Published in final edited form as:

J Pediatr Urol. 2013 December ; 9(6): . doi:10.1016/j.jpurol.2012.09.003.

Childhood Vesicoureteral Reflux Studies: Registries and Repositories *Sources and Nosology*

Russell W. Chesney and Andrea B. Patters

Department of Pediatrics, University of Tennessee Health Science Center, Memphis, TN

Abstract

Despite several recent studies, the advisability of antimicrobial prophylaxis and certain imaging studies for urinary tract infections (UTIs) remains controversial. The role of vesicoureteral reflux (VUR) on the severity and re-infection rates for UTIs is also difficult to assess. Registries and repositories of data and biomaterials from clinical studies in children with VUR are valuable. Disease registries are collections of secondary data related to patients with a specific diagnosis, condition or procedure. Registries differ from indices in that they contain more extensive data. A research repository is an entity that receives, stores, processes and/or disseminates specimens (or other materials) as needed. It encompasses the physical location as well as the full range of activities associated with its operation. It may also be referred to as a biorepository. This report provides information about some current registries and repositories that include data and samples from children with VUR. It also describes the heterogeneous nature of the subjects, as some registries and repositories include only data or samples from patients with primary reflux while others also include those from patients with syndromic or secondary reflux.

Keywords

urinary tract infection; vesicoureteral reflux; registry; repository; reflux nephropathy

Introduction

Appropriate methods for the evaluation and treatment of children with vesicoureteral reflux (VUR) remain a knotty problem [1]. Doubts have been raised about the role of long-term antibiotic prophylaxis in preventing urinary tract infection (UTI) and renal scarring in children with VUR [2]. Surgical intervention trials using re-implantation or endoscopic injection of biologically inert materials have been associated with high success for the resolution of reflux, but do not always translate to reduction in the frequency of urinary tract infections or scarring [3]. A number of prospective, interventional clinical trials that aim to examine the role of VUR as a risk factor for UTI and renal scarring have either recently been completed or are ongoing. Some are randomized and controlled [1, 4, 5], and all

© 2012 Journal of Pediatric Urology Company. Published by Elsevier Ltd. All rights reserved.

Correspondence to: Russell W. Chesney, MD Le Bonheur Chair of Excellence Chair, Department of Pediatrics Le Bonheur Children's Hospital The University of Tennessee Health Science Center 50 N. Dunlap Memphis, TN 38103 Tel: 901-287-6106 Fax: 901-287-5028 rchesney@uthsc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

For the RIVUR Trial investigators: Ranjiv Mathews, Saul Greenfield, Tej Mattoo, Alejandro Hoberman, Ron Keren, Myra Carpenter and Marva Moxie-Mims

potentially contain a sufficient number of subjects to allow for complex analysis. Several of these studies form the basis of national or international registries and/or repositories that potentially allow for further and ongoing analysis of well characterized patient populations. In this review of registries and repositories we endeavor to clarify these, to compare prospective registries and to explain the nature of the patients herein.

Patient or disease registries are defined as collections of secondary data related to patients with a specific diagnosis, condition or procedure, and they contain a substantial amount of patient information [6]. Registries differ from indices in that they contain more extensive data: an index is generally a list of cases that contains minimal information. A repository is an entity that receives, stores, processes and/or disseminates specimens and other items, such as images, as needed. It encompasses the physical location as well as the full range of activities associated with its operations. It may also be referred to as a biorepository [6]. In general, a repository has a “repository allocation committee” (RAC), which is responsible for ascertaining if requests for datasets and biospecimens meet the criteria for valid research studies. The RAC is also responsible for assuring that critical last remaining specimens are not removed without valid scientific justification. Repositories, therefore, contain biological material from patients often described in registries. This paper will define the locations and describe the fundamental nature of the patient populations of a number of substantial registries and repositories.

Methods

All of the studies evaluated relate to VUR in children of specified age ranges: no adults were included. The inclusion and exclusion criteria were those of the underlying studies and can vary from study to study. Most of the registries and repositories examined were recently convened and have readily available and fairly extensive data, either published or web-based, concerning patient demographics, primary and secondary outcomes, length of follow-up, and whether or not the trial was interventional. Several of these trials have been closed, but others are ongoing [4, 7-12].

Because the purpose of this report is to catalog some of the registries and repositories available, and to discuss their heterogeneous nature, no information regarding the primary or secondary outcomes of the patient groups was evaluated or analyzed. In general, we sought registries and repositories from national or international multi-center studies.

Results

Registries: location and features

Some of the extant national patient registries for children who have established VUR at the time of study entry are shown in Table 1 and arise from several countries, including Australia (ANZDATA), Italy (ItalKid), Greece (Patras), Sweden (the Swedish Reflux Trial in Children), and other European nations, as well as the United States and South America. One large, all-encompassing registry is the United States Renal Data System (USRDS), a large data set that has “de-identified” information on subjects of all ages who are receiving renal replacement therapy or have undergone a renal transplant. In this system, pediatric data are divided into several age categories: 0 - 4 yrs, 5 - 10 yrs, 11 - 15 yrs, and 16 - 20 yrs. This data set includes children with VUR and end stage renal disease. Each year a new group of patients enters the data set and a group of patients leaves due to death or entering adulthood (> 20 years of age).

One distinction of VUR registries is that several, such as ANZDATA, USRDS, Patras and RIVUR continue to collect data prospectively, whereas the International Reflux Study, the

Swedish Reflux Trial in Children, and the studies of Roussey-Kesler, Pennisi, Montini and Garin are closed [4, 9-13]. All potentially offer data sources for analysis. Moreover, some of these large national registries contain data from subjects with renal disorders other than VUR, but do include children with reflux nephropathy. Hence, certain registries contain data from subjects where only primary VUR is considered (e. g., RIVUR and ItalKid), while others categorize patients with either primary or syndromic reflux and/or no reflux (USRDS, ANZDATA, the Swedish Reflux Trial, the Roussey-Kesler study and the Garin study). This creates a problem in nosology, or the classification of disease, of which potential investigators should be cognizant. Tables 1 and 2 list several national registries and their study characteristics.

The International Reflux Study in Children compared the long-term outcome of medical versus surgical treatment of children with severe VUR in 438 patients initially followed over five years. Some of the children in the European limb of the study (306) were followed for a longer period of time, and 252 were included in the final 10-year report [13]. The ANZDATA registry contains data from all children under the age of 18 who have received renal replacement therapy (RRT) since the inception of RRT in Australia and New Zealand. Of those 1485 children, 35.8% were diagnosed with structural anomalies including hypoplasia/dysplasia, posterior urethral valves, or reflux nephropathy [14]. This registry did not include children with primary reflux. The prospective and population-based CKiD and ItalKid [15, 16] registries have examined more than 1750 children with a variety of kidney diseases over a period of time (ItalKid > 10 years; CKiD > 3years). In each of the registries those patients with VUR can be assessed separately as a subset. The ItalKid Primary Reflux Study is a published example of analysis of such a subset [17]. A large retrospective review of 176 children with renal hypo/dysplasia, many of whom had VUR, showed that they had progressed to end stage renal disease by the end of puberty [18]. In the ESCAPE trial, 385 European children with chronic kidney disease (CKD) were treated with an angiotensin-converting enzyme inhibitor for blood pressure control and evaluated [19]. The patients in this trial included 264 with renal hypoplasia/dysplasia. This represents a trial in which the primary outcome is not recurrence of UTI or evaluation of reflux, but one in which patients with the potential for re-infection of the urinary tract happen to be included. Because of the data recorded in this registry, it could well provide useful information with regard to VUR, especially in children with congenital anomalies of the kidney and urinary tract (CAKUT).

Some recent prospective, randomized trials of antibiotic prophylaxis or imaging need to be described in greater detail so that these registries can be compared. The study of Roussey-Kesler *et al.* was a prospective, randomized antibiotic prophylaxis study of 225 children, ages 1-3 years, with low grade (I-III) reflux [12]. There was no difference in the time to first infection between children treated with placebo or antibiotic (cotrimoxazole), except that prophylaxis was beneficial in boys (23 boys, 31% of the study population) with grade III reflux. A UTI was defined by $>10^5$ colony forming units (CFU) of a single organism obtained from sterile bags in non-toilet-trained children or clean midstream catch in older children.

The study of Garin *et al.* was a prospective, randomized trial of antibiotic prophylaxis (sulfamethoxazole/trimethoprim or nitrofurantoin) of 236 patients (113 with VUR) with reflux from the United States, Chile and Spain [9]. Children with grades of VUR higher than I-III were excluded. All patients had evidence of pyelonephritis, as ascertained by DMSA scintigraphy. Urine was obtained by bladder catheterization or clean catch in toilet-trained children. The age range was 3 months to 17 years, with a median age of 3 years in patients with VUR and 2 years in those without reflux. There was no difference in re-infection rate between the treatment and non-treatment groups.

The Swedish Reflux Trial in Children was a prospective, randomized controlled trial of 203 children, aged 1-2 years, with grade III/IV reflux followed for 2 years [4]. The population consisted of 128 girls and 75 boys and three treatment arms – antibiotic prophylaxis, endoscopic surgery and a surveillance group – were enrolled. The antibiotics employed for prophylaxis were trimethoprim (first choice) or nitrofurantoin or cefadroxil. In this controlled trial, a high rate of recurrence of febrile UTI was found in girls with high grade reflux, but in boys antibiotic prophylaxis and endoscopic intervention reduced the infection rate [20]. All patients with reflux had primary reflux with no evidence of secondary or syndromic reflux.

In a randomized trial in Italy 100 patients with grades II, III, IV reflux were assigned to receive sulfamethoxazole/trimethoprim or to serve as controls [11]. Patients were aged 1 to 30 months and urine was obtained by sterile bag technique. The males (50%) were not circumcised. There was no evidence of benefit from antibiotic prophylaxis, but control patients were not given a placebo.

In a multicenter, randomized, controlled, noninferiority trial from Italy that enrolled 338 children with primary reflux, aged 2 months to < 7 years and 69% female, participants received either co-trimoxazole or co-amoxiclav or no prophylaxis for 12 months [10]. The grades of reflux were none to I-III. There was no difference in the primary outcome of reduction of recurrence of febrile UTI between groups. Urine was collected by sterile urinary bag and two consecutive and concordant urinalyses were necessary to rule out false-positive tests.

A large (576 children) placebo-controlled trial regarding the efficacy of antibiotics was performed in Australia in children under 18 years [5]. The median age at entry was 14 months; 64% of patients were female and 42% had known VUR while in the study. A UTI developed in 55 of 288 patients on placebo and 36 of 288 receiving trimethoprim/sulfamethoxazole ($p < 0.02$), demonstrating the value of continuous antibiotic prophylaxis. Urine was collected by suprapubic aspiration, urinary catheter or midstream clean catch in children who were toilet-trained.

The RIVUR study has enrolled a baseline population of 607 patients with grades I-IV VUR in a randomized, placebo-controlled trial designed to measure recurrence of UTI (primary outcome). Participants were aged 2 months to 6 years, predominantly female (92%) and Caucasian (81%), and most commonly had grades II/III reflux (80%). Outcome of patients randomized to placebo or trimethoprim/sulfamethoxazole will be analyzed after 24 months with initial 12 month and 24 month DMSA scan to determine rate of scarring. Quality of life and dysfunctional voiding scores were measured in all patients. Urine was obtained by bladder catheterization or midstream collection in toilet-trained children. The outcome results await the conclusion of the study in 2013.

Several large national registries are available, including ANZDATA, ItalKid, USRDS, CKiD and the ESCAPE trial (Tables I and II). These registries contain patients with heterogeneous renal disorders, including glomerulonephritis, renal dysplasia/hypoplasia, and reflux nephropathy. In contrast to the previously mentioned trials, these registries do not focus on UTIs or VUR, but do contain many patients with these disorders, especially syndromic VUR.

A non-interventional study of reflux (Patras, Greece) assessed 296 children by use of DMSA scan to determine the value of scan following a febrile UTI to identify dilating VUR [8]. Patients were < 24 months of age (47% female) and urine was collected by suprapubic aspiration or bladder catheterization. The data from this study suggested that acute DMSA scan has limited overall ability to identify VUR.

Biomaterial repositories

There exist several biomaterial repositories that are listed in Table 3. The biorepositories of the Irish Primary VUR repository, the UK/Slovenia Repository, the Dutch Italian Repository, the New York City – Columbia University Repository, the Iowa – Ohio State – Pittsburgh Repository and the Montreal Children's Hospital Repository all contain biologic materials obtained from children with VUR. These repositories are often, but not always, separate from the large registries. The Urologic Diseases Database and Repository for Biosamples is sponsored by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH). Both the CKid and the RIVUR repositories are part of this system. Among the features of the listed repositories are the following: they include samples from subjects with primary VUR and without obstruction, or subjects with CAKUT. All subjects have a positive VCUG as an entry criterion and they may include familial VUR or index cases only. Subjects are North American, European or Chilean. No ethnic groups are excluded. The biomaterials stored include blood, urine, immortalized cells, hair, and fingernail clippings. Hair and nails are not always kept, but can be used to assess environmental toxins.

Discussion

The purpose of this report is to clarify the nature of extant registries and repositories, and to briefly summarize the makeup of the populations studied. The aim is to make students of reflux aware of the heterogeneous nature of the patients studied, as well as the rich sample size.

One of the dilemmas in understanding the association of VUR, renal scarring, and the natural course of CKD progression in reflux nephropathy is the paucity of studies of the natural history of syndromic and non-syndromic VUR [7, 21, 22]. Many studies have examined children with a variety of kidney diseases. In these registries those patients with VUR can often be assessed separately as a subset. This overall picture of CAKUT and renal hypodysplasia progressing to ESRD versus the apparently more benign course of children with primary VUR defines the nosologic problem in considering VUR. With increasing evidence that VUR is not a prerequisite for the development of pyelonephritis, reflux nephropathy may represent mainly an embryologically derived renal parenchymal abnormality [7]. Simply put, not all VUR has the same biologic profile.

The aim of creating registries with data from children with VUR is not only to understand the short-term outcomes, but also to potentially evaluate long-term outcomes if cohort studies are undertaken. Similarly, the aim of creating repositories with stored genetic material is to understand genotype/phenotype correlations and the genetic bases of long-term outcomes.

An examination of these registries shows heterogeneity within these patients on whom extensive data are kept, with some patients not having VUR (Tables 1 and 2). Again, this heterogeneity leads to nosologic issues. Older registries of VUR subjects tended to include children with CAKUT and reflux nephropathy. Newer registries are more likely to evaluate primary, non-syndromic VUR. In addition, the extensive changes in urinary tract imaging mean that the data from techniques such as DMSA, radionuclide imaging and radionuclide voiding studies are not always found in older registries, but are likely found in newer ones. For example, only in the final (10-year) follow-up of the International Reflux Study were DMSA scans performed to identify new scars. Finally, another heterogeneous feature is that the period of follow-up of patients in these registries can vary from one year to more than 10 years.

There is considerable value in several recent studies (listed in Tables 1 and 2) because they have prospectively recruited and well defined patients, and the age, gender, VUR grade and outcomes are well described [4, 5, 8-12]. All these subjects were followed for a definite predetermined time period. Studies emanating from Europe and Australia have more males than American trials do, which has been attributed to the lower rates of circumcision in these populations [1]. An ideal study should obtain urine by bladder catheterization or suprapubic aspiration in non-toilet-trained children [5, 8, 9] rather than sterile-bag urine collection [4, 10-12], an opinion also expressed by Hoberman and Keren [1]. Another issue can be insufficient statistical power to detect clinically important differences: in order to detect a reduction in the absolute risk of recurrent UTI of 10%, a study would need to enroll roughly 600 children [1, 23]. Several of these registries have fewer than 300 patients enrolled (Tables 1, 2).

Biorepositories also contain materials from patients with CAKUT and reflux nephropathy or primary non-syndromic VUR [24]. Several repositories include material from affected and non-affected relatives of patients with familial VUR, while others only include samples from the index case. Material from a repository may not be made available until a study has finished enrolling subjects or when the study is closed (when baseline and primary outcome results are published). Also, access to a gold standard biorepository with electronic data management is not always possible. Frequently, a grant from the NIH or other agency and/or an agreement to collaborate with the investigative team is required.

The greater the diversity and amount of materials available for genetic or other studies, the more the results of studies that utilize the materials can be generalized. As a goal for future large cohort studies of VUR, an attempt should be made to create both a registry and a repository where relevant data and material from subjects and family members can be stored. These materials will have to be “de-identified” to meet privacy guidelines. In the future, more complex genetic analyses will be performed as techniques for genome-wide searches become more rapid and less expensive. Two additional themes of study should be an examination of genes of interest in the entire urinary tract and correlation of genetic/genomic information with imaging results. Because of the manner in which renal development occurs, genes of interest should always include those evident in the urethra, bladder and ureters as well as the kidney. Mutations or polymorphisms in developmental genes should be examined as well as those relevant to the mature kidney. When properly stored urine is available, urine proteomics can be correlated with both genetic/genomic information and the results of imaging studies.

One of the many issues with the use of registries is at what point in time the material and data are made available to the scientific community. Data and materials remain the property of the primary investigators until the study is deemed closed. This is typically considered to have occurred once the baseline and main outcomes publications are accepted and published. At this time, data collected under the aegis of national funding agencies is made available to other investigators. A mechanism for investigators to access registry data or repository biomaterials is to submit a grant application to the funding agency for an ancillary study. These ancillary studies generally ask questions that are not the primary or secondary outcomes of the parent study.

For individuals wishing to access data for analyses, the question as to who “owns” the data is also pertinent. While a study is still active the data are under the guardianship of the data-coordinating center. Once the primary outcome studies are performed and published the data become public or available through limited access. The studies that underlie these registries are funded by national research agencies rather than pharmaceutical or device companies.

The request for material should be in the form of an ancillary study for up to two years after the study outcome is published. Following that time period, applications to obtain repository samples should be reviewed by the repository allocation committee and the institutional review board.

With improvement in data collection, imaging techniques, and the evaluation of genetic and proteomic biomaterials, the information from patients enrolled in VUR studies can be analyzed in many ways and new questions can be asked. To accomplish these goals, a standardization of the operation of registries and repositories would be optimal, including a web-based portal of access.

Acknowledgments

The authors thank the RIVUR participants, their families and the participating physicians, investigators and staffs for making this research possible. The authors have no financial or personal conflicts of interest to disclose. Ethical approval was not required for this review. The Randomized Intervention for Children with Vesicoureteral Reflux trial was supported by cooperative agreements U01 DK074059 (Carpenter), U01 DK074053 (Hoberman), U01 DK074082 (Mathews), U01 DK074064 (Keren), U01 DK074062 (Mattoo), U01 DK074063 (Greenfield) from the National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services. The trial was also supported by the Children's Hospital of Philadelphia Clinical and Translational Science Award (UL1TR000003) from the National Center for Research Resources, now at the National Center for Advancing Translational Sciences, National Institutes of Health. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Diabetes and Digestive and Kidney Diseases or the National Institutes.

References

- [1]. Hoberman A, Keren R. Antimicrobial prophylaxis for urinary tract infection in children. *N Engl J Med*. 2009; 361:1804–6. [PubMed: 19864680]
- [2]. Keren R, Carpenter MA, Hoberman A, Shaikh N, Mattoo TK, Chesney RW, et al. Rationale and design issues of the randomized intervention for children with vesicoureteral reflux (RIVUR) study. *Pediatrics*. 2008; 122(Suppl 5):S240–50. [PubMed: 19018048]
- [3]. American Urological Association. Policies, Guidelines & Quality. 2010. <http://www.auanet.org/content/guidelines-and-quality-care/guidelines-and-quality-carecfm>
- [4]. Brandstrom P, Esbjorner E, Herthelius M, Holmdahl G, Lackgren G, Neveus T, et al. The Swedish reflux trial in children: I. Study design and study population characteristics. *J Urol*. 2010; 184:274–9.
- [5]. Craig JC, Simpson JM, Williams GJ, Lowe A, Reynolds GJ, McTaggart SJ, et al. Antibiotic prophylaxis and recurrent urinary tract infection in children. *N Engl J Med*. 2009; 361:1748–59. [PubMed: 19864673]
- [6]. National Heart Lung and Blood Institute. Biologic specimen and data repository information coordinating center. 2010. <https://biolinccnhlbinihgov/glossary/>
- [7]. Craig JC, Williams GJ. Denominators do matter: it's a myth--urinary tract infection does not cause chronic kidney disease. *Pediatrics*. 2011; 128:984–5. [PubMed: 21987711]
- [8]. Fouzas S, Krikelli E, Vassilakos P, Gkentzi D, Papanastasiou DA, Salakos C. DMSA scan for revealing vesicoureteral reflux in young children with urinary tract infection. *Pediatrics*. 2010; 126:e513–9. [PubMed: 20679300]
- [9]. Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A, Young L. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. *Pediatrics*. 2006; 117:626–32. [PubMed: 16510640]
- [10]. Montini G, Rigon L, Zucchetta P, Fregonese F, Toffolo A, Gobber D, et al. Prophylaxis after first febrile urinary tract infection in children? A multicenter, randomized, controlled, noninferiority trial. *Pediatrics*. 2008; 122:1064–71. [PubMed: 18977988]
- [11]. Pennesi M, Travan L, Peratoner L, Bordugo A, Cattaneo A, Ronfani L, et al. Is antibiotic prophylaxis in children with vesicoureteral reflux effective in preventing pyelonephritis and renal scars? A randomized, controlled trial. *Pediatrics*. 2008; 121:e1489–94. [PubMed: 18490378]

- [12]. Roussey-Kesler G, Gadjos V, Idres N, Horen B, Ichay L, Leclair MD, et al. Antibiotic prophylaxis for the prevention of recurrent urinary tract infection in children with low grade vesicoureteral reflux: results from a prospective randomized study. *J Urol*. 2008; 179:674–9. discussion 9. [PubMed: 18082208]
- [13]. Jodal U, Smellie JM, Lax H, Hoyer PF. Ten-year results of randomized treatment of children with severe vesicoureteral reflux. Final report of the International Reflux Study in Children. *Pediatr Nephrol*. 2006; 21:785–92. [PubMed: 16565873]
- [14]. Orr NI, McDonald SP, McTaggart S, Henning P, Craig JC. Frequency, etiology and treatment of childhood end-stage kidney disease in Australia and New Zealand. *Pediatr Nephrol*. 2009; 24:1719–26. [PubMed: 19373494]
- [15]. CKiD. A prospective cohort study of kidney disease in children. 2010. <http://www.statepijhsph.edu/ckid/>
- [16]. Ardissino G, Dacco V, Testa S, Bonaudo R, Claris-Appiani A, Taioli E, et al. Epidemiology of chronic renal failure in children: data from the ItalKid project. *Pediatrics*. 2003; 111:e382–7. [PubMed: 12671156]
- [17]. Marra G, Oppezzo C, Ardissino G, Dacco V, Testa S, Avolio L, et al. Severe vesicoureteral reflux and chronic renal failure: a condition peculiar to male gender? Data from the ItalKid Project. *J Pediatr*. 2004; 144:677–81. [PubMed: 15127014]
- [18]. Gonzalez Celedon C, Bitsori M, Tullus K. Progression of chronic renal failure in children with dysplastic kidneys. *Pediatr Nephrol*. 2007; 22:1014–20. [PubMed: 17380351]
- [19]. Wuhl E, Trivelli A, Picca S, Litwin M, Peco-Antic A, Zurowska A, et al. Strict blood-pressure control and progression of renal failure in children. *N Engl J Med*. 2009; 361:1639–50. [PubMed: 19846849]
- [20]. Brandstrom P, Esbjorner E, Herthelius M, Swerkersson S, Jodal U, Hansson S. The Swedish reflux trial in children: III. Urinary tract infection pattern. *J Urol*. 2010; 184:286–91. [PubMed: 20488494]
- [21]. Montini G, Tullus K, Hewitt I. Febrile urinary tract infections in children. *N Engl J Med*. 2011; 365:239–50. [PubMed: 21774712]
- [22]. Shaikh N, Ewing AL, Bhatnagar S, Hoberman A. Risk of renal scarring in children with a first urinary tract infection: a systematic review. *Pediatrics*. 2010; 126:1084–91. [PubMed: 21059720]
- [23]. Mathews R, Carpenter M, Chesney R, Hoberman A, Keren R, Mattoo T, et al. Controversies in the management of vesicoureteral reflux: the rationale for the RIVUR study. *J Pediatr Urol*. 2009; 5:336–41. [PubMed: 19570724]
- [24]. Lambert HJ, Stewart A, Gullett AM, Cordell HJ, Malcolm S, Feather SA, et al. Primary, nonsyndromic vesicoureteric reflux and nephropathy in sibling pairs: a United Kingdom cohort for a DNA bank. *Clin J Am Soc Nephrol*. 2011; 6:760–6. [PubMed: 21441121]

Table 1

Details of some registries that are no longer enrolling participants and are considered closed.

Study	Site	Format	No. enrolled	% Female	Urologic imaging	Reference
International Reflux Study in Children (IRSC)	United States, Canada, Europe	Long-term outcome of medical or surgical treatment of children < 11 y with grade III/IV VUR	438 (252 followed for 10 y)	76.1	Urography, VCUG, DMSA scan for selected pts in 5-10 yrs of follow-up	<i>Pediatr Nephrol</i> (2006) 21:785 ulf.jodal@pediat-gu.se
The Swedish Reflux Trial in Children	Sweden	Prospective, randomized, controlled trial of grade III/IV reflux followed for 2 y	203, non-syndromic reflux	63.1	VCUG, DMSA scan with follow-up	<i>J Urol</i> (2010) 184: 274-304 (several articles) sverker.hansson@gu.se
Chronic Kidney Disease in Children (CKiD)	USA	Prospective observational cohort with mild to moderately impaired renal function	586 enrolled; 87 with reflux nephropathy (mainly 2°); CAKUT	33	VCUG	Clinicaltrials.gov; NCT00327860
The ESCAPE Trial	Europe	Prospective, randomized, controlled study of intense vs standard blood pressure control in children with CKD	385 (264 with hypo/dysplasia)	41		<i>New Engl J Med</i> (2009) 361:1639 franz.schaefer@med.uni-heidelberg.de
Ab prophylaxis, UTI and VUR study	France	Prospective, randomized; antibiotic prophylaxis for low grade VUR in children 1 mo to 3 y	225	69	Ultrasound, VCUG	<i>J Urol</i> (2008) 79:674 gwenaelle.roussey@chunantes.fr
VUR, Ab prophylaxis and UTI after pyelonephritis study	USA, Chile, Spain	Prospective, randomized, controlled, 3-18 y old with primary VUR	236 (113 with VUR)	75	Ultrasound, VCUG, DMSA scan	<i>Pediatr</i> (2006) 117:626 garineh@peds.ufl.edu
Antibiotic prophylaxis and recurrent UTI in children	Australia New Zealand	Prospective, low-dose controlled continuous SX/TMP vs placebo to prevent reinfection; 42% of pts with reflux; ages 1 mo to 10 y	576	64%	Not required; most had ultrasound, VCUG and DMSA scan	<i>NEJM</i> (2009) 361:1748 jonathan.craig@sydney.edu.au
Italian Renal Infection Study Group (IRIS) (Montini study)	Northeast Italy	Multicenter randomized, controlled, open label prophylaxis after first UTI; co-trimazole or co-amoxiclav or no therapy, ages 2 mo to < 7 y	338	69%	Ultrasound, VCUG, DMSA	<i>Pediatr</i> (2008) 122:1064 montini@pediatria.unipd.it

Study	Site	Format	No. enrolled	% Female	Urologic imaging	Reference
Effect of prophylaxis in children with reflux on preventing pyelonephritis and renal scarring (Pennesi study)	Northern Italy	Prospective SX/TMP vs no antibiotic; grades II-IV reflux; ages 1-30 mo	100	50%	Repeated VCUG and DMSA scan	<i>Pediatr</i> (2008) 121:e1489 pennesi@burlo.trieste.it

Ab, antibiotic; CAKUT, congenital anomalies of the kidney and urinary tract; DMSA, dimercaptosuccinic acid; ESRD, end stage renal disease; GFR, glomerular filtration rate; mo, months; ps, patients; TMP/SX, trimethoprim/sulfamethoxazole ; VCUG, voiding cystourethrography; VUR, vesicoureteral reflux; y, years

Table 2

Details of some registries that are currently enrolling participants and are considered open.

Registry	Site	Format	No. enrolled	Gender	Urologic imaging	Reference
Australia New Zealand Dialysis and Transplant Registry (ANZDATA)	Australia, New Zealand	ESRD in children since 1963. Originally retrospective, now real-time event-based reporting/annual survey	1485 (280 with reflux nephropathy, but number declined with recognition of CAKUT)	45.4% female	Urography, VCUG	<i>Pediatr Nephrol</i> (2009) 24:1719 ANZDATA.org
Italian Pediatric Registry of Chronic Renal Failure in Children (Italkid)	Italy	Chronic renal failure in children with GFR <75 ml/min/1.73 m ² ; 1° & 2° reflux, all grades	1197 (hypoplasia with reflux in 309)	33% female, but includes posterior urethral valves and CAKUT	VCUG	Italkid@italkid.org
Randomized Intervention for Children with Vesicoureteral Reflux (RIVUR)	USA	Prospective UTI with 1° VUR, interventional 2 months <6 years Grades I-IV VUR	607	92% female	Ultrasound, VCUG, DMSA scan with follow-up	Clinicaltrials.gov; NCT00405704
Patras	Greece	Prospective UTI, Grades I-V VUR	296 (reflux in 62)	46.8% female	Ultrasound, VCUG, DMSA scan	<i>Pediatrics</i> (2010) 126:e513 sfouzas@gmail.com
United States Renal Data System (USRDS)	USA	Information and data from children with ESRD since 1988; all pts on dialysis - all reflux	425 with reflux nephropathy in 2000 - 2009	60% females	Not always specified	USRDS@usrds.org

Table 3

Biomedical repositories

Repository	Number of samples	Reference
Urologic Diseases Database and Repository for Biosamples and Data	Many studies, thousands of samples	http://www.niddkrepository.org
CKiD - 2008	586	Clinicaltrials.gov; NCT00327860
RIVUR - 2010	600 anticipated	Clinicaltrials.gov; NCT00405704
Irish Primary VUR Repository - 2007	609	<i>J Med Genet</i> (2007) 44:710 david.barton@olchc.ie
UK/Slovenia Repository - 2001 - 2010	661	<i>J Am Soc Nephrol</i> (2010) 21:113 j.a.goodship@ncl.ac.uk
Dutch - Italian Repository - 2008	95	<i>J Am Soc Nephrol</i> (2008) 19:825 a.bertoliavella@erasmusmc.nl
New York City - Columbia University Repository - 2010	3144	<i>Nat Genet</i> (2011) 43:321 Ali Gharavi (ag2239@columbia.edu), Richard Lifton (richard.lifton@yale.edu)
Iowa-Ohio State - Pittsburgh Repository - 2010	380 (100 with reflux)	david.hains@nationwide.org
Montreal Children's Hospital - McGill University - 2010	142	indra.gupta@muhc.mcgill.ca