HHS Public Access

Author manuscript

Kidney Int. Author manuscript; available in PMC 2020 November 01.

Published in final edited form as:

Kidney Int. 2019 November ; 96(5): 1071–1076. doi:10.1016/j.kint.2019.06.024.

Chronic Kidney Diseases in Agricultural Communities Report from a Workshop

Susan R. Mendley[1], **Adeera Levin**[2], **Ricardo Correa-Rotter**[3], **Bonnie Joubert**[4], **Elizabeth Whelan**[5], **Brian Curwin**[5], **Erik Koritzinsky**[1], **Denise Gaughan**[1], **Paul L. Kimmel**[1], **Shuchi Anand**[6], **Pedro Ordunez**[7], **Ludovic Reveiz**[7], **Diane S. Rohlman**[8], **Carla Saenz**[7], **Madeleine K. Scammell**[9], **Robert O. Wright**[10], **Robert A. Star**[1]

[1]Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, NIH (US)

[2]University of British Columbia (Canada)

[3]Instituto Nacional de Ciencas Médicas y Nutrición Salvador Zubirán (Mexico)

[4]Population Health Branch, National Institute of Environmental Health Sciences, NIH

[5]National Institute for Occupational Safety and Health, CDC (US)

[6]Stanford University School of Medicine

[7]Pan American Health Organization

[8]College of Public Health, University of Iowa

[9]Boston University School of Public Health

[10]Mount Sinai School of Medicine

Abstract

In June 2018, the National Institute of Diabetes and Digestive and Kidney Diseases and the National Institute of Environmental Health Sciences sponsored a workshop to identify research gaps in an increasingly common form of chronic kidney disease in agricultural communities, often termed CKDu. The organizers invited a broad range of experts who provided diverse expertise and perspectives, many of whom had never addressed this particular epidemic. Discussion was focused around selected topics including: identifying and mitigating barriers to research in CKDu, creating a case definition, and defining common data elements. All hypotheses regarding etiology were entertained, and meeting participants discussed potential research strategies, choices in study design, and novel tools that may prove useful in this disease. Achievements of the workshop included robust cross-disciplinary discussion and preliminary planning of research goals and design. Specific challenges in implementing basic and clinical research and interventions in Low

Corresponding author: Susan R. Mendley susan.mendley@nih.gov.

and Middle Income Countries were recognized. A balanced approach to leveraging local resources and capacity building without overreaching was emphasized.

Keywords

Chronic Kidney Disease of uncertain/nontraditional etiology; Mesoamerican Nephropathy; Chronic Interstitial Nephritis of Agricultural Communities; Kidney Disease of Unknown Cause in Agricultural Laborers; tubulointerstitial; environmental exposure; low and middle income countries

Context and Background Rationale for Workshop:

A devastating and increasingly common form of early onset chronic kidney disease (CKD) is recognized in distinct agricultural regions, resulting in a large death toll among young working age men as well as other members of the community. Despite many reports of this form of CKD of undetermined origin, there remain numerous open questions and untested hypotheses about its causes and treatment. Areas of high disease prevalence include regions of Nicaragua, El Salvador, Costa Rica, Guatemala, Mexico, Panama, Sri Lanka, India, and other areas, although the full extent of the disease worldwide is not known. The disease has been termed Chronic Kidney Disease of uncertain/nontraditional etiology (CKDu/CKDnt), Mesoamerican Nephropathy (MEN), Chronic Interstitial Nephritis of Agricultural Communities (CINAC), or Kidney Disease of Unknown Cause in Agricultural Laborers (KDUCAL), and the heterogeneity of nomenclature may have hindered our understanding of the condition. It is characterized by tubulointerstitial pathology and the absence of traditional risk factors, such as diabetes, hypertension and aging. Whether this condition represents a single disease or a group of diseases with similar histopathology and who share some characteristics is unknown, and its cause or causes remain obscure. The condition was initially described in Central America in the early 2000s, although models suggest that the disease began in the mid-1970s. It was seen predominantly in workers from sugarcane plantations [1, 2], although the range of locations and occupations is very wide and likely still incomplete. [3–6]

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute of Environmental Health Sciences (NIEHS) planned and supported a workshop in Bethesda, Maryland on June 25–26, 2018 to enable better understanding of the epidemic of chronic kidney diseases in agricultural communities around the world and to inform research goals.

The organizing committee took an unbiased and agnostic approach to promote a broad scientific framework, in order to engage diverse perspectives and ensure that the scientific approach would include many avenues of investigation. A broad international group of experts with a wide range of skills, interests and perspective participated. Supplemental Table 1 shows the areas of expertise and interest of speakers and participants and Supplemental Table 2 shows the countries represented by the speakers, poster presenters and participants, which added to the diversity of opinion and perspective. Details of the meeting, including agenda, speaker abstracts and poster presenters can be found at: https://

www.niddk.nih.gov/news/meetings-workshops/2018/chronic-kidney-diseases-in-agricultural-communities-2018.

The meeting was structured as a series of short talks to provide context and to inform facilitated discussion groups. Topics were chosen to cover epidemiology, the science of investigating complex conditions, the techniques and application of toxicology, the history of other “geographically-identified kidney conditions”, environmental sciences, ethics, surveillance mechanisms, pathologic findings and potential mechanisms for CKDu. After an overview of the features and extent of CKDu[7–19], the pitfalls of creating too narrow or too broad a case definition were discussed. Geographic distribution has defined our thinking about CKDu and the value of surveillance data such as United States Renal Data System (https://www.usrds.org/) for end stage renal disease (ESRD) and the Centers for Disease Control and Prevention Chronic Kidney Disease Surveillance System (https://nccd.cdc.gov/ckd/) was recognized. Observations and renal biopsies in migrant agricultural workers in the U.S. and in Sri Lanka, El Salvador, India and France suggest a link to a history of exposure to pesticides and herbicides, and speakers proposed potential tubulo-toxic mechanisms. Bacterial and viral pathogens were considered as potential etiologies, although compelling evidence is lacking.

The broad concept of the exposome and the challenges in applying exposomic research to CKDu were brought forth, yet speakers acknowledged that the research community has not addressed the difficulty of measuring past exposures, the lack of data on a wide array of potentially relevant chemicals and the lack of analytical tools to evaluate ‘omic’ interactions. Conference speakers reviewed study designs appropriate for research on environmental exposures, with an understanding of work practices and agricultural exposure sampling. Soil and water analysis methods for chemicals and metals were discussed and, as an example, U.S. soil geochemistry and mineralogy databases were shared (https://mrdata.usgs.gov/soilgeochemistry/#/summary), but similar data are not available in regions of high CKDu prevalence.

Geographic hotspots and familial clustering of CKDu make genetic studies an important component of understanding this disease. There are specific epidemiological challenges when studying agricultural communities, with particular emphasis on biases introduced by the “healthy worker effect” and loss to follow-up. These have not received sufficient attention and will be critical to study design.

Break-out groups were given specific charges and preparation by the planning committee and facilitators around the topics occurred before the meeting. The key areas of focused discussion were:

1. Identifying and mitigating barriers to research
2. The importance of standardizing and implementing a case definition
3. Defining common data elements

1. Identifying and Mitigating Barriers to Research

Research in CKDu is uniquely complicated because of scientific, economic, political, sociocultural and resource barriers which confront disadvantaged populations in remote areas of Low and Middle Income Countries (LMIC).

Scientific and technical barriers include the lack of baseline epidemiologic surveillance data in the LMIC where the disease is prevalent. Often local health systems are limited in their ability to capture information on the broad population or to characterize the full extent of the disease. Therefore much of our data come from recognized clusters and small samples, which may lead to biased approaches to evaluation. Further, the scientific research infrastructure within affected countries appears inadequate to approach a problem of this magnitude, and financial constraints of LMIC may preclude them from devoting significant economic resources for research. Nonetheless, researchers must partner with local ministries of health, universities, and academic communities which can provide critical support. They will play an important role in the success of any research effort to understand CKDu. In particular, one speaker described her success in establishing a strong partnership with a Ministry of Agriculture and with faculty at a local collaborating university to build local research capacity; this permitted environmental health studies to continue through political unrest and travel restrictions.

Workshop attendees were aware of the importance of gaining and maintaining trust with participants, within the research community, and with international stakeholder groups. Potential study participants are dependent upon continued employment to support their families and participation in research should not impair their livelihood. While researchers have an obligation to inform participants if they recognize disease that was previously unknown, employers may discharge those who are recognized to be affected by CKDu. This risk of disclosure to the employer places study participants in a vulnerable position. Protections must be in place to safeguard confidentiality of potential research subjects, while allowing them the autonomy to choose to participate in research of value for their community. In addition, genetic studies of the affected populations are still in their earliest stages; as these become more common, it will be increasingly important to respect the culture and perspective of the communities. Many members of affected communities have limited health literacy and education. Some workers are migrants which makes follow-up challenging. Language and cultural barriers may compromise the ability to explain the purpose of and procedures involved in research, imperil the accuracy of information gathered and impede understanding of results and opportunities for interventions. Ethics review committees will need to understand local cultural expectations and harmonize local standards with the expectations of often foreign funding agencies.

The influence of agribusiness in government and policymaking cannot be ignored. The agricultural industry has an important role in protecting its employees, has been a partner in attempts to decrease the burden of disease, and has supported research in CKDu. Some large-scale agricultural corporations have permitted access to workers and local resources, including field hospitals with laboratory facilities. In this manner, important surveillance data can be obtained and mechanistic and preventive studies could be proposed. However,

the large economic impact of CKDu, and potentially the findings of CKDu research, on the agricultural and agrochemical industries means that industry collaborations must be scrutinized for conflicts of interest. Transparency and full disclosure of relationships will be expected.

Establishing trust within the research community requires objectivity and openness to multiple theories of etiologies of CKDu; ethical conduct of research including respect for participant privacy, autonomy and dignity; transparency in disclosure of funding and collaboration; and data sharing.

An additional ethical challenge in conducting research in resource poor areas is the scarcity of renal replacement therapy, including dialysis and kidney transplantation. While the ultimate goal is to prevent and develop effective treatment for CKDu, in the interim one must anticipate the identification of more affected participants and likely more premature deaths. Access to and delivery of appropriate healthcare, and advocacy for improved working conditions are essential human rights. Activities in those domains should not be delayed, but rather accomplished in parallel with research[20].

2. Creating a Case Definition

The lack of consensus regarding clinical features of CKDu in different regions of the world has been an impediment to progress in understanding the etiology and the extent of the disease. Overlapping and conflicting definitions in the literature limit comparability and data sharing. A clinical diagnosis of CKDu in an individual with chronic kidney disease requires the highest level of certainty, including nephrology consultation, laboratory testing and likely a renal biopsy for confirmation. Such a degree of diagnostic certainty is not possible for surveillance in LMIC or for an observational study, and therefore a research definition is needed. Heterogeneous approaches have been applied to identify CKDu in the known hotspots, and in regions suspected of having diseases akin to CKDu. A systematic approach to defining cases could facilitate research focused on etiology by:

1. Allowing comparisons of prevalence and incidence in regions with confirmed or suspected disease
2. Standardizing entry criteria for case-control or case-cohort studies
3. Enabling the systematic identification of high prevalence locations for geographic mapping with potential exposures (including, but not limited to, water source, average temperatures, metals and agrochemicals) and generation of new hypotheses
4. Supporting a basis for prevention and intervention activities of public health professionals.

The Pan American Health Organization in collaboration with the Latin American Society of Nephrology and Hypertension and the U.S. Centers for Disease Control [4, 21, 22] and World Health Organization in Sri Lanka[23] have proposed working definitions, although there remain resource constraints on laboratory testing and obtaining biopsies and renal imaging. A format to define possible, probable and confirmed cases is presented in Table 1,

informed by recent consensus reports, published case series and biopsy reports of CKDu.[7, 17–19]

The commonly used case definitions require laboratory features characteristic of tubulointerstitial disease, i.e., reduced eGFR, yet they use variable thresholds to exclude persons on the basis of proteinuria; they do not address a particular age range; and they do not specify an appropriate method for calculating eGFR in affected populations nor the threshold at which eGFR would be considered abnormal. There will need to be a balance between the sensitivity and specificity of an ideal case definition because the positive and negative predictive value of a case definition depends upon disease prevalence in the community and the prevalence of mimicking and masking conditions, such as diabetic nephropathy or cardiovascular disease; these coexisting diseases must be accounted for in research studies. While a narrow “clean” definition may be most useful to focus research efforts, excluding persons with diabetes and hypertension may result in a falsely low disease prevalence and would also miss important disease interactions. Further, using a particular geographic locale in a case definition may hinder the identification of additional disease clusters. A framework was agreed upon as shown in Table 1, fitting the best current knowledge regarding CKDu. However, as circumstances and knowledge in the field change, the framework for definition should be periodically reviewed and updated.

3. Defining Common Data Elements for Research in CKDu/CKD in agricultural communities

Widely accepted common data elements are needed to conduct research in all areas of public health including CKDu. The biomedical research community has recognized the importance of the FAIR guiding principles for data stewardship (findability, accessibility, interoperability, and reusability). Common data elements (CDE), defined as “a combination of a defined variable paired with a specified set of similarly coded responses to questions that are common to multiple data sets or used across different studies,” allow data to be more easily analyzed, shared and combined across studies to derive knowledge and accelerate scientific discovery[24]. The FAIR principles and CDEs are particularly relevant to efforts in CKDu since the current state of research in this area includes small series reports, lack of comparable data elements, ad hoc tools and inconsistent reporting of methods. Relevant domains of data are noted in Table 2, but this cannot be considered a comprehensive list. They are suggested CDE for active surveillance of populations and affected workers, including comparison of disease burden between agricultural workers and those who work in the home or in nonagricultural settings, and between parents and children. Such approaches have provided reliable data in higher income countries and in LMIC with established public health systems, but passive surveillance strategies may be more feasible in low resource settings.

Occupation is an important potential exposure that is challenging to capture systematically. While some validated tools exist, they are largely untested in the agricultural practices in affected communities, and exposures likely vary over the course of planting and harvest seasons. Data collection, reporting and analytic methods to capture this granularity need to

be planned, and soil, water and air sampling data will need to be obtained with appropriate metadata to permit linkage to local community exposures.

Urine and blood analyses require standardized methodology, balancing the value of ‘gold standard’ testing against clinically available tests (e.g. IDMS standardized serum creatinine concentration vs point of care), in the context of precision, accuracy and utility. Biopsy samples, including indications, clinical phenotype and circumstances, are important core data elements, which may not be possible obtain in all settings. Sharing of images will maximize the value of biopsy tissue and permit validation of findings.

An annotated compendium of standardized tools to sample the domains listed in Table 2 is needed. Ideally terminology standards could be developed from published studies, but this may not be possible with existing literature. While it would be desirable to use the PhenX Toolkit (https://www.phenxtoolkit.org), funded by the National Human Genome Research Institute of NIH, as a platform, at present this toolkit is incomplete for chronic kidney disease research and limited for environmental exposure assessment. This deficiency should be addressed in order to enhance data sharing and validation. Researchers must clearly specify how and when the data (including documentation, metadata, case report forms and protocols) will be shared. International privacy laws must be accommodated in developing a repository of health and occupational data and digital pathology images.

Moving Forward / Next Steps

Finally, breakout groups worked together to develop a research agenda which could address the topics considered on Day 1. Group discussions were guided by the following questions: How can we move from epidemiologic observation to causal hypotheses? How can environmental sampling and exposure assessment be used to drive and answer research questions? How can we prove causality? How should clinical/epidemiologic studies be designed?

The advantages and disadvantages of different study designs were debated and are shown in Table 3. The importance of human studies in early and established disease to generate testable hypotheses which could be validated in animal models, organoids and microchips was recognized. If CKDu is viewed as a model for tubulointerstitial disease, it remains to be determined if changes in the renal interstitium are a response to repeated tubular cell injury. Further, when biopsied at an advanced stage, primary tubulointerstitial kidney disease with secondary glomerular changes can be difficult to distinguish from end-stages of a primary glomerular process. Hypotheses for etiologic factors include, but are not limited to: environmental nephrotoxicants, genetic predisposition, climactic factors, recurrent episodes of dehydration, and unrecognized infectious agents. Interplay of different potential renal injuries and gene-environment interactions remains likely. The role of episodic acute interstitial nephritis driving progression of this chronic disease is likely in some settings. Careful planning of statistical methodology and data elements will be needed to compare different cohorts across geographic regions and time, and to incorporate multiple risk factors into analytic strategies. Obtaining biological samples, including renal biopsies, urine sediment, shed cells and exosomes, will be critical for testing hypotheses of etiology. The

challenge of uniform specimen preservation, transport and storage for future analysis will need to be addressed.

In order to implement a research agenda, investigators and funding agencies need to address the biomedical research infrastructure and trained workforce in LMIC where the diseases are most prevalent. A balanced approach to leveraging local resources and capacity building without overreaching will be appropriate.

While identification of causality is a research priority, there remains a strong desire to develop prevention and treatment strategies concomitantly, although specific recommendations are lacking. General improvements in agricultural working conditions including access to shade, rest and hydration are appropriate. If such improvements decrease the incidence or severity of the disease, the possibility of a ‘natural experiment’ that supports some of the current hypotheses should not be missed and the need for exposure analysis, standardized data sets and definitions remains relevant.

Key questions remain. Why are “hotspots” hot? Who gets this disease and who is protected? What is the role of acute and chronic exposures, and how can we identify and quantify them? What tools and model systems will prove most valuable in the understanding of this condition? How can we plan scientifically rigorous, culturally sensitive, multi-disciplinary clinical research in different regions and communities?

The diverse group of experts in methodologies, kidney disease, occupational and environmental science who attended the workshop provided valuable insights to move the field of enquiry forward. This report serves to synthesize the key discussion items, areas of consensus and controversy. The authors encourage the scientific community to embrace the challenge of understanding this condition, using a collaborative framework, as outlined here.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The faculty and organizing committee:

Kevin Abbott, Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Liz Amos, National Library of Medicine, NIH, Shuchi Anand, Stanford University, Kate Applebaum, George Washington University, John Balbus, NIEHS-WHO Collaborating Centre for Environmental Health Sciences, National Institute of Environmental Health Sciences, NIH, Ricardo Correa-Rotter, Instituto Nacional de Ciencas Médicas y Nutrición Salvador Zubirán (Mexico), Brian Curwin, National Institute for Occupational Safety and Health, CDC, Marc De Broe, University of Antwerp, José Escamilla, Pan American Health Organization, David Friedman, Harvard Medical School, Denise Gaughan, Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Jason Glaser, La Isla Network, Arthur Grollman, Stony Brook University School of Medicine, David Sheikh Hamad, Baylor College of Medicine, Bonnie Joubert, Population Health Branch, National Institute of Environmental Health Sciences, NIH, Paul Kimmel, Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Erik Koritzinsky, Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Ty Lawson, NIEHS-WHO Collaborating Centre for Environmental Health Sciences, National Institute of Environmental Health Sciences, NIH, Adeera Levin, University of British Columbia (Canada), Susan Mendley, Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Kathleen Michels, Division of International Research and Training, Fogarty International Center, NIH, Murray

Mittelman, Harvard University, Ana Navas-Acien, Columbia University, Geoff Plumlee, U.S. Geological Survey, Ludovic Reveiz, Pan American Health Organization, Diane Rohlman, University of Iowa, Pierre Rollin, Viral Special Pathogens Branch, National Center for Emerging and Zoonotic Infectious Diseases, CDC, Carla Saenz, Pan American Health Organization, Dale Sandler, Epidemiology Branch, National Institute of Environmental Health Sciences, NIH, Rajiv Saran, University of Michigan, Madeleine Scammell, Boston University, Carol Shreffler, Exposure, Response, and Technology Branch, National Institute of Environmental Health Sciences, NIH, William Suk, Hazardous Substances Research Branch, National Institute of Environmental Health Sciences, NIH, Brittany Trottier, Hazardous Substances Research Branch, National Institute of Environmental Health Sciences, NIH, Elizabeth Whelan, National Institute for Occupational Safety and Health, CDC, Robert Wright, Icahn School of Medicine at Mount Sinai, Yining Xie, Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, NIH.

Disclaimer:

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention or the Pan American Health Organization.

References:

1. Trabanino RG, et al., [End-stage renal disease among patients in a referral hospital in El Salvador]. Rev Panam Salud Publica, 2002 12(3): p. 202–6. [PubMed: 12396639]
2. Kupferman J, et al., Acute Kidney Injury in Sugarcane Workers at Risk for Mesoamerican Nephropathy. Am J Kidney Dis, 2018 72(4): p. 475–482. [PubMed: 30042041]
3. Johnson RJ, Wesseling C, and Newman LS, Chronic Kidney Disease of Unknown Cause in Agricultural Communities. N Engl J Med, 2019 380(19): p. 1843–1852. [PubMed: 31067373]
4. Hoy W and Ordunez P, Epidemic of Chronic Kidney Disease in Agricultural Communities in Central America. Case definitions, methodological basis and approaches for public health surveillance. 2017, Pan American Health Organization: Washington, D.C.
5. Wesseling C, et al., Resolving the enigma of the mesoamerican nephropathy: a research workshop summary. Am J Kidney Dis, 2014 63(3): p. 396–404. [PubMed: 24140367]
6. Wegman D, et al., Report from the Second International Research Workshop on Mesoamerican Nephropathy. 2015, SALTRA/IRET-UNA.
7. Anand S, et al., Prospective Biopsy-Based Study of Chronic Kidney Disease of Unknown Etiology in Sri Lanka. Clin J Am Soc Nephrol, 2019.
8. Caplin B, et al., International Collaboration for the Epidemiology of eGFR in Low and Middle Income Populations - Rationale and core protocol for the Disadvantaged Populations eGFR Epidemiology Study (DEGREE). BMC Nephrol, 2017 18(1): p. 1. [PubMed: 28049448]
9. Caplin B, et al., The International Society of Nephrology's International Consortium of Collaborators on Chronic Kidney Disease of Unknown Etiology: report of the working group on approaches to population-level detection strategies and recommendations for a minimum dataset. Kidney Int, 2019 95(1): p. 4–10. [PubMed: 30606428]
10. Fischer RSB, et al., Early detection of acute tubulointerstitial nephritis in the genesis of Mesoamerican nephropathy. Kidney Int, 2018 93(3): p. 681–690. [PubMed: 29162294]
11. Herrera R, et al., Clinical characteristics of chronic kidney disease of nontraditional causes in Salvadoran farming communities. MEDICC Rev, 2014 16(2): p. 39–48. [PubMed: 24878648]
12. Ordunez P, et al., Chronic kidney disease mortality trends in selected Central America countries, 1997–2013: clues to an epidemic of chronic interstitial nephritis of agricultural communities. J Epidemiol Community Health, 2018 72(4): p. 280–286. [PubMed: 29437864]
13. Athuraliya TN, et al., Prevalence of chronic kidney disease in two tertiary care hospitals: high proportion of cases with uncertain aetiology. Ceylon Med J, 2009 54(1): p. 23–5. [PubMed: 19391454]
14. Gonzalez-Quiroz M, et al., Decline in Kidney Function among Apparently Healthy Young Adults at Risk of Mesoamerican Nephropathy. J Am Soc Nephrol, 2018 29(8): p. 2200–2212. [PubMed: 29907699]

15. Nanayakkara S, et al., An integrative study of the genetic, social and environmental determinants of chronic kidney disease characterized by tubulointerstitial damages in the North Central Region of Sri Lanka. J Occup Health, 2014 56(1): p. 28–38. [PubMed: 24351856]
16. Peraza S, et al., Decreased kidney function among agricultural workers in El Salvador. Am J Kidney Dis, 2012 59(4): p. 531–40. [PubMed: 22300650]
17. Nanayakkara S, et al., Tubulointerstitial damage as the major pathological lesion in endemic chronic kidney disease among farmers in North Central Province of Sri Lanka. Environ Health Prev Med, 2012 17(3): p. 213–21. [PubMed: 21993948]
18. Wijkstrom J, et al., Morphological and clinical findings in Sri Lankan patients with chronic kidney disease of unknown cause (CKDu): Similarities and differences with Mesoamerican Nephropathy. PLoS One, 2018 13(3): p. e0193056. [PubMed: 29513702]
19. Wijkstrom J, et al., Clinical and pathological characterization of Mesoamerican nephropathy: a new kidney disease in Central America. Am J Kidney Dis, 2013 62(5): p. 908–18. [PubMed: 23850447]
20. Ordunez P, et al., Chronic kidney disease epidemic in Central America: urgent public health action is needed amid causal uncertainty. PLoS Negl Trop Dis, 2014 8(8): p. e3019. [PubMed: 25101669]
21. Ferreiro A, et al., Confirmed clinical case of chronic kidney disease of nontraditional causes in agricultural communities in Central America: a case definition for surveillance. Rev Panam Salud Publica, 2016 40(5): p. 301–308. [PubMed: 28076578]
22. Lozier M, et al., Chronic kidney disease of nontraditional etiology in Central America: a provisional epidemiologic case definition for surveillance and epidemiologic studies. Rev Panam Salud Publica, 2016 40(5): p. 294–300. [PubMed: 28076577]
23. Rajapakse S, Shivanthan MC, and Selvarajah M, Chronic kidney disease of unknown etiology in Sri Lanka. Int J Occup Environ Health, 2016 22(3): p. 259–264. [PubMed: 27399161]
24. Corwin EJ, et al., Feasibility of Combining Common Data Elements Across Studies to Test a Hypothesis. J Nurs Scholarsh, 2017 49(3): p. 249–258. [PubMed: 28231416]

Table 1.

Proposed criteria to identify cases of CKDu

	Possible	**Probable**	**Confirmed**
CKD EPI eGFR < 60 ml/min/1.73m^2 but higher threshold would be appropriate if younger subjects are included	X	X	X
Urine dipstick negative for protein, or no greater than 1+	X	X	X
Age 18–60 years with consideration of including adolescents in future studies	X	X	X
3-month repeat CKD EPI eGFR < 60 ml/min/ 1.73m^2		X	X
Ultrasound demonstrating absence of cystic disease or large stone burden.			X
Renal biopsy showing primary tubulointerstitial disease			X
Diabetes: Diabetic subjects are not excluded (may coexist with CKDu). Studies of CKDu prevalence or incidence should be stratified by presence of diabetes			
Location. If in a region where CKDu or a phenomenon akin to CKDu is suspected, the current approach could be used to estimate relative prevalence. Ideally a subset of patients should undergo biopsy to confirm, but that may be impossible in low resource settings.			
Supportive features: Absence of edema; presence of hypokalemia and hyperuricemia. Ultrasound findings of loss of cortico-medullary differentiation or bilateral small kidney size.			

Table 2.

Domains and Sources of Data Elements

Potentially Relevant Data Domains	Proposed Sources
Health history	Medical records, Questionnaires, Kidney function measures
Occupational history	Surveys, Questionnaires, Wearable devices
Birth history	Medical records, Questionnaires
Pharmaceutical and Herbal Medication use	Medical records, Surveys, Dispensary records
Environmental exposure	Local sample collection, Wearable devices, Environmental surveillance databases, questionnaires
Meteorology	Wet Bulb Globe temperature measurement, Meteorological records
Geography	GPS, Satellite

Table 3.

Study Design Considerations

Study designs	Advantages *regarding CKDu*	Disadvantages *regarding CKDu*
Prospective longitudinal studies	• Better view of the natural history of disease-*incompletely understood in CKDu* • Permit collection of a broader range of biomarkers over time • Exposure analysis over time • Test different hypotheses-*etiology of CKDu is unknown*	• Expensive-*insufficient sample size may limit scope or power of study* • Require stable residential populations-*many affected workers are migrants* • Results available only after years of follow-up
Retrospective case-control studies	• Comparisons of different locales and populations-*which may explain different presentations in different regions* • Comparisons of affected and unaffected members of the same community • Define susceptibility factors	• Depends heavily on the case definition-*which is still being debated* • Focus on late stage disease-*interventions may be more valuable early in younger, less affected individuals* • Survivor bias
Flexible study designs	• Case-only or case-control studies could be embedded within a prospective study	• Need sufficient power to examine variety of etiologies and biospecimens