International Expert Consultation on Chronic Kidney Disease of Unknown Etiology

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Presidential Task Force for Prevention of Chronic Kidney Disease

World Health Organization
COUNTRY OFFICE FOR Sri Lanka

International Expert Consultation on Chronic Kidney Disease of Unknown Etiology

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Report of the International Expert Consultation on Chronic Kidney Disease of unknown etiology (CKDu) in Sri Lanka

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I. Title

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Contents

Acronyms

AAN	aristolochic acid nephropathy
As	arsenic
BEN	Balkan endemic nephropathy
BMI	body mass index
Cd	cadmium
CKD	chronic kidney disease
CKDu	chronic kidney disease of unknown etiology
ESRD	end-stage renal disease
IERG	independent expert review group
Ig	immunoglobulin
IT	information technology
KDIGO	Kidney Disease: Improving Global Outcomes
MeN	Mesoamerican nephropathy
MRL	maximum residues limit
NCD	noncommunicable disease
NSAID	non-steroidal anti-inflammatory drug
RO	reverse osmosis
SLN	Sri Lanka nephropathy
UEN	Uddanam endemic nephropathy
WSP	water safety plan

Executive Summary

Chronic kidney disease of unknown etiology (CKDu) is a serious public health problem in Sri Lanka and several other countries, particularly in Mesoamerica. CKDu appears to disproportionally affect poor, rural, male farmers in hot climates. Despite more than 20 years of study in Sri Lanka and globally, the problem of CKDu is not well understood. The Government of Sri Lanka accords a very high priority to addressing CKDu. A Presidential Task Force on CKDu was set up in 2014 to provide oversight and coordinate the efforts of various sectors, agencies and ministries towards the prevention and treatment of CKDu. In this context, the World Health Organization (WHO) Country Office for Sri Lanka and the Presidential Task Force jointly convened a three-day international expert consultation to guide future direction for addressing CKDu in Sri Lanka.

The consultation aimed to develop consensus on research priorities and cost-effective interventions for prevention and management. The objective was to review the knowledge on CKDu globally and in Sri Lanka, identify gaps, prioritize an interdisciplinary collaborative research agenda and recommend interventions based on the available evidence. The Consultation also aimed to develop consensus on the monitoring and accountability framework for implementation of the recommendations.

Participants comprised 54 national and international clinicians, researchers, epidemiologists, toxicologists, agriculture scientists, social scientists, hydrologists and other experts who represented the geographical and etiological dimensions of the disease. Experts came from Sri Lanka, India, the United Kingdom, Australia, Cuba, El Salvador, Finland, Sweden, Canada and Costa Rica adding a wealth of experience to the Consultation. The International Society of Nephrology, Sri Lanka Society of Nephrology, international and national universities, public and private research institutes, National Science Foundation, Coordinating Secretariat for Science, Technology and Innovation and WHO were the key organizations represented.

A series of background papers commissioned for the Consultation provided the current state of the problem of CKDu and the gaps that needed to be filled. These provided overviews of the disease both in Sri Lanka and globally, the clinical aspects, available evidence on the possible role of various agents in the etiopathogenesis of the disease, and the social impact of CKDu.

Strong support to the Consultation was expressed by the Director of the Presidential Task Force on CKDu and Secretaries and other senior officials of key ministries at the opening session, highlighting the commitment of the Government of Sri Lanka to solving the problem of CKDu through a multisectoral approach. To set the stage, two presentations were made on the status of CKDu in Sri Lanka and globally. Participants were then divided into four groups according to their areas of expertise, asked to review the available evidence on specified topics, and arrive at a series of recommendations by consensus.

On the first day, the groups were tasked with defining future research priorities in four key areas: (i) Clinical aspects: early detection, treatment and care; (ii) Role of agrochemicals; (iii) Role of water/heavy metals; and (iv) Role of heat stress/dehydration and miscellaneous hypotheses. On the second day, the four groups had to identify priority cost–effective interventions in the following areas: (i) Prevention; (ii) Early detection, treatment and care; (iii) Integrated surveillance and CKD registry; and (iv) Social interventions, as CKDu has a huge social impact on patients and their families.

The outputs of the group work were consolidated into key recommendations by consensus. These recommendations will be incorporated into the forthcoming National Action Plan on CKDu for Sri Lanka. In order to implement the National Action Plan on CKDu, a framework for monitoring, implementation and accountability was proposed based on the “Every woman Every child” accountability concept of the United Nations that was put in place in 2010 to accelerate the progress towards achievement of the Millennium Development Goals by 2015. The existing framework consists of a National Committee on CKDu, which can provide the overall oversight. The Presidential Task Force can be the focal point for the proposed intersectoral coordinating mechanism. In addition, constitution of an Independent Expert Review Group was discussed, which could independently review the ongoing interventions and report to the National Committee. All participants agreed to this three-tier approach.

Open discussions in the plenaries led to final consensus recommendations, which were presented on the final day of the meeting to the Director of the Presidential Task Force in the concluding session.
The recommendations of the Consultation are based on the consensus of all 54 experts who participated in the meeting.

Recommendations

- Develop a robust surveillance system to understand the burden, geographical distribution and time trends of CKDu in Sri Lanka. The surveillance system should be linked to monitoring of potential toxins in food, water and the environment, and provide a platform for long-term research to understand the role of potential risk factors and document the usefulness of ongoing interventions.

- Establish a consortium of national/international researchers to conduct long-term interdisciplinary research. CKDu is a complex disease and there is a need for sharing expertise across disciplines and countries to accelerate knowledge dissemination, guide the research agenda and help solve the mystery of "u" (unknown) in CKDu. WHO will facilitate researchers from global CKDu hotspots to engage in research exchange.

- Strengthen the implementation of available interventions; namely, early detection and management of CKDu in the early stages and dialysis in the late stages. In addition, prioritize the provision of safe drinking water and food in the affected areas and ensure sustainable agricultural practices based on the current status of knowledge and evidence. An evaluation component should be built into these interventions to understand their impact and modify the interventions if needed.

- Provide social support at three levels – patient, family and community. Build the capacity of existing community-level workers, appoint trained paramedical personnel and social workers in appropriate locations, and expand and strengthen social support services and resources. Develop a sound communication strategy to destigmatize the disease. Livelihood generation in affected areas was also recommended.

- Strengthen/expand human resources at various levels, such as nephrologists, renal care nurses, social workers at the nephrology units and field level to enhance the coverage of renal care services and provide psychosocial support to patients and families.

- Develop a framework for monitoring and accountability to ensure timely implementation of the activities. A three-tier system was proposed, consisting of a National Committee on CKDu, an intersectoral coordinating mechanism coordinated by the Presidential Task Force and an Independent Expert Review Group. The framework will have its set of performance indicators based on the National Action Plan. This will enable open and transparent measurement as well as communication.

Report of the Consultation

Background

Chronic kidney disease (CKD) is one of the noncommunicable diseases (NCDs) of public health importance due to its high burden and high cost of treatment in the advanced stages. CKD in adults is predominantly caused by diabetes and hypertension. Autoimmune and systemic conditions also cause CKD, as do inherited conditions. Nephrotoxic drugs, herbal medications, toxins and infections are other causes of CKD in developing countries. The prevalence of CKD ranges from 9% to 11% in developed countries. An increased prevalence of CKD has been observed in select geographical areas in several countries over the past two decades. The countries included El Salvador, Nicaragua, Costa Rica, Egypt, Sri Lanka and India. As the etiology was not clear, the term "chronic kidney disease of unknown etiology" (CKDu) has been used in the literature since the early 2000s.

In Sri Lanka and Mesoamerica, CKDu is a serious public health problem that appears to disproportionally affect poor, rural, male farmers in hot climates. Despite more than 20 years of research in Sri Lanka and globally, the problem of CKDu is not well understood. The Government of Sri Lanka accords a very high priority to addressing CKDu. A Presidential Task Force on CKDu was set up in 2014 to provide oversight and coordinate the efforts of various sectors, agencies and ministries towards the prevention and treatment of CKDu. In this context, the World Health Organization (WHO) Country Office for Sri Lanka and Presidential Task Force jointly convened a three-day international consultation to guide future direction for addressing CKDu in Sri Lanka.

Objectives

The Consultation aimed to develop consensus on research priorities and priority interventions for the prevention and management of CKDu. The objective was to review the knowledge on CKDu globally and in Sri Lanka, identify gaps, prioritize an interdisciplinary collaborative research agenda and recommend interventions based on the available evidence. The Consultation also aimed to develop consensus on a monitoring & accountability framework for implementation of the recommendations.

Methods

Nine background papers were commissioned during the preparatory phase of the Consultation. These papers covered areas such as a global overview of CKDu, overview of CKDu in Sri Lanka, and various other topics relevant to the causes of and interventions for CKDu. These papers were circulated to all experts prior to the meeting and provided background information to facilitate discussions during the meeting.

Broad themes of the Consultation were research priorities and priority interventions for CKDu for the first two days. The experts were divided in four groups on Days 1 and 2. Each group was led by two co-chairs – one international and one national expert. A note with detailed objectives, key areas of discussion and expected outcomes was given to each of the groups to facilitate the discussion. The Chair summarized the information from the relevant background paper to set the stage for group discussion. The group reviewed the available information, identified gaps and agreed on a set of recommendations.

Following a presentation on "Principles of testing hypotheses in epidemiological research" on the first day, each of the groups was tasked with defining future research priorities in four key areas: (i) Clinical aspects: early detection, treatment and care; (ii) Role of agrochemicals; (iii) Role of water/heavy metals; and (iv) Role of heat stress/dehydration and miscellaneous hypotheses.

On the second day, the four groups had to identify priority cost–effective interventions in the following areas: (i) Prevention; (ii) Early detection, treatment and care; (iii) Integrated surveillance and CKD registry; and (iv) Social interventions, as CKDu has a huge social impact on patients and their families.

The framework for monitoring, implementation and accountability was discussed on the last day of the meeting. At the end of each of the three sessions – research priorities, priority interventions and monitoring/accountability – each group presented the outcome of their deliberations to all the experts. An open discussion was held after each presentation, and comments and suggestions were given by the audience. These were incorporated in the final recommendations. All the experts submitted WHO Declaration of Interest forms.

Day 01

Opening session

The Director of the Presidential Task Force on CKDu, Mr Asela Iddawela, welcomed the participants and gave the background of the Presidential Task Force, which was set up in 2014 to limit the spread of CKDu. Guided directly by the President, its task is to provide oversight and coordinate all activities related to the control of CKDu in Sri Lanka. He hoped that the deliberations from the three-day meeting would help in formulating the National Action Plan and a monitoring framework for its implementation. He wished the participants success.

The presence of Secretaries and other senior officials of the Ministries of Health, Nutrition and Indigenous Medicine; Science, Technology and Research; City Planning and Water Supply; Social Empowerment and Welfare; and the Chairperson of the University Grants Commission highlighted the commitment of the Government of Sri Lanka to combating the problem of CKDu. Each of them discussed the initiatives and interventions being undertaken by their respective ministries and collaboratively.

The WHO Representative to Sri Lanka described the objectives of the meeting and the expected outcomes. He explained why this forum, with its diverse range of experts and expertise, was well suited to look for solutions to the problem of CKDu. He urged participants to work as a team, as solutions are easier to find when people share expertise and resources.

Setting the scene

An overview of the status of CKDu in Sri Lanka apprised participants of the scale of the problem and what was being done to alleviate it. The presentation covered factors that may have a bearing on the origin of CKDu, the epidemiology of the disease, areas ("dry zone") where the disease is found, number of patients, the profile of a typical patient (poor, male paddy farmer, 40–70 years of age, familial preponderance), existing screening programmes and methods used to diagnose the disease. Management of the early and late stages of the disease, the national response, available facilities and services, and plans for expansion of services were also elaborated.

The ensuing discussion generated many questions. Some were related to laboratory findings such as urinary sediments, level of creatinine, ultrasonographic appearance and morphology of the kidneys, which patients were considered suitable for biopsy, and what histopathological findings were commonly seen. Other queries were on whether fluorosis and drinking water had a role in causation, differences in clinical and pathological findings between men and women, and whether renal satellite clinics were located close to patients. A query was also raised about the type of persons used as controls for various studies, and whether one or more control groups were required.

The global burden of CKDu and the characteristics of the various epidemics around the world was presented next. Various types of CKDu were discussed, namely Mesoamerican nephropathy (MeN) in the Central American countries, Balkan endemic nephropathy (BEN) in the Balkan States, Itai–itai nephropathy in Japan (caused by ingesting rice contaminated with cadmium), aristolochic acid nephropathy (AAN) in Taiwan, China, Belgium and other countires worldwide among users of herbal medicines, Uddanam endemic nephropathy (UEN) in India, and Sri Lanka nephropathy (SLN) in Sri Lanka. The geography, similarities and differences between these types of CKDu with respect to climate, age, sex, occupation, clinical features, main and alternative hypotheses related to causation, were compared. MeN, SLN and UEN are diseases of the tropics and have some common features, while Itai–itai, BEN and AAN differ from these. Ongoing research collaboration and initiatives between various countries facing this problem, such as through the Consortium on the Epidemic of Nephropathy in Central America and Mexico (CENCAM) and the Central American Programme on Work , Health and the Environment (SALTRA) were presented together with the existing and suggested policy responses, and technological solutions. The need for interdisciplinary and international research collaboration by parties independent of conflicts of interest was highlighted, as was the need for research to take into account socioeconomic factors and the role of governments and international and professional organizations such as the World Health Organization (WHO) and the International Society of Nephrology.

The presentation was followed by questions pertaining to the sociodemographic characteristics of the patients and role of various risk factors and their combinations.

Group work: Defining future research priorities

Group 1: Clinical aspects: early detection, treatment and care

Although CKDu was first identified in Sri Lanka in the 1990s, one of the main gaps identified by the group was the absence of a uniform case definition, both within the country and internationally. This impairs the ability to answer key questions, such as the true estimate of the burden of disease, the risk factors for progression, impact of interventions, and comparability across jurisdictions. The natural history of the disease needs to be studied further.

The group discussed the need for modifying the existing case definition and using inclusion instead of the exclusion criteria used currently. CKD could be the overarching disease, and cases subdivided into CKDu and CKD due to other causes, such as hypertension, diabetes and others. An international group of experts from various disciplines (not limited to those involved in clinical care) should formulate a uniform case definition. This should include epidemiological, clinical and etiopathological criteria. It was also suggested that cases be divided into possible, probable and definite CKDu on the basis of the presence of defined criteria. The present staging system of the Kidney Disease: Improving Global Outcomes (KDIGO) (stages 1–5) could be retained. Sri Lanka should use one method of calculating the estimated glomerular filtration rate (eGFR), and it was suggested that the CKD-EPI formula be used. With respect to screening, the group felt that biomarkers could not be used at present outside of the research context, but it was important to establish screening methods compatible with the regular surveillance programme using point-of-care testing machines, and testing for urine albumin/creatinine ratio and serum creatinine.

Research questions identified during the group work

Group 1: Clinical aspects: early detection, treatment and care

- What is the case definition of CKDu?
- What are the indications for renal biopsy and criteria for pathological diagnosis of CKDu?
- What is the eGFR formula used in various laboratories and how can it be standardized based on the CKD-EPI formula? What is the population-adjusted expected normal rage for eGFR and other relevant laboratory tests?
- What are the valid point-of-care testing technologies that can be introduced in the screening programme?

Group 2: Role of agrochemicals

The group identified gaps in knowledge regarding the availability of various agrochemicals, patterns of use, safe levels of agrochemicals in the environment and their health effects on humans. It reviewed the information on nephrotoxicity of various agrochemicals including such as glyphosate, propanil, chlorpyrifos, diazinon, carbofuran, profenofos, carbosulfan, carbaryl, etc. and the potential contaminants in agrochemicals such as cadmium (Cd) and arsenic (As). The available evidence for their association with CKDu was reviewed including evidence regarding nephrotoxicity in vitro, in animals and in humans at high and low doses. Annex 3 provides a summary of the outcomes of the review. Cd was nephrotoxic as per the literature; however, existing data from studies that measured Cd in water and biological samples was not conclusive and the clinical characteristics of the Cd-induced nephropathy seemed different from the CKDu in Sri Lanka. Per se, levels of Cd in water from studies in Sri Lanka were unlikely to account for the epidemic.

Inorganic As is nephrotoxic in vitro and in animals at high doses but there is no evidence of nephrotoxicity in humans for increased risks of CKD from the epidemiological studies. There are no reports of CKDu in other populations with high As levels in water. The group consensus was that As alone is unlikely to be the causative agent of CKDu in Sri Lanka.

Nephrotoxicity has been documented in the literature for humans at high doses for specific glyphosate formulations (in combination with certain adjuvants), propanil and chlorpyrifos. Association of individual pesticides with CKDu has been reported in only two studies in Sri Lanka. The evidence of causality of this association was considered inconclusive due to lack of consistency of the findings, lack of temporality where association was observed and limitations in the methods used for measuring exposures. Longitudinal well-designed studies that include healthy individuals in endemic and non-endemic areas, with bio banks, will be needed to assess the possible role of agrochemicals in causation and progression of CKDu.

Research questions identified during the group work

Group 2: Role of agrochemicals

- Can existing information regarding importation, distribution and use patterns of agrochemicals be linked to the CKDu incidence?
- Can low doses of Cd (from food or other sources) be nephrotoxic among individuals with other risk factors (e.g. malnutrition, low birth weight) and other diseases (e.g. diabetes)?
- As individual agrochemicals do not seem to explain the CKDu, can synergies between individual agrochemicals or between agrochemicals and other risk factors play a role in the causation of CKDu?

Group 3: Water and heavy metals

Several hypotheses have been put forward linking the causation of CKDu to various heavy metals and the quality and quantity of water. The group first weighed the available evidence for water and heavy metals as causative factors for CKDu. With regard to heavy metals, the group felt that the levels of these in water in Sri Lanka, particularly As and Cd, are not high enough to cause disease. Fluoride and its interaction with other constituents that add to the hardness of water is a concern. The increased risk of developing CKDu among those who drink well water as against those who drink spring water is based on anecdotal evidence and needs verification. The male preponderance of the disease is not explained by water as a major cause.

In affected areas, water quality needs to be assessed, particularly combinations of various constituents, such as fluoride and the effect of hardness in combination. The effect of type of water consumed (well water versus spring water) on the occurrence of CKDu, the quantity of water consumed, exposure to other substances through water and the results of interventions to provide clean drinking water (before–after studies) should be examined through well-designed studies. The long-term effect of consuming water that has undergone reverse osmosis (RO) treatment is another possible area of study.

The geochemical atlas of Sri Lanka should be updated and a single body, the Water Information System for Sri Lanka (WISSL), should maintain an updated database on water quality. Standardized study protocols (by the College of Community Physicians) as well as standardized prevalence protocols for CKDu should be established.

Research questions identified during the group work

Group 3: Water and heavy metals

- What is the prevalence of CKDu among communities drinking different types of water (shallow/deep/tube wells, spring, surface, rain water)?
- What is the impact of provision of safe water (treated by RO or other filters) on CKDu patients?
- How much water do people drink, especially those who work in the field, are the water sources the same as used by family members, and how long have they been using the water sources?
- Does silica, other chemicals and physical parameters such as taste, colour, smell (palatability) in water play a role in the causation of CKDu?
- Does fluoride play a role in combination with other factors, such as hardness of water, in causing CKDu?
- What are the roles of possible cofactors, including ionicity/Hofmeister series in CKDu?

Group 4: Heat stress and other hypotheses

The group reviewed the available evidence regarding heat stress hypothesis for Mesoamerican nephropathy. Research studies in sugarcane workers documented the physiological effects of heat stress after working for long hours in high temperatures. Exercise, heat and recurrent dehydration could lead to repeated acute kidney injury and eventually chronic kidney disease. The group discussed the relevance of the hypothesis in the context of Sri Lanka. Many non-endemic districts in Sri Lanka have similar or higher temperatures; however, CKDu has not been reported in these districts. The working hours and the work load of farmers in the endemic areas might be lower than that of the cane cutters in Mesoamerica. The group agreed that heat stress as a cause of CKDu in Sri Lanka is less clear than in Mesoamerica. However, further research is needed to understand its contribution.

The group discussed the role of infections in the etiology of CKDu. Leptospirosis has a high incidence in Sri Lanka and it can cause acute interstitial nephritis and acute kidney injury. Studies from Sri Lanka have documented a high prevalence of immunoglobulin (Ig)G antibodies against *Leptospira* in the population; however, data on IgM were lacking. The role of leptospirosis and hantavirus infection as a potential risk factor should be explored further. Two available studies from Sri Lanka have reported the role of genetic susceptibility as a risk factor. The group consensus was that a shared environment probably played a more important role as compared to genetic susceptibility. The majority of the patients with CKDu were found to have a low body mass index (BMI). However, it was not certain whether it was cause or the effect of CKDu. The role of low birth weight might be is difficult to study these due to lack of good-quality historical data. The use of non-steroidal anti-inflammatory drugs (NSAIDs), another well-established risk factor for renal injury, was common not only in endemic areas but also in other areas and therefore it may not be a major contributory factor for CKDu. Overall, heat stress and leptospirosis were identified as two potential risk factors for further research.

Research questions identified during group work

Group 4: Heat stress and other hypotheses

Heat stress hypotheses

- What were the work conditions a few decades ago and is there a change in work conditions since then?
- Has the climate of Sri Lanka changed over the past 30 years? Has the CKDu hotspot map changed over time?
- Do workers experience symptoms and signs (signs of dehydration, signs of heat exposure such as rise in core temperature, heart rate, etc. and signs of acute kidney injury) of heat exposure? What is the degree of heat exposure in each region and season as measured using heat stress indices?
- What kind of fluids do farmers drink , from which source and what is the quantity consumed during working hours?

Other hypotheses

- Is *Leptospira* DNA detectable in the biopsies done for CKDu?
- What is the incidence of CKDu among patients who have had leptospirosis on long-term follow up as compared with non-infected individuals?
- Is there a role of maternal malnutrition and low birth weight in causing CKDu?
- What is the nutritional status of early CKD populations?

Day 02

Group work: Priority cost–effective interventions

Group 1: Prevention

The group discussed the challenges in recommending specific interventions for prevention due to lack of a clear understanding of the etiology of CKDu. The major areas of discussion were water, agrochemicals and heat stress. The role of heavy metals in drinking water as a causative factor for CKDu has not been established; however, access to safe drinking water is a basic human right and therefore efforts to provide safe drinking water should be accelerated in endemic areas. Various technologies such as RO water, rain water harvesting, etc. are being used in endemic areas and feasibility studies need to be conducted to identify technologies that are cost effective and appropriate and sustainable.

With regard to agrochemicals, those with known nephrotoxic effects could be gradually phased out to reduce exposure in endemic areas – noting, however, that they should not be replaced with products with some other important toxicity. A comprehensive programme involving regulators, retailers and farmers is needed to reduce exposure to agrochemicals. The group also emphasized the need to promote sustainable farming practices.

Although the evidence for heat stress hypothesis has not been established as a causative factor for CKDu in Sri Lanka, exposure to heat should be reduced in high-risk groups in the endemic areas. There is a need to link planned interventions with improved surveillance mechanisms and information on prevalence to build an evaluation component and understand the impact. Evaluation of interventions may also provide insights regarding causes and risk factors for the disease.

Group 2: Early detection, treatment and care

Early detection results in early treatment. For this, screening is necessary, and the current guidelines on screening for CKD are applicable to CKDu patients as well. To encourage patients to undergo screening, awareness of CKDu should be raised via the media, and efforts made by local authorities to increase participation in screening. Reduction of stigma is also necessary to encourage people to come for screening. In addition, facilities need to be provided for testing.

With regard to treatment, the group felt that the current screening and management guidelines on CKD and CKDu should be revisited so that they could be adapted for use at all levels of health facilities (primary, secondary and tertiary). For those with end-stage renal disease (ESRD), a policy of "dialysis for all" should be followed, and patients undergoing dialysis supported in various ways.

Group 3: Surveillance

The group reviewed the differences between screening and surveillance. The primary goal of surveillance is to have population-level information, while screening is meant for detection of disease/risk at the individual level. Surveillance requires high participation from the population for reliable estimates using simple tests. Screening tests need to have a good balance of sensitivity, specificity and predictive values. The existing data sources for CKD were the community-based screening programme, the national registry maintained by the Ministry of Health and a renal registry maintained by the Sri Lanka Nephrology Association. The major gaps were lack of community-based surveillance and lack of linkage between the screening programme and registry. In addition, data from the two available registries need to be reconciled. The group reviewed the current status of the national renal registry and identified gaps such as lack of use of a uniform case definition, delays in data entry and inadequate analysis to inform policy-makers, and poor dissemination. The lack of robust population-level surveillance data was regarded as a hindrance to fully understanding the nature of the disease and and drawing comparisons with outbreaks in other countries.

The group agreed on the need for community-based surveillance in addition to the registry through periodic surveys to monitor the disease burden in endemic and non-endemic districts. Because accurate measurement of glomerular filtration rate is not possible in field conditions there is a need to rely on the estimated glomerular filtration rate (eGFR). For eGFR, a prerequisite of a meaningful community-based surveillance is the generation of population–specific baseline data which will allow the estimation of the distribution of eGFR values and monitoring of trends over time. The objectives of community-based surveillance would be to generate baseline data for eGFR, measure the proportion of individuals below a defined cut-off and monitor trends over time. Three districts could be selected – one from an endemic area, one from a non-endemic area and one from a moderately endemic area. Surveillance sites could be selected in each of the districts and a minimum of 1000 randomly selected individuals per site or all individuals in the defined geographical area should be surveyed. The need for high coverage was emphasized for the selected sites to generate reliable estimates. The ideal scenario would be to have a large number of sites to get a representative estimate at the district level; however, the time and resources required to complete one round of the survey need to be considered while finalizing the number of sites. The heterogeneity of the disease in endemic districts needs to be considered while selecting surveillance sites. The experts shared an available international protocol that could be potentially used for surveillance in Sri Lanka and would enable comparisons with other endemic countries, and facilitate identification of areas for active collaboration. The surveillance sites would then form a basis to develop research studies on various exposures of interest, such as heat stress, sources of drinking water, agrochemicals, etc. (*see* figure in Annex 4). Longitudinal cohort studies could also be conducted at these sites to understand the unknown aspects of CKDu.

Group 4: Social interventions

CKDu has a devastating effect on individuals, families and the community. Intense stigma is attached to the disease and the high costs of treatment push affected people into poverty, which leads to further social and health problems. There are huge gaps in knowledge among patients, and gaps in service provision.

Priority interventions should be provided at three levels – patient, family and community. The needs of patients and families should be elucidated through a consultative process, and patients' views taken into consideration when planning interventions. Patients' working conditions can be improved by speaking with their employers. Families can be provided psychosocial counselling, and children helped through school-based interventions such as foster families, and bank accounts for children so that their studies are not interrupted due to poverty/death of a parent. Self-help groups can be formed at both the family and community levels, and assistance provided to vulnerable families. In the community, trained social workers can help to support patients. In addition, informal counselling networks can be strengthened by calling upon community and religious leaders, and traditional medicine practitioners to provide support. Existing community-level workers can also be mobilized. In hospitals, clinical psychosocial workers can provide counselling and support.

The group also discussed interventions that the government could provide at various levels. These should start with putting in place an organizational structure to tackle the social issues due to CKD at the national and provincial levels. An intersectoral body should be set up headed by the President/Prime Minister and coordinated by the Ministry of Health, with a Deputy Director General specially appointed for CKD, supported by a dedicated budget and intersectoral team. The fund for CKDu should be augmented, and subsidies provided for transport/medications/overnight stay for patients, especially those undergoing dialysis. Support should also be provided for children and women-headed households. A national-level communication strategy to provide information on CKDu and destigmatize the disease should be worked out. If required, brand ambassadors could be used to leverage multinational support.

Day 03

Framework for monitoring, implementation and accountability (I-AM)

The outcome of the Consultation will inform and feed into the forthcoming National Action Plan on CKDu for Sri Lanka. In order to ensure and facilitate implementation of the National Action Plan, a framework for monitoring, implementation and accountability (I-AM) was presented. The proposed framework was developed on the basis of the "Every woman Every child" accountability framework model of the United Nations, which was put in place in 2010 to accelerate progress towards achievement of the Millennium Development Goals 4 and 5 by 2015.

The proposed framework would be three-pronged: a national committee on CKDu, an intersectoral coordinating mechanism and oversight by an independent expert review group (IERG)(***Fig 1***). Initial steps towards establishment of a national committee on CKDu have already been taken. The Chair would be the President/ Prime Minister, and members would include ministers and secretaries of relevant ministries, experts in the relevant areas, chairs of the IERG and Presidential Task Force, heads of international agencies and donors. The purpose would be to review implementation of the recommendations, identify challenges in implementation, mobilize the resources required and communicate the progress made in a transparent manner through the media and other channels. The Committee should meet at least twice a year to review progress.

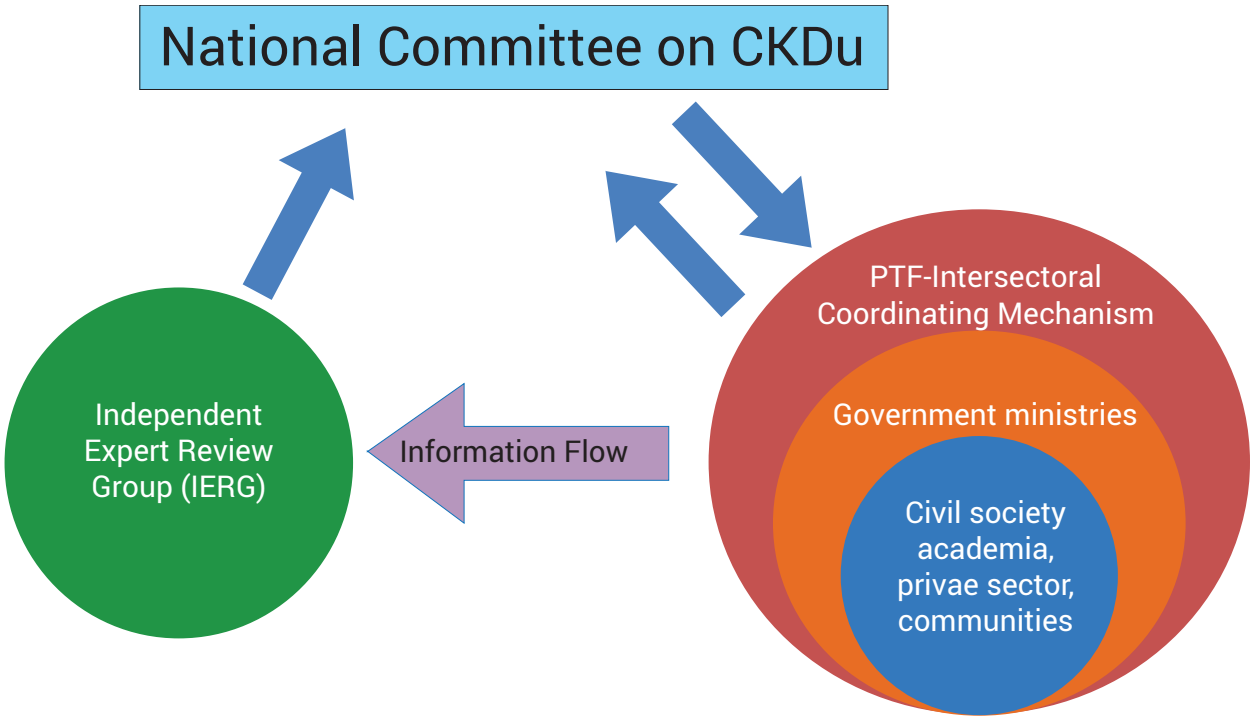


Fig. 1. Proposed structure of the framework for monitoring, implementation and accountability (I-AM).

The intersectoral coordinating mechanism would comprise heads of the various implementing departments at national, provincial and district levels, experts such as clinicians, epidemiologists and sociologists, principal investigators of research studies, administrators of hospitals in the affected areas, and representatives of civil society and patients, among others. It would be chaired by the director of the Presidential Task Force.
Its purpose would be to prepare a National Action Plan, and develop indicators to assess progress. It should meet at least four times a year.

The role of the IERG would be crucial, as it would provide an independent assessment of the progress and allow for mid-course corrections of the National Action Plan. It would report annually to the President and the general public. Its composition would include about 8–10 national members of high standing and knowledge, selected through a transparent process.

Moving forward

At the end of the sessions, each group presented the outcome of their deliberations to all the experts and an open discussion was held. The final consensus recommendations were shared with all the participants on the third day of the meeting and with the Director of Presidential Task Force in the concluding session. Therefore, the recommendations of the consultation are based on the consensus of all experts who participated in the meeting.

Recommendations

Surveillance: Develop a robust surveillance system to understand the burden, geographical distribution and time trends of CKDu in Sri Lanka.

- Establish community-based disease surveillance to understand the burden, geographical distribution and time trends of CKDu in Sri Lanka.
- Develop national/international consensus on a case definition for CKDu at three levels – suspected CKDu, probable CKDu and confirmed CKDu.
- Include monitoring the use of agrochemicals in the areas under surveillance.
- Strengthen ongoing water quality surveillance, with a focus on nephrotoxic chemicals in the affected areas. Use a web-based platform to consolidate, analyse and share the water quality data collected by the National Water Supply and Drainage Board, Ministry of City Planning and Water Resources and Ministry of Health, Nutrition and Indigenous Medicine.
- Strengthen the National Renal Registry for completeness, timely analysis and dissemination. Reconcile and improve linkages of screening programmes and the registry maintained by the Sri Lanka Society of Nephrology with the National Renal Registry.

Research: Share expertise across disciplines and countries to accelerate knowledge dissemination, guide the research agenda and help solve the mystery of "u" (unknown) in CKDu, as it is a complex disease.

- Establish a consortium of national/international researchers to conduct long-term interdisciplinary research. The consortium can provide technical support in developing research protocols to address the research questions that emerged during group work.
- Develop mechanisms and a framework for sharing the information and resources within the country and research programmes outside the country.
- Conduct further research on water, agrochemicals, infections and heat stress, as these have been identified as potential risk factors.
- Use community-based surveillance as a platform for planning research in priority areas. (*See* Annex 4.)

Priority interventions: Strengthen the implementation of available interventions and evaluate them to understand their impact and modify the interventions if needed.

- Evaluate the effectiveness of ongoing interventions

  Build in an evaluation component into each of the interventions to understand their usefulness and modify the intervention if needed. Evaluation of interventions may also provide insights into the causes and risk factors for the disease.

- Provide safe drinking water to the affected population

  Accelerate efforts to provide safe drinking water in the short term and long term, mainly focusing on technologies that are affordable and sustainable.

  Conduct a feasibility study to introduce cost–effective and appropriate water treatment systems and rapid assessment of water treatment technologies, e.g. RO plants (community and household) and water sources used in endemic areas.

  Formulate and enforce regulations on the use of various water treatment units in affected areas. Implement water safety plans (WSP) and water quality surveillance in endemic areas.

- Reduce exposure to agrochemicals

  Give priority to the adaptation of sustainable agricultural practices. Prohibit entry of and/or phase out agrochemicals with known nephrotoxic active ingredients or contaminants based on proven scientific evidence.
  Implement a comprehensive programme involving regulators, retailers and farmers to control the use of agrochemicals. Key components of the programme may include,
  (i) periodic assessment of the quality at retailer level,
  (ii) assessment of volumes/quantities applied and contamination in food,
  (iii) regular monitoring of agrochemicals and their residues in food, water and the environment,
  (iv) limiting the number of agro-pesticide formulations with the same active ingredient,
  (v) regulations to involve trained personnel in handling agrochemicals at the “agrochemical dealer shops”,
  (vi) training programmes for farmers and extension officers on the appropriate use of agrochemicals.

- Develop, recommend and implement alternate pest control methods and sustainable farming practices, with a special focus on CKDu-endemic areas.

- Establish and update the maximum residues limits (MRL) data for pesticides based on total diet studies carried out in Sri Lanka.

- Minimize exposure to heat/thermal stress

  Implement a programme of rehydration, adequate rest and shade in occupations at high risk for heat stress/dehydration and assess their effectiveness in preventing CKDu.

- Early detection and management

  Simplify the existing CKD and CKDu screening and management guidelines, and adapt them for primary-, secondary- and tertiary-care facilities.

  Enhance screening coverage by improving awareness and providing point-of-care testing units (mobile) for each district.

  Enhance the capacity of primary care units to function as satellite renal clinics to improve access to renal care, and develop guidelines for referral from primary to tertiary care facilities.

  Ensure the availability of drugs and consumables. Dispense outpatient drugs for two months at a time and provide long-acting erythropoietin to reduce the number of patient visits.

  Discourage smoking, betel chewing and illicit use of alcohol, and include vaccination in the existing guidelines to delay the progression of renal disease.

  Implement a “dialysis for all” policy to ensure access to treatment for all patients with end-stage renal disease (ESRD). Explore the feasibility of innovative solutions, e.g. mobile dialysis units.

  Seek international assistance in establishing a “deceased donor programme” to strengthen the transplant programme.

Social services: Provide social support at three levels – patient, family and community.

- Strengthen the informal local support network (Ministry of Social Welfare) and involvement of community leaders.
- Develop school-based social interventions to increase accessibility and social support for children of CKDu patients.
- Develop a specific communication strategy to destigmatize and demystify the disease.
- Expand social support services and resources such as transport/medicines/overnight stay for patients, and provide appropriate financial assistance to patients.
- Enhance livelihood generation in affected areas and plan special initiatives to empower women who are heads of families.

Capacity building: Strengthen/expand human resources at various levels.

- Increase the number of nephrologists from the present 1/million to about 4/million population as well as the number of nursing staff to enhance the coverage of renal services.
- Enhance the capacity of existing community-level workers and increase the number of community-level health workers to provide outreach services such as screening and follow up.
- Appoint trained social workers/counsellors in appropriate locations such as renal clinics and dialysis units to provide psychosocial support to patients and families.

Monitoring and accountability : Develop a framework for monitoring and accountability to ensure timely implementation of activities.

- Establish a three-tier system, consisting of a National Committee on CKDu, an intersectoral coordinating mechanism coordinated by the Presidential Task Force and an Independent Expert Review Group.
- Develop a set of performance indicators for the framework based on the National Action Plan.
- Ensure open and transparent measurement as well as communication.

Annex 1: Agenda of the meeting

Day 1 : 27 April 2016

Registration : 8.30 am–9.00 am

Inaugural session	
9.00–10.00 am	• Welcome and opening remarks – Director, Presidential Task Force on CKDu • Remarks by dignitaries • Introducing the participants • Objectives and expected outcomes of the meeting: WHO Country Office (WCO) Sri Lanka
10.00–10.30 am	End of inauguration with tea/coffee
Opening Plenary : Setting the scene – Mr Asela Iddawela (Chair)	
10.30–11.30 am	Presenter – Dr Tilak Abeysekera An overview of CKDu in Sri Lanka (25 minutes) Discussion
11.30–12.30 pm	Presenter – Dr C. Wesseling CKDu: Global overview (25 minutes) Discussion
12.30–12.45 pm 12.45–02.00 pm	Group photograph Lunch

CONCURRENT GROUP WORK: Defining future research priorities	
2.00 pm	Principles of testing hypotheses in epidemiological research – Dr Prabhdeep Kaur
2.10–5.30 pm (with a 15-minute tea break)	The background paper on available evidence and gaps in the evidence will serve as the base for discussions and will be presented by group co-chair Each group will further discuss available research evidence and based on gaps in the evidence, identify a list of future research questions.
	Group 1: Clinical aspects: Early detection, treatment and care
	Group 2: Role of agrochemicals
	Group 3: Role of water/heavy metals
	Group 4: Role of heat stress/dehydration and other miscellaneous hypotheses
7.00–9.00 pm	RECEPTION

Day 2 : 28 April 2016

GROUP WORK PRESENTATIONS: Defining future research priorities	
9.00–10.30 am	Chair : Professor Sirimali Fernando Group work presentations: (15 min presentation and 30 min for discussion)
10.30–11.00 am	Tea break
11.00 am–12.30 pm	Group presentations: contd (15 min presentation and 30 min for discussion)
12.30–1.30 pm	Lunch
1.30–2.00 pm	Conclusions on future research priorities
CONCURRENT GROUP WORK: Priority cost–effective interventions	
2.00–5.30 pm (with a 15 minute tea break)	The background papers on existing priority interventions and gaps in the interventions will serve as the base for discussions and will be presented by group co-chairs Each group will further discuss priority interventions based on current evidence and suggest priority interventions and mechanisms for their implementation
	Group 1: Preventive interventions
	Group 2: Early detection, treatment and care
	Group 3: Integrated surveillance & CKD Registry
	Group 4: Social interventions

Day 3: 29 April 2016

GROUP WORK PRESENTATIONS: Priorities for interventions	
9.00–11.00 am	Chair – Professor Adeera Levin Group work presentations (Each group will have 10 minutes for presentation and 20 minutes for discussion)
11.00–11.45 am	**Tea break**
11.45–12.15 pm	Chair – Professor Adeera Levin Conclusion of set of recommendations on priority interventions
12.15–1.15 pm	Chair – Professor Saroj Jayasinghe Framework for monitoring, implementation and accountability (20 minute presentation followed by discussion) – by Dr Jacob Kumaresan and Professor Ajith de Alwis
1.15–2.30 pm	Lunch
Moving forward—CLOSING CEREMONY	
2.30–3.30 pm	Chair – Mr Asela Iddawela • Set of recommendations on research priorities • Set of recommendations on priority interventions • Summary of the framework on monitoring and accountability
	Vote of thanks, WCO Sri Lanka
3.30–4.00 pm	**Tea/coffee**

Annex 2: List of participants and organizers

Professor Adeera Levin	International Society of Nephrology – President
Dr David Harris	International Society of Nephrology – President, President Elect
Dr Marcello Tonelli	International Society of Nephrology – University of Alberta, Director, Global Research Portfolio ISN
Dr Catherina Wesselling	Institute of Environmental Medicine (IMM), Solnavagen, Sweden
Dr Wendy Hoy	Director/Professor, Centre for Chronic disease, University of Queensland,Australia
Professor Raúl Herrera Valdés	Nephrology Institute, Havana, Cuba
Professor Antero Aitio	Finnish Institute of Occupational Health, Helsinki, Finland (retired)
Professor Neil Pearce	London School of Hygiene and Tropical Medicine, UK
Dr Kristina Jakobssen	Gothenburg University, Sweden
Professor Vidhya Venugopal	Department of Environmental Health Engineering, Sri Ramachandra University, India
Dr Carlos Manuel Orantes Navarro	Nephrologist, MD, National coordinator for Kidney Diseases, El Salvador
Dr Prabhdeep Kaur	National Institute of Epidemiology, Indian Council of Medical Research, India
Dr Lesley Onyon	Regional Adviser, Occupational and Environmental Health, WHO Regional Office for South-East Asia
Dr Gampo Dorji	Temporary International Professional, Noncommunicable Diseases, WHO Regional Office for South-East Asia
Mrs Payden	Regional Adviser, Water, Sanitation and Hygiene, WHO Regional Office for South-East Asia

Dr Nihal Abeysinghe	Acting Coordinator, Immunization Department, WHO Regional Office for South-East Asia
Dr Thamarangsi Thaksaphon	Director SE/NDE Noncommunicable Diseases & Environmental Heath, WHO Regional Office for South-East Asia
Dr Agnes Soares De Silva	Regional advisor – Environmental Epidemiology, Pan American Health Organization
Dr Bandana Malhotra	Chief Rapporteur, India
Professor Buddhi Marambe	Faculty of Agriculture, University of Peradeniya
Professor Kamani Wanigasuriya	Faculty of Medical Sciences, University of Sri Jayawardenepura
Dr Parakrama Waidyanatha	Centre for Education, Training and Research on Kidney Diseases, Peradeniya
Dr Latiff Nazar	Consultant Nephrologist, President-Sri Lanka Society of Nephrology
Dr Chandika Gamage	Senior Lecturer, Faculty of Medicine, University of Peradeniya
Dr Nishantha Nanayakkara	Consultant Nephrologist, General Hospital, Kandy
Dr Tilak Abeysekera	Honorary Visiting Fellow, Faculty of Medicine, University of Peradeniya
Professor Rezvi Sheriff	Senior Professor, Kotalawala Defence University
Professor Sisira Siribaddana	Dean, Faculty of Medicine, Rajarata University of Sri Lanka
Dr Eranga Wijewickrama	Senior Lecturer, Faculty of Medicine, University of Colombo
Mr Manju Gunawardana	Senior Research Scientist/ Head of Business Development/Head of Business Incubation Centre, Sri Lanka Institute of Nanotechnology
Dr Chula Herath	Consultant Nephrologist, President Elect-Sri Lanka Society of Nephrology
Dr Mathu Selvarajah	Consultant Nephrologist, Sri Lanka Society of Nephrology

Professor Ajith de Alwis	Project Director, Coordinating Secretariat for Science, Technology and Innovation (COSTI)/ Faculty of Engineering, University of Moratuwa
Professor Rajitha Wickramasinghe	Professor of Public Health, Faculty of Medicine, University of Kelaniya
Dr Asanga Ranasinghe	National Coordinator, Renal Disease Prevention and Research, Ministry of Health, Nutrition and Indigenous Medicine
Dr Nalaka Herath	Ministry of Health, Nutrition and Indigenous Medicine
Dr Pubudu de Silva	Ministry of Health, Nutrition and Indigenous Medicine
Dr Thilanga Ruwanpathirana	Ministry of Health, Nutrition and Indigenous Medicine
Professor Sirimali Fernando	Chairperson, National Science Foundation/Faculty of Medical Sciences, University of Sri Jayawardenepura
Professor Saroj Jayasinghe	Professor in Clinical Medicine, Faculty of Medicine, University of Colombo
Dr Herath Manthrithilake	International Water Management Institute
Dr Channa Jayasumana	Head/Department of Pharmacology, Faculty of Medicine, Rajarata University of Sri Lanka
Professor Chandani Liyanage	Department of Sociology, Faculty of Arts, University of Colombo
Mr Sumitha Sumanaweera	Deputy General Manager, Corporate Planning, National Water Supply & Drainage Board
Professor DM Dissanayaka	Faculty of Medicine, University of Peradeniya
Dr Sanjaya Heyyanthuduwa	Consultant Nephrologist, Sri Lanka Society of Nephrology
Professor Ramanie Jayathilake	Department of Sociology, Faculty of Arts, University of Colombo
Mr M Ramamoorthy	Ministry of Social Empowerment and Welfare, Sri Lanka
Dr Sarath Amunugama	Deputy Director General, Public Health Services, Ministry of Health, Nutrition and Indigenous Medicine

Co-organizers

Mr Asela Iddawela	Project Director, Presidential Task Force on prevention of CKDu
Dr Jacob Kumaresan	WHO Representative to Sri Lanka
Dr Arturo Pesigan	WHO Technical Officer
Dr Nishirani Lanka Jayasuriya Dissanayake	WHO, National Professional Officer for Noncommunicable Diseases
Professor Nalika Gunawardena	WHO, National Consultant (Noncommunicable Diseases)
Mr Tirupathi Suveendran	WHO, National Programme Officer – Mental Health
Dr Sachie Panawala	Coordinator – International Expert Consultation on CKDu / Project Scientist – COSTI
Mr Lalith Bandara	Assistant Secretary to President
Mr Jagath Nayanapriya	Project Coordinator, PTF on prevention of CKDu
Mr Stefhan Fonseka	Project Coordinator, PTF on prevention of CKDu

Annex 3: Summary of evidence on risk factors for CKDu

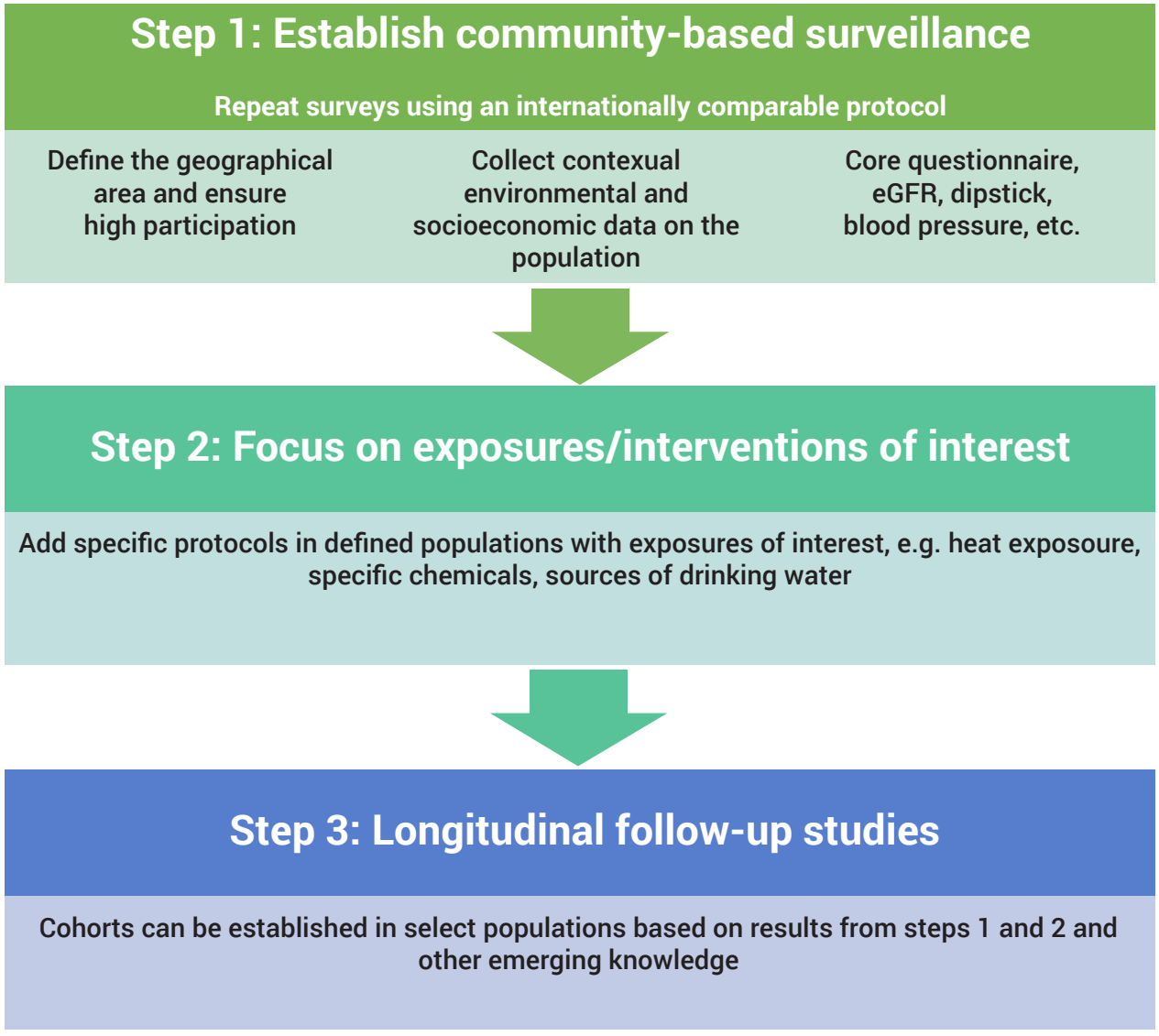
Risk factor	Availability of research evidence on association with CKDu	Strength of evidence	Need for further research
Cadmium in water	Data available from multiple case–control studies	Inconclusive*	Not a research priority
Arsenic in water	Data available from multiple case–control studies	Unlikely	Not a research priority
Water (fluoride, hardness and high ionicity)	No data from analytical studies	Inconclusive	Yes
Genetic susceptibility	Data available from two studies in Sri Lanka	Unlikely	Not a research priority
Low birth weight	No data from analytical studies	No studies	Not a research priority
Heat stress	Only one case–control study in Sri Lanka	Inconclusive	Yes
Leptospirosis/hantavirus	No data from analytical studies	No studies	Yes
Non-steroidal anti-inflammatory drugs	No data from analytical studies	Unlikely	Not a research priority

Agrochemicals	Nephrotoxicity in humans at low or high doses	Strength of evidence
Glyphosate with specific adjuvants**	Yes	Inconclusive*
Paraquat**	Not known	No studies
Parathion-methyl**	Not known	Inconclusive
Propanil***	Yes	No studies
Carbofuran***	Not known	Inconclusive
Carbaryl***	Not known	Inconclusive
Chlorpyrifos***	Yes	Inconclusive
Profenofos	Not known	Inconclusive
Carbosulfan	Not known	Inconclusive
Neonicotinoids	Not known	Inconclusive
MCPA	Not known	Inconclusive
Diazinon	Not known	Inconclusive
Pretilachlor	Not known	No studies
Pyribenzoxim	Not known	No studies
Glufosinate ammonium	Not known	No studies

*Inconclusive: Research studies available but evidence not conclusive either for or against the risk factor being studied.
**Banned in Sri Lanka. ***Import license has not been issued since 2015.

Annex 4: Framework for community-based surveillance and research

Conceptual framework for establishing community-based surveillance and longitudinal cohorts: a step-wise approach to CKDu in Sri Lanka



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