

3.13 CHRONIC KIDNEY DISEASE OF UNKNOWN AETIOLOGY (CKDu) NATIONAL RESEARCH PROGRAMME MINISTRY OF HEALTH

NATIONAL RESEARCH PROJECT
CHRONIC KIDNEY DISEASE OF UNKNOWN ORIGIN

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CAUSES OF CKD IN SRI LANKA

- In Sri Lanka, common causes of CKD are similar to that described in most part of the world (diabetes, hypertension etc) - **Other than for certain regions in dry zone**
- For most of the CKD cases reported from the dry zone, primary cause is not known
CKD OF UNKNOWN ORIGIN

THE CONCERNS

- Increasing number of CKD cases & uneven distribution
 - Case load more in certain areas i.e. regional clustering
 - Affect low socioeconomic group i.e. young male farmers
- Slowly progressive disease - Patients seek treatment at late stages & often require dialysis/ transplantation
- High economical cost for patient, family & state
 In 2005, 350 million rupees was spent for management of patients with renal disease (dialysis, transplant etc.)



PUBLIC HEALTH PROBLEM

CKD of unknown origin (CKDu) is an important public health problem for Sri Lanka

- **Disease burden is high** in terms of premature mortality & morbidity, quality of life and cost
- It is **perceived as a threat** by the public
- It is **distributed unfairly** i.e. regional clustering of cases & the prevalence is comparatively high among lower socioeconomic class
- There is evidence that **upstream preventive strategies** i.e. strategies that target socioeconomic & environmental factors could substantially reduce the burden of this condition
- Such preventive **strategies have not been well formulated**

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ECONOMIC PERSPECTIVE

- Every year about 2000 new patients seek treatment for End Stage Kidney Disease (i.e. dialysis or transplantation)
- Failure to find solutions may cost millions of rupees worth of productivity due to premature morbidity & mortality
- Around 4% - 5% of the annual health budget is currently spent on management of patients with renal disease
- Collaborative national research effort needs comparatively very much less resources - **IT IS COST EFFECTIVE !!**

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JUTIFICATION FOR A NATIONAL RESEARCH EFFORT

- A considerable amount of background work has been done
- However, no systematic surveys have been conducted to get best available estimates of prevalence
 - Issues with the case definition of CKDu
 - Unclear from published data, whether the samples were representative of the population (? Selection bias, ? Response bias)
 - Lack of appropriate validation for most of the data available especially lab data
 - It's difficult to take policy decisions based on such data
- Urgent need for epidemiological data based on scientific studies

KEY RESEARCH QUESTIONS

- What is the incidence/prevalence of CKDu?
- What is the exact geographical distribution?
- What is/are the definite causative factors?
- Which strategies could prevent the condition?

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Prevention is the most cost-effective & affordable approach

- However, prevention is not an option at present as the cause/s is / are still unknown
- If the aetiology is known only, well focused preventive strategies can be developed & implemented

Urgent need for a comprehensive globally conceivable study with a multisectoral & multidisciplinary approach to launch a national public health response for prevention of CKDu

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INVOLVEMENT OF WHO

- In 2007, a request was made to WHO by then Hon. Minister of Health to provide technical assistance
- A series of scientific committee meetings & extensive draft proposal reviews were conducted in 2008 & the research proposal was finalized in July 2009
- National Research Project finally commenced in late 2009
- Role of WHO (HQ/ SEA Regional Office/ Country Office)
 - Technical, management & logistical assistance
 - Ensuring quality & ethical standards of research
 - Fund mobilization & fund management
 - Secretarial support

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RESEARCH PROPOSAL

- Build upon existing information/ study findings
- Consist of coordinated series of studies
- Ensure multisectoral & multidisciplinary approach
- Ensure quality control of analytical data by internationally accredited centers & comprehensive data analysis
- Designed to generate conclusive evidence on determinants of CKDu
- Main objective is to **make prevention an option**

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CKD Scientific Committee Meeting

NATIONAL COLLABORATIVE RESEARCH EFFORT

- MoH (Epidemiology Unit, Environmental Health Division & NCD Unit)
- Provincial/Regional Health Authorities
- Universities & Research Institutes
- Clinicians/Nephrologists/ Pathologists
- Public Health/ Community Physicians
- National Science Foundation
- National Water Supply & Drainage Board
- Office of Registrar of Pesticides

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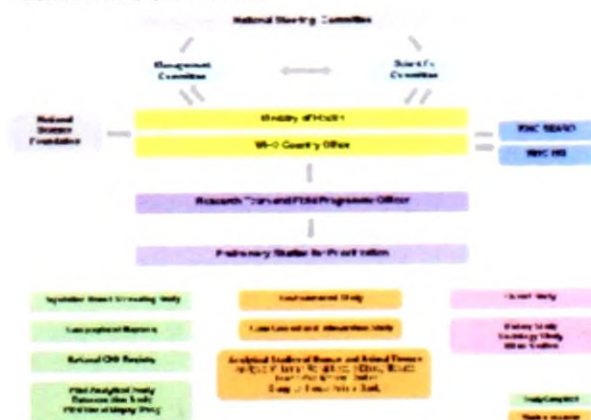
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Multisectoral, multidisciplinary research effort built upon on existing evidence

- Population prevalence study
- Hospital-based CKD registry
- Environmental study (high & low prevalence areas)
- Postmortem study (cases & controls)
- Case control study - Urine metal analysis
- Case control study - Nail & hair analysis for arsenic
- Study on herbal remedies (aristolochic acid)
- Socioeconomic & productivity impact study
- Randomized clinical trial (efficacy of ACEI in CKDu patients)

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CKDu Research Study Operational Structure

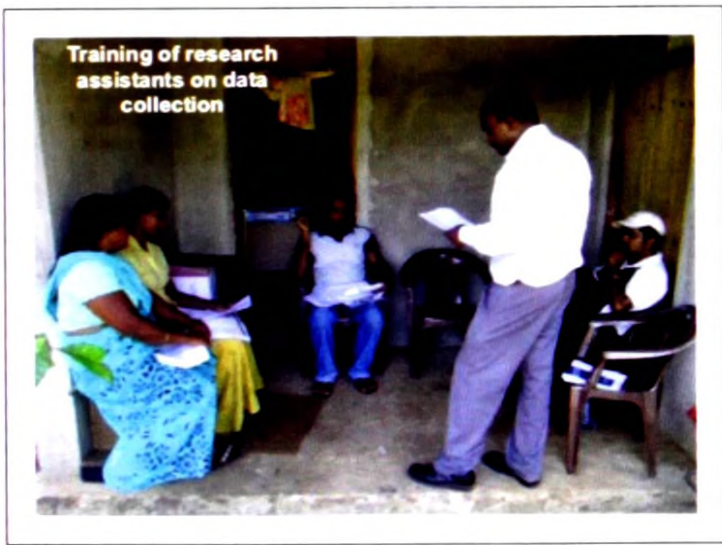
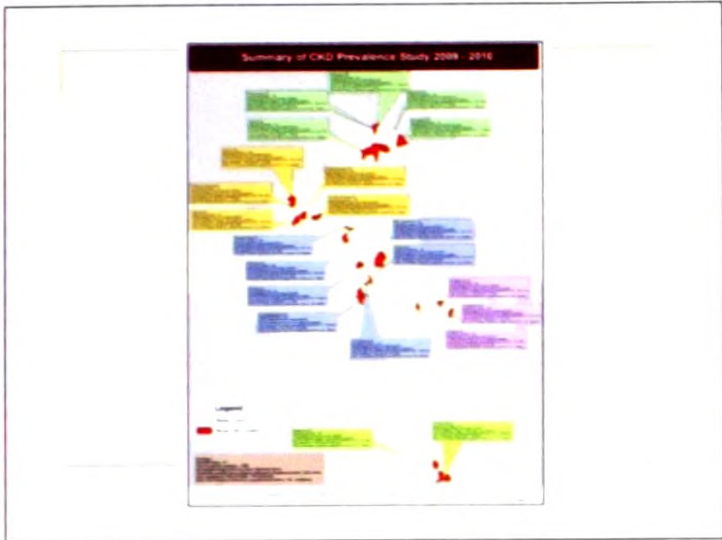


POPULATION PREVALENCE STUDY

Objectives:

- To confirm or refute previously reported wide ranges in the prevalence of CKDu
- To identify the factors associated with CKDu
- To facilitate the conduct of other research components (e.g. case control studies, analyses of potential environmental toxins, clinical trial etc.)
- A well acceptable standard case definition of CKDu was first time used
- All CKDu cases in the study areas geographically mapped (GPS)
- Results currently available

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HOSPITAL - BASED CKD REGISTRY

- Database has information on basic socio-demographics, lifestyle factors, environmental factors, clinical history, anthropometry & laboratory investigations for 1997 patients registered in selected hospitals
- It's an ongoing activity
- Will serve as a resource to the academic & clinical medicine communities

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ENVIRONMENTAL STUDY

Objective:

- To estimate quantitatively the potential toxicants in wide range of environmental samples obtained from high & low prevalent areas of CKDu

Study components:

- Analysis at University of Kelaniya
- Analysis at International reference Laboratory (University of Antwerp, Belgium)
- Study on agrochemicals

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ENVIRONMENTAL STUDY ANALYSIS AT UNIVERSITY OF KELANIYA

- Samples taken from the environment of 50 randomly selected CKDu patients (from hospital registry)
- Cadmium, lead & iron levels of samples (drinking & irrigation water, rice, pulses, fresh water fish, lotus, foliar vegetables, breast milk, cow & buffalo milk) analyzed at Kelaniya University
- Analysis results available

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ENVIRONMENTAL STUDY - ANALYSIS AT UNIVERSITY OF ANTWERP, BELGIUM

- Drinking water samples of 99 CKDu cases (stage III & IV) analyzed for cadmium, lead & arsenic (Results available)
- Environmental samples (reservoir sediments, water from different sources, soils of agricultural & non-agricultural lands, rice, locally grown pulses & vegetables, freshwater fish and fertilizers/pesticides) from CKDu high prevalent areas & control areas (Hambantota) analyzed for metal analysis (Most of the results available)
- Completed GPS mapping of tube wells in 22 GN divisions (study area)

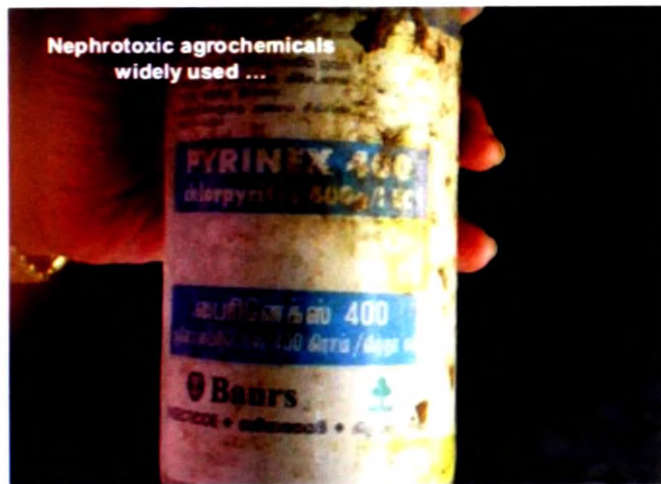
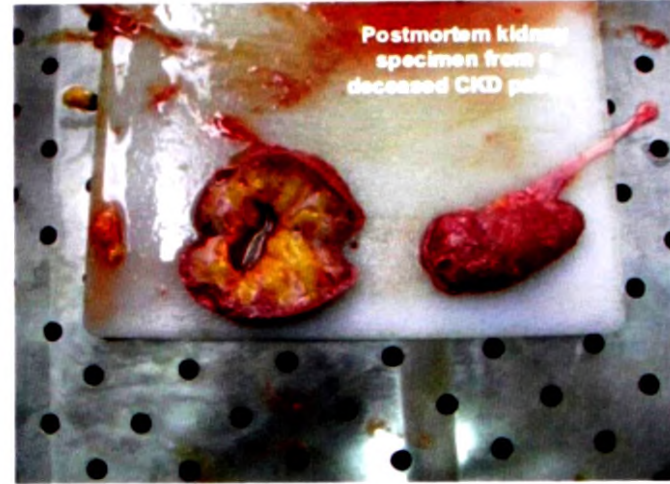
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ENVIRONMENTAL STUDY STUDY ON AGROCHEMICALS

- A comprehensive list of pesticides used in CKDu prevalent areas (Anuradhapura, Polonnaruwa & Mahiyangana) and control area (Hambantota) has been prepared
- Soil samples (from paddy field, vegetable plots & Chena cultivation), fertilizer & pesticide samples collected from the study area
- Soil samples and fertilizer & pesticide samples collected from control area (Hambantota)
- All the samples dispatched to Belgium for metal analysis (arsenic, cadmium, selenium & lead)
- Awaiting for results

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CASE CONTROL STUDY METAL ANALYSIS OF URINE

- Objective: To compare and contrast CKDu cases & controls in relation to exposure to heavy metals/ metalloids in the environment
- Cases & controls identified from the population prevalence study
- Urine samples of randomly selected 94 CKDu (stage III & IV) & 401 CKDu (stage I & II) cases analyzed for metals (cadmium, lead & arsenic) at the University of Antwerp, Belgium (results available)
- Urine samples of controls (n = 132, M:F = 1:1) from non-CKDu households sent to Belgium for metal analysis (awaiting results)

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POSTMORTEM STUDY

University of Antwerp, Belgium

- Pilot Study: PM specimens of 06 CKDu patients & 03 controls from NCP and 01 CKD patient (known aetiology) & 02 controls from WP analyzed for metals (results available)
- PM specimens of 20 CKDu patients & 11 controls analyzed for metals (awaiting results)
- Postmortem specimens included kidney, liver & bone

University of Peradeniya

- PM specimens (kidney & bone) of 06 CKDu patients & 03 controls will be analyzed for aluminium, lead, cadmium, arsenic & fluoride

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CASE CONTROL STUDY - ANALYSIS OF HAIR & NAIL SAMPLES FOR ARSENIC

- Objective: To compare and contrast CKDu cases and controls in relation to exposure to arsenic in the environment
- Hair & nail samples from
 - 77 CKDu cases (stage I - 16, stage II - 19, stage III - 22 & stage IV - 20 cases)
 - 50 Controls (M:F = 1:1) from non-CKDu households
- Samples sent for arsenic analysis at the University of Antwerp, Belgium (awaiting results)

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SOCIOECONOMIC & PRODUCTIVITY IMPACT STUDY

- Objective is to estimate the socio-economic impact of CKDu & recommend mitigation measures
 - Estimation of costs of CKDu to the affected households & community and the health system
 - Description of modes of coping adapted to mitigate adverse socio-economic impacts
 - Estimation of economic impact of CKDu on the GDP
 - Evaluation of different mechanisms of social support & recommend the best options for implementation
- Community-based survey has been completed & the hospital-based survey is currently undergoing

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STUDY ON NEPHROTOXIC HERBAL REMEDIES

- Aristolochic acid nephropathy (AAN) is characterized by interstitial fibrosis
- Reports of AAN from some countries mainly attributed to the use of herbal remedies
- Expected outputs: List of aristolochic acid containing herbal remedies used in Sri Lanka & their prescription pattern
- Study results available

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RANDOMIZED CLINICAL TRIAL

- A double blind clinical trial to examine the renal effects of an Angiotensin Converting Enzyme Inhibitor (enalapril) by comparing & evaluating the effect of enalapril to a placebo in CKDu patients
- Hypothesis: Enalapril would significantly reduce progression of renal disease in CKDu patients
- Trial is currently undergoing in Anuradhapura & Polonnaruwa with the participation of 266 CKDu patients

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Visiting CKD patients



Updating regional health officials

ISSUES & CONCERNS

- "Fatigue" observed among the general public in 'high risk areas' towards new research initiatives
- While accepting the need for the involvement of international reference laboratories, due consideration has been given to capacity development at country level
- Reluctance shown by some researchers to jointly submit research proposals, sharing their knowledge & expertise and lab capacity for a national cause
- Need for individual researchers & groups to work together under the national research effort

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ISSUES & CONCERNS

- Delay in getting the results from international reference laboratories due to stringent quality control measures and long processes involved in analysis especially for heavy metals
- Pressure from different stakeholders, media, general public and also from groups with vested interests for 'quick' results
- Piecemeal release of study findings may jeopardize the research project
- Sharing hypotheses/ findings to the media/ public without complete scientific evidence may bring serious repercussions in different fronts (economical, political etc)

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THANK YOU