinine, proteinuria, micro- or macro-albuminuria, and renal structural abnormalities. We also accepted definitions which included some patients with ESRD among the patients with CKD, but excluded definitions which were exclusively patients receiving renal replacement therapy.

Outcomes of interest were relative risk estimates of acute community-acquired LRTIs, UTIs, CNS infections or sepsis. We accepted outcomes describing incidence of severe infections (such as hospitalisation with pneumonia).

We restricted our search to published studies which were sufficiently large to include at least 30 participants with and without kidney disease, to allow reasonable precision of the study estimate. Detailed eligibility criteria are listed in **Supplementary Table 4.**

Data Extraction and Quality Assessment

Data were extracted from relevant studies using a pre-specified collection form. Study characteristics extracted included study design, data source, any participant exclusion criteria, number of participants, age, gender, baseline renal function, definition of renal impairment, definition of the outcome infection. An estimate of relative risk (rate ratio, risk ratio or odds ratio) with any measures taken to address confounding was extracted from each eligible independent analysis in each study. Studies with no confidence intervals and for which the standard error was not calculable from the data presented were included in the review but not considered for meta-analysis.

When multiple estimates were available from a study but were not independent, a single estimate was identified for potential meta-analysis by selecting the estimate best adjusted for confounding, using the most recent data, comparing the level of CKD most common in the general population with no CKD.

Study quality was assessed using a pre-specified tool adapted from Higgins *et al*. for observational studies.[14] Studies were assigned a high, low or uncertain risk of each of: selection bias, non-differential measurement error for exposure and outcome, information bias in exposure and outcome, confounding and reverse causation. The minimum requirement for a low risk of bias from confounding was appropriate management of confounding by age, sex and diabetes. Specific criteria used are detailed in **Supplementary Table 5**.

Data Synthesis and Analysis

The relationship between CKD and UTIs was considered likely to differ from that of CKD to other infections, due to potential reverse causality. For example, repeat UTIs may cause kidney disease, or structural kidney disease may be identified though investigation of repeat UTIs. Therefore in all quantitative analysis, UTIs were analysed separately from other infections.

Estimates were examined for heterogeneity using Cochran's Q statistic and the I^2 statistic as described by Higgins *et al*.[15] If I^2 was less than 50% and Cochran's Q statistic p≥0.1, fixed-effects meta-analysis was considered for each of the two categories (UTI, and other infections). Funnel plots were constructed to look for publication bias. All analysis was conducted using STATA version 12.0.

RESULTS

The database searches identified 10,380 citations, of which 1,204 were duplicates (**Figure 1**). Both reviewers had 100% agreement on which studies to extract for full-text analysis from screening a random sample of 100 abstracts (Cohen's K= 1).

We identified 14 eligible studies, with varying study characteristics (**Table 1**). Four studies were case-control studies,[16-19] and ten were cohort studies.[20-29] Seven studies investigated a range of risk factors for infection,[16-19, 21, 28-29] two studies reported the effect of CKD on infection as a confounder of the effect of interest,[24-25] and five studies investigated the effect of CKD on infection risk as their primary research question.[5, 20, 22, 26-27]

Seven studies were based among the general population.[5, 16, 19, 21, 23, 28-29] Other study populations included: attendants at a specialist renal clinic,[22] patients with diabetes mellitus,[25] patients admitted to hospital for an acute cardiovascular event or an arterial revascularisation procedure, [24] and the Navajo Nation – a population which experiences 3–5 times higher rates of invasive pneumococcal disease than the general US population.[17] The population of the cohort studies in Calgary, Canada were adults with a serum creatinine test result available in their medical records.[26-27] There is some overlap in the study populations of these two cohort studies: residents aged over 65 years with a serum creatinine measurement between 1 July 2001 and 31 December 2001 and also between 1 July 2003 and 30 June 2004 would have been included in both studies for the period from the second creatinine measurement until 31 December 2004.[26-27]

Definitions of kidney disease included medical diagnoses of chronic renal disease, elevated creatinine levels, impaired creatinine clearance, and structural abnormalities of the kidney. Five studies excluded patients with ESRD, and one specified the number included, but for the

remaining eight studies it was unclear how many of the included patients received renal replacement therapy **(Table 1)**.

Three studies recorded infections diagnosed in primary care or outpatients,[16, 19, 29] two recorded infections identified from a positive culture result,[17, 26] one included infections diagnosed in the emergency department,[18] seven required hospital admission for infection,[5, 21, 23-25, 27-28] and for one study the definition and severity of infection was unclear.[22]

For two studies, the results extracted had no confidence interval or standard error and these could not be calculated from the reported data. From the remaining 12 studies, 17 independent effect estimates with standard errors were available for meta-analysis, among which UTI was the outcome in three estimates.

For all infections there was strong evidence of considerable heterogeneity (Cochran's Q statistic p<0.001, I^2=96.5%). This persisted when estimates for UTIs were excluded (p<0.001, I^2=97.2%), when considering LRTIs alone (p<0.001, I^2=98.2%), when limited to cohort studies (p<0.001, I^2=97.3%), and when stratified by exclusion of patients with ESRD (ESRD excluded, p<0.001, I^2=88.9%: ESRD not excluded p<0.001, I^2=97.2%). Due to this heterogeneity, meta-analysis was not performed.

All results are displayed in the Forest plot (**Figure 2**). Despite the quantitative heterogeneity, the results were qualitatively similar: all estimates were compatible with a positive association between kidney disease and infection. The four studies which compared different stages of CKD found a graded association of increased risk of infection with more severe CKD. These studies all excluded patients with end-stage renal disease.[22-23, 26-27] One study found that the effect of CKD on infection risk was modified by age, with a declining effect of CKD on infection risk as age increased.[27] This effect was consistent with the

lower effect of CKD on UTI incidence found among 86–90 year olds (0.90, 95% CI 0.50–1.77) compared with an adult study population with a mean age of 66 years (1.50, 95% CI 1.10–1.90).[25, 29]

The funnel plot was sparsely populated, with widely scattered effect estimates, and provides no clear evidence for or against publication bias (**Supplementary Figure 1**).

Study quality was variable. Relying on routine medical diagnosis introduced a potential source of misclassification of kidney disease status for seven studies.[5, 16-19, 21, 24] There was variable adjustment for confounding, from unadjusted crude estimates to estimates adjusted for a range of comorbidities, demographic and socio-economic factors. Six studies did not meet this review's minimal requirements.[19, 21-22, 25, 28-29] The summarised results are displayed in **Table 2**, and the full quality assessment is in **Supplementary Table 5**.

Table 1: Characteristics of eligible studies (n=14)

Case-control studies												
	Study			Kidney disease			Infection			Kidney disease prevalence		Odds ratio (95% CI)
	Date	Setting	Population Age % Female	Defined	ESRD included	Ascertained	Type	Defined	Ascertained	Cases	Controls	
Vinogradova 2009[16]	1996 - 2005	UK	General population Any age Median age band 45-64 years Cases 49.3%, controls 49.1%	Chronic renal disease	Unclear	Primary care medical record diagnosis code in previous 5 years	Pneumonia	Medical diagnosis recorded in primary care records	READ code in primary care medical records	203/ 17,172 (1.2%)	386/ 71,299 (0.5%)	1.72 (1.3 – 2.07)[1]
Watt 2007[17]	1999 - 2002	The Navajo Nation USA	Navajo adults ≥18 years Summary age and sex n/r	Chronic renal failure	17 participants receiving dialysis	Medical record abstraction	Invasive pneumococcal disease	S.pneumoniae isolated from a normally sterile body fluid during illness	Active laboratory surveillance system[2]	20/118 (16.9%)	12/353 (3.4%)	2.6 (0.87 – 7.7)[3] P=0.087
Loeb 2009[18]	2002 - 2005	Ontario & Alberta Canada	General population ≥ 65 years Mean age: cases 79.1, controls 74.4 years. Cases 39.6%, controls 68.5%	Renal disease	Unclear	Cases: hospital interview. Controls: telephone interview at home.	Pneumonia	Consistent chest X-ray and ≥2 of: chest pain, shortness of breath, productive cough, temperature >38°C, crackles on auscultation.	Recruited patients attending emergency departments	127/690 (18.4%)	38/82 (4.4%)	4.06 (1.98–8.35)[4] P<0.001
Schnoor	2002	Germany	General	Chronic	Unclear	Cases:	Pneumonia	(1) Infiltrate on chest	Community-	49/1128	27/1044	1.7 (1.1–2.8)

2007[19]	– 2005		population >18 years Mean age: cases 57, controls 57.5 years Cases 44.8%, controls 54.7%	renal disease		reporting physician. Controls: self-reported questionnaire.		X-ray or (2) temperature ≥38.3°C with any of: cough, purulent sputum, positive auscultation. Excluded if hospitalised within prior 4 weeks, or immunodeficient.	acquired pneumonia network registry reports (primary and secondary care)	(4.3%)	(2.6%)	(unadjusted) P<0.05	

Cohort studies

	Study			**Kidney disease**			**Comparison group**	**Infection**			**Risk or rate ratio (95% CI)**	
	Date	**Setting** **Follow up time**	**Population** **Number** **Age** **Sex**	**Defined** **Number with kidney disease**	**ESRD**	**Ascertained**	**Defined**	**Type**	**Defined**	**Ascertained**		
Higgins 1989[22]	1985	Oxford UK 1 year	Patients attending a Renal Unit with chronic renal failure n=211 17-77 years Mean 50.5 years % female n/r	Creatinine ≥250 µmol/l Number n/r	Excluded	Serum creatinine	Creatinine <250 µmol/l	UTI	>10[5] organism/ml and ≥10 leucocytes /hpf in clean catch urine specimen	Medical record review	Creatinine µmol/l	
											<250	1
											250-500	1.5 [5]
											>500	2[5]
Dalrymple 2012[23]	1989 – 2007	United States Mean 11.5 years	General community-dwelling population[6] n=5,142 >65 years Mean 72 years	Baseline eGFR<90 mL/min/1.73 m^{2} [7] n=3,863	Excluded	Baseline cystatin C	Baseline eGFR ≥90 mL/min/1.73 m^{2} [7]	Pulmonary	Hospital admission with a principal discharge diagnosis of the relevant infection (ICD-9-CM codes)	Medical record review following patient report of hospital admission in cohort study	eGFR mL/min/1.73m^{2}	
											≥90	1
											60–89	1.22 (0.99–1.54)[8]
											45–59	1.27 (0.94–1.71)[8]
											15–44	1.81 (1.25–2.63)[8]
								Genitourinary			≥90	1
											60–89	1.08 (0.75–1.56)[8]
											45–59	1.17 (0.67–2.05)[8]
											15–44	2.63 (1.40–4.96)[8]

			61% female					Bacteremia and sepsis			≥90	1
											60–89	1.10 (0.77–1.58) [8]
											45–59	1.55 (0.93–2.57) [8]
											15–44	0.77 (0.29–2.03) [8]
Hackam 2006[24]	1997 - 2002	Ontario Canada Mean 2.2 years	Patients with cardiovascular disease n=69,168 >65 years Mean 74.1 years 44% female	Chronic renal insufficiency n=7,169	Unclear	Health record databases[9]	No chronic renal insufficiency	Sepsis	Hospital admission with a diagnosis of sepsis[10]	Health record database[11]	1.47 (1.27–1.72)[12]	
Karunajeewa 2005[25]	1999 - 2000	Western Australia Mean 2.9 years	Patients with diabetes n=496 >10 years Mean 66.1 years[13] 46.2% female	Albuminuria; serum urea; serum creatinine	Unclear	Baseline urinary albumin: creatinine ratio (ACR), serum urea, serum creatinine	Hazard ratio per 2.72-fold increase in ACR or serum urea	Urinary sepsis and non-urinary sepsis	Hospitalisation diagnosis codes (principal diagnosis, or principal or secondary diagnosis)[14]	Health record database[15]	Urinary sepsis (principal code)	
											Ln(ACR)	1.5 (1.1 – 1.9) [16] p=0.004
											Urinary sepsis (principal or secondary code)	
											Ln(ACR)	1.3 (1.1 – 1.6) [17] p=0.005
											Non-urinary sepsis (principal)	
											Ln(ACR)	1.4(1.1-1.9) [16]
											Non-urinary sepsis (principal or secondary code)	
											Ln(urea)	4.6 (2.3-9.4) [16] p<0.001
James 2008[26]	2001 - 2004	Calgary Canada Mean 3.2 years	General population n=25,675 >65 years Mean by eGFR [18] 55.9% female	Baseline eGFR<60 mL/min/1.73 m^2 [19] n=6,941	Excluded	Calgary Laboratory Services records	Baseline eGFR ≥60 mL/min/1.73 m^2 [19]	Bloodstream infection	Any pathogenic organism isolated from ≥1 blood cultures submitted from the community or ≤2 days of hospital admission	Calgary Laboratory Services records	eGFR mL/min/1.73m^2	
											≥60	1
											45-59	1.17 (0.92–1.49)[20]
											30-44	1.60 (1.20–2.13) [20]
											<30	2.95 (2.11–4.14) [20]
James 2009[27]	2003 -	Calgary Canada	General population	Time updated	Excluded	Calgary Laboratory	eGFR 60-104 mL/min/1.73	Pneumonia	ICD-10 code for pneumonia any	Hospital discharge	eGFR mL/min/1.73m^2	
											18-54 years	

	2006	Median 2.5 years	n=252,516 ≥18 years Mean by eGFR[21] 42.3% female	eGFR<60 mL/min/1.73 m^2 [22] n=35,948		Services records	m^2 [22]		position in hospital discharge report	reports	60-104	1
											45-59	3.23 (2.40–4.36) [23]
											30-44	9.67 (6.36–14.69) [23]
											<30	15.04 (9.64–23.47) [23]
											Age 55 – 64 years	
											60-104	1
											45-59	1.43 (1.11–1.84) [23]
											30-44	1.94 (1.32–2.87) [23]
											<30	5.50 (3.83–7.92) [23]
											Age 65 – 74 years	
											60-104	1
											45-59	1.18 (0.99–1.40) [23]
											30-44	2.24 (1.84–2.73) [23]
											<30	3.23 (2.52–4.13) [23]
											Age ≥75 years	
											60-104	1
											45-59	0.95 (0.85–1.05) [23]
											30-44	1.03 (0.92–1.16) [23]
											<30	1.79 (1.55–2.06) [23]
Wang 2012[28]	2003 – 2011	United States Mean .7 years	General population sample (weighted by age, geography and ethnicity) [24] n=30,239 ≥45 years 69%>60 years 55% female	Baseline eGFR<60 mL/min/1.73 m^2 [25]	Unclear	Baseline serum creatinine	Baseline eGFR ≥60 mL/min/1.73 m^2 [25]	Sepsis	Among hospitalisations attributed by participants to serious infection, medical record review [26]	Initially reported by study participants, confirmed with medical record review	1.99 (1.73–2.29) [27]	

Caljouw 2011[29]	1998 - 2004	Leiden The Netherlands Mean 2.6 years	General population n= 479 86-90 years All aged 86 years at entry 67.2% female	Creatinine clearance <30mL/min[28] n=43	Unclear	Baseline serum creatinine	Creatinine clearance ≥30mL/min[28]	UTI	Diagnosed by treating physician based on signs, symptoms and urine analysis; or death records[29]	Physician interview and medical record review. Statistics Netherlands for cause of death data.	0.9 (0.5–1.7) (unadjusted) p=0.794
Campbell 2011[21]	2009 - 2010	England UK 9 months	General population n=43.9 million 6 months - 64 years Summary age and sex n/r	Chronic kidney disease n=182,000	Unclear	Cases: consultant microbiologist report. Denominator: primary care population estimate.[30]	No pre-existing conditions [30]	Pandemic influenza A(H1N1)	Polymerase chain reaction (PCR) test confirmation of pandemic influenza A (H1N1) from a hospital inpatient.	Consultant microbiologist report to national surveillance system.	17.5 (13.4 – 22.9) [31]
USRDS 2010[20]	2008	USA 1 year [32]	Medicare patients 66+ years	Chronic kidney disease	Excluded	Insurance database ICD-9_CM codes [33]	No CKD	Pneumonia	Principal cause of hospital admission using hospital insurance claim records	ICD-9-CM codes 480-486	2.76 (unadjusted)
								UTI		ICD-9-CM codes [34]	3.15 (unadjusted)
								Bacteraemia/ septicaemia		ICD-9-CM codes 038.0 – 038.9	3.90 (unadjusted)

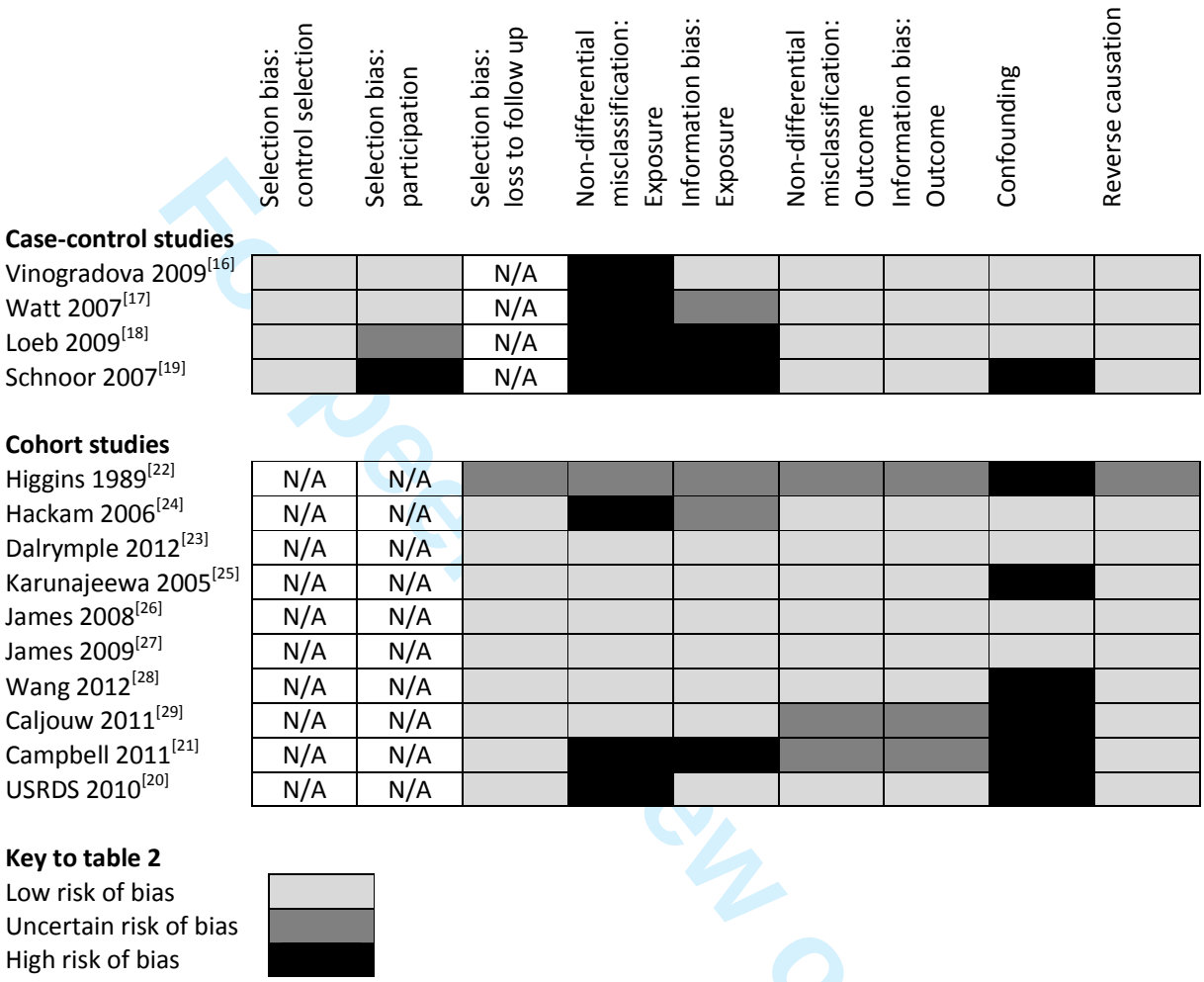
95% CI = 95% confidence interval; n/r = not reported; CKD= chronic kidney disease; UTI = urinary tract infection

1. Controls matched to cases on age at index data (within 1 year), sex, general practice, and calendar time. Estimate adjusted for smoking status, Townsend deprivation score, use of influenza vaccine in previous 12 months, use of pneumococcal vaccine in previous 5 years, number of years of medical records data available in database, and comorbidities including: diabetes, chronic heart disease, chronic respiratory disease, asplenia, cerebrospinal shunt, chronic liver disease, sickle cell disease or coeliac disease, cochlear implant, HIV/AIDS, immunosuppression, stroke or transient ischaemic attack, rheumatoid arthritis, Parkinson's disease, multiple sclerosis, dementia, osteoporosis, and any cancer.
2. Center for American Indian Health surveillance system.

3. Cases and controls matched by gender and age group. Adjusted for age, receipt of pneumococcal polysaccharide vaccine, congestive heart failure, alcohol use, body mass index and unemployment.
4. Adjusted for age, non-English language spoken most at home, living in detached house, living alone, congestive heart failure, chronic obstructive pulmonary disease, dysphagia, functional status using Barthel Index, immunosuppressive medications, nutritional score, tobacco use (lifetime history and secondhand smoke), alcohol consumption and history of regular exposure to gases, fumes or chemicals at home, or at work.
5. Approximate numbers, read from bar graph in publication. No confidence intervals available.
6. Cohort selected for the Cardiovascular Health Study. Exclusion criteria included: inability to provide informed consent or communicate with the interviewer, institutionalisation, being homebound, receipt of hospice care, treatment with radiation or chemotherapy for cancer, or plans to move out of the community within 3 years.
7. Serum cystatin C measured by particle-enhanced immunonephelometic assay, and eGFR calculated using: $eGFR=6.7xCysC^{-1.19}$.
8. Adjusted for age, sex, race, tobacco use, body mass index, diabetes mellitus, coronary heart disease, stroke, heart failure, cancer, chronic obstructive pulmonary disease, serum albumin, C-reactive protein, interleukin-6.
9. Canadian Institute for Health Information Discharge Abstract database or Ontario Health Insurance Plan database
10. ICD-9 codes 003 1, 036 2 and 038 0 – 038 9.
11. Canadian Institute for Health Information Discharge Abstract database.
12. Adjusted for statins, age, sex, nature of index event, charlson index, healthcare use, malignant disease, chemotherapy, neutropaenia, diabetes mellitus, oral steroids, antineoplastics, other immunosuppressants, history of aspiration, structural lung disease, previous infection (respiratory, GI, skin/soft tissue or other), recent trauma, transplant recipient, heart failure, stroke, chronic liver disease, chronic obstructive pulmonary disease, alcoholism, dementia, Parkinson's disease. Statin and non-statin users matched using propensity scoring for the above factors.
13. Mean age among the 460 participants without asymptomatic bacteriuria, 66.1years (SD11.0): mean age among the 36 participants with asymptomatic bacteriuria, 67.7 years (SD 10.5).
14. ICD-9 or ICD-10 codes for urinary sepsis were those encoding UTI, cystitis, pyelonephritis, orchitis, epididymitis and prostatitis; codes for non-urinary sepsis were those for sepsis, septicaemia and/or abscess.
15. Western Australia Data Linkage System.
16.Adjusted for presence of asymptomatic bacteriuria.
17. Adjusted for presence of asymptomatic bacteriuria and age.
18. Mean age ±SD by eGFR. >=60: 74.4±6.5years. 45-59: 77.5±7.2 years. 30-44: 79.3±7.4years. <30: 78.6±7.4 years.
19. eGFR calculated using abbreviated Modification of Diet in Renal Disease Study equation (omitting ethnicity) from single outpatient serum creatinine result.
20. Adjusted for age, sex, diabetes mellitus, comorbidity score and care in a CKD clinic.
21. Mean age ±SD by eGFR. >=105: 38.7±14.6. 60-104: 50.9±15.4. 45-59: 67.0± 14.1. 30-44: 74.5±12.9. <30: 73.3±15.2.
22. eGFR calculated using abbreviated Modification of Diet in Renal Disease Study equation (omitting ethnicity) from most recent outpatient serum creatinine result.
23. Adjusted for age, sex, socio-economic status, ethnicity, diabetes mellitus, Charlson comorbidity score.
24. Cohort selected for the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study. Population weighted by age, ethnicity and geography according to local stroke incidence rates.
25. eGFR calculated using CKD-EPI equation.

26. Medical record review confirming (1) serious infection as major reason for admission and (2) ≥2 of heart rate >90 beats/minute, temperative>383°C or <36°C, tachypnoea >20 breaths/minute or leucocytosis.
27. Adjusted for age, sex, race, education, income, geographic region, alcohol use and smoking status.28. Creatinine clearance calculated from serum creatinine concentration and weight using Cockcroft-Gault formula.
29. Cause of death recorded as UTI (ICD-10 code N39.0)/
30. Department of Health-Health Protection Agency influenza vaccine uptake primary care monitoring system data.
31. Adjusted for age.
32. Smoothed estimate: Models include data from the stated year and the two years proceeding it, applying weights of 1, ¼ and 1/8 with increasing distance in time.
33. ICD-9-CM diagnosis codes recorded in insurance claims during the preceding year: 585.1 – 585.5 (chronic kidney disease stages 1-5); or 585.6 with no ESRD 2728 form or other indication of ESRD.
34. Principal hospital admission ICD-9-CM codes: 590-590.9, 595-595.4, 597-597.89, 598, 599.0, 601-601.9, 604-604.9, 607.1-2, 608.0, 608.4, 616.1, 616.3-4, and 616.8.

Table 2: Summary of risk of bias within studies (quality assessment tool adapted from Higgins *et al.*)[14]



DISCUSSION

Our comprehensive search strategy identified 14 studies describing an association between kidney disease and acute community-acquired infection. Although between-study heterogeneity precluded meta-analysis, all were consistent with a positive direction of association. The four studies which reported estimates on more than one category of kidney disease all found a graded association in which risk of infection increased with greater severity of CKD. These four studies all excluded patients with end-stage renal disease, and three were at low risk of bias in all categories of quality assessment.[22-23, 26-27]

To our knowledge, this is the first review to address this research question systematically. We used a sensitive search strategy, with a broad definition of kidney disease, for a thorough and inclusive search. The results are consistent with the conclusion of previous narrative reviews: that an association between CKD and infection incidence is likely, but that there is a paucity of evidence.[10-12]

Heterogeneity between the studies precluded meta-analysis of results. Variable study designs and biases may have contributed to heterogeneity: for example, the three case-control studies calculated odds ratios, which may differ from equivalent rate ratios for common infections.[16-18] Failure to control the confounding effects of age, sex and diabetes would be likely to result in overestimation of the effect of CKD on infection. Non-differential misclassification of kidney disease status in studies which relied on routine medical diagnosis would be expected to underestimate the effect of CKD on infection risk. In general the risk of ascertainment bias from increased monitoring for infection among patients with CKD is probably low, although one study assessed risk factors for hospitalisation with influenza during an influenza pandemic, in which context patients with influenza-like symptoms may have been more likely to be tested for influenza A(H1N1) if they also had CKD.[21]

The heterogeneity may reflect true differences in effect size between the studies.

Firstly, the studies considered a range of outcomes. CKD may have a different effect on the incidence of different infections. For all but three studies, detection of infection required either hospital attendance for the infection or a positive blood culture. CKD may affect severity of infection, as an alternative or in addition to any effect on infection incidence. CKD may also increase the probability of hospital admission for management of a moderately severe infection. Either would result in a larger effect of CKD on the risk of severe infectious outcomes (such as hospitalisation for sepsis) than on less severe infections (such as community-diagnosed LRTI), and could result in the graded association we observed, with increasing hospitalisation for patients with more severe stages of CKD.

Secondly, the studies included a variety of definitions of kidney disease. For example, proteinuria (and renal loss of complement) may represent a separate mechanism for risk of infection than uraemia. For the nine studies which did not exclude patients with ESRD it is unclear to what extent the results reflect the effect of treatments associated with dialysis, such as vascular or peritoneal access for dialysis, on infection incidence.

Thirdly, the association of CKD with infection may be modified by age. James *et al.* observed a weaker association of CKD with hospitalisation for pneumonia as age increased. They suggested that such an observation could be explained by a lower baseline rate of hospitalisation for pneumonia among younger adults, the natural decline in renal function by age, and inaccuracy in the estimation of renal function using the Modification of Diet in Renal Disease (MDRD) Study equation in older populations.[27] As their study population included only adults who had had a creatinine test result, reasons for testing creatinine could also be relevant confounders. As age-increases, more comorbidities accrue which require creatinine tests to guide therapy. Hence, younger people who receive a creatinine test may be

at an unusually high risk for both infections and CKD due to the reasons associated with getting a creatinine test. A real age-dependency of the CKD-infection association would be consistent with the lower effect of CKD on UTI incidence found among 86–90 year olds (0.90, 95% CI 0.50–1.77) compared with an adult study population with a mean age of 66 years (1.50, 95% CI 1.10–1.90). However, it may be that the study among the older adults measured a less severe outcome, and CKD may be associated with other factors that eventually lead to hospitalisation for UTI.[25, 29]

CKD was not a component of the primary study question for nine of the 14 studies, thus there is a risk that this association may have been reported and published only when CKD was found to be a risk factor for infection or an important confounder of another relationship. This would result in selective reporting bias, with a subsequent overestimation of the association of CKD with infection risk. This bias would be expected to affect smaller studies to a greater extent, and a funnel plot might show an asymmetry of relative risk estimates about the central pooled estimate among smaller studies. The sparsely populated funnel plot (**Fig S1**) provides no clear evidence for or against selective reporting bias, but some evidence of selective reporting bias comes from within the individual studies. For example, the crude hazard ratio for the association of creatinine clearance with UTI incidence is reported in Caljouw *et al.* (0.9, 95% CI 0.5–1.7) but as creatinine clearance was not found to be significant in the multivariable model the adjusted association is not reported.[29]

The overlap in the study populations of the two large cohort studies based in Calgary, Canada could result in more similar estimates than if the study populations were independent.[26-27] Outcomes in the two studies are likely to be correlated with each other: hospitalisation with pneumonia could cause a positive blood culture, which would result in one infection being included as an outcome in both studies. This is unlikely to have a large effect, particularly in

qualitative assessment of the combined evidence, as the potential overlap of person-time is limited.

Although we excluded study populations routinely treated with specialist medication (unless for kidney disease), some study populations may have been at higher risk of infection than the general population, and this may have affected the relationship of CKD to infection. For example, the cohort of patients admitted for an acute cardiovascular event or an arterial revascularisation procedure will have had a higher prevalence of co-morbidities (such as diabetes) than the general population and excluded patients with severe co-morbidities who did not survive an acute cardiovascular event, or who were not fit enough to undergo the procedure.[24] Each of the selected study populations limits the generalisability of the individual study result, but the qualitatively similar findings across the variety of study populations, and their qualitative consistency with the four studies based among the general population,[5, 16, 21, 29] support a positive association between CKD and infection risk in a variety of study populations.

A few large, high quality studies which excluded patients with ESRD have found a graded association between pre-dialysis CKD and risk of hospitalisation with infection. All studies identified in this review were compatible with a positive association of CKD with increased infection risk. There are little data available on the association of CKD with infection incidence using less severe outcome measures than hospitalisation, and it is not possible in most studies to distinguish an effect on susceptibility to infection from an effect on the severity of infection.

The potential age-dependency of the relationship between CKD and infection is intriguing and needs further research. There is also currently no evidence on the relationship between proteinuria and infection incidence independently of glomerular filtration rate. Future studies

should identify infections in the community in addition to hospitalisations for infection, characterise the association of proteinuria adjusted for glomerular filtration rate, explore the age-dependency of the association, and assess vaccine efficacy among older people with CKD.

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FIGURE LEGENDS

Figure 1: Flow chart of study selection

Figure 2: Forest plot of all estimates of the association of CKD with infection(n=17) from all 14 studies identified

UTI: urinary tract infection
The estimates from Higgin 1985 and USRDS 2010 did not include standard errors.
Dalrymple 2012: Presented estimates compare eGFR 45-59 with eGFR ≥90 mL/min/1.73m^2
James 2009: Presented estimates compare eGFR 45-59 with eGFR 60-104 mL/min/1.73m^2
James 2008: Presented estimates compare estimated glomerular filtration rate (eGFR) 45-59 with eGFR ≥60 mL/min/1.73m^2

Contributor statement:

All authors designed the study strategy including the search terms, inclusion and exclusion criteria. HM performed the search, study selection and data extraction. DN screened the randomly selected sample of 100 abstracts. All authors agreed quality assessment of included papers and interpretation of results by discussion. HM drafted the article, which DN and ST revised. All authors approved the final version of the manuscript.

Competing interests statement:

H I McDonald: None. S L Thomas: None. D Nitsch: None to declare.

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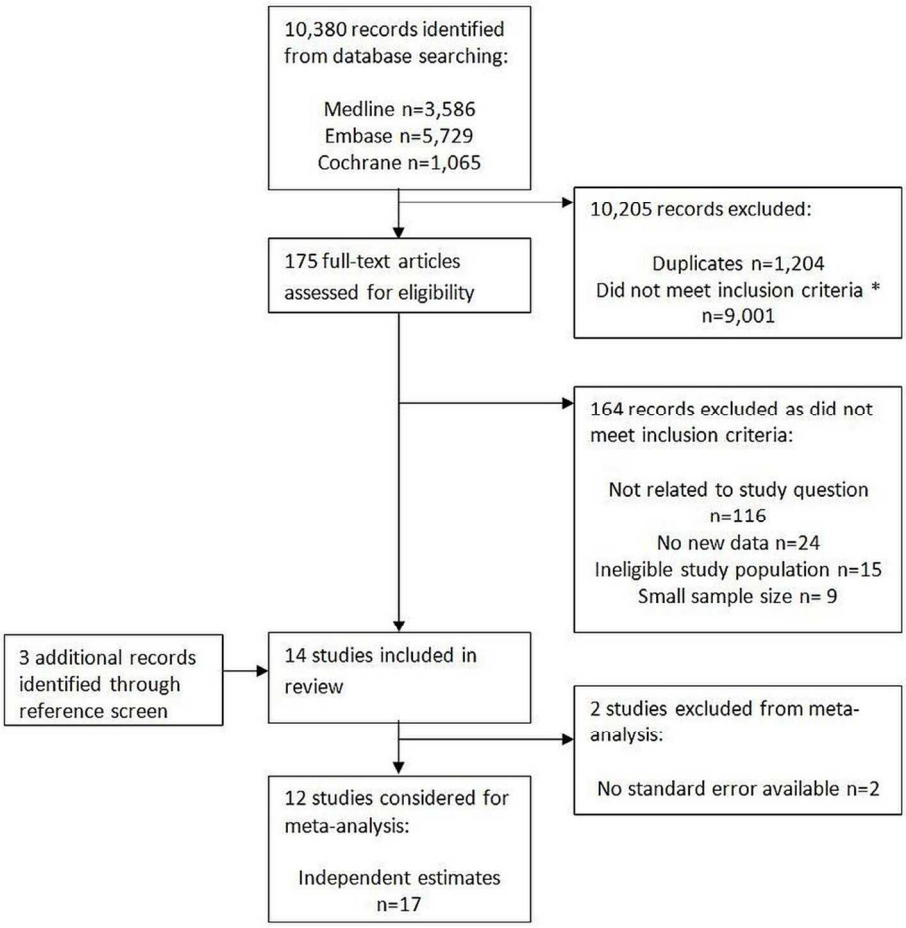
Data sharing statement:

All data, including full search terms and eligibility criteria, are available either in the article or as online supplementary material submitted with this manuscript.



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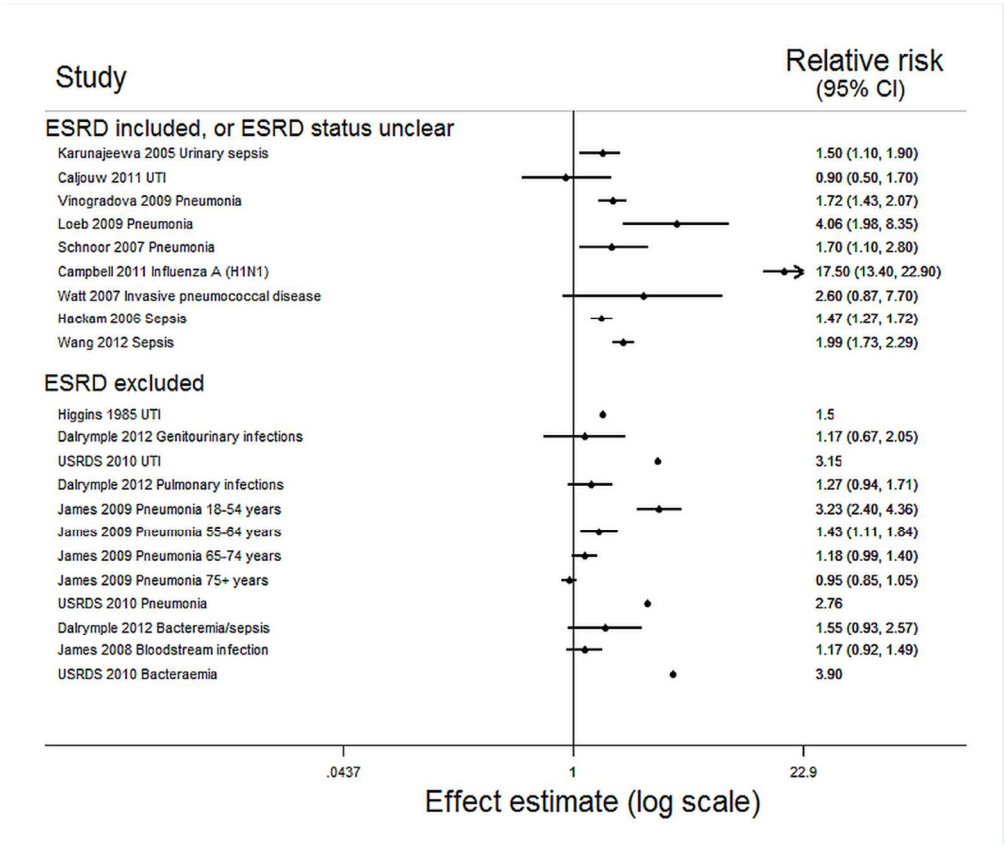


90x75mm (300 x 300 DPI)

Supplementary Table 1: Medline search strategy

	Search	Results
1	(sepsis* or septic?emia or bacter?emia or fung?emia or pneumonia* or bronchopneumonia* or pleuropneumonia* or LRTI or empy?ema or influenza* or legionell* or bacteriuri* or pyelonephriti* or cystitis* or pyelocystitis* or pyelitis* or urethriti* or UTI or meningiti* or meningococc* or encephaliti* or poliomyeliti* or septic shock).tw.	343181
2	(CNS adj4 infection*).tw.	2545
3	(central nervous adj4 infection*).tw.	3805
4	exp cerebral phaeohyphomycosis/ or central nervous system infections/ or exp brain abscess/ or exp toxoplasmosis, cerebral/ or central nervous system bacterial infections/ or exp empyema, subdural/ or exp epidural abscess/ or exp lyme neuroborreliosis/ or exp meningitis, bacterial/ or exp meningitis, escherichia coli/ or exp meningitis, haemophilus/ or exp meningitis, listeria/ or exp meningitis, meningococcal/ or exp meningitis, pneumococcal/ or exp central nervous system fungal infections/ or exp meningitis, fungal/ or exp meningitis, cryptococcal/ or exp neuroaspergillosis/ or central nervous system viral diseases/ or exp encephalitis/ or exp encephalitis, viral/ or exp encephalitis, arbovirus/ or exp encephalitis, california/ or exp encephalitis, japanese/ or exp "encephalitis, st. louis"/ or exp encephalitis, tick-borne/ or exp west nile fever/ or exp encephalitis, herpes simplex/ or exp encephalitis, varicella zoster/ or exp encephalomyelitis, equine/ or exp meningitis, viral/ or exp lymphocytic choriomeningitis/ or exp meningitis, aseptic/ or exp paraparesis, tropical spastic/ or poliomyelitis/ or exp poliomyelitis, bulbar/ or exp encephalomyelitis/ or exp meningitis/	102876
5	exp endocarditis, bacterial/ or exp endocarditis, subacute bacterial/ or exp pneumococcal infections/ or catheter-related infections/ or exp coinfection/ or communicable diseases/ or exp community-acquired infections/ or exp sepsis/ or exp bacteremia/ or exp hemorrhagic septicemia/ or exp fungemia/ or exp shock, septic/ or exp empyema/ or exp viremia/ or exp parasitemia/	139752
6	((renal or kidney) adj4 chronic adj4 failure*).tw.	21053
7	((renal or kidney) adj4 chronic adj4 disease*).tw.	15978
8	((renal or kidney) adj4 chronic adj4 insufficienc*).tw.	4448
9	((renal or kidney) adj4 chronic adj4 injury).tw.	454
10	((renal or kidney) adj4 chronic adj4 impairment*).tw.	336
11	(creatinine* or GFR or eGFR or albuminuri* or proteinuri* or microalbuminuri* or	194742

	nephropath* or glomerulo* or nephr#ti* or nephrosi* or ur?emia or ESRD or CKD or cardio-renal or Kimmelstiel-Wilson).tw.	
12	Creatinine/bl [Blood]	25724
13	Kidney Diseases/co, ep [Complications, Epidemiology]	11809
14	exp diabetic nephropathies/ or exp hypertension, renal/ or exp nephritis/ or exp anti-glomerular basement membrane disease/ or exp glomerulonephritis, iga/ or exp glomerulonephritis, membranoproliferative/ or exp glomerulonephritis, membranous/ or exp lupus nephritis/ or exp nephrosclerosis/ or exp nephrosis/ or exp renal insufficiency/ or exp cardio-renal syndrome/ or exp uremia/ or exp azotemia/ or exp proteinuria/	234481
15	kidney function tests/ or exp glomerular filtration rate/	44837
16	Animals/	4889105
17	Humans/	12139628
18	16 not (16 and 17)	3594930
19	Adult/	3567838
20	exp child/ or exp child, preschool/ or exp infant/	1849722
21	20 not (19 and 20)	1265383
22	Case reports/	1557478
23	developing countries/ or exp africa/ or cuba/ or dominica/ or dominican republic/ or grenada/ or guadeloupe/ or haiti/ or jamaica/ or exp central america/ or "gulf of mexico"/ or latin america/ or exp south america/ or exp asia, central/ or borneo/ or cambodia/ or east timor/ or indonesia/ or laos/ or malaysia/ or mekong valley/ or myanmar/ or philippines/ or thailand/ or vietnam/ or bangladesh/ or india/ or afghanistan/ or iran/ or iraq/ or jordan/ or lebanon/ or syria/ or turkey/ or yemen/ or nepal/ or pakistan/ or sri lanka/ or exp china/ or "democratic people's republic of korea"/ or mongolia/ or albania/ or latvia/ or lithuania/ or bosnia-herzegovina/ or bulgaria/ or "republic of belarus"/ or romania/ or exp russia/ or serbia/ or ukraine/ or yugoslavia/ or exp transcaucasia/ or exp indian ocean islands/ or fiji/ or papua new guinea/ or vanuatu/ or palau/ or hawaii/	620630
24	developed countries/ or bahamas/ or barbados/ or netherlands antilles/ or puerto rico/ or "trinidad and tobago"/ or "virgin islands of the united states"/ or canada/ or greenland/ or united states/ or brunei/ or singapore/ or bahrain/ or israel/ or kuwait/ or oman/ or qatar/ or saudi arabia/ or united arab emirates/ or hong kong/ or macau/ or exp japan/ or "republic of korea"/ or bermuda/ or exp australia/ or andorra/ or austria/ or belgium/ or estonia/ or croatia/ or czech republic/ or hungary/ or poland/ or	1800832

	slovakia/ or slovenia/ or finland/ or exp france/ or exp germany/ or gibraltar/ or exp great britain/ or greece/ or iceland/ or ireland/ or exp italy/ or liechtenstein/ or luxembourg/ or cyprus/ or malta/ or monaco/ or netherlands/ or portugal/ or san marino/ or exp scandinavia/ or spain/ or switzerland/ or new zealand/ or new caledonia/ or guam/	
25	23 not (23 and 24)	556094
26	Postoperative complications.sh.	263650
27	(incidence* or odds ratio or risk ratio or risk factor or relative risk).tw.	608698
28	(respiratory adj3 infection*).tw.	28563
29	(lower respiratory adj3 infection*).tw.	4633
30	(urinary adj3 infection*).tw.	28333
31	(upper urinary adj3 infection*).tw.	312
32	6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	366856
33	(exp incidence/ or exp multivariate analysis/ or exp odds ratio/ or exp logistic models/ or exp risk factors/ or exp epidemiologic studies/).sh.	1799348
34	(exp pyelitis/ or exp pyelocystitis/ or exp pyelonephritis/ or exp urethritis/ or cystitis or urinary tract infections or exp pyuria/).sh.	50526
35	(respiratory tract infections or exp bronchiolitis/ or exp bronchiolitis, viral/ or empyema, pleural or exp influenza, human/ or exp legionellosis/ or exp legionnaires' disease/ or exp lung abscess/ or exp lung diseases, fungal/ or exp lung diseases, parasitic/ or exp pneumonia/ or exp bronchopneumonia/ or exp pleuropneumonia/ or exp pneumonia, bacterial/ or exp chlamydial pneumonia/ or exp pneumonia, mycoplasma/ or exp pneumonia, pneumococcal/ or exp pneumonia, rickettsial/ or exp pneumonia, staphylococcal/ or exp pneumonia, pneumocystis/ or exp pneumonia, viral/ or exp severe acute respiratory syndrome/ or exp tracheitis/ or exp whooping cough/).sh.	155035
36	1 or 2 or 3 or 4 or 5 or 28 or 29 or 30 or 31 or 34 or 35	585963
37	27 or 33	2098986
38	32 and 36 and 37	5940
39	38 not 18 not 21 not 22 not 25 not 26	3514
40	limit 39 to (english or french or german)	3163

Supplementary Table 2: Embase search strategy

	Search	Results
1	kidney failure/co, ep [Complication, Epidemiology]	13218
2	chronic kidney failure/co, ep [Complication, Epidemiology]	10827
3	exp proteinuria/co, ep [Complication, Epidemiology]	5456
4	uremia/co, ep [Complication, Epidemiology]	3030
5	glomerulus filtration rate/	43185
6	creatinine clearance/	17973
7	glomerulosclerosis/co, ep [Complication, Epidemiology]	450
8	kidney disease/co, ep [Complication, Epidemiology]	10406
9	analgesic nephropathy/co, ep [Complication, Epidemiology]	39
10	chronic kidney disease/co, ep [Complication, Epidemiology]	1733
11	diabetic nephropathy/co, ep [Complication, Epidemiology]	9683
12	allergic glomerulonephritis/co, ep [Complication, Epidemiology]	109
13	immune complex nephritis/co, ep [Complication, Epidemiology]	77
14	immunoglobulin A nephropathy/co, ep [Complication, Epidemiology]	678
15	kidney amyloidosis/co, ep [Complication, Epidemiology]	228
16	nephritis/co, ep [Complication, Epidemiology]	1053
17	glomerulitis/	456
18	Goodpasture syndrome/co, ep [Complication, Epidemiology]	31
19	immune complex nephritis/co, ep [Complication, Epidemiology]	77
20	interstitial nephritis/co, ep [Complication, Epidemiology]	901
21	lupus erythematosus nephritis/co, ep [Complication, Epidemiology]	850
22	nephrosis/co, ep [Complication, Epidemiology]	189
23	nephrotic syndrome/co, ep [Complication, Epidemiology]	2133
24	exp glomerulopathy/co, ep [Complication, Epidemiology]	5475
25	exp glomerulonephritis/co, ep [Complication, Epidemiology]	4296
26	exp kidney dysfunction/co, ep [Complication, Epidemiology]	1322
27	(creatinine* or GFR or eGFR or albuminuri* or proteinuri* or microalbuminuri* or nephropath* or glomerulo* or nephr#ti* or nephrosi* or ur?emia or ESRD or CKD or	282722

	cardio-renal or Kimmelstiel-Wilson).tw.	
28	((renal or kidney) adj4 chronic adj4 failure*).tw.	28639
29	((renal or kidney) adj4 chronic adj4 disease*).tw.	23893
30	((renal or kidney) adj4 chronic adj4 insufficienc*).tw.	6425
31	((renal or kidney) adj4 chronic adj4 injury).tw.	631
32	((renal or kidney) adj4 chronic adj4 impairment*).tw.	501
33	exp infectious pneumonia/ or bacterial pneumonia/ or chlamydial pneumonia/ or group b streptococcal pneumonia/ or legionnaire disease/ or mycoplasma pneumonia/ or pneumocystis pneumonia/ or pulmonary candidiasis/ or severe acute respiratory syndrome/ or staphylococcal pneumonia/ or virus pneumonia/	50671
34	respiratory tract infection/ or exp influenza/ or laryngotracheobronchitis/ or lower respiratory tract infection/ or parainfluenza virus infection/ or respiratory syncytial virus infection/ or viral respiratory tract infection/	106624
35	avian influenza/	5081
36	chest infection/ or pertussis/	13997
37	bronchiolitis/ or laryngotracheobronchitis/ or tracheobronchitis/	10003
38	pleura empyema/	3703
39	pyuria/ or urinary tract infection/	66023
40	candiduria/ or kidney infection/	1502
41	kidney abscess/ or pyonephrosis/	1666
42	cystitis/	11865
43	pyelonephritis/ or acute pyelonephritis/	22138
44	brain infection/ or brain abscess/ or herpes simplex encephalitis/ or herpes zoster encephalitis/ or subdural empyema/ or tick borne encephalitis/ or virus encephalitis/	24862
45	central nervous system infection/ or epidural abscess/ or poliomyelitis/	38386
46	meningitis/ or bacterial meningitis/ or exp fungal meningitis/ or haemophilus meningitis/ or lymphocytic choriomeningitis/ or subdural empyema/ or virus meningitis/	57864
47	encephalitis/ or brain ventriculitis/ or eastern equine encephalitis/ or encephalomyelitis/ or epidemic encephalitis/ or meningoencephalitis/ or panencephalitis/ or primary amebic meningoencephalitis/	47288
48	exp meningococcosis/	11231
49	exp pneumococcal infection/	5729

50	exp group b streptococcal infection/ or group b streptococcal pneumonia/	405
51	exp bacteremia/ or staphylococcal bacteremia/	29638
52	bloodstream infection/	2518
53	candidemia/	1358
54	systemic mycosis/ or fungemia/ or invasive aspergillosis/ or invasive candidiasis/	5182
55	sepsis/ or bacteremia/ or septic shock/ or septicemia/ or urosepsis/	140091
56	viremia/	12287
57	parasitemia/	6918
58	(sepsis* or septic?emia or bacter?emia or fung?emia or pneumonia* or bronchopneumonia* or pleuropneumonia* or LRTI or empy?ema or influenza* or legionell* or bacteriuri* or pyelonephritis or cystitis or pyelocystitis or pyelitis or urethriti* or meningiti* or meningococc* or encephaliti* or poliomyeliti* or septic shock).tw.	497436
59	(CNS adj4 infection*).tw.	3591
60	(central nervous adj4 infection*).tw.	4861
61	UTI.tw.	6684
62	bronchopneumonia/	8394
63	arachnoiditis/ or aseptic meningitis/ or epidemic meningitis/ or group b streptococcal meningitis/ or meningoencephalitis/ or pneumococcal meningitis/	21305
64	exp epidemiology/ or exp incidence/	1705072
65	exp risk factor/	513022
66	exp attributable risk/	1487
67	exp hazard ratio/	11362
68	statistical model/	87903
69	(odds adj1 ratio).tw.	101865
70	(relative adj2 ratio).tw.	2736
71	case report/	1892302
72	developing country/	71459
73	developed country/	25618
74	postoperative complication/ or postoperative infection/ or surgical infection/	272218
75	exp Africa/	196804

76	argentina/ or bolivia/ or brazil/ or chile/ or colombia/ or ecuador/ or french guiana/ or guyana/ or paraguay/ or peru/ or suriname/ or uruguay/ or venezuela/	98392
77	exp Central America/	15618
78	china/ or mongolia/ or philippines/	82530
79	borneo/ or cambodia/ or indonesia/ or laos/ or malaysia/ or myanmar/ or papua new guinea/ or thailand/ or timor-leste/ or viet nam/	53670
80	North Korea/	237
81	latvia/ or lithuania/	3316
82	albania/ or armenia/ or azerbaijan/ or belarus/ or "bosnia and herzegovina"/ or bulgaria/ or "georgia (republic)"/ or "macedonia (republic)"/ or romania/ or russian federation/ or serbia/ or ukraine/	83374
83	USSR/	50149
84	iran/ or iraq/ or jordan/ or lebanon/ or "turkey (republic)"/ or yemen/	49920
85	kazakhstan/ or kyrgyzstan/ or tajikistan/ or turkmenistan/ or uzbekistan/	5682
86	afghanistan/ or bangladesh/ or india/ or nepal/ or pakistan/ or sikkim/ or sri lanka/	105351
87	cuba/ or dominica/ or dominican republic/ or grenada/ or guadeloupe/ or haiti/ or jamaica/	11346
88	fiji/ or philippines/ or polynesia/	8607
89	exp Indian Ocean/	2505
90	Mexico/	28748
91	72 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90	789122
92	exp Western Europe/	911511
93	croatia/ or czech republic/ or hungary/ or poland/ or slovakia/ or slovenia/	73494
94	Estonia/	2056
95	canada/ or united states/	1031054
96	japan/ or macao/	115065
97	South Korea/	4982
98	bahrain/ or cyprus/ or israel/ or kuwait/ or oman/ or qatar/ or saudi arabia/ or united arab emirates/	37707
99	exp "Australia and New Zealand"/	129186

100	brunei darussalam/ or hong kong/ or singapore/	21427
101	73 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100	2259038
102	91 not (91 and 101)	710496
103	treatment outcome/	579285
104	editorial/	438527
105	embryo/	177038
106	infant/	533322
107	child/	1295310
108	preschool child/	469034
109	school child/	217344
110	adolescent/	1180705
111	adult/	4186945
112	105 or 106 or 107 or 108 or 109 or 110	2546570
113	112 not (112 and 111)	1658687
114	animal model/	630310
115	animal experiment/	1606715
116	nonhuman/	3807183
117	animal/	1773703
118	human/	13422168
119	114 or 115 or 116 or 117	5921124
120	119 not (119 and 118)	4747089
121	pneumonia/	97950
122	lung infection/ or hantavirus pulmonary syndrome/ or lung abscess/ or viral bronchiolitis/	21795
123	(respiratory adj3 infection*).tw.	43371
124	(lower respiratory adj3 infection*).tw.	6553
125	(urinary adj3 infection*).tw.	44177
126	(upper urinary adj3 infection*).tw.	444
127	(epidemiolog$ or incidence).tw.	878025
128	(relative adj risk*).tw.	55195
129	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18	364340

	or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32	
130	33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 121 or 122 or 123 or 124 or 125 or 126	851259
131	64 or 65 or 66 or 67 or 68 or 69 or 70 or 127 or 128	2659100
132	129 and 130 and 131	7357
133	132 not 120 not 113 not 104 not 71 not 74 not 102	4970
134	limit 133 to (english or french or german)	4602
135	limit 134 to embase	4247

Supplementary Table 3: Cochrane library search strategy

	Search	Results
1	sepsis* or septic*mia or bacter*mia or fung*mia or pneumonia* or bronchopneumonia* or pleuropneumonia* or LRTI or empy*ma or influenza* or legionell* or bacteriuri* or pyelonephriti* or cystitis* or pyelocystitis* or pyelitis* or urethriti* or UTI or meningiti* or meningococc* or encephaliti* or poliomyeliti* or "septic shock"	19098
2	CNS near/4 infection*	47
3	"central nervous" near/4 infection*	92
4	[mh "cerebral phaeohyphomycosis"] or [mh ^"central nervous system infections"] or [mh "brain abscess"] or [mh "toxoplasmosis, cerebral"] or [mh ^"central nervous system bacterial infections"] or [mh "empyema, subdural"] or [mh "epidural abscess"] or [mh "lyme neuroborreliosis"] or [mh "meningitis, bacterial"] or [mh "meningitis, escherichia coli"] or [mh "meningitis, haemophilus"] or [mh "meningitis, listeria"] or [mh "meningitis, meningococcal"] or [mh "meningitis, pneumococcal"] or [mh "central nervous system fungal infections"] or [mh "meningitis, fungal"] or [mh "meningitis, cryptococcal"] or [mh neuroaspergillosis] or [mh ^"central nervous system viral diseases"] or [mh encephalitis] or [mh "encephalitis, viral"] or [mh "encephalitis, arbovirus"] or [mh "encephalitis, california"] or [mh "encephalitis, japanese"] or [mh "encephalitis, st. louis"] or [mh "encephalitis, tick-borne"] or [mh "west nile fever"] or [mh "encephalitis, herpes simplex"] or [mh "encephalitis, varicella zoster"] or [mh "encephalomyelitis, equine"] or [mh "meningitis, viral"] or [mh "lymphocytic choriomeningitis"] or [mh "meningitis, aseptic"] or [mh "paraparesis, tropical spastic"] or [mh ^poliomyelitis] or [mh "poliomyelitis, bulbar"] or [mh encephalomyelitis] or [mh meningitis]	1015
5	[mh "endocarditis, bacterial"] or [mh "endocarditis, subacute bacterial"] or [mh "pneumococcal infections"] or [mh ^"catheter-related infections"] or [mh coinfection] or [mh ^"communicable diseases"] or [mh "community-acquired infections"] or [mh sepsis] or [mh bacteremia] or [mh "hemorrhagic septicemia"] or [mh fungemia] or [mh "shock, septic"] or [mh empyema] or [mh viremia] or [mh parasitemia]	4033
6	respiratory near/3 infection*	4398
7	urinary near/3 infection*	3732
8	[mh pyelitis] or [mh pyelocystitis] or [mh pyelonephritis] or [mh urethritis] or [mh ^cystitis] or [mh ^"urinary tract infections"] or [mh pyuria]	2143
9	[mh ^"respiratory tract infections"] or [mh bronchiolitis] or [mh "bronchiolitis, viral"] or [mh ^"empyema, pleural"] or [mh "influenza, human"] or [mh legionellosis] or [mh	5402

	"legionnaires' disease"] or [mh "lung abscess"] or [mh "lung diseases, fungal"] or exp [mh "lung diseases, parasitic"] or [mh pneumonia] or [mh bronchopneumonia] or [mh pleuropneumonia] or [mh "pneumonia, bacterial"] or [mh "chlamydial pneumonia"] or [mh "pneumonia, mycoplasma"] or [mh "pneumonia, pneumococcal"] or [mh "pneumonia, rickettsial"] or [mh "pneumonia, staphylococcal"] or [mh "pneumonia, pneumocystis"] or [mh "pneumonia, viral"] or [mh "severe acute respiratory syndrome"] or [mh tracheitis] or [mh "whooping cough"]	
10	(renal or kidney) near/4 chronic near/4 failure*	4476
11	(renal or kidney) near/4 chronic near/4 disease*	1647
12	(renal or kidney) near/4 chronic near/4 insufficienc*	510
13	(renal or kidney) near/4 chronic near/4 injury	29
14	(renal or kidney) near/4 chronic near/4 impairment*	34
15	creatinine* or GFR or eGFR or albuminuri* or proteinuri* or microalbuminuri* or nephropath* or glomerulo* or nephr?ti* or nephrosi* or ur*mia or ESRD or CKD or cardio-renal or Kimmelstiel-Wilson	16810
16	[mh ^creatinine/BL]	2042
17	[mh ^"kidney diseases"/CO,EP]	341
18	[mh "diabetic nephropathies"] or [mh "hypertension, renal"] or [mh nephritis] or [mh "anti-glomerular basement membrane disease"] or [mh "glomerulonephritis, iga"] or [mh "glomerulonephritis, membranoproliferative"] or [mh "glomerulonephritis, membranous"] or [mh "lupus nephritis"] or [mh nephrosclerosis] or [mh nephrosis] or [mh "renal insufficiency"] or [mh "cardio-renal syndrome"] or [mh uremia] or [mh azotemia] or [mh proteinuria]	7117
19	[mh ^"kidney function tests"] or [mh "glomerular filtration rate"]	2417
20	{or #1-#9}	25511
21	{or #10-#19}	21120
22	{and #20-#21}	1422
23	incidence* or "odds ratio" or "risk ratio" or "risk factor" or "relative risk"	69239
24	[mh incidence] or [mh "multivariate analysis"] or [mh "odds ratio"] or [mh "logistic models"] or [mh "risk factors"] or [mh "epidemiologic studies"]	122866
25	{or #23-#24}	165844
26	{and #22, #25}	953

Supplementary Table 4: Inclusion and exclusion criteria for determining study eligibility

	Included	Excluded
Participants	Adult human participants.	Populations exclusively of: - pregnant women; - kidney transplant recipients or patients receiving renal replacement therapy; - patient groups usually managed in secondary care unless this was for chronic kidney disease, or routinely treated with immunosuppressive medication.
Study settings	High income countries (World Bank classification).(13) Community settings, including adults living in institutional care.	
Exposure of interest	Chronic acquired kidney disease, indicated by any of the following: - medical diagnosis; - reduced estimated glomerular filtration rate; - reduced creatinine clearance; - elevated creatinine; - proteinuria, micro- or macro-albuminuria; - renal structural abnormalities. Where there was no 'unexposed' group without kidney disease, comparison between stages 1-2 and stages 3-5 CKD was accepted.	
Outcomes of interest	Incidence rate ratio, risk ratio or odds ratio estimates of the effect of kidney disease on any of the following community-acquired acute infections: - lower respiratory tract infections; - urinary tract infections (UTIs); - central nervous system infections; - sepsis. Urinary catheter-associated UTIs from community settings, and incidence of severe disease (such as hospitalisation for infection) were accepted.	Outcomes not accepted: - infection prevalence; - hospital-associated infection rates; - post-operative follow up outcomes; - incidence of infection-related mortality; - prognosis among infected patients.
Study methodology	Trials, case-control studies, cohort studies or other observational study designs containing original data. Relevant review articles without original data were identified for reference list screening.	Case reports. Descriptive studies without a comparison group. Studies with fewer than 30 participants in either the exposed or unexposed categories.
Publication details	Any publication date. Languages: English, German, French.	

Supplementary Table 5: Quality assessment of studies including rationale (n=14)

	Case-control studies				Cohort studies									
	Vinogradova 2009 (16)	Watt 2007 (17)	Loeb 2009 (18)	Schnoor 2007 (19)	Higgins 1989 (22)	Hackam 2006 (24)	Dalrymple 2012 (23)	Karunajeewa 2005 (25)	James 2008 (26)	James 2009 (27)	Wang 2012 (28)	Caljouw 2011 (29)	Campbell 2011 * (21)	USRDS 2010(20)
Selection bias														
Selection of controls [1]	Low: matched selection of primary care registered patients	Low: neighbourhood controls selected systematically by proximity	Low: random digit dialling of hospital catchment area residents	Low: random selection from population register	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study
Participation bias [2]	Low: automatic participation	Low: participation 83% of cases, 84% of controls	Uncertain: participation rate not reported	High: Participation <60% overall	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study	N/A: cohort study
Loss to follow up [3]	N/A: case-control study	N/A: case-control study	N/A: case-control study	N/A: case-control study	Uncertain: not reported and clinically determined. May be differential, but study period only one year.	Low: automated follow up	Low: >80% follow up	Low: automated follow up	Low: automated follow up	Low: automated follow up	Low: >80% follow-up	Low: followed up 479 of 551 participants alive aged 86 years: 86% follow up	Low: active case-finding applied to national census figure (no follow up required)	Low: automated follow up
Non-differential misclassification of exposure [4]	High: relies on medical diagnosis of chronic renal disease in medical records.	High: relied on medical diagnosis of chronic renal disease in medical records.	High: ascertained medical diagnosis of chronic renal disease in participant interview.	High: ascertained medical diagnosis of chronic renal disease in questionnaire for controls	Uncertain: not reported when creatinine measured.	High: relies on medical diagnosis of chronic renal disease in medical records.	Low: determined prospectively from blood results	Low: determined prospectively from test results	Low: determined prospectively from blood results	Low: determined prospectively from blood results	Low: determined prospectively from blood results	Low: determined prospectively from blood results	High: relies on medical diagnosis of chronic renal disease in medical records.	High: relies on medical diagnosis of chronic renal disease in insurance claims
Information bias: exposure														
Recall bias [5]	Low: kidney disease diagnosis ascertained from pre-	Low: kidney disease diagnosis ascertained from pre-	High: ascertained medical diagnosis of kidney	High: ascertained medical diagnosis of kidney	Low: determined from serum creatinine with clear	Low: kidney disease diagnosis ascertained from pre-	Low: determined prospectively from blood results.	Low: determined prospectively from test results.	Low: determined prospectively from blood results.	Low: determined prospectively from blood results.	Low: determined prospectively from blood results.	Low: determined prospectively from blood results.	Low: kidney disease diagnosis ascertained from pre-	Low: kidney disease diagnosis ascertained from pre-

	existing medical records	existing medical records	disease in participant interview in hospital for cases and at home for controls	disease at home for controls	cut-off (objective measure)	existing medical records							existing medical records	existing insurance records
Observer bias [6]	Low: used pre-specified codes to define kidney disease status	Uncertain: Medical record abstractors not blinded to case-control status and criteria for assigning kidney disease status not reported	High: interviewers aware of case status (interviewed in hospital) or control status (telephone interview at home)	High: decision to list diagnosis of kidney disease in case report made in context of illness for cases	Low: determined from serum creatinine with clear cut-off (objective measure)	Uncertain: source of kidney disease status data not reported. If hospital records are used, decision to list diagnosis in discharge record made in context of illness for cases.	Low: determined from serum cystatin C (objective measure)	Low: determined from blood and urine test results (objective measure)	Low: determined from serum creatinine (objective measure)	Low: determined from serum creatinine (objective measure)	Low: determined from serum creatinine (objective measure)	Low: determined from serum creatinine (objective measure)	High: decision to list diagnosis of kidney disease in case report made in context of illness for cases	Low: used pre-specified codes to define kidney disease status
Ascertainment [7]	Low: chronic kidney disease diagnosis would have to predate current acute infection	Low: chronic kidney disease diagnosis would have to predate current acute infection	Low: chronic kidney disease diagnosis would have to predate current acute infection	High: ascertainment entirely different for cases than controls	Uncertain: not reported when creatinine measured, or whether this is recurrent/ prompted by illness	Uncertain: source of kidney disease status data not reported. If hospital records used, patients with infection-related hospitalisations more likely to have CKD status recorded.	Low: all participants tested at baseline.	Low: participants monitored annually.	Low: baseline measure used (that only patients with a result were eligible was considered a limitation to generalisability)	Low: sensitivity analysis using only the baseline creatinine test found similar results to the last-carried forward method	Low: all participants tested at baseline.	Low: all participants tested at baseline.	High: ascertainment entirely different for cases than non-cases	Low: kidney disease status ascertained in year prior to study
Non-differential misclassifica	Low: medical diagnosis of severe	Low: active surveillance with clear	Low: severe outcome with clear	Low: severe outcome with clear	Uncertain: methods for ascertaining	Low: severe outcome with widely	Low: severe outcome with clear	Low: severe outcome with widely	Low: severe outcome with clear	Low: severe outcome with widely	Low: severe outcome with clear	Uncertain: kidney disease	Uncertain: sending of PCR test	Low: severe outcome unlikely to

tion of outcome [8]	outcome	criteria	criteria	criteria	infection not reported	accepted clinical criteria	criteria	accepted clinical criteria	criteria	accepted clinical criteria	criteria	status may affect healthcare attendance for minor illness such as UTI	during influenza pandemic vulnerable to be influenced by kidney disease status	be missed
Information bias: outcome														
Recall bias [9]	Low: cases identified from medical records based on GP diagnosis	Low: cases identified by laboratory surveillance	Low: cases determined by medical diagnosis in hospital	Low: Low: realtime reporting system through established surveillance network	Uncertain: methods for ascertaining infection not reported	Low: monitoring of all hospital discharge reports	Low: semi-annual cohort monitoring	Low: monitoring of all hospital discharge reports	Low: monitoring of all biochemistry results	Low: monitoring of all hospital discharge reports	Low: semi-annual cohort monitoring	Low: annual clinician interviews supplemented with medical record review	Low: realtime case finding system through laboratory results	Low: monitoring of all hospital insurance claims
Observer bias [10]	Low: clinical diagnosis of severe outcome unlikely to be severely affected by kidney disease comorbidity	Low: Laboratory based surveillance system with clear criteria for cases	Low: CKD status unlikely to severely affect physician application of clear criteria	Low: surveillance system with clear criteria for cases	Uncertain: standard definition of APN is vague and not reported whether any observer blinded to renal status	Low: kidney disease status unlikely to affect choice of hospital diagnosis code for severe outcome	Low: kidney disease status unlikely to affect choice of hospital diagnosis code for severe outcome	Low: kidney disease status unlikely to affect choice of hospital diagnosis code for severe outcome	Low: objective definition of outcome independent of exposure status	Low: kidney disease status unlikely to affect choice of hospital diagnosis code for severe outcome	Low: CKD status unlikely to severely affect application of clear criteria	Low: kidney disease status unlikely to strongly influence diagnosis of UTI at age 86-89 years, given case criteria include symptoms and urinary analysis	Low: objective criteria for cases once tested	Low: kidney disease status unlikely to affect choice of hospital diagnosis code for severe outcome
Ascertainment [11]	Low: kidney disease status unlikely to affect primary care attendance with severe outcome	Low: active surveillance with clear criteria, testing for IPD unlikely to be markedly influenced by CKD	Low: kidney disease status unlikely to affect hospital attendance with severe outcome	Low: kidney disease status unlikely to affect primary care or hospital attendance with severe outcome	Uncertain: methods for ascertaining infection not reported	Low: kidney disease status unlikely to affect diagnosis of severe outcome with widely accepted	Low: kidney disease status unlikely to affect hospital attendance with severe outcome	Low: kidney disease status unlikely to affect hospital attendance with severe outcome	Low: sending of blood culture unlikely to be influenced by kidney disease in context of severe	Low: kidney disease status unlikely to affect diagnosis of severe outcome with widely accepted	Low: kidney disease status unlikely to affect hospital attendance with severe outcome	Uncertain: kidney disease status may affect healthcare attendance for minor illness such as UTI	Uncertain: sending of PCR test during influenza pandemic vulnerable to be influenced by	Low: kidney disease status unlikely to affect hospital attendance with severe outcome

		status in context of known high incidence among the Navajo Nation				clinical criteria			illness	clinical			comorbidities	
Confounding	Low: controls matched to cases on age and sex, estimate adjusted for wide range of confounders including diabetes[13]	Low: controls matched for age and sex. Diabetes eligible for inclusion in final model [14]	Low. Age, sex and diabetes eligible for inclusion in final model [15]	High: unadjusted	High: unadjusted estimate. In particular, high immunosuppressant use among the study population	Low: adjusted for age, sex, nature of index event, charlson index, healthcare use, and other comorbidities	Low: adjusted for age, sex, race, smoking, BMI, diabetes mellitus, and multiple co-morbidities.	High: no adjustment for sex [16]	Low: adjusted for age, sex, diabetes, comorbidity score, care in a dedicated renal clinic	Low: adjusted for age, sex, socio-economic status, ethnicity, diabetes mellitus, Charlson comorbidity score	High: adjusted for age, sex, alcohol, smoking and demographic factors but no comorbitidies.	High: no adjustment for sex or diabetes [17]	High: adjusted for age only	High: unadjusted [19]
Reverse causation [18]	Low: pre-existing kidney disease reported at time of infection	Low: pre-existing kidney disease reported at time of infection	Low: pre-existing kidney disease reported at time of infection	Low: pre-existing kidney disease reported at time of infection	Uncertain: Timing of creatinine measurement relative to infections not specified	Low: chronic renal failure should not be diagnosed within one hospital episode for infection	Low: baseline serum cystatin C used	Low: serum biochemistry tested at screening	Low: baseline creatinine used	Low: only followed to first outcome event, creatinine result predates qualifying infection	Low: baseline creatinine used	Low: baseline creatinine used	Low: pre-existing kidney disease reported at time of infection	Low: kidney disease status established in year prior to study

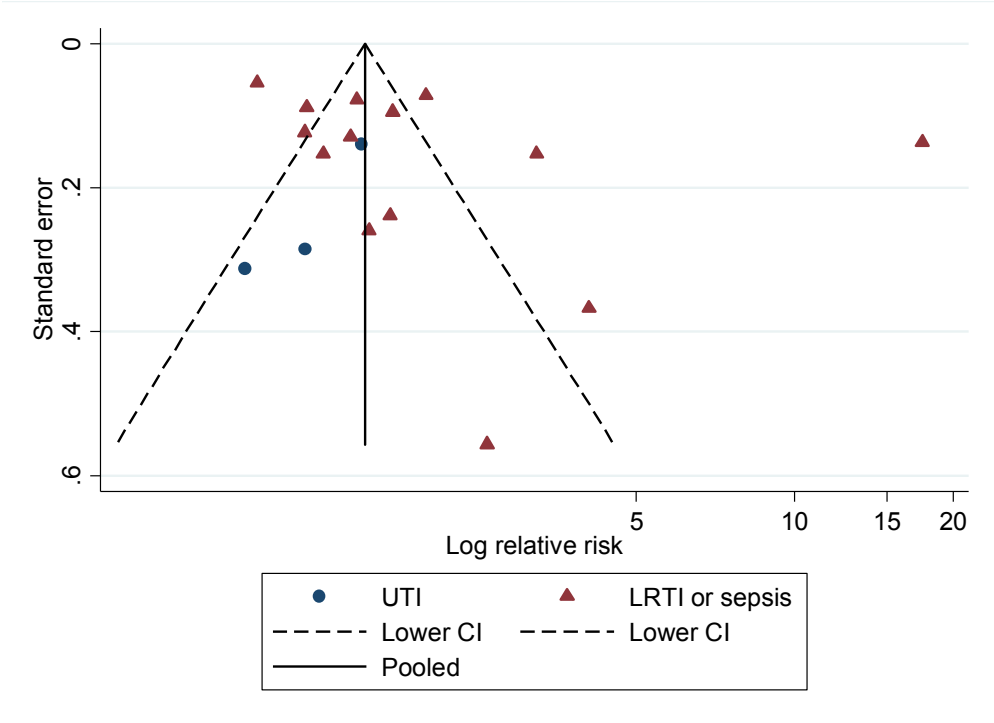
*The unusual design of the artificial cohort study by Campbell *et al*. is worth clarification. During the 2009–2010 influenza pandemic, hospitalised cases of laboratory confirmed pandemic influenza A (H1N1) were reported by a laboratory-based national surveillance system. The surveillance report, completed by the microbiologist, asked whether the case had a diagnosis of CKD. Denominators for infection rates were obtained from primary care registers of patients eligible for pandemic influenza vaccination by virtue of a CKD diagnosis (for CKD): and from the national census (for non-CKD).(29) The effect of CKD on influenza may be overestimated in this study, because CKD was advertised as a possible risk factor for pandemic influenza to encourage vaccine uptake among this group, and patients with flu-like symptoms could have been more likely to attend hospital or be tested for pandemic influenza A (H1N1) if they had a diagnosis of CKD.

1. High risk: probability of selection as a control likely to be affected by kidney disease status (known or unknown).
Low risk: controls selected using random sampling (or other system unlikely to be biased by kidney disease status) from the population from which the cases arose.

2. Low risk: (1) automated participation (e.g. medical record review), or (2) ≥80% participation, or (3) 70-80% participation with a comparison (min age, sex, death/morbidity) showing similar characteristics between those included and those not included in the study.
3. Low risk: (1) automated follow up (e.g. through record linkage), or (2) ≥80% follow up, or (3) 70-80% follow up with a comparison (min age, sex, death/morbidity) showing similar characteristics between those included and those not included in the study.
4. High risk: allocation of kidney disease status relies on existing kidney disease having been diagnosed as part of routine medical care.
Low risk: All members of study assessed for kidney disease at baseline.
5. High risk: kidney disease status defined by patient recall of CKD diagnosis in context of recent infection.
6. High risk: kidney disease status defined by observer unblinded to case status, without clear objective criteria to apply.
7. High risk: participants with infections are more or less likely to be tested for kidney disease.
8. Low risk: Active screening for infection, or severe outcome unlikely to be missed or presents validation results of >70% sensitivity and specificity
9. High risk: infection status defined by patient recall of infection in context of kidney disease e.g. participants with kidney disease asked to recall infections while at renal clinic.
10. High risk: infection status defined by observer in context likely to be influenced by kidney disease status (assumed that clinical diagnosis of severe infections was unlikely to be strongly influenced by awareness of CKD as a comorbidity but that less severe infections may be influenced by this in the absence of clear diagnostic criteria).
11. High risk: ascertainment of infections likely to be influenced by kidney disease status (assumed that attendance to healthcare facility for severe infections was unlikely to be strongly influenced by awareness of CKD as a comorbidity but that attendance for less severe infections may be influenced by this in the absence of active surveillance).
12. Low risk: At least age, sex and diabetes must have been eligible and considered for the final model.
13. Controls matched to cases on age at index data (within 1 year), sex, general practice, and calendar time. Estimate adjusted for smoking status, Townsend deprivation score, use of influenza vaccine in previous 12 months, use of pneumococcal vaccine in previous 5 years, number of years of medical records data available in database, and comorbidities including: diabetes, chronic heart disease, chronic respiratory disease, asplenia, cerebrospinal shunt, chronic liver disease, sickle cell disease or coeliac disease, cochlear implant, HIV/AIDS, immunosuppression, stroke or transient ischaemic attack, rheumatoid arthritis, Parkinson's disease, multiple sclerosis, dementia, osteoporosis, and any cancer.
14. Controls matched for age and sex. Diabetes eligible for inclusion in final model, which was adjusted for age, pneumococcal vaccine, congestive heart failure, alcohol use, BMI and unemployment.
15. Age, sex and diabetes eligible for inclusion in final model. Final model adjusted for age, non-English language at home, living in a detached house, living alone, congestive heart failure, chronic obstructive pulmonary disease, dysphagia, Barthel index of functional status, immunosuppressive medications, nutritional score, tobacco use, alcohol use, and exposure to fumes.

16. The best adjusted estimate for urinary sepsis is adjusted for asymptomatic bacteriuria and age, and restricted to diabetics, but not adjusted for sex.
17. High risk: age-restricted and stratified by long term care facility (LCTF) residency, but no management of confounding by sex or co-morbidities.
18. High risk: exposure defined after the infection defined as the study outcome.
19. Rate ratios for hospitalisation with UTI, pneumonia and bacteraemia/ sepsis unadjusted. Rate ratios for hospitalisation with any infection calculated as the ratio of the rate among participants with CKD, compared with no CKD, each rate having been adjusted for gender, prior hospitalisation, ASHD, CHF, CVA, PVD, dysrhythmia, other cardiac disease, diabetes, COPD, hypertension, liver disease, gastrointestinal disease, cancer, and anemia.

Supplementary Figure 1: Funnel plot showing the relationship between relative risk and standard error for the 17 estimates from all 12 studies considered for meta-analysis (all infections combined)



UTI = urinary tract infection

Other infections comprised lower respiratory tract infections and sepsis.

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	7
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	8 and Appendix Table 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix Tables 1-3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	9
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9

PRISMA 2009 Checklist

Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (I^2) for each meta-analysis.	10

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	10
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	12 and figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	12 and Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	14 and Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13 and Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13 and Figure 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	14 and Appendix Figure 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	22
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	22,24
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	25-26
FUNDING			

PRISMA 2009 Checklist

Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	31

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