

Chronic Kidney Disease of Unknown Origin (CKDu)

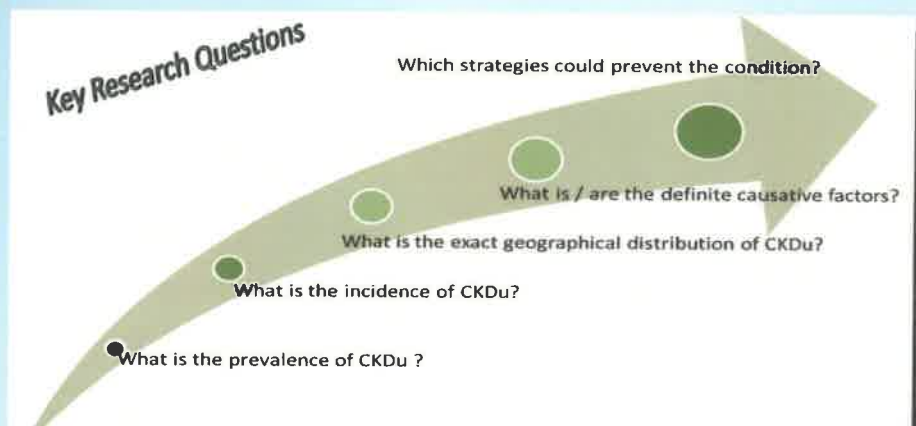
DECEMBER 2009

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National Research Programme for Chronic Kidney Disease of unknown origin (CKDu) in Sri Lanka

Chronic Kidney Disease (CKD) is an emerging health problem and is often combined with poor health outcomes and high economical cost on patient, family, community and health system. In recent years, a significant increase in CKD cases has been observed in some parts of the country especially in North Central, North Western, Uva and Eastern Provinces. For a significant proportion of CKD cases reported from these areas, aetiology of the disease remains a mystery. To resolve this public health issue, the Government of Sri Lanka requested the World Health Organization to coordinate a multisectoral, multidisciplinary research effort, which built upon on existing information. This coordinated series of research activities is designed to generate conclusive evidence within a specified time period to make prevention an option.



CKDu—Case Definition : Health Ministry Circular

A circular was issued by the Ministry of Health to all preventive and curative health institutions with regard to the definition of CKDu.

The aetiology of chronic kidney disease will be considered as "Uncertain or Unknown" only if all the criteria stated below are satisfied:

No past history of or current treatment for diabetes mellitus or chronic and/or severe hypertension, snake bite, urological disease of known aetiology or glomerulonephritis

Normal HbA1C (< 6.5%)

BP < 160/100 mm Hg untreated or < 140/90 mm Hg on up to two antihypertensive agents

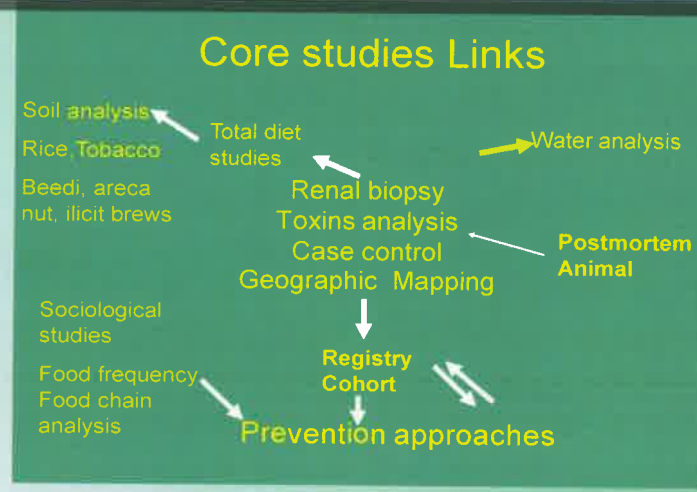
The staging of CKDu into Grades 1–4 will be based on the classification system recommended by the National Kidney Disease Outcomes Quality Initiative but modified for logistic and financial reasons.

CKDu Study Groups

The National Research Programme for CKDu consists of a series of coordinated studies, each of which will potentially contribute to elucidating key determinants of CKDu. However, due to limited resources it is not possible to carry out all the studies listed simultaneously. Hence, the studies were considered in order of priority as shown below and the first four studies have been commenced in the latter part of 2008.

- Systematic survey to identify low and high prevalence CKDu areas.
- Geographic mapping of cases and water sources and establish registry
- Preliminary studies to assist further prioritization; Pilot analytical study (post mortem), Retrospective study on histology, Pilot renal biopsy study (analytical and electron microscopy)
- Environmental studies: sub-sampling of all relevant local foods, water supplies, soil, etc for analyses of potential environmental toxins
- Comparison of high and low prevalence CKDu areas
- Case-control study
- Human renal biopsy analyses (electron microscopy and metal mapping)
- Human Post-mortem Studies
- Cohort study to commence with cases from the systematic survey
- Analytical studies on animal tissues

National CKDu Research Programme—Core Studies



National Coordination mechanism for CKDu

To ensure smooth functioning of the research programme, it is of vital importance to outline the functions and responsibilities of different stakeholders. In order to achieve this, three committees have been constituted at different levels namely the National Steering Committee, Management Committee and the Scientific Committee with clearly defined terms of reference. In addition to these committees, there is a panel of International Experts who has provided technical inputs into finalization of the research proposal. Further, this panel of experts will help to ensure quality and ethical standards of research together with peer reviewing of protocols, reports and publications.

National Steering Committee	Management Committee	Scientific Committee
<p>This is chaired by the secretary of the Ministry of Healthcare & Nutrition and consists of Secretaries from different ministries inclusive of DM, Agriculture, Education, Higher education, Environment, Indigenous Medicine, Science & Technology, Public Administration & Home Affairs & Social Services & Social Welfare. In addition Chief Epidemiologist and WHO, UNDP Country Representative will also be present. The main aim of this committee is to advice on policy, technical, legal, scientific & administrative issues related to CKDu</p>	<p>This is chaired by the DDG – PHS 1 and consists of the Regional Directors of Health Services of the affected areas, Heads of the Institutions under the different ministries like Central Environment Authority, Disaster Management Centre, National Science Foundation, Water supply & drainage Board, Registrar of pesticides. They are the implementers of the decisions taken at the National Steering committee and ensures multisectoral participation.</p>	<p>This is chaired by the chief epidemiologist and consists of group leaders of the different research groups including cohort study, Renal Biopsy study, Environmental study, Sociology & Diet study, Geographical mapping & Animal tissue study. This committee ensures execution of the studies at community level.</p>

Population Prevalence study

The main purpose of this cross-sectional study is identifying the prevalence of chronic kidney disease of unknown origin (CKDu) in selected areas of Sri Lanka. This study is currently being conducted in Anuradhapura, Polonnaruwa and Badulla Districts.

A total of 6698 subjects aged between 15 to 70 years (both inclusive) from 22 GN divisions were found to be eligible for the study according to the selection criteria. Representativeness of this study population was assured by strictly adhering to the scientifically sound methodology including sampling procedure. At the beginning of the study, all selected households were mapped using the global positioning

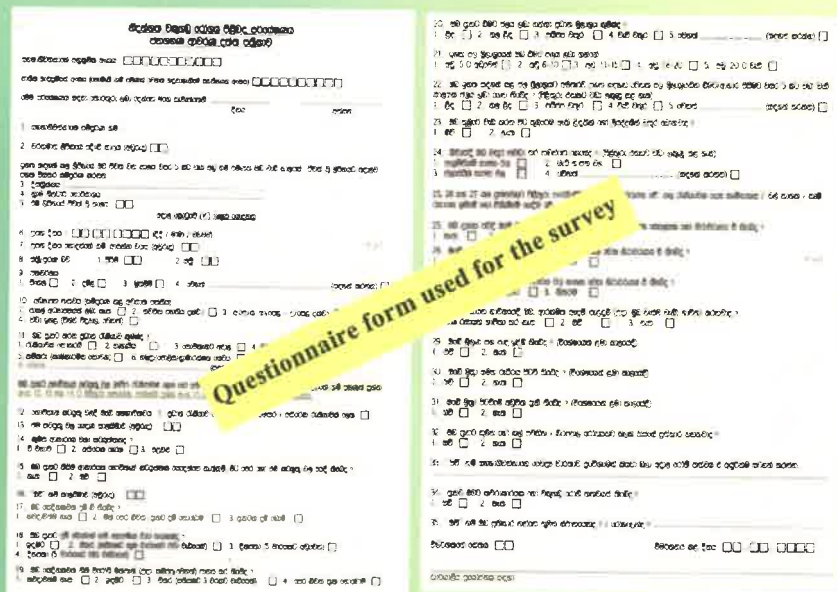
system (GPS).

The field assistants were able to interview 6132 subjects (92% of the eligible). Early morning urine samples for albumin creatinine ratio (ACR) were collected from 4941 subjects (74% of eligible). Those who found to be having urine ACR of equal or more than 30 mg/g were subjected to anthropometric measures, blood pressure measurement and biochemical investigations (serum creatinine and glycosylated hemoglobin).

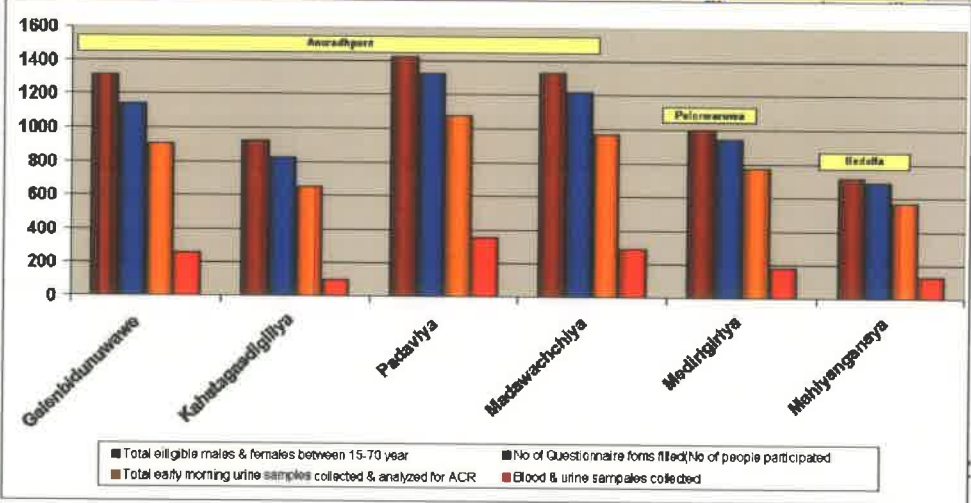
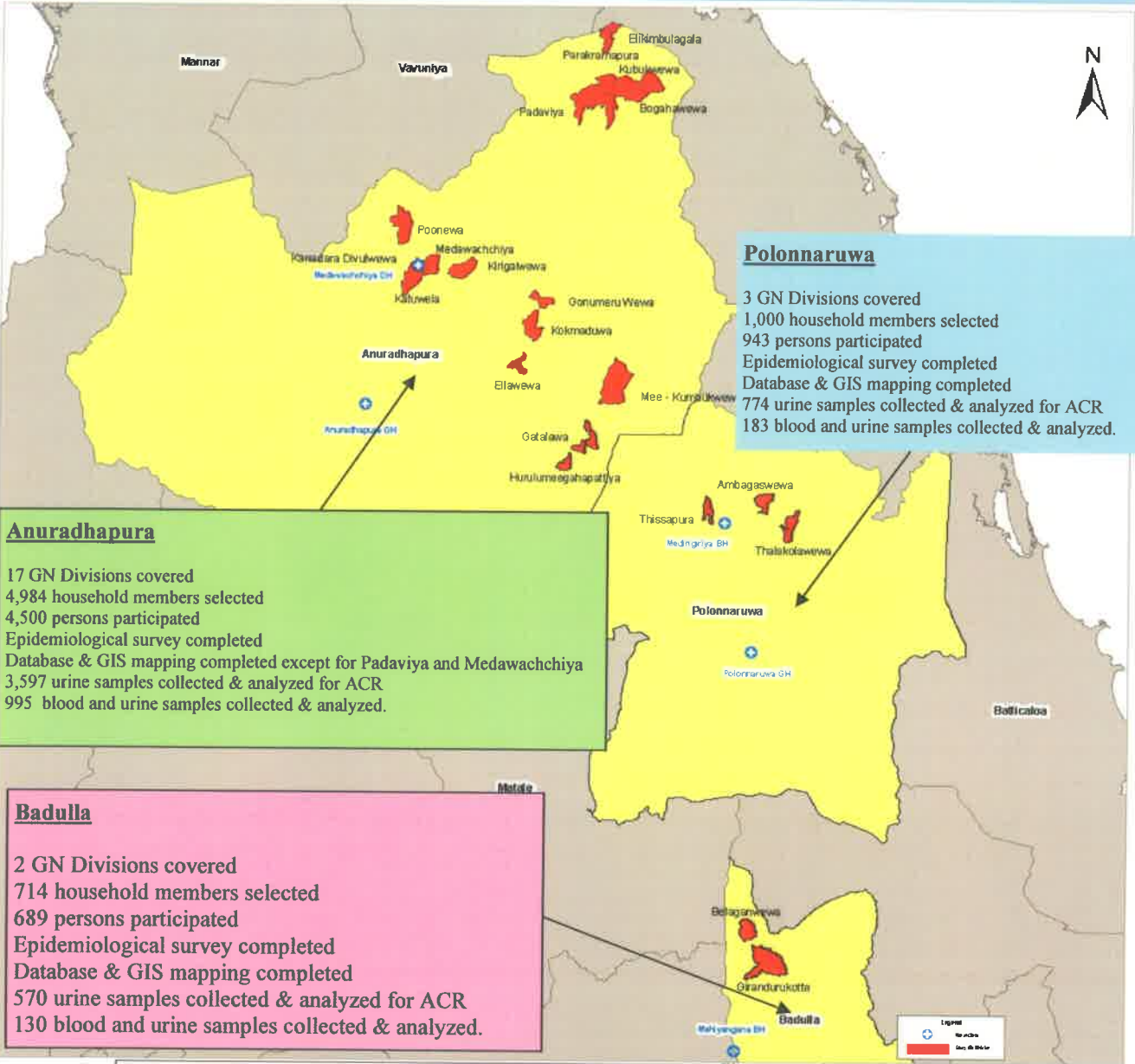
All the field activities related to this research component have been completed with the support of District & Divisional Secretaries, MOHs and Grama Niladaris, and now we are in the process of identifying subjects with chronic kidney disease of un-

known aetiology (CKDu) according to the case definition agreed upon.

By identifying the prevalence of CKDu in different areas, this study will help to get an estimate of the diseases burden in the country. Further, the 'cases' identified from this study will be used for a case control study planned for this year and the serum specimens of the subjects currently stored at -70°C at the Epidemiology Unit cold room complex will also be subjected to further biochemical analysis (levels of cadmium, aluminium, lead, fluoride etc).



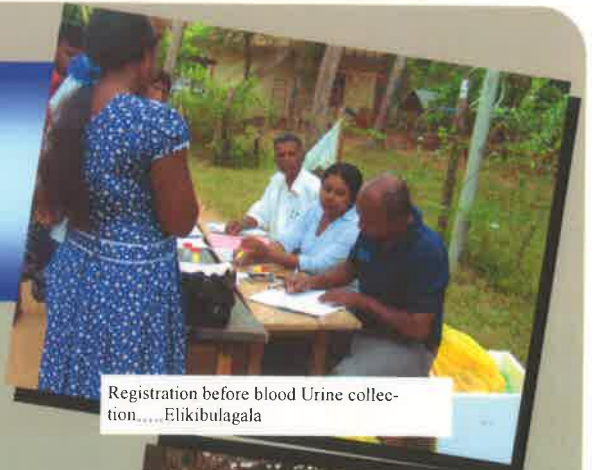
Summary of CKD Prevalence Study - December 2009



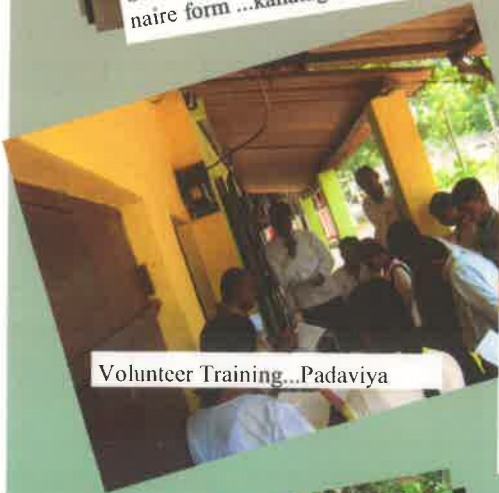
The Team at Work....



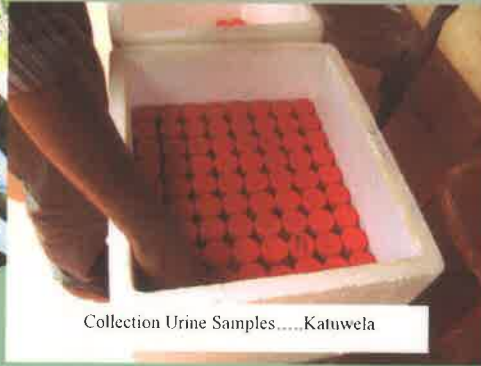
Selected field workers being trained on questionnaire form ...kahatagasdigiliya



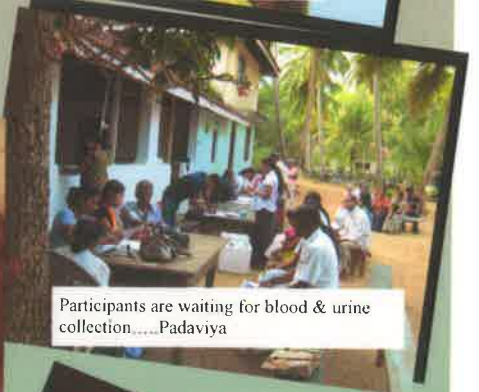
Registration before blood Urine collection....Elikibulagala



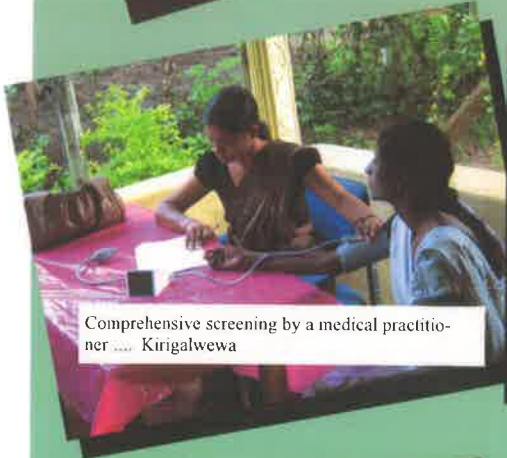
Volunteer Training...Padaviya



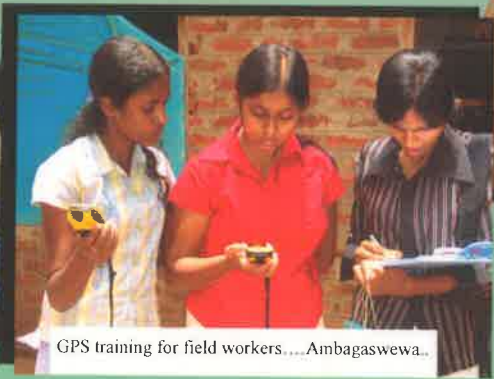
Collection Urine Samples....Katuwela



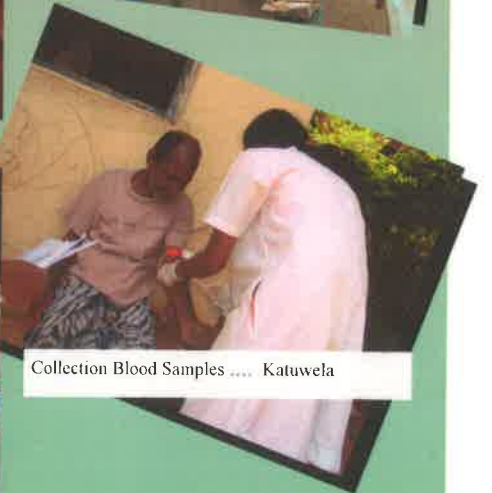
Participants are waiting for blood & urine collection....Padaviya



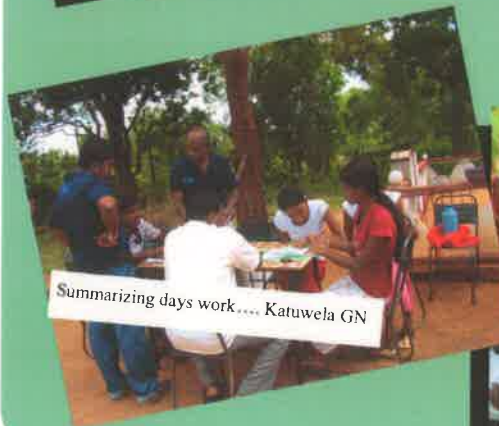
Comprehensive screening by a medical practitioner Kirigalwewa



GPS training for field workers....Ambagaswewa..



Collection Blood Samples Katuwela



Summarizing days work.... Katuwela GN



Team at Gonumeruwewa GN....urine collection...



Visiting CKDu patient households Ellawewa GN

Hospital Based CKD Registry

The main objectives of this registry are to characterize CKD/CKDu populations; to estimate prevalence and incidence of CKD/CKDu based on hospital data; to enable geographic mapping of CKD patients; to help in identifying new areas for special renal studies and to support investigator-initiated research.

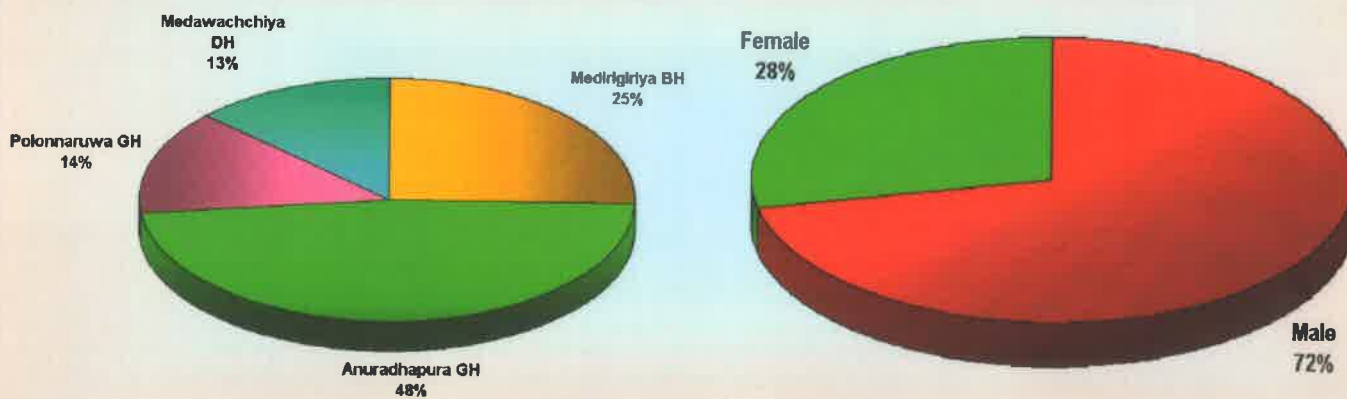
The hospital-based CKD registry has been established in four hospitals in

the North-Central Province namely TH Anuradhapura, DGH Polonnaruwa, BH Medirigiriya and DH Medawachchiya.

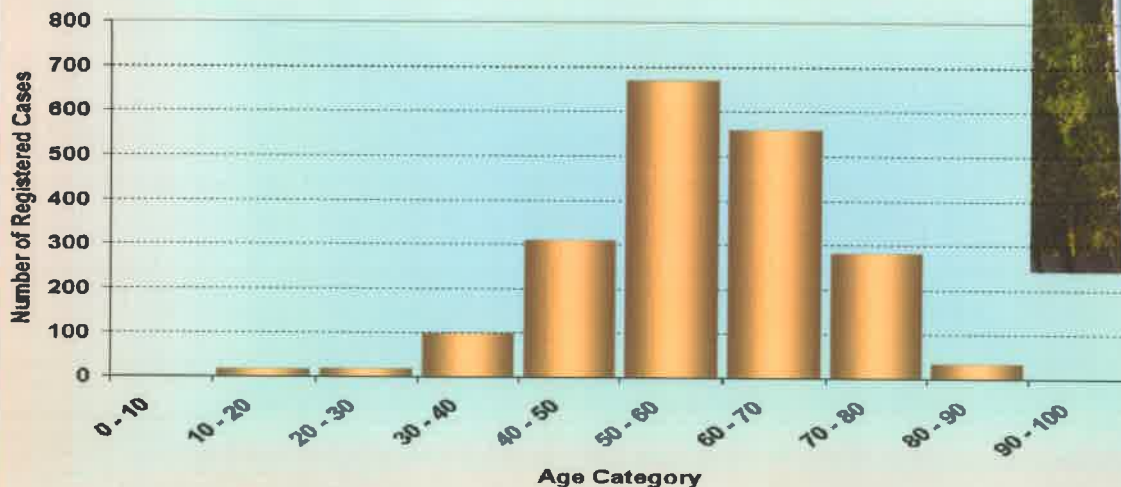
At present the registry is having the details of 1997 patients. For each patient in the registry, the database includes information on basic socio-demographics, primary medical diagnosis that led to CKD, treatment records and transplant information if available.

It is an ongoing activity and steps have been taken to expand this activity in a stepwise manner to other hospitals also (i.e. towards a national registry). The database will be linked with all renal centres in Sri Lanka. An annual report containing descriptive and analytic epidemiologic data on CKD patients will be published in future.

Cases registered in the hospital registry - 1,997 CKDu Cases—775(39%)



Age Breakdown of Registered CKD Cases



Environmental Study Group—Sample collection & analysis

Details of 606 CKDu patients identified from the hospital-based registry were shared with the Environmental Study Group by the Epidemiology Unit of the Ministry of Health. Fifty patients from this list were randomly selected and their houses were visited for sample collection. From each household, 15 -

20 different types of samples were collected. They were analysed for Cadmium (Cd), Lead (Pb) and Iron (Fe) using internationally accepted, standard pre-preparation and analysing methods. Samples were subjected to wet washing acid digestion prior to analyse by the flame and graphite furnace

Atomic Absorption Spectrophotometer. A total of 670 samples collected from above households and the analysis was done at the Department of Chemistry, University of Kelaniya.

Environmental Study

The samples collected consisted of following:

- * *Nelumbo nucifera (Lotus)*
- * *Beatle*
- * *Sediments of reservoirs*
- * *Soils of agricultural lands*
- * *Soils of non agricultural lands*
- * *Irrigation water*
- * *Drinking well water*
- * *Agro-well water*
- * *Pipe borne water*
- * *Tube well water*
- * *Rice*
- * *Pulses - locally grown*
- * *Fish - Tilapia*
- * *Fish - Lula (Seasonal)*
- * *Pasture - onsite / from the farmers*
- * *Milk - cows and buffaloes*
- * *Milk - mothers*
- * *Nelumbo nucifera (Lotus)*
- * *Beatle*
- * *Tobacco*
- * *Leafy vegetable consumed in the region*
- * *Lasia spinosa (Kohila)*
- * *Urine*
- * *Weeds*
- * *Field products*



GPS coordinates of the selected households were obtained. Entire dermal, dental and other variations among the patients were recorded and other information such as food habits and water usage were obtained.



Pilot Analytical Study (Post Mortem Study)

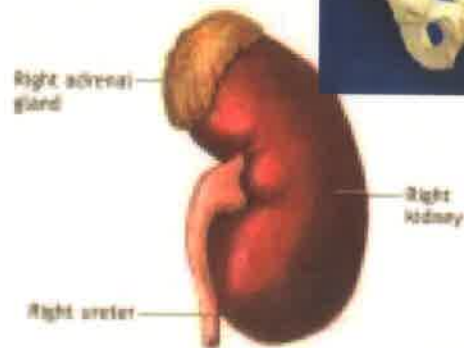
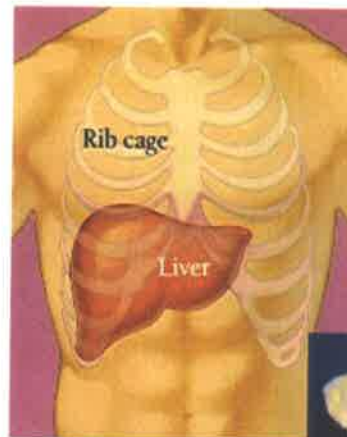
As the metal analysis is very expensive, this component of the research programme will be conducted initially as a pilot study. The postmortem study is expected to give the direction for future studies on which particular element/s will be focused.

Postmortem specimens (kidney cortex, liver and bone) are currently being collected from the following:

- * Six chronic kidney disease patients who had dialysis and were residents of Colombo
- * Six chronic kidney disease patients who had dialysis and were residents of North Central Province
- * Three apparently healthy adults aged between 40 and 60 years, killed in accidents and were residents of North Central Province
- * Three apparently healthy adults aged between 40 and 60 years, killed in accidents and were residents of Colombo

The specimens collected will be subjected to trace metal analysis at an international reference laboratory located at the University of Antwerp, Belgium. The "Collaboration and Material Transfer Agreement" between the Ministry of Health and the reference laboratory in Belgium has been already signed. The collected

specimens are currently stored at -70C at the Cold Room Complex, Epidemiology Unit.



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Fund Mobilization — CKDu

The collaborative national research effort is expected to cost around USD 1 million. To raise the necessary funds, two donor forums were organized with the participation of national and international donor agencies. These forums were chaired by the Hon. Minister of Healthcare & Nutrition.

As the Ministry of health deemed this issue as a public health priority, the WHO Country Office has managed to raise USD 75,000 by re-programming some of the funded activities. In addition, WHO - SEARO (South East Asia Region) has contributed USD 240,000 up to December 2009.

WHO Country office has also supported the Ministry of Health to submit a proposal to Department of National Planning of the General Treasury, through the National Science Foundation, which has a mandate to carry out research and development for socio economic development of Sri Lanka. This effort was successful in securing USD 700,000 for research activities in 2010.

In 2005, 3.5 million USD (4.6%) of the annual health budget was spent on management of patients with renal disease