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**Long-term consequences of urinary tract infection in Childhood (LUCI): Electronic population-based cohort study**

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## **How this fits in:**

Studies have estimated the risk of renal scarring following childhood urinary tract infection (UTI) to be 5.6%-15%, but these were generally conducted in hospital with selected populations of children who were seriously ill or with additional risk factors. The risk of renal scarring from less severe UTI, without additional risk factors, and in the majority of children commonly seen in primary care, is not known.

This study has found that childhood UTI, including UTI diagnosed in primary care, is associated with renal scarring, even in the absence of other risk factors such as vesicoureteric reflux (VUR), but the rate of diagnosed renal scarring is only around 1%. It has also found that childhood UTI, in the absence of other risk factors, is not associated with chronic kidney disease (CKD), hypertension or end-stage renal failure (ESRF) up to age ten.

## **Abstract**

### *Background*

Childhood urinary tract infection (UTI) can cause renal scarring and possibly hypertension, chronic kidney disease (CKD) and end-stage renal failure (ESRF). Previous studies focus on selected populations, with severe illness or underlying risk factors. The risk for most children with UTI is unclear.

### *Aim*

Examine the association between childhood UTI and outcomes in an unselected population of children.

### *Design and setting*

Retrospective population-based cohort study using linked GP, hospital and microbiology records; Wales, UK.

### *Method*

Participants: All children born 2005-2009. Follow-up until 31/12/2017.

Exposure: Microbiologically confirmed UTI before age five.

Key outcomes: Renal scarring, hypertension, CKD, ESRF.

### *Results*

Of 159,201 children, 48.7% female, 11,099 (7%) had UTI. 245 (0.15%) were diagnosed with renal scarring by age seven. Odds of renal scarring were higher in children with UTI (1.24%; adjusted odds ratio 4.60, 95% CI: 3.33 to 6.35).

Mean follow-up was 9.53 years. Adjusted hazard ratios (95% CI) were: 1.44 (0.84 to 2.46) for hypertension; 1.67 (0.85 to 3.31) CKD; 1.16 (0.56 to 2.37) ESRF.

### *Conclusions*

The prevalence of renal scarring in an unselected population of children with UTI is low. Without underlying risk factors, UTI is not associated with CKD, hypertension or ESRF by age 10. Further research with systematic scanning of children's kidneys including those with less severe UTI and without UTI, is needed to increase certainty of these results, as most children are not scanned. Longer follow-up is needed to establish if UTI, without additional risk factors, is associated with hypertension, CKD or ESRF later in life.

### *Introduction*

Urinary tract infection (UTI) is a common cause of serious illness and hospital admission in children.<sup>1,2</sup> Childhood UTI can also cause renal scarring and has been associated with long-term complications such as hypertension, pre-eclampsia and renal failure.<sup>3-6</sup> However, the evidence for this association is weak and has been questioned.<sup>2,7-10</sup> In addition, the risk of renal scarring in children with less severe UTI or without underlying risk factors is not clear.

This needs to be clarified as it informs the correct approach to urine sampling and diagnosis of UTI in children.

A systematic review, published in 2010, found that the prevalence of renal scarring following first childhood febrile UTI was 15%.<sup>5</sup> Another systematic review, in 2019, examining antibiotic prophylaxis for recurrent UTI, found renal scarring in 5.7% of children.<sup>11</sup> The studies in these reviews, and those on which much of the current practice is based, were generally conducted in secondary care, where children tend to have serious illness, or in selected populations where a high proportion of children have other risk factors such as vesicoureteral reflux disease (VUR). One study included recruitment from primary care and reported that of 143 children with UTI and without VUR, 5.6% had renal scarring.<sup>12</sup> However, only 19.7% of eligible children were enrolled in the study suggesting significant selection bias.<sup>12</sup> Studies examining risk factors for renal scarring, including a meta-analysis of 1280 children, are also limited to children with febrile UTI, those with serious illness in hospital, and with a high proportion of VUR.<sup>13-18</sup>

The risk of renal scarring for the majority of children, not necessarily febrile and without additional risk factors, frequently seen in primary care, is not known. The long-term follow-up of children with UTI has been highlighted by the National Institute for Health and Care Excellence (NICE) as a research priority.<sup>2</sup> The importance of understanding the risk of complications following UTI in most children, without underlying congenital abnormalities has also been highlighted.<sup>8</sup>

The aim of this study was to determine, whether children who have experienced a UTI in childhood (before the age of five years) from any setting and of any severity, have worse

outcomes compared to children who have not experienced a UTI, across the whole of the population of Wales.<sup>19</sup> A secondary objective was to identify which factors were associated with renal scarring in children who have had one or more childhood UTIs.

## Methods

This was a retrospective observational study using anonymised routinely collected data from the Secure Anonymised Information Linkage (SAIL) Databank with person-level linkage across datasets.<sup>20-22</sup>

### *Data sources*

SAIL is a repository for routinely collected health and population data in Wales.<sup>20-22</sup> All data were accessed via the secure, remote access, SAIL Gateway following Information Governance Review Panel approval.<sup>20-22</sup> Public Health Wales provided a data extract of urine microbiology culture results from all microbiology laboratories in Wales (Datastore) for use in this project.

### *Study design and participants*

The cohort were children born and resident in Wales during their first five years of life, and under five years old between 1999 and 2012. The main cohort for analysis were children born between 1 January 2005 and 31 December 2009 to ensure that the first five years of life were covered by the dates when microbiology data was available. The study end date was 28 February 2017.



### *Exposure*

UTI cases were based on National Health Service (NHS) laboratory results from microbiological culture. These data represented samples, from primary and secondary care, classified as positive or negative by NHS laboratories according to their standard operating procedures. Exposure was at least one microbiologically confirmed UTI before fifth birthday. As exposure (to UTI) can change over the study period, exposure status was taken at the time of outcome or age five where no outcome was recorded before this time.

### *Outcomes*

The primary outcome measure was renal scarring identified in the medical records. There was no single ICD-10 code for renal scarring, so following discussion with the medical coding department and consultant paediatric nephrologist (JVdV), we included ICD-10 codes where renal scarring or chronic pyelonephritis were specified and where coders indicated renal scarring may be coded (N11.0, N11.1, N13.7, N28.8). The secondary outcomes were hypertension, chronic kidney disease (CKD), end-stage renal failure (ESRF), hospital admissions, GP consultations, antibiotic prescriptions, microbiologically confirmed UTI aged 5-7, dysfunctional voiding, renal imaging, renal/urological surgery and day case admissions. Sources of data and clinical codes to define outcomes, and analysis approach are in Supplementary Tables 1 and 2.

GP consultations related to an actual clinician contact rather than planned consultations such as immunisations or medication reviews.<sup>23</sup>

### *Risk factors for renal scarring*

A Directed Acyclic Graph informed our choice of variables to include in the main analysis (Supplementary Figure 1). We considered sex, deprivation, comorbidities, VUR and other congenital malformations, and perinatal factors, as known or possible potential confounders (Supplementary Table 3). As we were interested in the effects of exposures that were not mediated through these factors, we adjusted for these in the models. Clinical codes for congenital malformations and comorbidities are listed in Supplementary Table 4.

Comorbidities were treated as time-varying covariates in the same way as exposure.

Congenital abnormalities (including VUR) were considered to have been there since birth even if recording of the diagnosis occurred later.

### Statistical analyses

The sample size was based on the outcome of renal scarring in children with microbiologically confirmed UTI and taken as 15% from the 2010 systematic review.<sup>5</sup> Full details can be found in the protocol paper.<sup>19</sup>

We used demographic and clinical codes to describe baseline characteristics by exposure status to summarise the study population and described the prevalence of renal scarring by age five and age seven. Where a lack of evidence of an event occurred in the data then this was taken as no event e.g. if no renal scarring code was found then we assume that no renal scarring occurred. For variables where we would expect data such as age, sex, ethnicity, missing data was not imputed and a complete case set used. We used logistic regression with discrete time-varying exposure covariates including the exposure variable and risk factors to model the odds of renal scarring in the first five and seven years of life. Odds ratios (ORs) were estimated with 95% confidence intervals (CIs) for exposure to UTI, adjusting for risk

factors. Cox regression with discrete time-varying exposure covariates was used to model time to first renal scarring admission. Models were censored at date of death, migration or end of study. A competing risks model was also run to take into account of any deaths that could modify the chance of renal scarring. Adjusted HRs with 95% CI for exposure to UTI were estimated for both time to event models.

Secondary outcomes were analysed using a combination of logistic, Poisson, or negative binomial regression, or time to event models, depending on the nature of data and were pre-specified (Supplementary Table 1). Poisson or negative binomial regression models were used where the outcome was a count of events.

Several sensitivity analyses were performed. (1) Due to uncertainty whether renal scarring codes were sufficiently sensitive to pick up all cases, the primary outcome was expanded to include renal pathology codes (Supplementary Table 5). (2) In children linked to GP data, any additional renal scarring diagnoses were determined using these data (Supplementary Table 5). (3) Two effect modifiers were pre-specified for sub-group analyses for the primary outcome: sex of child and presence of any renal/urological congenital anomalies. We also identified risk factors for renal scarring in children with at least one childhood UTI.

#### *Post-hoc analyses*

Two post-hoc analyses were performed. The first, analysed children with only one UTI separately to those with more than one UTI. A second analysed the association between UTI and renal scarring excluding children with congenital anomalies, as advised by the independent study steering committee.

SPSS v26.0 and Stata SE (version 16.0) were used for all statistical analyses.

## Results

The study population was 627,107 eligible children born in Wales between 1999 and 2012. After excluding children with incomplete exposure period before the age of five, 159,201 (25.4%) remained with full exposure data available for all five years (Figure 1). Of these, 43,584 (27.4%) children had at least one urine sample analysed between birth and age five. In 32,485 (74.5%) of these children, representing 20.4% of the whole cohort, all of the samples analysed were negative. 11,099 (7.0% of the whole cohort), had at least one positive sample (microbiologically confirmed UTI). 115,617 (72.6%) had no urine samples analysed by the age of five.

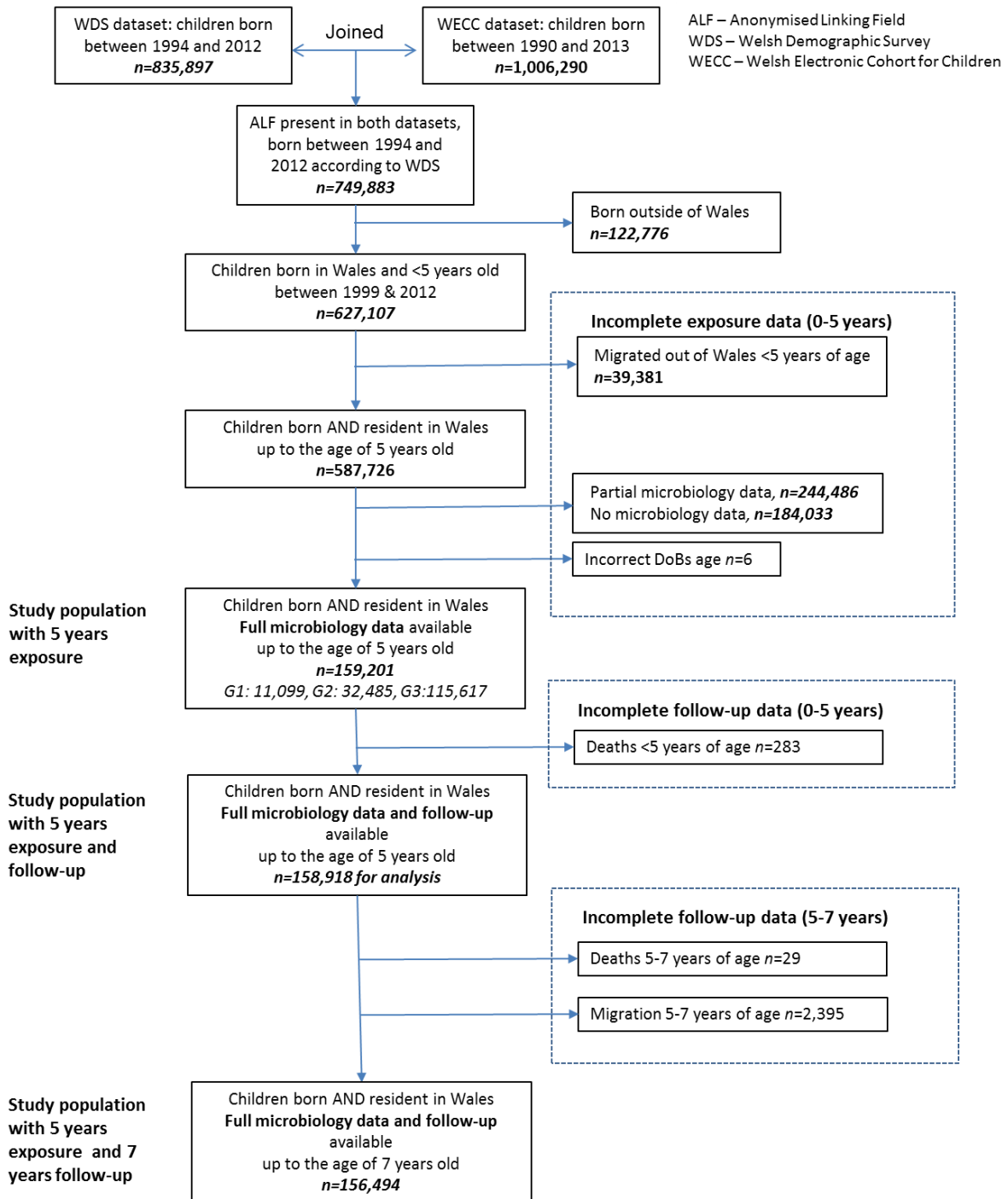
The mean follow-up period per child, from birth was 9.53 years (SD=1.54). 158,918 (99.8%) children had at least five years, and 156,494 (98.3%) had at least seven years follow-up. The final study cohort were consistent with the population excluded from analysis (Table 1).

### *Renal scarring*

The prevalence of diagnosed renal scarring by age five was 0.13% (n=208), and by age seven was 0.15% (n=245). In children with at least one UTI, the prevalence of diagnosed renal scarring by age five was 0.99% (n=109/11,023) and by age seven was 1.24% (n=135/10,875) (Table 2). The majority of those with UTI and renal scarring had also been diagnosed with VUR (n=91/135, 83%). The association between a UTI and a subsequent diagnosis of renal scarring up to age five was evident (adjusted OR (aOR) 4.03 (95% CI 2.81 to 5.79); table 2). Similar associations were found with renal scarring up to 7 years of age (Table 2). When time to diagnosed renal scarring was examined, the aOR was 2.76 (95% CI 2.07 to 3.68). A competing risks model produced similar results. Utilising all 159,201 children in the analysis, when time to renal scarring was examined (or in those that did not have renal scarring, time

to death, migration or end of study), the crude hazard ratio (HR) was 16.34 (12.93 to 20.66) and after adjustment for the same confounders reduced to 2.76 (2.07 to 3.68). Using a competing risks model (where the competing risk was death), the crude sub-HR was found to be similar (16.31 (12.91 to 20.62)).

**Figure 1. Flow of patients from initial identification in the database through to final cohort**



**Exposure**  
G1: At least one mcUTI, G2: Negative samples, G3: No samples sent

**Table 1. Comparison between study population by exposure group and the excluded population**

|                                    | At least one microbiologically confirmed UTI n=11,099 Group 1 | No UTI (Group 2+3)                           |                                    | Final study cohort n=159,201 Group 1+2+3 | Excluded population* n=428,515 |
|------------------------------------|---|--|------------------------------------|--|--------------------------------|
|                                    |   | Only negative urine samples n=32,485 Group 2 | No urine samples n=115,617 Group 3 |  |                                |
| Sex N(%)                           |   |  |                                    |  |                                |
| Male                               | 3,359 (30.3)  | 15,093 (46.5)                                | 63,225 (54.7)                      | 81,677 (51.3)                            | 219,867 (51.3)                 |
| Female                             | 7,740 (69.7)  | 17,392 (53.5)                                | 52,392 (45.3)                      | 77,524 (48.7)                            | 208,648 (48.7)                 |
| <b>Deprivation quintile N(%)</b>   |   |  |                                    |  |                                |
| Missing data                       | 286 (2.6)   | 908 (2.8)                                    | 3254 (2.8)                         | 4,448 (2.8)                              | 14,463 (3.4)                   |
| Data available                     | 10,813 (97.4)   | 31,577 (97.2)                                | 112,363 (97.2)                     | 154,753 (97.2)                           | 414,052 (96.6)                 |
| 1 – Least deprived                 | 2,980 (27.6)  | 7,961 (25.2)                                 | 29,576 (26.3)                      | 40,517 (26.2)                            | 108,889 (26.3)                 |
| 2                                  | 2,425 (22.4)  | 6,698 (21.2)                                 | 25,057 (22.3)                      | 34,180 (22.1)                            | 90,340 (21.8)                  |
| 3                                  | 2,040 (18.9)  | 6,161 (19.5)                                 | 21,008 (18.7)                      | 29,209 (18.9)                            | 78,909 (19.1)                  |
| 4                                  | 1,666 (15.4)  | 5,232 (16.6)                                 | 19,086 (17.0)                      | 25,984 (16.8)                            | 69,542 (16.8)                  |
| 5 – Most deprived                  | 1,702 (15.7)  | 5,525 (17.5)                                 | 17,636 (15.7)                      | 24,863 (16.1)                            | 66,372 (16.0)                  |
| Maternal age at birth (years) N(%) |   |  |                                    |  |                                |
| Missing data                       | 5 (0.05)  | 11 (0.03)                                    | 50 (0.04)                          | 66 (0.04)                                | 927 (0.2)                      |
| Data available                     | 11,094 (99.95)  | 32,474 (99.97)                               | 115,567 (99.96)                    | 159,135 (99.96)                          | 427,588 (99.78)                |
| Less than 24                       | 3,687 (33.2)  | 10,384 (32.0)                                | 36,182 (31.3)                      | 50,253 (31.6)                            | 132,425 (31.0)                 |
| 25-29                              | 3,074 (22.7)  | 9,021 (27.8)                                 | 30,722 (26.6)                      | 42,817 (26.9)                            | 126,987 (29.7)                 |
| 30-34                              | 2,601 (23.4)  | 8,018 (24.7)                                 | 28,755 (24.9)                      | 39,374 (24.7)                            | 110,724 (25.9)                 |
| 35 or above                        | 1,732 (15.6)  | 5,051 (15.6)                                 | 19,908 (17.2)                      | 26,691 (16.8)                            | 57,452 (13.4)                  |
| Birth weight (g) N(%)              |   |  |                                    |  |                                |
| Missing data                       | 28 (0.3)  | 61 (0.2)                                     | 128 (0.1)                          | 217 (0.1)                                | 535 (0.1)                      |
| Data available                     | 11,071 (99.7)   | 32,424 (99.8)                                | 115,489 (99.9)                     | 158,984 (99.9)                           | 427,980 (99.9)                 |
| Low (<2500)                        | 1,065 (9.6)   | 2,616 (8.1)                                  | 7,090 (6.1)                        | 10,771 (6.8)                             | 28,665 (6.7)                   |

|  |               |                  |                   |                   |                   |
|--|---------------|------------------|-------------------|-------------------|-------------------|
| Normal (2500 to <4500)                   | 8,877 (80.2)  | 26,267<br>(81.0) | 94,280<br>(81.6)  | 129,424<br>(81.4) | 348,890<br>(81.5) |
| High (4000 to <7000)                     | 1,129 (10.2)  | 3,541 (10.9)     | 14,119<br>(12.2)  | 18,789<br>(11.8)  | 50,425 (11.8)     |
| Gestational age at birth (weeks)<br>N(%) |               |                  |                   |                   |                   |
| Missing data                             | 81 (0.7)      | 225 (0.7)        | 1,182 (1.0)       | 1,488 (0.9)       | 19,565 (4.6)      |
| Data available                           | 11,018 (99.3) | 32,260<br>(99.3) | 114,435<br>(99.0) | 157,713<br>(99.1) | 408,950<br>(95.4) |
| Less than 33                             | 384 (3.5)     | 760 (2.4)        | 1,255 (1.1)       | 2,399 (1.5)       | 6,409 (1.6)       |
| 33 to <37                                | 700 (6.4)     | 2,085 (6.5)      | 6,042 (5.3)       | 8,827 (5.6)       | 23,547 (5.8)      |
| 37 to 43                                 | 9,934 (90.2)  | 29,415<br>(91.2) | 107,138<br>(93.6) | 146,487<br>(92.9) | 378,994<br>(92.7) |
| Ever breastfed** N(%)                    |               |                  |                   |                   |                   |
| Missing data                             | 736 (6.6)     | 1,739 (5.4)      | 7755 (6.7)        | 10,230 (6.4)      | 148,445<br>(34.6) |
| Data available                           | 10,363 (93.4) | 30,746<br>(94.6) | 107,862<br>(93.3) | 148,971<br>(93.6) | 280,070<br>(65.4) |
| No                                       | 4,555 (44.0)  | 12,667<br>(41.2) | 47,378<br>(43.9)  | 64,600<br>(43.4)  | 127,851<br>(45.6) |
| Yes                                      | 5,808 (56.0)  | 18,079<br>(58.8) | 60,484<br>(56.1)  | 84,371<br>(56.6)  | 152,219<br>(54.4) |

\* Partial (n=244,486) or no (n=184,033) microbiology data, incorrect date of birth (n=6)

\*\*At birth or at 6-8 weeks post-partum



**Table 2: Renal scarring diagnosis to age of 5 and 7 by exposure group N(%)**

|  | <b>No renal scarring<br/>N=158,710<br/>(99.87%)</b> | <b>Renal scarring<br/>N=208<br/>(0.13%)</b> | <b>Crude OR (95% CI)</b> | <b>Adjusted* OR (95% CI)</b>  |
|--|---|---|--------------------------|-------------------------------|
| <b>Analysis to age 5<br/>N=158,918</b> |   |   |                          |                               |
| No UTI n=147,895                       | 147,796 (99.93)                                     | 99 (0.07)                                   | ref                      | ref                           |
| UTI n=11,023                           | 10,914 (99.01)                                      | 109 (0.99)                                  | 14.91 (11.35 to 19.59)   | 4.03 (2.81 to 5.79)           |
|  | <b>No renal scarring<br/>N=156,249<br/>(99.84%)</b> | <b>Renal scarring<br/>N=245<br/>(0.16%)</b> | <b>Crude OR (95% CI)</b> | <b>Adjusted** OR (95% CI)</b> |
| <b>Analysis to age 7<br/>N=156,494</b> |   |   |                          |                               |
| No UTI n=145,619                       | 145,509 (99.92)                                     | 110 (0.08)                                  | ref                      | ref                           |
| UTI n=10,875                           | 10,740 (98.76)                                      | 135 (1.24)                                  | 16.63 (12.92 to 21.40)   | 4.60 (3.33 to 6.35)           |

\*adjusted for sex, comorbidities, known congenital anomalies and vesicoureteral reflux (VUR)

\*\* adjusted for comorbidities and vesicoureteral reflux (VUR)

### *Post-hoc analysis*

Children with only one UTI did not have a higher odds of renal scarring diagnosis than those without UTI (aOR=1.34 (95% CI:0.91 to 1.98) whereas children with more than one UTI did have a higher odds of renal scarring (7.09 (4.39 to 11.45; Supplementary Table 6). The effect of UTI on renal scarring in children without any congenital anomalies, was reduced but still observed (2.18 (1.49 to 2.87); Supplementary Table 7).

### *Sensitivity analyses*

#### *Renal pathology*

Using any renal pathology codes showed a stronger relationship with UTI than renal scarring codes alone (aOR =5.68 (4.47 to 7.21)) (Supplementary Table 8).

### *GP diagnosis of renal scarring*

There were 118,167 (74.2%) children with GP data available in SAIL; however only 25 were additionally picked up in GP records and so additional analyses were not performed.

### *Subgroup analyses*

There was little evidence to show that the effect of UTI was different in males compared to females (interaction term p-value =0.06) (Supplementary Table 9a).

Children with a renal/urological congenital anomaly were a rare subgroup, but had a much higher rate of renal scarring compared to those with no congenital anomalies (Supplementary Table 9b). There was little evidence to show that the effect of UTI differed between groups (interaction term p=0.068).

### *Secondary outcomes*

Renal/urological surgery, day case admissions, dysfunctional voiding, receiving at least one antibiotic, and experiencing further microbiologically confirmed UTI (age five to seven) were all associated with UTI. (Tables 3 and 4). After adjustment, there was no association between UTI and hypertension, CKD or ESRF up to age five or when all available data was used (up to average age of ten; Tables 3 and 4).

Children with UTI experienced more GP consultations than those without (median 27 versus 19 respectively, adjusted IRR=1.39 (1.37 to 1.42), Table 3); and received more antibiotic prescriptions (median 5 vs 3 respectively, adjusted IRR=1.50 (1.47 to 1.53), Table 4).

*Exploratory: Factors associated with renal scarring in Group 1*

In 11,023 children with at least one UTI before the age of five, VUR, having a UTI under the age of one, and three or more UTIs before the age of five had the strongest association with renal scarring (Supplementary Table 10)

Table 3: Secondary outcomes

|   | <b>Hypertension</b>         | <b>Chronic kidney disease</b> | <b>Renal failure</b>       | <b>Hospital admissions</b> | <b>GP consultations</b>     | <b>Renal/urological surgery</b> |
|---|-----------------------------|-------------------------------|----------------------------|----------------------------|-----------------------------|---------------------------------|
| <b>Children with a 5 year follow up N<sup>a</sup></b>                 | <b>158,930</b>              | <b>158,918</b>                | <b>158,923</b>             | <b>159,136</b>             | <b>132,721</b>              | <b>158,921</b>                  |
| N(%) with an event  |                             |                               |                            |                            |                             |                                 |
| Negative/no sample <sup>b</sup>                                       | 61/147,890 (0.04)           | 33/147,882 (0.02)             | 44/147,880 (0.03)          | 89,938/153,610 (58.6)      | 4,126/123,522 (96.7)        | 107/147,910 (0.07)              |
| UTI <sup>b</sup>  | 15/11,040 (0.14)            | 13/11,036 (0.12)              | 7/11,043 (0.06)            | 3,106/5,477 (56.7)         | 298/8,901 (96.8)            | 73/11,011 (0.66)                |
| <i>Missing</i>  | ..                          | ..                            | ..                         | 49 <sup>c</sup>            | 0                           | ..                              |
| Crude OR (95% CI)   | 3.30 (1.87 to 5.80), <0.001 | 5.28 (2.78 to 10.04), <0.001  | 2.13 (0.96 to 4.73), 0.063 | 0.93 (0.88 to 0.98), 0.007 | 1.03 (0.92 to 1.16), 0.603  | ..                              |
| Adjusted <sup>d</sup> OR (95% CI)                                     | 1.84 (0.95 to 3.58), 0.072  | 0.70 (0.29 to 1.72), 0.442    | 0.92 (0.36 to 2.34), 0.855 | 0.97 (0.91 to 1.02), 0.239 | 1.01 (0.90 to 1.14), 0.838  | ..                              |
| Count of events Median (25 <sup>th</sup> to 75 <sup>th</sup> centile) |                             |                               |                            |                            |                             |                                 |
| Negative/no sample <sup>b</sup>                                       | ..                          | ..                            | ..                         | 2 (1 to 3)                 | 19 (12 to 29)               | ..                              |
| UTI <sup>b</sup>  | ..                          | ..                            | ..                         | 2 (1 to 3)                 | 27 (17 to 40)               | ..                              |
| Crude IRR <sup>e</sup> (95% CI), p-value                              | ..                          | ..                            | ..                         | 1.06 (1.02 to 1.10), 0.003 | 1.40 (1.38 to 1.42), <0.001 | ..                              |
| Adjusted <sup>d</sup> IRR (95% CI), p-value                           | ..                          | ..                            | ..                         | 1.04 (1.00 to 1.08), 0.047 | 1.39 (1.37 to 1.42), <0.001 | ..                              |
| <b>Time (years) to first event<br/>N=159,201</b>                      |                             |                               |                            |                            |                             |                                 |

|  |                                |                                 |                                |                                |    |                                 |
|--|--------------------------------|---------------------------------|--------------------------------|--------------------------------|----|---------------------------------|
| Crude HR (95% CI), p-value                 | 3.14 (1.97 to 5.00),<br><0.001 | 7.70 (4.61 to<br>12.87), <0.001 | 3.83 (2.20 to<br>6.67), <0.001 | 0.94 (0.90 to<br>0.97), <0.001 | .. | 8.95 (6.91 to<br>11.61), <0.001 |
| Crude SHR <sup>f</sup> (95% CI), p-value   | 3.13 (1.97 to 4.99),<br><0.001 | 7.69 (4.60 to<br>12.85), <0.001 | 3.82 (2.19 to<br>6.66), <0.001 | 0.94 (0.91 to<br>0.97), <0.001 | .. | 8.94 (6.90 to<br>11.58), <0.001 |
| Adjusted <sup>d</sup> HR (95% CI), p-value | 1.44 (0.84 to 2.46),<br>0.189  | 1.67 (0.85 to<br>3.31), 0.140   | 1.16 (0.56 to<br>2.37), 0.693  | 0.96 (0.93 to<br>0.997), 0.034 | .. | 1.40 (1.00 to<br>1.96), 0.050   |

*UTI = urinary tract infection, OR=Odds ratio, IRR=Incidence risk ratio, HR=Hazard ratio; SHR = Subdistribution hazard ratio*  
*a N excludes children who die before the age of 5 unless they have an outcome event (e.g. hospital admission); b Exposure taken at end of follow-up period (5 or 7 years) or at time of outcome; c no exposure group since date of hospitalisation was before date of birth; d Adjusting for sex, index of multiple deprivation quintile, birthweight, gestational age (weeks), maternal age (years), ever breastfed, known or possible congenital anomalies and time varying risk factors: comorbidities (diabetes, malignancies, circumcision, renal surgery, immunosuppression), and any vesicoureteral reflux (VUR). Note: renal surgery outcome excluded renal surgery from comorbidities.*  
*e Negative binomial regression model; f SHR estimate comes from a competing risk (CR) analysis where the competing risk is death.*

Table 4: Secondary outcomes

|   | Renal imaging in GP               | Dysfunctional Voiding          | Microbiologically confirmed UTI (5-7yrs follow up) | Antibiotics                    | Day cases                      |
|---|-----------------------------------|--------------------------------|--|--------------------------------|--------------------------------|
| <b>Children with a 5 year follow up N<sup>a</sup></b>                 | <b>132,721</b>                    | <b>132,721</b>                 | <b>156,494<sup>b</sup></b>                         | <b>132,721</b>                 | <b>158,947</b>                 |
| N(%) with an event  |                                   |                                |  |                                |                                |
| Negative/no sample <sup>c</sup>                                       | 500/123,589 (0.40)                | 918/123,560 (0.74)             | 1,746/145,593 (1.2)                                | 101,322/123,522 (82.0)         | 11,227/148,338 (7.57)          |
| UTI <sup>c</sup>  | 446/9,132 (4.89)                  | 127/9,161 (1.39)               | 686/10,901 (6.3)                                   | 8,267/9,199 (89.9)             | 1,191/10,605 (11.23)           |
| <i>Missing</i>  | <i>0</i>                          | <i>0</i>                       | <i>0</i>   | <i>0</i>                       | <i>4</i>                       |
| Crude OR (95% CI)   | 12.64 (11.11 to 14.39),<br><0.001 | 1.88 (1.56 to 2.26),<br><0.001 | 5.53 (5.05 to 6.06),<br><0.001                     | 1.94 (1.81 to 2.08),<br><0.001 | 1.55 (1.45 to 1.65),<br><0.001 |
| Adjusted <sup>d</sup> OR (95% CI)                                     | 11.80 (10.27 to 13.57),<br><0.001 | 1.78 (1.46 to 2.16),<br><0.001 | 3.96 (3.59 to 4.37),<br><0.001                     | 1.92 (1.79 to 2.07),<br><0.001 | 1.43 (1.34 to 1.54),<br><0.001 |
| Count of events Median (25 <sup>th</sup> to 75 <sup>th</sup> centile) |                                   |                                |  |                                |                                |
| Negative/no sample <sup>c</sup>                                       | ..                                | ..                             | ..   | 3 (1 to 6)                     | ..                             |
| UTI <sup>c</sup>  | ..                                | ..                             | ..   | 5 (2 to 9)                     | ..                             |
| Crude IRR <sup>c</sup> (95% CI), p-value                              | ..                                | ..                             | ..   | 1.49 (1.46 to 1.51),<br><0.001 | ..                             |
| Adjusted <sup>d</sup> IRR (95% CI), p-value                           | ..                                | ..                             | ..   | 1.50 (1.47 to 1.53),<br><0.001 | ..                             |

UTI = urinary tract infection, OR= Odds ratio; IRR = incidence risk ratio; HR=Hazard ratio; SHR = Subdistribution hazard ratio

a N excludes children who die before the age of 5 unless they have an outcome event (e.g. hospital admission);

b Children with a 7 year follow-up;

c Exposure taken at end of follow-up period (5 years) or at time of outcome; c no exposure group since date of hospitalisation was before date of birth;

d Adjusting for sex, index of multiple deprivation quintile, birthweight, gestational age (weeks), maternal age (years), ever breastfed, known or possible congenital anomalies and time varying risk factors: comorbidities (diabetes, malignancies, circumcision, renal surgery, immunosuppression), and any VUR (congenital and non-congenital). Note: renal surgery outcome excluded renal surgery from comorbidities.

*e Negative binomial regression model*

## Discussion

### *Summary of main findings*

This study describes the outcomes for 159,201 children, including 11,099 with at least one microbiologically confirmed UTI before their fifth birthday, and reflects routine clinical practice across all settings, including primary care. Children who had UTI were more than four times as likely to have a subsequent diagnosis of renal scarring. Children who had at least one UTI before the age of five received more antibiotic prescriptions and were more likely to be diagnosed with dysfunctional voiding and further UTIs (aged 5-7 years) than those without. The strongest predictors of subsequent renal scarring in children experiencing one or more UTI were: VUR, a UTI under the age of one, and three or more UTIs under the age of five. After adjustment for risk factors, we found no association between microbiologically confirmed UTI and subsequent CKD, hypertension or ESRF in children up to a mean age of 10 years.

### *Strengths and limitations*

Although large numbers of children were included in the study, the outcomes of interest were uncommon. We adjusted for many risk factors, however there could be others, unrecognised. Using routine data, clinical features such as fever could not be examined and the numbers having DMSA scans were not coded in hospital data. There was no single ICD-10 code for renal scarring and the validity of using the ICD-10 codes which we used has not been tested. This could have resulted in some renal scarring diagnoses being missed or some incorrectly categorised as renal scarring. The association between VUR and renal scarring may have been over-estimated due to the codes used to define them.



As this is a whole population study reflecting standard clinical practice, imaging was not systematically performed on all children. Therefore, some cases of renal scarring may not have been identified; and those who were scanned would have been more likely to have had recurrent or more serious UTI, or known risk factors, as current guidance does not recommend scanning children with only one uncomplicated UTI.<sup>2,24</sup> Equally, some children may have had undiagnosed VUR, other risk factors or unsuspected UTI. Although having microbiological confirmation for UTI was a strength of this study, we did not explore UTIs which were clinically suspected but not confirmed microbiologically. Studying an unselected population and including all UTIs, diagnosed from any setting, allowed assessment of the impact of multiple UTIs and UTIs of any severity.

#### *Comparison with existing literature*

We found that UTI was not associated with ESRF, CKD or hypertension in the absence of underlying risk factors. Previous evidence is inconclusive, however, the previously held belief that UTI leads to these long-term complications has more recently been questioned.<sup>4,7-10</sup> Our study is large and includes all children with microbiologically confirmed UTI before age five. However, we only have follow-up to an average age of 10 years old, so cannot be sure that UTI is not associated with these outcomes at an older age.

The prevalence of renal scarring in our study was lower than in previously published studies, although to our knowledge, no other studies have attempted to estimate the prevalence in a large unselected population of children. Previous studies include systematic DMSA scanning but are limited to small, select populations of children with febrile UTIs, usually conducted in hospital, reflecting more severe illness, and a higher proportion with VUR (64-76%).<sup>5,11,25-27</sup> These studies vary widely in reported rates of renal scarring, ranging from 2.8% to

15%.<sup>5,11,12,25,26</sup> One study included 50 children with afebrile UTI and found no renal scarring, but the 95% confidence interval was wide (0%-7%).<sup>25</sup> Not all children with UTI would have been scanned in our study, so the true prevalence may be higher; although we had follow-up to an average age of 10 years covering a long period of time during which a scan could have occurred. We also cannot be sure that some children without UTI did not have undiagnosed renal scarring as this would require children without UTI or underlying risk factors to have a DMSA scan. On review of the literature, we could find no studies which include a group of children without UTI or risk factors, undergoing DMSA scanning.

Very few children in our study had VUR or underlying risk factors, reflecting more closely the majority of children likely to be seen in primary care (VUR in 0.4% of the study population and in 5.6% of children with at least one UTI).<sup>28</sup>

#### *Implications for research and practice*

Childhood UTI, even in the absence of other risk factors, is associated with renal scarring suggesting the importance of prompt diagnosis and treatment of UTIs in all children. However, the prevalence of renal scarring appears to be low, and it is not certain that renal scarring leads to poor outcomes in the majority of children, so whether urine sampling strategies in primary care need to be modified, and to what extent, is not clear.<sup>8</sup>

Our finding that UTI is not associated with longer-term complications except in the presence of other risk factors means that it may not be necessary to further image and follow-up children without risk factors, particularly given improvements in antenatal scanning to detect congenital abnormalities. However, as our average follow-up was only 9.58 years, it is

possible that there was insufficient time for complications to have developed, and studies with longer follow-up are needed to confirm our findings.

To be sure that renal scarring diagnoses are not being missed in standard clinical practice, and to determine the true relationship between UTI and renal scarring, a large study with systematic DMSA scanning in a low-risk population of children, including those with self-limiting UTI and without UTI, is needed. However, as DMSA scans are invasive tests which do not alter clinical management of the individual in most cases, this may be difficult to justify; and selection bias is likely to remain a significant challenge.

### *Conclusion*

Our paper shows that childhood UTI is associated with a diagnosis of renal scarring but the prevalence is low. UTI is not associated with CKD, hypertension or ESRF by age 10 after adjusting for underlying risk factors. Systematic scanning of children's kidneys including those with less severe UTI and without UTI, is needed to increase certainty of these findings, as most children without UTI are not scanned. Longer follow-up is needed to establish if UTI, without additional risk factors, is associated with hypertension, CKD or ESRF later in life.

### **Ethics approval:**

The study was approved by the Wales REC3 Ethics committee on 9/6/16. REC reference: 16/WA/0166

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This work uses data provided by patients and collected by the NHS as part of their care and support #datasaveslives

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**Conflicts of interest:**

All authors declare that they have had no conflicts of interest, following the guidelines of the ICMJE.

**Data sharing**

The data for this study cannot be shared as it is held in the Secure Anonymised Information Linkage (SAIL) system. The protocol for this paper has been published:

Lugg-Widger FV, Angel L, Cannings-John R, Jones H, Lau M, Butler C, et al. Long-term outcomes of urinary tract infection (UTI) in Childhood (LUCI): protocol for an electronic record-linked cohort study. *BMJ Open*. 2019;9(4):e024210.

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Kathryn Hughes and Rebecca Cannings-John are guarantors for the study. The guarantors accept full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish.

The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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