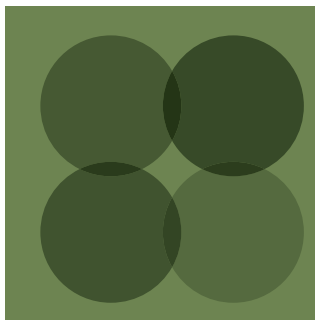
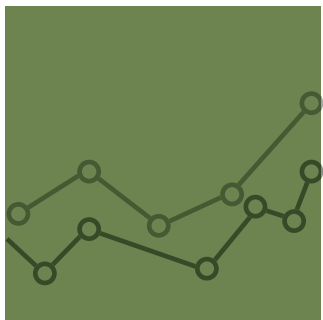
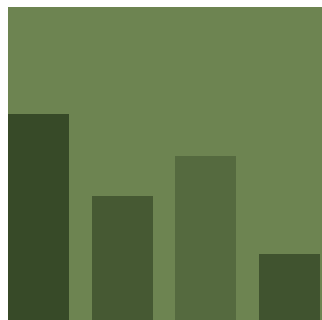
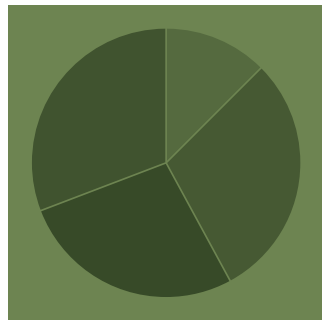


# EPIDEMIC OF CHRONIC KIDNEY DISEASE IN AGRICULTURAL COMMUNITIES IN CENTRAL AMERICA

CASE DEFINITIONS,  
METHODOLOGICAL BASIS  
AND APPROACHES FOR  
PUBLIC HEALTH SURVEILLANCE



Pan American  
Health  
Organization



World Health  
Organization  
REGIONAL OFFICE FOR THE Americas





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METHODOLOGICAL BASIS,  
AND APPROACHES FOR  
PUBLIC HEALTH SURVEILLANCE

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**Pan American  
Health  
Organization**



REGIONAL OFFICE FOR THE

**World Health  
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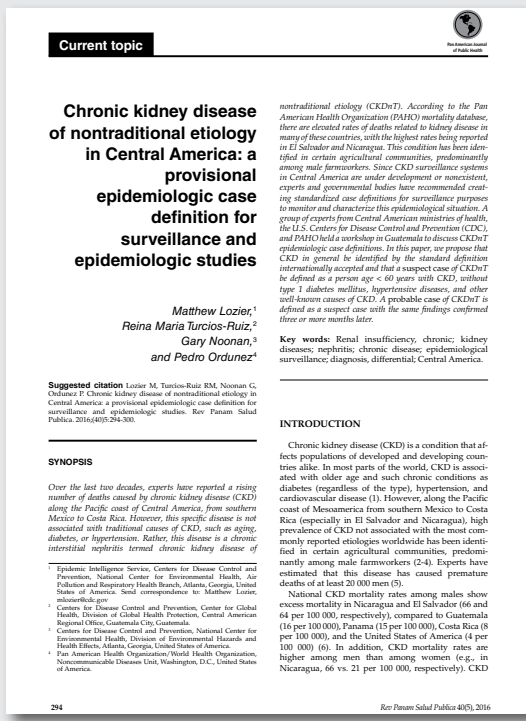
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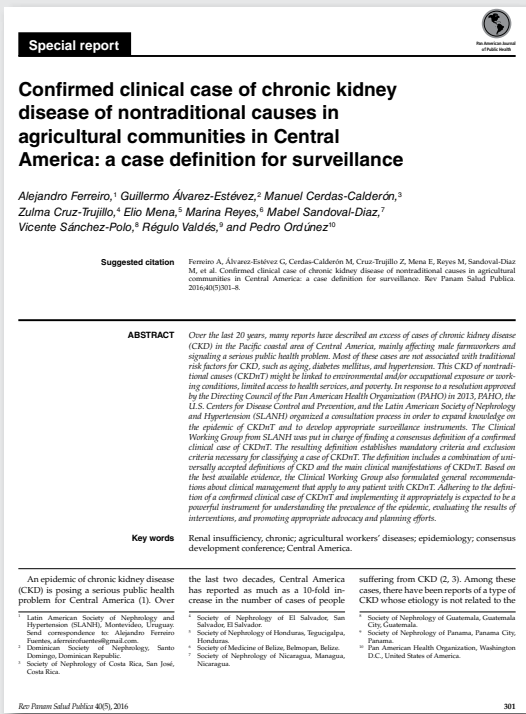
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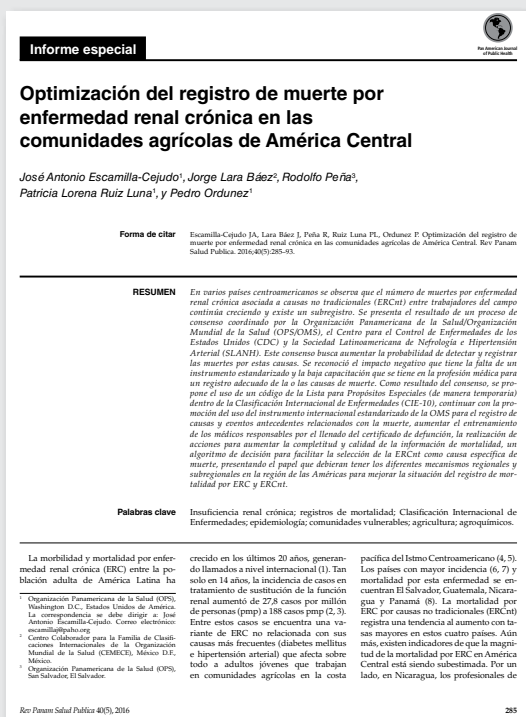
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# Pan American Health Organization 52nd Directing Council

Washington, DC, USA  
30 September – 4 October 2013





PAN AMERICAN HEALTH ORGANIZATION  
WORLD HEALTH ORGANIZATION



## 52nd DIRECTING COUNCIL 65th SESSION OF THE REGIONAL COMMITTEE

Washington, D.C., USA, 30 September-4 October 2013

### RESOLUTION

#### CD52.R10

### CHRONIC KIDNEY DISEASE IN AGRICULTURAL COMMUNITIES IN CENTRAL AMERICA

#### THE 52nd DIRECTING COUNCIL,

Having considered the concept paper *Chronic Kidney Disease in Agricultural Communities in Central America* (Document CD52/8);  
Recalling the importance that the Member States place on the objective of achieving universal health coverage and equitable access to health services;

Aware of the Political Declaration of the High-level Meeting of the General Assembly of the United Nations on the Prevention and Control of Noncommunicable Diseases (A/66/L.1);

Recognizing the inordinate burden of chronic kidney disease in agricultural communities in Central America and that additional research is urgently needed to inform an evidence-based response;

Taking into account the Declaration of San Salvador, which recognizes this chronic kidney disease as a serious public health problem that requires urgent action;

Aware of the obligation of the Member States to provide a comprehensive, integrated, and solidarity-based response to the health problems of its populations,

#### RESOLVES:

1. To take note of the concept paper *Chronic Kidney Disease in Agricultural Communities in Central America*.
2. To urge the Member States, as appropriate, to:
  - (a) support the Declaration of San Salvador, which recognizes chronic kidney disease from non-traditional causes in Central America as a serious public health problem;
  - (b) promote the design and implementation of domestic and regional research agendas for chronic kidney disease in order to bridge the knowledge gap;
  - (c) promote partnerships with other sectors of government, development agencies, civil society, affected communities, academia, private enterprise, and other interested parties, to coordinate efforts, mobilize resources, establish plans at the regional, national, and subnational levels, and promote sustainable, evidence-based public policies, programs and actions to mitigate, on an urgent basis, the health, social, and economic consequences of this disease;
  - (d) strengthen surveillance for chronic kidney disease, with emphasis on at-risk populations and communities;
  - (e) strengthen their capacities in environmental and occupational health and preventive interventions, including health education, taking into account the regulatory frameworks and international commitments and standards;
  - (f) strengthen health services to enhance quality of care and patient safety, the availability of human resources, medicines, and health technologies, and the financing of evidence-based services.
3. To request the Director to:
  - (a) continue to advocate for effective resource mobilization and to encourage Member States to play an active role in the implementation of this resolution;

**(b) lend technical support to Member States to strengthen surveillance systems and facilitate advancement of research priorities for chronic kidney disease;**

- (c) promote the strengthening of countries' capabilities in regard to environmental and occupational health and preventive interventions, taking into account the regulatory frameworks and international commitments and standards;
- (d) support country efforts to take a comprehensive evidence-based approach to address chronic kidney disease, including human resource management and procurement mechanisms for medicines and other critical public health supplies, such as the PAHO Strategic Fund, in order to increase coverage, access, and quality of care;
- (e) continue to alert countries to the increased risk of chronic kidney disease in at-risk populations and communities;
- (f) submit a biennial progress report to the Governing Bodies on the implementation of this resolution.



# EXECUTIVE SUMMARY

In the last four decades, increasing numbers of young people, in clusters of vulnerable farming communities in several Central American countries, have developed a severe form of kidney failure of uncertain etiology (thus termed chronic kidney disease of nontraditional causes, or CKDnT, in this publication). This type of chronic kidney disease, primarily a form of chronic interstitial nephritis, has reached epidemic proportions, devastating entire communities and overwhelming health systems. A recent analysis estimated that more than 60,000 renal failure (a proxy of CKDnT) deaths (41% among those younger than 60 years of age) occurred between 1997 and 2013 in Central America. CKDnT is characterized by progressive renal insufficiency, often diagnosed at a very late stage, in the absence of early symptoms, necessitating renal replacement therapy if the patient is to survive.

Although the etiology of this epidemic is not completely clear, consensus is building around the chronic and multifactorial nature of the origins of the disease

and the epidemic. A multideterminant model, consistent with life course and social determinants of health approaches, is presented in this document. It brings together biological, environmental, occupational, and socio-ecological factors to contextualize the lives of those most affected, who live in conditions of social vulnerability and with limited access to health services, as is characteristic of many farming communities in Central America.

This document presents a background to this epidemic, including its epidemiology and main hypothetical risk factors of CKDnT. It also includes a description of clinical and pathological characteristics, the case definitions for CKDnT surveillance, and the methodological basis and approaches for public health surveillance.

The Pan American Health Organization (PAHO) Resolution on Chronic Kidney Disease in Agricultural Communities in Central America has recommended a set of priorities to address this epidemic; this





document specifically addresses the request for a framework for systematic surveillance of CKD and CKDnT to be developed in the region, particularly for affected countries. This document presents a surveillance framework which includes: (a) passive surveillance, with the main components based on mortality registries and on a population registry of dialysis or end-stage kidney disease; (b) active surveillance that could be based mainly on sentinel surveillance in communities and in selected occupations; and (c) population-based surveillance, through repeated cross-sectional surveys such as the WHO STEPS, which is a stepwise approach to surveillance for non-communicable diseases (NCDs).

The fundamental purpose of this document is to guide countries in the strengthening—and in some cases, in creating—a surveillance system with a focus on CKDnT, and chronic kidney disease in general, as part of a broader strategic effort on NCD surveillance. The framework presented focuses on CKDnT case definitions and the methodological basis and

approaches for public health surveillance for the most affected countries to date, but may be useful in other high-risk scenarios for CKDnT. Hence, its aim is to provide public health officials and health care professionals with a conceptual framework for public health surveillance. Moreover, understanding that the operationalization of this type of surveillance requires much more detailing of the how-to processes, a manual of operations will be produced to guide the implementation. An additional document will be produced to focus exclusively on environmental and occupational surveillance.

This document has been developed in consultation with a wide range of experts, from PAHO technical areas and external surveillance content experts, through an extended iterative process, where multiple rounds of consultations were carried out and in conjunction with the data and evidence currently available. These considerations will be revised and updated as new evidence becomes available.

# SETTING THE CONTEXT

*Wendy Hoy, Gloria Giraldo,  
Ramon Martinez, Ludovic Reveiz,  
Pedro Ordunez*



## Background of the Epidemic and PAHO Response

Although there are no standardized reliable data, it is estimated that in the last four decades, thousands of people in several Central American countries have developed kidney failure of uncertain etiology, which is clinically and histopathologically compatible with a chronic interstitial nephritis (5–13). This condition, described in clusters of vulnerable agricultural communities, is most frequent among male workers, and is particularly severe in sugarcane cutters. Women are also at increased risk in these areas. This disease does not appear to be related primarily to the usual predominant risk factors for CKD such as diabetes, high blood pressure, obesity, and glomerulonephritis or to other well-defined kidney syndromes (5–12). Therefore, PAHO and others have been using the provisional term of chronic kidney disease of nontraditional causes (CKDnT) to refer to this condition.

The Pan American Health Organization (PAHO) estimates that more than 60,000 renal failure deaths (41% among those younger than 60 years of age) occurred in Central America between 1997 and 2013. These kidney-related death rates, specifically deaths coded as CKD-N18 of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) (14), which is a proxy for that form of chronic interstitial nephritis, are extremely elevated in Central America compared to the rest of the countries of the Americas (6). El Salvador and Nicaragua report the highest rates of mortality, but the condition is evident in Costa Rica, Guatemala, Honduras, Panama, Belize, and some regions of Mexico (15, 16).

In 2013, several high-level meetings were held, in which Member States of Central America and the

Dominican Republic in the Central American Integration System (SICA) along with the Council of Ministers of Health of Central America and the Dominican Republic (COMISCA) recognized, in the Declaration of San Salvador, that this type of non-traditional chronic kidney disease is a significant public health problem and requires urgent action to curb the epidemic (16). Subsequently, the 52<sup>nd</sup> Directing Council of PAHO, which met on September 30, 2013, approved the Resolution on Chronic Kidney Disease in Agricultural Communities in Central America (16), where it further supported the Declaration of San Salvador. The Resolution called, among many strategic actions, for lending technical support to strengthen surveillance systems (PAHO Resolution, request 3.b) with an emphasis on at-risk populations and communities (16). This document responds primarily to this specific mandate.

This document aims to provide public health officials and health care professionals, including physicians, nurses, epidemiologists, and hospital and health unit administrators, with a conceptual framework that includes an overview of the epidemic, the clinical and pathological characteristics of this specific type of CKD, the case definitions, and the methodological basis and approaches for public health surveillance.

The operationalization of surveillance will require additional work which may include a manual of operations to detail the processes here described. Similarly, other important topics, such as occupational and environmental surveillance, will be presented in a separate document.



## Epidemiology of CKD and CKDnT in Central America

In Central America, the prevalence of CKD and end-stage renal disease (ESRD), the known risk factors for CKD in the entire population, and the net burden of disease attributable to CKD are not well known. However, estimates from the Institute of Health Metrics and Evaluation (IHME) (17) showed that CKD was among the top 10 causes of age-standardized disability-adjusted life years (DALYs) in Central Latin America (which included Central America, Colombia, Mexico, and Venezuela). In fact, CKD-attributable DALYs doubled (increasing by 102%) in this region between 1990 and 2015, and their rank as causes of DALY rose from 18<sup>th</sup> to 5<sup>th</sup> place. This increase is five times higher than the CKD-attributable DALYs globally during the period, which were 18%. In Central Latin America, CKD-attributable DALYs present a more serious problem among men, although with notably high rates in women; rates in women have increased by 95% over the 25-year period, compared to 108% among men (17). Consistent with this pattern, over the past 20 years many reports have been published describing an excess of cases of CKDnT in Central America (5–13).

As is well known, CKD is not homogeneously distributed. CKD hotspots are defined as countries, regions, communities, or ethnicities with a higher than average prevalence of CKD (18). For instance, decades ago, an interstitial nephritis was described in the Balkans, now attributed to the contamination of grain with *Aristolochia* (19), which has also caused interstitial nephritis and renal failure in China and some areas in Europe. Epidemic levels of chronic interstitial nephropathies of uncertain etiology have also appeared in agricultural communi-

ties in Pakistan, Egypt, Tunisia, and India (7, 12, 20). In the dry north-central zone of Sri Lanka, a similar situation to the one in Central America, both clinically and epidemiologically, has been extensively reported (12).

In the specific case of Central America, rates of CKDnT are generally highest in males of working age, and the disease is usually in the advanced stages when diagnosed. However, community-based screening studies show that females are also affected, particularly in countries with highest mortality (21). Moreover, there are suggestions of early life manifestations of disease. Children and adolescents in one sugarcane-cutting Nicaraguan community with high rates of CKDnT in adults have elevated markers of renal tubular injury (22), while almost half the children in the Pediatric Central Renal Disease referral center in Guatemala have CKD of unknown etiology, and are largely referred from regions where CKDnT has been reported in adult groups (23). Similarly, the Pediatric NefroSalva study conducted in CKDnT high-prevalence area of El Salvador among children and adolescents showed a prevalence of CKD of 4.3% in girls and 3.8% in boys (24).

Many affected communities and regions in Central America are at lower altitudes and high temperatures and closer to the Pacific coast; this geographical zone contains the largest portion of arable land and farming, particularly the cultivation of sugarcane, has become more intense in the last few decades, resulting in more area under cultivation, a greater yield per hectare, and greater harvesting productivity (25).



A recent mortality analysis shows elevated and increasing death rates of recorded CKD N-18 in Central American countries from 1997 to 2013 (Table 1). The same analysis shows the striking difference in mortality trends among Central American countries with extremely elevated rates in El Salvador and Nicaragua, especially among men (Figure 1). When the analysis zooms in on those younger than 30 years of age, as shown in Figure 2, it is clear that death rates due to CKD N-18 in the high-risk countries rise considerably relative to those in the USA and Cuba (ref-

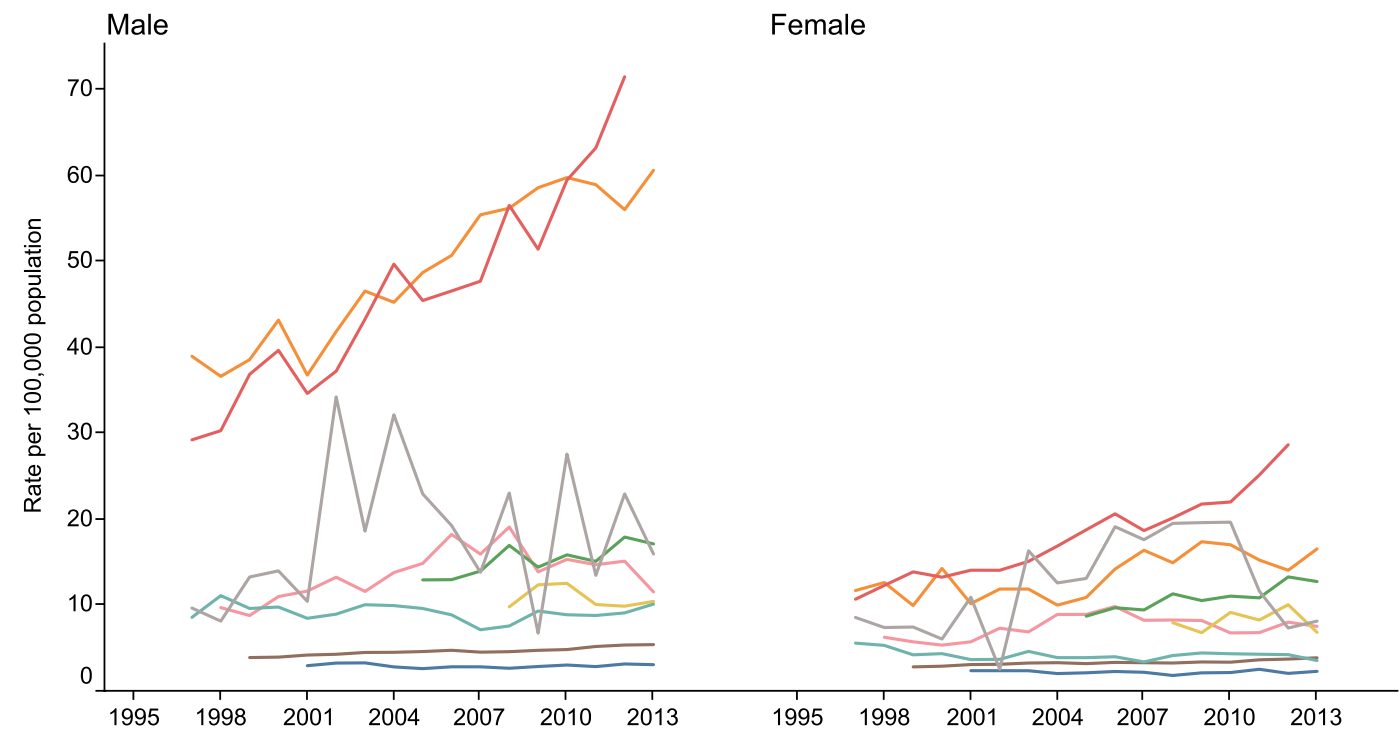
erence countries) from the youngest ages, with boys and girls equally affected. Beyond 10–14 years of age, rates increase exponentially, presumably sometime after they enter the work force. Only as adults do rates in males exceed those of females. These mortality data are also similar to the mortality pattern reported for the Guanacaste Province of Costa Rica, where the mortality rate increased almost nine-fold over four decades (1970 to 2012) from 4.4 to 38.5 per 100,000 among men and from 2.3 to 10.7 per 100,000 among women (26).

**Table 1.** Chronic kidney disease deaths; numbers, age-standardized mortality rates, and average annual percent change, in all ages population, by time-period, for Central American countries, Cuba and the United States

Country	Population 2013	Period	First available year			Last available year			Cumulative		
			Age-standardized death Rate (x100,000 pop)	Total Deaths	Deaths <60 years (% of total deaths)	Age-standardized death Rate (x100,000 pop)	Total Deaths	Deaths <60 years (% of total deaths)	AAPC (95% CI)	Total Deaths	Deaths <60 years (% of total deaths)
<b>Belize</b>	344,193	1997-2013	9.27	13	5 (38%)	11.51	21	11 (52%)	10.4 [1.4, 20.3]	365	148 (41%)
<b>Costa Rica</b>	4,706,433	1997-2013	6.99	180	53 (29%)	6.64	333	86 (26%)	-2.2 [-4.8, 0.4]	4,060	1,193 (29%)
<b>El Salvador</b>	6,089,644	1997-2012	18.69	684	283 (41%)	47.36	2,582	905 (35%)	17.6 [15.5, 19.6]	22,537	8,482 (38%)
<b>Guatemala</b>	15,690,793	2005-2013	10.68	774	302 (39%)	14.7	1,442	565 (39%)	12.9 [7.6, 18.5]	9,970	3,909 (39%)
<b>Honduras</b>	7,849,059	2008-2013	8.77	397	227 (57%)	8.59	477	280 (59%)	-1.1 [-13.6, 13.1]	2,836	1,517 (53%)
<b>Nicaragua</b>	5,945,646	1997-2013	23.85	536	246 (46%)	36.67	1,552	796 (51%)	9.7 [7.0, 12.5]	16,566	8,574 (52%)
<b>Panama</b>	3,805,683	1998-2013	8.04	167	60 (36%)	9.52	344	100 (29%)	7.3 [2.2, 12.6]	4,722	1,284 (27%)
<b>Subtotal</b>				2,751	1,176 (43%)		6,751	2,743 (41%)		61,056	25,107 (41%)
<b>Cuba</b>	11,362,505	2001-2013	2.71	358	103 (29%)	2.72	494	124 (25%)	-0.7 [-3.6, 2.3]	5,301	1,401 (26%)
<b>United States of America</b>	317,135,919	1999-2012	3.3	14,130	2,072 (15%)	4.58	27,417	3,103 (11%)	6.0 [4.9, 7.1]	294,332	40,950 (14%)

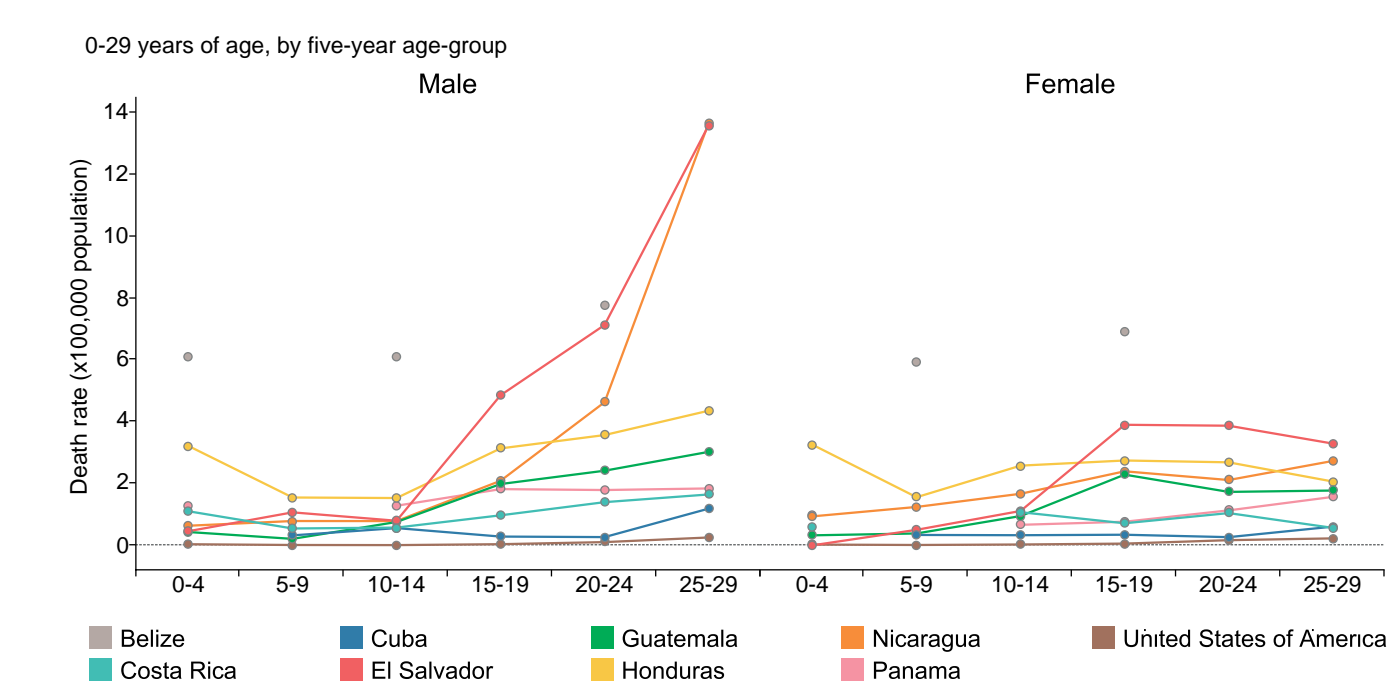


**Figure 1.** Chronic kidney disease age-standardized mortality rate trends in all ages population, by sex in Central American countries, from 1997 to 2013



Source: Regional mortality information system. Pan American Health Organization (PAHO).

**Figure 2.** Chronic kidney disease mortality rate in 0-29 year-old population by sex and age group in Central American countries, Cuba, and United States, 2010-2012



Source: Regional mortality information system. Pan American Health Organization (PAHO).

# Main Hypothetical Mechanisms and a Multideterminant Model for CKDnT

To understand the pathogenesis of most chronic non-communicable diseases, and its public health impact, requires a multideterminant model of causation. A multideterminant model of chronic kidney disease in general has recently been developed (see Conceptual Model, Staging, and Diagnosis of CKD). However, the etiology of CKDnT is not yet completely understood. Although it is generally accepted that CKDnT has multideterminant origins, there are currently two hypothetical mechanisms under discussion, most likely interdependent: exposures to agrochemicals and agricultural working practices. Both are related to precarious working conditions in the context of social vulnerability and a tropical climate.

## Toxic exposures

Exposures to toxins can occur through ecosystem pollution (soil, water, air, food) as well as directly through workplace exposures. They can jeopardize fertility, fetal development, and gestational outcomes, as well as damage organ systems throughout postnatal life (27, 28). In the case of CKDnT, a growing number of studies provide clues to a potential link between CKDnT and agricultural working practices, including agrochemical use. For instance, Orantes et al. (2015) cite very high levels of CKD in both sexes in a region in El Salvador where there is little current agricultural laboring activity, but where leaking containers around an abandoned former storage site have contaminated the environment with agrochemicals that were banned more than 20 years ago, and where high

levels of toxaphene, arsenic, and paraquat have been documented widely in local well water (21, 29). Environmental contaminants are also potential explanations, at least in part, for CKD biomarkers in non-laboring community members in high-risk communities (22, 23, 30).

Toxic exposure has been proposed as a potential causative factor of CKD in other regions beyond Central America. For instance, a recent US study of 32,000 wives of pesticide applicators, who had themselves never applied pesticides, showed their ESRD risk to be significantly correlated with their husbands' cumulative pesticide exposure, suggesting that exposures to spray drift carried by their husbands may be involved (31). In Sri Lanka, a case control study conducted among 125 confirmed CKDnT cases and 180 controls showed that CKDnT was associated with lifetime exposure to different kinds of pesticides. Glyphosate was the most widely used pesticide among Sri Lankan farmers in both groups. In general, subjects who sprayed glyphosate were four times more likely to have CKDnT compared to those without such a history (32). Additional work supports the hypothesis that glyphosate could damage the kidneys, as reported by Jayasumana et al. (2015, 2014), who showed a highly increased risk for CKDnT in male farm workers and exposure-response from water consumption from wells polluted with glyphosate (33, 34).

Central America has a long-standing and well-documented history of agrochemical misuse (35–37). The fact that some pesticides used regularly in Central America are clearly nephrotoxic (37–39) should be sufficient reason to take them into account in



the causation pathway of this epidemic, although much further research is needed to elucidate the specific mechanisms.

## Agricultural working practices

Working and employment conditions, specifically those associated with sugarcane harvesting and processing, can be extreme, particularly where there is incomplete mechanization and deficient occupational health and safety regulations. Stressors include excessive energy expenditure as well as heat stress and dehydration. Demands for greater crop yields, lack of secure employment, and payment by daily harvest weight drive workers to maximize exertion and minimize time for rest and rehydration, in a tropical climate (high temperature and humidity) where conditions may be further exacerbated by climate change (20, 40–43).

Severe working conditions of high temperature and

dehydration have been documented in sugarcane workers in Costa Rica, Nicaragua, and El Salvador (41–48). The severity of such stressors has been compared with that of marathon running, forced military marches for several days, and desert military campaigns (45); however, the cited study highlights that, for agricultural workers, these events are not intermittent, but are repeated every working day during the harvest season. Effects could be expressed through a multitude of symptoms, including, at the severe end of the spectrum, heat stroke and death. Excessive use of analgesics, especially NSAIDs (non-steroidal anti-inflammatory drugs), used to treat or prevent adverse symptoms related to harsh working conditions, could be additionally harmful. Dehydration itself might have specific harmful effects on the kidneys, mediated through several pathways, including vasopressin toxicity, hyperosmolarity-induced activation of aldose reductase pathways and sorbitol toxicity, hyperuricemia, and accumulation of renally excreted nephrotoxins (47, 48).

## A multideterminant model for the CKDnT epidemic

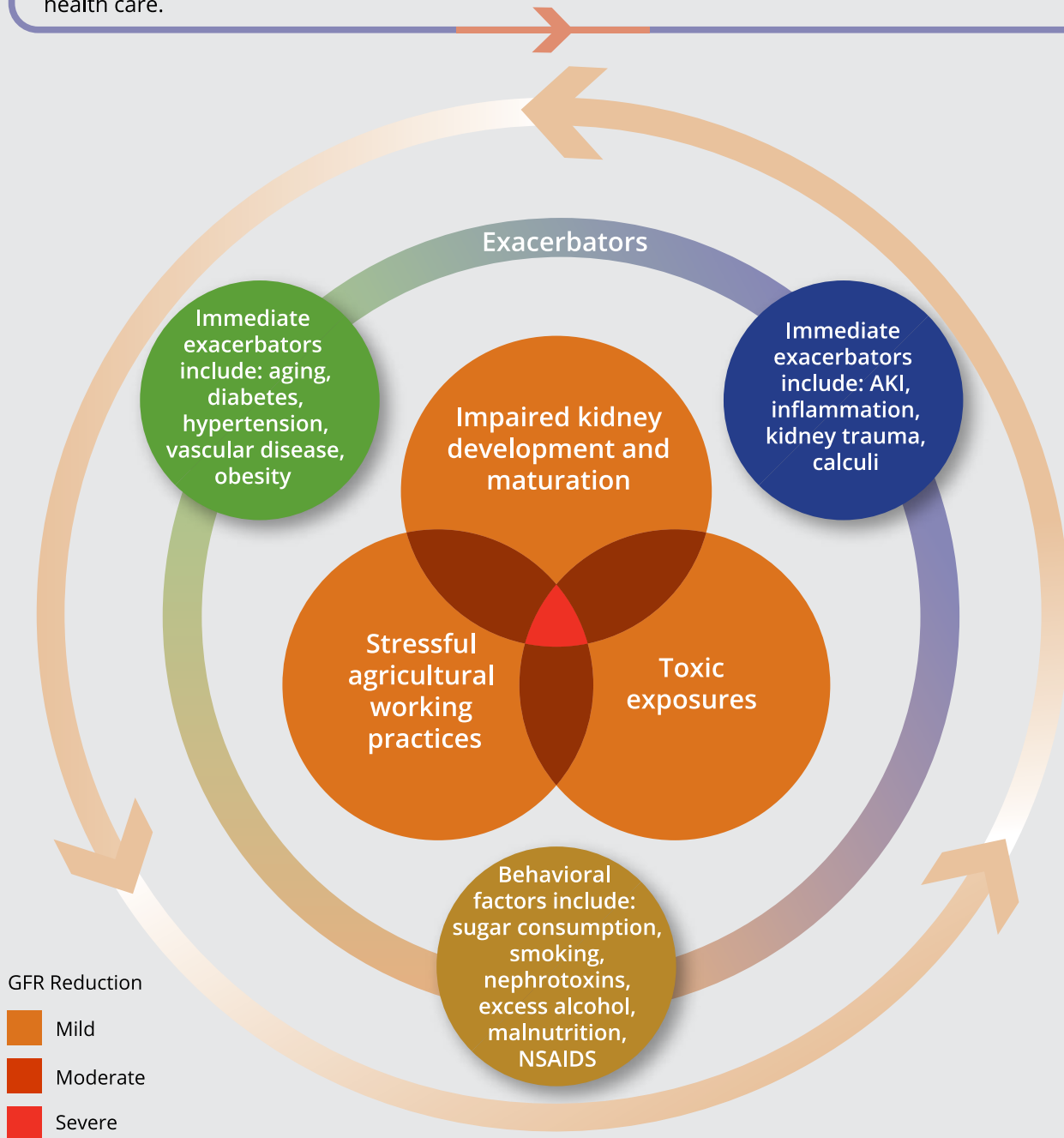
Categories of various risk factors for CKD need not be mutually exclusive. Instead, they can operate in multideterminant or “multi-hit” (49–51) disease frameworks. This implies that organ damage can result from multiple risk factors, acute and chronic, which can act simultaneously or sequentially to amplify the injury caused by each. Multideterminant frameworks allow contemplation of all feasible risk factors, acting alone or in concert, and can thus reconcile different theories of causation. Distinctions between precipitating and facilitating factors are often blurred. Attributable fractions for a defined outcome can be estimated for all risk factors measured. In multideterminant disease models, mitigation of any factor with a significant contribution to risk could reduce ongoing end-organ damage.

A multideterminant model seems appropriate for the CKDnT epidemic. Exposure to pesticides, when combined with strenuous working conditions, intake of contaminated water, and dehydration, in a

context of social vulnerability, could be part of a comprehensive model (12). Beyond toxic exposures and stressful agricultural working practices, and consistent with a life course and social determinants approach to chronic disease, a major category of risk could be added: impaired kidney development and maturation (51). A more comprehensive potential model is shown in Figure 3. Orbiting around the main risk categories are more immediate exacerbators of kidney injury, such as aging, diabetes, hypertension, vascular disease, and obesity. Similarly, acute kidney injury (AKI), infection, inflammation, kidney trauma, calculi, and behavioral factors such as sugar consumption, smoking, and alcohol use are also taken into account. Genetic factors (not shown in the figure) probably influence individual susceptibility through all those pathways. Finally, the social context—low socioeconomic status (SES), unsustainable agricultural practices such as over-reliance on synthetic fertilizers and pesticides, lack or inadequacy of a regulatory system for occupational and environmental hygiene and safety, and absent or poor-quality health services—could potentiate the expression and progression of the disease and the epidemic.

**Figure 3.** A theoretical multideterminant framework for CKDnT

**Context:** Social determinants of health, low socioeconomic status, unsustainable agricultural working practices, lack of regulatory systems for occupational and environmental hygiene practices, and lack of health care.





# TOWARDS CASE DEFINITIONS FOR SURVEILLANCE OF CKDnT

*Wendy Hoy, Pedro Ordunez*





# Conceptual Model, Staging, and Diagnosis of CKD

## Conceptual model

CKD is not a specific disease, but an expression of kidney damage or reduced kidney function which can result from a wide variety of afflictions. A CKD diagnosis relies on abnormalities of the kidneys, protein and/or albumin in the urine, and/or reduced estimated excretory kidney function.

The model developed within the last 10 years includes consideration of risk, disease stages, and complications including renal failure and death. Early stages of disease are often asymptomatic, are detected during the assessment of comorbid disorders, and may be reversible. Rapidly progressive diseases can lead to kidney failure within months; however, most diseases evolve over decades and some patients do not progress during many years of follow-up (52).

Current definitions of CKD are based on the most recent Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines formulated in 2005 and published in 2013 (53), which build on previous guidelines of the National Kidney Foundation of the United States (54–57).

Although there has been increasing application of epidemiological perspectives to the study of kidney disease (58), significant methodological obstacles remain. Perneger and colleagues' discernment of the situation in 1995 still offers a valid view of CKD. Obstacles described include lack of sensitive markers of early renal insufficiency, uncertainty regarding cause-of-death certification in persons with kidney diseases, ambiguous criteria for diagnosing specific renal diseases, inconsistent

risk factor assessments, and inadequate conceptual models for causation of kidney failure. Perneger and colleagues recommended development of a global framework, to include a definition of diagnostic criteria for renal diseases, etiologic studies of “all-cause” end-stage renal disease, systematic collection of data on risk factors for renal injury, and distinction between initiators and promoters of renal insufficiency and between proximate and distal risk factors (59). The nascent CKDnT model presented in the previous section incorporates many of these recommendations.

## Staging of CKD

It is now customary to divide CKD into “stages,” which express the presence of kidney abnormality and the extent of kidney functional loss at any point (Figure 4). These stages are somewhat arbitrary, but provide common reference points for health care providers and researchers (60). For any serum creatinine level in a given individual, the estimated glomerular filtration rate (eGFR) inevitably decreases with age, because higher age in the formulae drives a lower eGFR. Beyond that “age-related” change, greater reductions in eGFR in an individual over time signal accelerated loss of kidney function, which can eventually result in death or kidney failure. Early stages of that progression are often silent; hence advanced kidney disease can develop without substantial symptoms.

In the usual forms of CKD, Stage 3 CKD and beyond often leads to premature death, including, but not exclusively, cardiovascular deaths, and many people die before progressing to terminal kidney

## Estimates of glomerular filtration rate in adults

Estimates of the glomerular filtration rate (eGFR) in adults (>18 years old), commonly calculated through the Chronic Kidney Disease Epidemiology Collaboration (CKD EPI) formula or the modified Modification of Diet in Renal Disease (MDRD) study formula (55, 56), are based on levels of serum creatinine, with adjustment for age, gender, and, in the USA, for African American race. Measurements of serum creatinine should be progressively standardized in individual laboratories, preferably by isotope dilution mass spectrometry (IDMS) methods. The CKD EPI formula is said to be more concordant with GFR measurements by gold standard tracer methods in lower ranges of serum creatinine concentrations (and therefore higher eGFR levels), while both perform equally well for higher levels of creatinine (or lower eGFR). Adjustments for race/ethnicity, if any, need to be group-specific: for example, no adjustment for race or “Black” status was indicated in a systematic study of eGFR in remote-living Aboriginal people in Australia (61). Values of eGFR from CKD EPI and MDRD are both said to represent eGFR standardized per 1.73 m<sup>2</sup> of body surface area (BSA). Those assumptions were derived from best-fit correlations of eGFR measures in grouped data of thousands of people, and apply only very approximately in a given individual (Figure 4).

Among individuals, there is only modest correlation of eGFR with their glomerular filtration rate measured by tracer studies. However, sequential eGFR measures in an individual are very useful and are the standard tool to follow trends in excretory kidney function over time.

failure. For those who progress through Stage 5 CKD, kidney failure death is inevitable unless they receive renal replacement therapy (RRT-dialysis or transplantation). Dialysis is laborious, expensive, and a scarce resource in developing countries. It can prolong life, but does not restore life expectancy to normal, and quality of life ranges from marginal to wretched.

It was once thought that CKD inevitably progressed. Longitudinal data, however, show that kidney function can stabilize over the intermediate term in many people with CKD, and can even increase substantially in some subjects (62). Stabilization or partial recovery can avert or delay the need for dialysis (or kidney death) or rescue patients from dialysis dependency, to live somewhat longer, and with an acceptable quality of life.

## Diagnosis of chronic kidney disease

Diagnosis of CKD relies on measurements of glomerular filtration rate (GFR), presence of albuminuria or proteinuria, and other kidney abnormalities. These include abnormalities in the urine sediment, abnormalities in the composition of blood and urine that define tubular syndromes, and abnormalities in imaging studies. With CKDnT, most of the early manifestations are associated with tubular syndromes or alterations in urine sediment before there is clinically evident proteinuria/albuminuria or a fall in GFR. It must be emphasized that, by the time eGFR is clearly decreased, half or more of functioning kidney mass has already been lost in young and middle-aged people.

In the absence of other defining features, CKD is identified by tests at two different time points, at

least 3 months apart, which demonstrate and then confirm the presence of

1. Albuminuria (ACR  $\geq 30$  mg/g) with or without decreased eGFR; or
2. eGFR  $< 60$  mL/min/1.73 m<sup>2</sup> with or without albuminuria. Albuminuria and eGFR provide the cut points for staging of CKD, as stated in the guidelines and defined in the previous topic (Figure 5). In the absence of proteinuria/albuminuria

or other defining features, a confirmed eGFR  $< 60$  mL/min/m<sup>2</sup> drives the diagnosis of CKD. However, a confirmed eGFR in the low range may be a manifestation of already advanced CKDnT.

Additionally, it is important to emphasize that the diagnosis of CKD does not imply causation. A cause can often be ascertained with careful evaluation, but in some cases remains uncertain.

**Figure 4.** Stages of Chronic Kidney Disease

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories (description and range)		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				$< 30$ mg/g $< 3$ mg/mmol	30-300 mg/g 3-30 mg/mmol	$> 300$ mg/g $> 30$ mg/mmol
GFR categories (mL/min/1.73 m <sup>2</sup> ) Description and range	G1	Normal or high	$\geq 90$			
	G2	Mildly decreased	60-89			
	G3a	Mildly to moderately decreased	45-59			
	G3b	Moderately to severely decreased	30-44			
	G4	Severely decreased	15-29			
	G5	Kidney failure	$< 15$			

Green: low risk (if no other markers of kidney disease, no CKD); yellow: moderately increased risk; orange: high risk; red: very high risk.

a Reprinted, with permission from Elsevier, from: Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney Int Suppl. 2013;3(1):1-150.



## Clinical and Pathological Characteristics of CKDnT

The full spectrum of CKDnT, its severity, the rates and determinants of progression to kidney failure, and the potential to arrest or reverse the process have not yet been fully defined. However, considerable progress has been achieved during the last 5 years. For instance, in their recent report, Jayasumana et al. (2016) summarized the main clinical characteristics of this condition in both El Salvador and Sri Lanka, where CKDnT epidemic has been documented extensively. Figure 5 shows the description for El Salvador (12, 29).

On examination by light microscopy of kidney tissue, at biopsy or autopsy, this condition, in both settings, shares the features of renal tubular epithelial cell injury and inflammation and scarring of the tubules and interstitium, ranging from mild to severe in degree (63, 64). Although this is sometimes mixed with changes in the vascular and glomerular compartments of the kidney, the condition does not seem to be a primary affliction of the glomeruli. Pathologic findings associated with glomerular

ischemia have also been described (65). The relatively minor involvement of glomeruli in this injury pattern explains the absence of heavy protein excretion as a primary marker of disease (64). With albuminuria or proteinuria less reliable markers of early disease, CKDnT is often diagnosed when eGFR has fallen to 50% or less of normal, or CKD Stages 3, 4, and 5. The kidney has substantial compensatory mechanisms to mask loss of functioning mass over the short and intermediate term (54), so that this degree of impairment already represents advanced disease. Thus, disease burdens are underestimated and opportunities for early intervention are missed due to late diagnosis.

Despite the progress on the clinical, histopathological, and epidemiological study of CKDnT, the absence of a widely acceptable standard case definition has become the main obstacle for the development of surveillance systems. The next section describes the approach and process to reach consensus on case definitions for surveillance.

# Approach for Consensus on Case Definitions of CKDnT for Surveillance

PAHO, the United States Centers for Disease Control and Prevention (CDC), and the Latin American Society of Nephrology and Hypertension (SLANH—Spanish acronym) convened a consultation process to develop case definitions for CKDnT surveillance in response to the Commission of Ministers of Health of Central America and the Dominican Republic (COMISCA) resolution (15) and the PAHO Resolution (16).

Subject matter experts in three key fields (epidemiology, clinical nephrology, and mortality and vital statistics) were invited from eight Central American countries: Belize, Costa Rica, the Dominican Republic, El Salvador, Guatemala, Honduras, Nicaragua, and Panama. These experts had been appointed by the Ministry of Health of each country. Nephrologists were designated by the national chapter of SLANH. Once delegates were appointed for each working group, a remote consultation was initiated following the Delphi technique. After the initial consultation, the working groups drafted documents that included the opinions of experts and concepts that emerged from an extensive literature review. Such consultation was repeated in two or more additional cycles. In December 2013, they convened an in-person workshop in Guatemala City to discuss and develop further case definitions. A total of 28 persons from the eight countries participated (11 nephrologists, 11 subject matter experts in surveillance, and 6 subject matter experts in mortality and vital statistics), with representation from each country. Additional technical staff from three public health agencies (CDC, PAHO, and COMISCA) also participated.

Figure 5. Description of CKDnT in El Salvador

Clinical features
Asymptomatic (early stages)
Loss of appetite
Lethargy
Backache
Insomnia
Arthralgia
Muscle ache
Cramps
Dysuria
Foamy urine
Neurological abnormalities
Sensorineural hearing loss
Tibial artery abnormalities
Normal liver enzyme level
Urine findings
Hypersuricosuria
Hypernatruria
Hypermagnesuria
Hyperphosphaturia
Hypercalciuria
Proteinuria (negative/trace, no active sediment)
B2-microglobulin, N-acetyl-glucosaminidase, neutrophil gelatinase-associated lipocalin
Blood
Hyperuricemia
Hyponatremia
Hypokalemia
Imaging
Bilateral small echogenic kidneys, decreased cortico-medullary ratio, irregular margins
Histopathology
Tubulo-interstitial nephritis
Interstitial fibrosis
Tubular atrophy
Interstitial mononuclear cell infiltration
Glomerular collapse
Fibrous intimal thickening and arterioral hyalinosi
Negative immunofluorescence tests

Figure adapted from Jayasumana C, Orantes C, Herrera R , et al. Chronic interstitial nephritis in agricultural communities: a worldwide epidemic with social, occupational and environmental determinants. Nephrol Dial Transplant. 2017;32(2):234–41.





The Epidemiologic Workgroup was charged with drafting epidemiologic case definitions of *suspect and probable CKDnT*. The discussion considered both the epidemiologic and operational aspects of the case definitions. Input was provided from the clinical case definition and harmonization of CKDnT mortality classification workgroups to obtain the final version of the case definition presented in this document.

The Clinical Nephrology Workgroup was charged with achieving a consensus definition for *confirmed clinical cases of CKDnT*. Suggestions were made by members of the other two discussion groups participating in the workshop. Final editing of the consensus proposal was done at a meeting organized by CDC, PAHO, and SLANH in Atlanta, USA, in July 2014, with the participation of delegates from each organization. The resulting document is the basis for the confirmed clinical case definition of CKDnT presented herein.

The workgroup to improve surveillance of mortality from CKDnT consisted of experts from PAHO/WHO and the WHO Collaborating Center for the Family of International Classifications in Mexico (CEMECE). CEMECE and PAHO/WHO have worked together for several years evaluating morbidity and mortality information systems in the region. At several on-site and virtual technical meetings, a proposal was drafted and sent to COMISCA, for consultations with its Member States. COMISCA forwarded the proposal to all its members. Participants were instructed to prepare recommendations to improve capture of deaths caused by CKDnT from information systems and the ICD-10 (14). Ultimately, this group agreed with a provisional code to classify deaths potentially attributed to CKDnT and an algorithm was developed to support coding and reporting.

The next sections cover the rationale for surveillance and the resultant case definitions.

**Rationale for case definition for surveillance purposes.** In the context of the epidemic of CKDnT in agricultural communities in Central America, the use of standard definitions of CKD and CKDnT will allow regions and countries to measure CKD- and CKDnT-related incidence and prevalence and compare these data with other regions and countries worldwide. The definitions will change over time as surveillance improves and more evidence is gathered about the epidemic, so that regular consensus meetings are recommended to discuss such potential changes to these definitions.



# Provisional epidemiologic case definitions for surveillance and epidemiologic studies

## **Suspect case of chronic kidney disease of nontraditional etiology (1)**

A suspect case of CKDnT is a person with one abnormal result that meets the KDI-GO CKD criteria AND who meets all of the following criteria:

1. No history of type 1 diabetes mellitus;
2. No history of hypertensive diseases (hypertensive heart disease, hypertensive chronic kidney disease, hypertensive heart and chronic kidney disease, secondary hypertension);
3. No history of other known cause(s) of CKD (e.g., congenital malformations, polycystic kidney disease, sickle cell disease, lupus, vasculitis, myeloma, and others); and
4. Age < 60 years.

## **Probable case of chronic kidney disease of nontraditional etiology**

A probable case of CKDnT is a suspect case with a second abnormal result, obtained at least three months after the first result, which meets the widely accepted criteria of CKD.

In some cases, CKD can be diagnosed in the absence of a second evaluation. Chronicity may be documented, or inferred by clinical judgment in the absence of past data or by eGFR or urine findings, or by imaging tests. The absence of an acute concomitant illness or the presence of small kidneys on imaging is a marker of chronicity, and a diagnosis does not need to await a second test.

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### **Chronic kidney disease of nontraditional etiology in Central America: A provisional epidemiologic case definition for surveillance and epidemiologic studies (1)**

Matthew Lozier (1), Reina Turcios-Ruiz (1), Gary Noonan (1), Pedro Ordunez (2) from the US Centers for Disease Control and Prevention (1) and the Pan American Health Organization (2).

*With acknowledgement of members of the Epidemiologic Workgroup in Guatemala City, 16–17 Dec, 2013: Marisol Aguilar, Ministry of Health, Panama; Patricia Alberto, Ministry of Health, El Salvador; Elsa Arenas de Kant, Ministry of Health, Panama; Englebert Emmanuel, Ministry of Health, Belize; Mario Gudiel, Council of Ministries of Health of Central America, (COMISCA); Carlos Orantes, National Institute of Health, Ministry of Health, El Salvador; Raquel Pimentel, Ministry of Health, Dominican Republic; and Berta Sam, Ministry of Health, Guatemala*

In addition to the clinical data and information needed to determine if a person has CKDnT, it is important to register individual characteristics (for instance, occupation: agricultural worker, pesticide applicator, among others), and population-level exposures (for instance, residing in a farming community or close to a source of agrochemicals), and other relevant characteristics to better understand potential causes of CKDnT.

Even though this can be a controversial issue, the expert group who developed the “suspect and probable case” definitions also stated their rationale in respect to age restrictions:

**Early ages:** Children are included in the CKDnT case definitions so that cases may be identified in the early stages of disease, allowing health care providers as well as researchers to explore development and progression of CKDnT.

**Older ages:** Due to the inverse association between age and eGFR, and the use of eGFR as the primary diagnosis criterion for CKDnT, the expert group proposed to exclude persons aged  $\geq 60$  years from the CKDnT case definition. However, it is important that CKD surveillance, registries, and epidemiologic studies include persons  $\geq 60$  years old to assess disease trends in all age groups. This will allow health authorities to assess the need for CKD treatment and for researchers to explore CKD progression in persons  $\geq 60$  years old. Finally, because there are key scientific uncertainties surrounding CKDnT, these case definitions are subject to change. They need to be validated in future studies and also using data from existing prevalence studies (1).

## Confirmed clinical case of CKDnT (2)

### 1. Mandatory criteria to classify a patient as having a confirmed clinical case of CKDnT:

- i. **Chronic kidney disease** (based on current consensus definition of CKD (3) and the clinical profile of CKDnT), defined and restricted to the following persistent alterations (for more than three months)
  - 1) Estimated glomerular filtration rate (eGFR)  $< 60$  mL/min/1.73 m<sup>2</sup> body surface area, preferably determined by the CKD EPI formula, based on standardized serum creatinine, or in its absence, by the four-variable MDRD formula or the Cockcroft-Gault formula and/or
  - 2) Kidney damage as defined by structural abnormalities or functional abnormalities other than decreased eGFR and/or
    - A) Non-nephrotic proteinuria (albuminuria  $> 30$  and  $< 3,000$  mg/24 hours, or albumin/creatinine ratio  $> 30$  and  $< 3,000$  mg/g) and/or
    - B) Urinary sediment abnormalities as markers of kidney damage (i.e., microscopic hematuria with abnormal erythrocyte morphology, or red blood cell casts, granular casts, or oval cells) and/or
    - C) Renal tubular disorders (i.e., renal tubular acidosis, nephrogenic diabetes insipidus, renal potassium wasting, other).
- ii. **Age:** 2 to 59 years.
- iii. **Ultrasonography of the urinary tract** demonstrating the presence of two morphologically symmetrical kidneys (eventually diminished in size), without urinary tract obstruction or renal polycystic disease.
- iv. Absence of any of the following exclusion criteria.

## 2. Exclusion criteria for classifying the CKD patient as having a confirmed clinical case of CKDnT:

i. A clinical history of:

- 1) **Diabetes mellitus** only if there is evidence of microangiopathy in other territories (diabetic retinopathy, diabetic neuropathy) or history (current or previous) of nephrotic proteinuria.
- 2) **Hypertension:** JNC 7 stage 2 ( $\geq 160/100$ ), or stage 1 hypertension with nonrenal target organ damage (cerebrovascular disease, ischemic heart disease, peripheral arteriopathy).
- 3) **Urologic pathology** (i.e., verified nephrolithiasis, nonlithiasic obstructive nephropathy, surgical or traumatic reduction of renal mass, other).
- 4) **Primary glomerulopathy** confirmed by renal biopsy or suspected due to presence of nephrotic-range proteinuria.
- 5) **Hematologic disease** (i.e., multiple myeloma, systemic amyloidosis, lymphoma, leukemia, sickle cell anemia, other).
- 6) **Genetic and/or heredofamilial renal disease** (i.e., Alport syndrome, polycystic renal disease, Fabry disease, familial glomerulopathy diagnosed by renal biopsy, other).
- 7) **Autoimmune disease** (i.e., systemic lupus erythematosus, systemic or renal-limited vasculitis, rheumatoid arthritis, mixed connective tissue disease, Goodpasture syndrome, primary antiphospholipid syndrome, other).
- 8) **Repeated exposure** to X-ray contrast media and/or administration of phospho-soda solutions, as preparation for colonoscopy.



### Confirmed clinical case of chronic kidney disease of nontraditional causes in agricultural communities in Central America: A case definition for surveillance (2)

Alejandro Ferreiro (1), Guillermo Álvarez-Estévez (2), Manuel Cerdas-Calderón (3), Zulma Cruz-Trujillo (4), Elio Mena (5), Marina Reyes (6), Mabel Sandoval-Díaz (7), Vicente Sánchez-Polo, Régulo Valdés (8), and Pedro Ordunez (9)

*Latin American Society of Nephrology and Hypertension (SLANH) (1), Dominican Society of Nephrology (2), Society of Nephrology of Costa Rica (3), Society of Nephrology of El Salvador (4), Society of Nephrology of Honduras (5), Society of Medicine of Belize (6), Society of Nephrology of Nicaragua (7), Society of Nephrology of Guatemala, and the Society of Nephrology of Panama (8) and Pan American Health Organization (9).*



The expert group for a confirmed clinical case also recommended recording in the registry each case:

- Residing or having resided for at least 6 months in an agricultural production area of Central America, or other similar environment.
- Working or having worked for at least 6 months in agricultural activities in Central America.

Furthermore, they recommended that:

- Children <2 years should not be included in the criteria for confirmed cases of CKDnT because the criterion of eGFR <60 mL/min does not apply under this age (they do not reach eGFR >60 mL/min, even adjusted to BSA), and most CKD under this age is related to urinary tract malformation or developmental renal abnormalities.
- Cases of CKDnT should be referred to a des-

ignated specialist, preferably a nephrologist, to complete the etiologic study of CKD and establish treatment guidelines (including histopathology if appropriate).

- All cases of CKD should be classified also by degree of decline in GFR and level of proteinuria or albuminuria.
- Clinical management and treatment of CKDnT cases should be adapted to the best available evidence. The best current strategy is using the recommendations in the SLANH CKD treatment guidelines for Stages 1 to 5 and the KDIGO Clinical Practice Guidelines (53, 66).
- Each case should be actively followed by a multidisciplinary team trained in management of these patients, evaluating the disease progression and benefit of therapeutic measures.



## Death attributed to CKDnT

Improving the completeness and quality of mortality data is an essential step in the construction of an accurate CKD and CKDnT surveillance system. Given that most Central American countries lack a standardized instrument for recording cause of death, the expert group strongly recommends that countries adopt as soon as possible the WHO International Form of Medical Certificate of Cause of Death. Moreover, physicians responsible for properly filling out death certificates may lack the appropriate training. Thus, failure to record this information or its improper recording limits the ability of the professional coder to accurately select and code the underlying cause of death. Added to these challenges is the fact that a specific ICD code for CKDnT does not currently exist.

In light of the aforementioned challenges, the expert group developed an algorithm to guide the process of recording and coding deaths attributed to CKDnT, using the official death certificate in a country, which records the underlying cause of death, as the base document. Since there is not a specific code for CKDnT, the expert group recommended implementing a procedure clearly delineated in the algorithm presented in Figure 6. Note that the main focus is on the group of “Acute Renal Failure,” which includes codes N17, N18, and N19. Under current coding practices most of the cases under the category of Renal Failure fall in the N18 category, which in the practical realm is the best proxy for CKDnT. The expert group suggested utilizing the temporary ICD-10 code, U50.X, which is the main result of this analysis, to notify deaths attributed to CKDnT.

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### Optimization of registry of deaths from chronic kidney disease in agricultural communities in Central America (3)

José Antonio Escamilla-Cejudo (1), Jorge Lara Báez,(2) Rodolfo Peña (1), Patricia Lorena Ruiz Luna (1), Pedro Ordunez (1) from Pan American Health Organization (1) and Family of International Classifications Collaborating Center in Mexico (CEMECE)(2)

*With acknowledgement of members of the Coding Mortality Workgroup in Guatemala City Guatemala City, 16–17 Dec, 2013: José Antonio Escamilla Cejudo, Marisol Aguilar, Jorge Lara, Rodolfo Peña, Patricia L. Ruiz Luna, José Monzón, Marisol Moreira, Francis Morey, David Rodríguez, Manuel Sagastume, Rosa María Vargas Alvarado, Pedro Ordunez. Representing the Pan American Health Organization/World Health Organization, (PAHO/WHO); Ministry of Health of Panama, Office of Health Statistics; WHO FIC [Family of International Classifications] Collaborating Center in Mexico (CEMECE); Executive Secretariat of the Council of Ministers of Health of Central America and the Dominican Republic (SE COMISCA); Ministry of Health of El Salvador, Bureau of Health Surveillance; Ministry of Health of Belize, Epidemiology Unit; Ministry of Health of El Salvador, Bureau of Statistics; Ministry of Health of Guatemala, National Center for Epidemiology; Ministry of Health of Costa Rica, Bureau of Health Surveillance, and acknowledging Drs. Juan José Amador, Patricia Soliz Sánchez, Gabriela Fernández Quintanilla for their contributions.*

**Under clinical and epidemiological assessment, consider that chronic kidney disease (CKD) is a chronic tubulo-interstitial nephropathy with a higher frequency of notification among agricultural workers and communities.**

**Scenario of multiple causes of death analysis**  
List of possible causes

**Start**  
Death Certificates

**Look specifically for underlying cause of death N17, N18, N19 and N28.9**

**Is it N17?**  
Yes: **Verify residency and epidemiological background information** → **Compatible with CKDnT definition?**  
No: **Is it N18?**

**Compatible with CKDnT definition?**  
Yes: **Classify as CKDnT (U50.X)** → **End**  
No: **Leave as N17 ARF and exclude from surveillance** → **End**

**Is it N18?**  
Yes: **Verify residency and epidemiological background information** → **Compatible with CKDnT definition?**  
No: **Verify residency and epidemiological background information** → **Compatible with CKDnT definition?**

**Compatible with CKDnT definition?**  
Yes: **Classify as CKDnT (U50.X)** → **End**  
No: **Leave as CKD N18** → **End**

**Compatible with CKDnT definition?**  
Yes: **Classify as CKDnT (U50.X)** → **End**  
No: **Leave as UKF (N19, N28.9)** → **End**

**Death cause acronyms:**  
ARF (N17) Acute renal failure  
CKD (N18) Chronic kidney disease  
UKF (N19, N28.9) Unspecified kidney failure  
CKDnT (U50) Chronic kidney disease non-traditional

**Pathways:**  
Initial assessment  
Group 1: Acute Renal Failure (ARF-N17)  
Group 2: Chronic Kidney Disease (CRF-N18)  
Group 3: Unspecified Kidney Failure (UKF N19, N28.9)

**End**

**Death cause acronyms:**

- ARF (N17)**  
Acute renal failure
- CKD (N18)**  
Chronic kidney disease
- UKF (N19, N28.9)**  
Unspecified kidney failure
- CKDnT (U50)**  
Chronic kidney disease  
non-traditional



## Further considerations regarding the implementation of case definitions

The discussion below applies to the case definitions related to CKDnT:

- 1) **a provisional epidemiologic definition of suspected and probable case,**
- 2) **a confirmed clinical case, and**
- 3) **death attributed to CKDnT.**

All case definitions presented herein respond to the need to have a standard definition for identification and classification. This is particularly important in the context of an epidemic of a relatively new and unidentified condition just barely considered by current ICD classification and surrounded by etiological uncertainty. Furthermore, standard case definitions allow for

trend and situational comparisons among countries and regions throughout time.

These case definitions, although provisional and evolving, are especially useful for public health surveillance in CKDnT high-prevalence scenarios such as farming communities in Central America and certain occupations. These definitions may also be applied in communities and groups that have not yet been identified as such but that could be considered at risk, even those outside Central America, if manifesting all or some of the following conditions: places where agriculture plays an economic role; where agrochemicals are widely used, independent of type of crop; where working conditions are precarious and strenuous including high-temperature exposure; and where health service infrastructure and health care access are limited, particularly in a context of social vulnerability. CKDnT case definitions may also be used in sentinel surveillance as a type of control in low- versus high-risk scenarios.





## High-Risk Scenarios for CKDnT

- Places where agriculture plays a relevant economic role  
AND
- Places where agrochemicals are widely used and/or stored, independently of crop
- Places where working conditions are precarious and strenuous in high-temperature environments
- Places where health service infrastructure and health care access are limited

An individual with CKD will have a higher probability of being classified as a case of CKDnT if the clinical pattern of his/her disease corresponds primarily with chronic tubular interstitial nephropathy and if the case originates from a high-risk scenario. However, even in high-risk scenarios, CKD cases can be found whose clinical pattern does not correspond primarily to chronic tubular interstitial nephropathy and hence they would not be classified as CKDnT cases.

It is important to highlight that classification of a CKD case as a CKDnT case could become even more complex in high-risk scenarios because the chance of observing mixed cases (CKDnT + CKD due to other causes such as diabetes, hypertension, etc.) might, in fact, be higher than in low-risk scenarios. In such cases, renal damage could progress more rapidly due to overlapping risk factors and heightened vulnerability. A robust surveillance system would ensure that all cases are registered and can be re-examined.

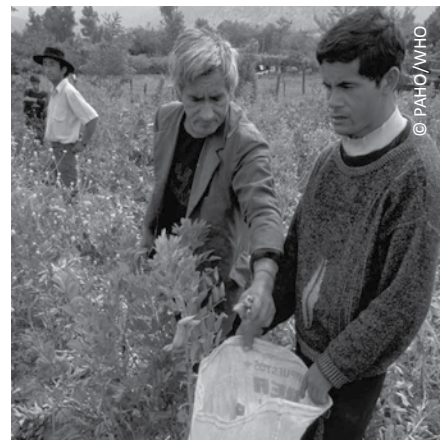


## Additional considerations regarding the case definitions by the editors of this document

1. The upper age exclusion, in any of the case definitions, may limit the view of CKDnT in older people. In many high-risk countries there are excessive and increasing rates of unexplained renal deaths continuing on through age 85 years. Thus, there will be many older people to consider as potential cases of CKDnT. This number will increase as populations age and when interventions are ultimately able to prolong the lives of people with CKDnT. Data of older people with CKDnT can reveal factors that are mitigating against a more aggressive course of renal disease, or associated with later onset disease. Such data might also shed light on historical trends in work practices, exposure, and environmental factors; it is noted that CKDnT may have a long latency period and older individuals may manifest symptoms later in life after working years. Finally, older people will have more comorbidities and are more likely to have admixtures of CKDnT with CKD of more traditional causes. It will be important to understand those mixes. To mitigate this issue, we recommend that surveillance systems should be able to register all cases without an upper age restriction.
2. Inclusion of children in the surveillance of CKD/CKDnT could pose extra difficulties for the implementation of a surveillance system. However, including children in the CKDnT case definitions will allow a broader view of a disease where early exposure to some risk factors might play a role in the origin of this epidemic. In addition, children's data will allow researchers to explore development and progression of CKDnT. Inclusion or exclusion of children in the surveillance system might require some ethical considerations based on country-specific standards, and special consideration of scenarios of high social vulnerability and places where child labor continues to be a challenge.
3. The exclusion of other conditions that predispose to or cause CKD might ultimately be relaxed. The frequency of obesity, the metabolic syndrome, hypertension, and type 2 diabetes will increase and they will potentially coexist with, or become superimposed on, CKDnT. Both CKD and CKDnT are disproportionately expressed in the most socioeconomically disadvantaged groups. Older people are more likely to have such admixtures. Excluding people with other potential causes of CKD will reduce the perceived CKDnT burden and diminish the opportunity to study the multideterminant nature of both CKD and CKDnT.
4. It is important not to lose track of people with initial unconfirmed characteristics of CKD. The patient might not be available for follow-up, or the repeat creatinine might not be confirmatory (error, borderline values, different hydration status, or different laboratories). Our recommendation is to enter and retain cases with a single laboratory test that meets the CKD criteria into registries as cases of interest. Their status can be updated to a suspect case of CKDnT if confirmatory data follow. Most cases with a depressed value of eGFR will ultimately be confirmed, and their retention in registries provides the opportunity to follow disease progression. Furthermore, their presence in registries can act as a reminder, minimizing the chance that they are lost to the system.
5. Defining an eGFR cut-off of less than 60 mL/min/1.73 m<sup>2</sup> for a CKDnT diagnosis might represent advanced disease in young adults; thus, development of markers allowing diagnosis at earlier stages is highly desirable.
6. The desirability of confirmation by a specialist will limit numbers of definitive diagnoses. As familiarity with this condition and its spectrum of manifestations grows, general physicians, primary care doctors, nurses, and health workers should be trained and certified to classify cases according to the case definitions for surveillance.

# METHODOLOGY FOR SURVEILLANCE OF CKD AND CKDnT

*Wendy Hoy, Pedro Ordunez*



## Investing in CKD/CKDnT Surveillance

Surveillance of CKD, in general, and CKDnT, particularly, and their risk factors is both necessary and urgent in the current context of the epidemic in agricultural communities in Central America. It will be a new component of public health practice in some countries, and should be integrated into health information systems already in place. Well-designed surveillance systems will provide the basis for the evaluation of policies and interventions aimed at curbing this epidemic, even when the causes are not completely clear.

### Surveillance of CKD and CKDnT may allow for

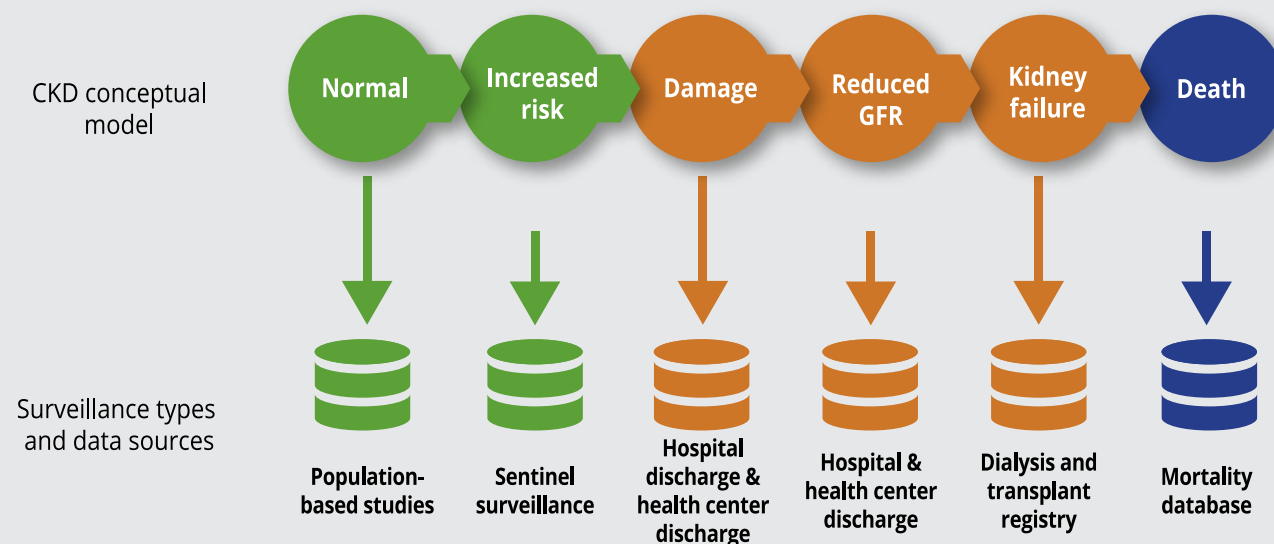
- Monitoring trends and the epidemiological distribution of CKD and CKDnT cases and related risk factors and conditions,
- Monitoring trends in the access—and factors related with the access—to renal replacement therapies for patients with end-stage renal disease,
- Monitoring trends and the epidemiological distribution of mortality due to CKD and CKDnT and related risk factors/conditions,
- Monitoring the impact of policies and interventions,
- Timely and appropriate dissemination and sharing of information,
- Monitoring aspects of working and employment conditions, and
- Monitoring social determinants of health in agricultural communities.

## Conceptual Basis for CKD and CKDnT Surveillance

Public health surveillance comprises the ongoing systematic collection, analysis, and interpretation of data, closely integrated with the timely dissemination of these data to those responsible for preventing and controlling disease (67). A surveillance system cannot be implemented successfully in the absence of a health system ready to act in a timely manner; otherwise, it would just be a data collection process operating in a vacuum, without integration into a larger coordinated public health response.

**CKDnT surveillance case definitions are not intended to be used to create a parallel and vertical surveillance system. Rather, we envision countries establishing a CKD surveillance system, as a component or as a subsystem of a broader NCD surveillance system, aligned with the comprehensive model of CKD (Figure 7) that would capture all CKD cases, irrespective of their etiology and inclusive of all geo-administrative units within the country. Then, the CKDnT case definitions criteria can be applied to characterize persons with CKD by most likely cause. Capturing all CKD cases is useful to estimate the impact of different risk factors for CKD, as well as for planning purposes.**

**Figure 7.** CKD conceptual model\* and corresponding CKD surveillance components



\*CKD model adapted from conceptual model published in Levey AS, Coresh J. Chronic kidney disease. *Lancet*. 2012 Jan 14;379(9811):165–80

An essential step would be to reach consensus among countries about a standard methodology for case definition, data collection, coding, and analysis. Data collection should be easy to apply, with a minimum set of information, and able to capture trends

of the distribution of the disease and death considering place, age, and gender, through time. Social determinants of health such as occupation and working conditions, and socioeconomic and demographic data such as migration status, should be included.

### Core sociodemographic data set to be collected for CKD and CKDnT surveillance.

- Demographic data: gender, date of birth, ethnic group, place of birth, place of residence;
- Socioeconomic data (housing, education, employment, income);
- Family health history, including history of kidney disease;
- Personal health history: diabetes, hypertension, kidney diseases, nephrotoxic medications, or other putative risk factors; and
- Occupational history: place of work (previous, current, duration), type, duration, seasonal/all year round, occupational exposures (e.g., for agricultural work: temperatures, types of crops, pesticides, herbicides, fertilizers, burn off).





A minimum and standardized set of core data is proposed to guarantee larger coverage, compliance, and sustainability of the surveillance system, which in addition would facilitate comparability between

countries. Other questions or modules could be added, but everyone would collect and analyze at least the agreed core set of information. Some sentinel surveillance sites could include additional modules.

### Attributes of a CKD/CKDnT Surveillance System

- ✓ Non-duplication but strengthening of existing surveillance systems.
- ✓ Core standardized components common to all countries and all time periods.
- ✓ Flexibility to incorporate additional items according to needs and resources of different countries, or at different times.
- ✓ Methods that can be implemented by various types of staff in various situations (not relying upon specifically trained medical personnel).
- ✓ Information stratified by age, gender, socioeconomic status, place of residence, and main occupation.
- ✓ Information collected, analyzed, and reported at a level directly relevant to the implementation and evaluation of interventions.
- ✓ Standardized quality control and quality assurance mechanisms at the data collection and data entry levels.
- ✓ Ability to generate reasonably valid and reliable estimates.
- ✓ Ability to generate timely and user-friendly reports for specific audiences.
- ✓ Simplicity and sustainability.

# APPROACHES TO ESTABLISHING A CKD/CKDnT SURVEILLANCE SYSTEM

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## Menu of Methodological Options for Surveillance

Understanding that there are similarities as well as differences among the various contexts where CKD and CKDnT epidemics are unfolding, this document presents a menu of options for national, subnational, local, or even supra-national surveillance systems. When selecting a methodology for surveillance, several factors need to be taken into account, including data needs and existing resources in the realms of human talent, technology, and finances.

We propose a surveillance methodology menu and data platform framework (Figure 8) with a potential combination of options composed by nonlinear approaches, from (a) passive surveillance, based on routinely collected mortality and morbidity registry data, to (b) active surveillance approaches, including sentinel surveillance, and (c) population-based surveys, through repeated cross-sectional surveys. Clearly, each country, based on its own resources and priorities, can decide which, when, and where of these components should be prioritized. Countries should continue to strengthen the passive surveillance component and, in parallel, start the sentinel surveillance in high-risk communities or in high-risk occupational groups. Most important, however, is to adopt the standard case definitions and put in place an acceptable and sustainable surveillance mechanism. Ethical and operational implications of active or passive methods of surveillance

should be considered carefully. Moreover, planning and executing a surveillance system entails taking into account an array of elements that start at the data source and continue through to the production of actionable surveillance products. Additionally, many operational aspects to be considered include governance and ownership of data, basic equipment, computer hardware and software, data management, costs, sustainability and integration systems, etc. In the next section, a conceptual framework for the data platform of a CKD/CKDnT surveillance system is provided; further details with clear practical guidance will be prepared as an independent forthcoming document.

## Framework for the Data Platform of the CKD/CKDnT Surveillance System

A framework for the data platform of the CKD/CKDnT surveillance system is illustrated in Figure 8. It supports the use of dynamic and large data sets from heterogeneous sources from several types of surveillance, to conduct comprehensive data analysis, produce effective data and information products (outputs), and improve information communication and dissemination. Ultimately, the format would be a modular and interdependent platform that would facilitate the addition of individual modules at later times as needs, capacity, and resources change.



The framework comprises five functional components (Figure 8):

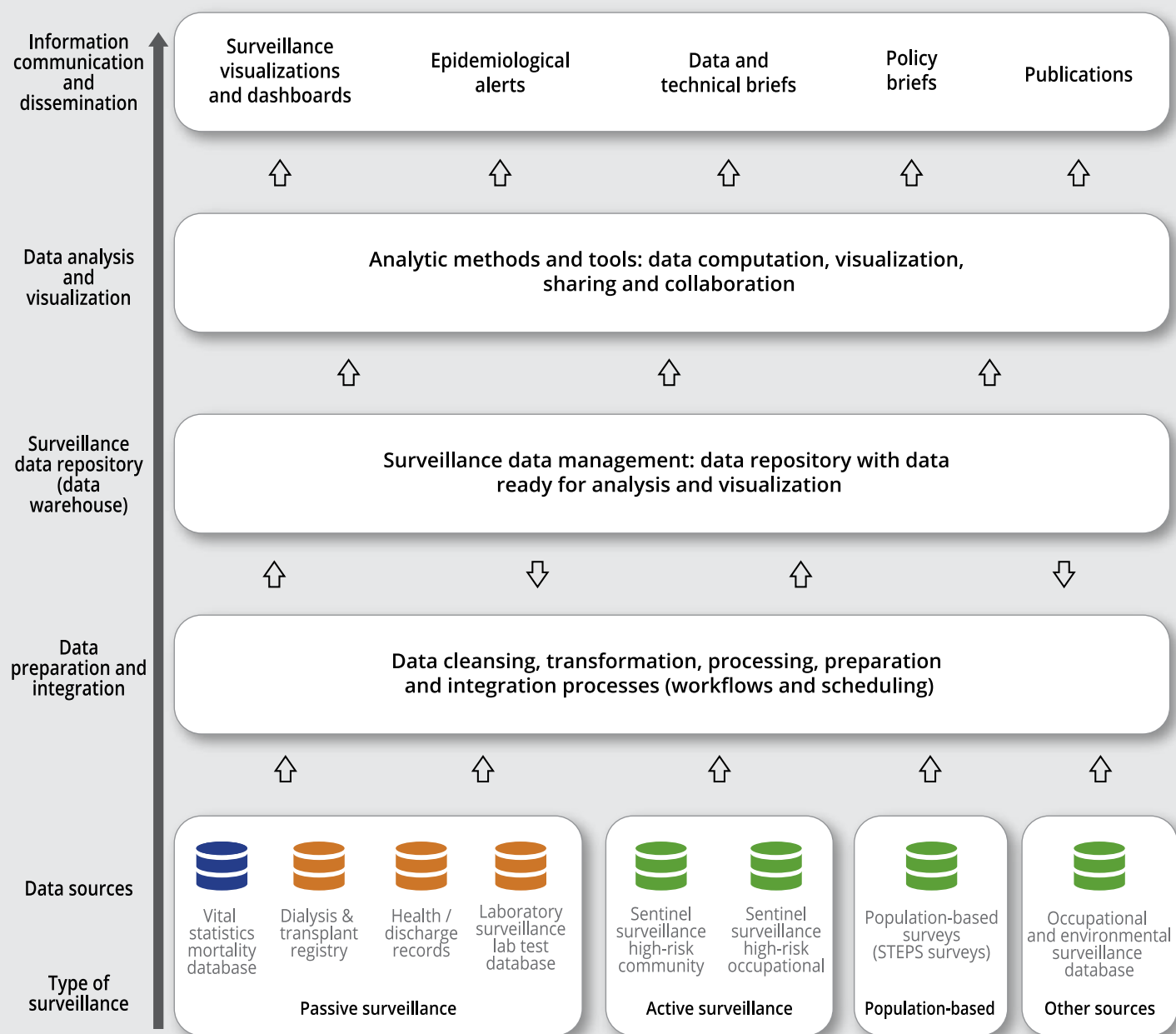
1. **Data Sources:** include the specification of data source from every surveillance component or subsystems, organized by type of surveillance.
2. **Data Preparation and Integration:** include the methods and tools for data cleansing, transformation, preparation, integration, and loading to the data repository.
3. **Surveillance Data Repository (Data Warehouse):** involves a database management system (DBMS) with methods, procedures, and tools for data storage, data querying, and database management.
4. **Data Analysis:** provides the tools and methods for data exploration and analysis; elaboration of data visualizations, dashboards, and reports; collaboration among team members; and content sharing.

5. **Communication and Dissemination:** include the methods, tools, and online applications to communicate and disseminate the information produced by the surveillance system to the audience.

A comprehensive data platform may not be available immediately; however, countries are encouraged to work towards building it. In the meantime, data to be collected for surveillance should be as minimal as possible, particularly active sentinel surveillance in communities and occupational groups. However, for passive surveillance, such as mortality analysis and community-based dialysis registries, many variables can be further examined by trained personnel using a standard protocol of analysis. Each component of the surveillance system has its own metric and will be able to produce a set of specific indicators useful for monitoring and evaluation (Table 2).



Figure 8. CKD/CKDnt surveillance system: framework for the information platform



**Table 2.** Recommended Key Metric for CKD and CKDnT Surveillance

Passive Surveillance		
Data sources: Mortality information systems/vital statistics		
Case definition: Death attributed to CKDnT (3)		
Core indicator: Mortality due to CKDnT (temporary code: U50.X)	$M_{\text{CKDnT}} = \frac{\text{CKDnT deaths}}{\text{Total population}} \times 100,000 \text{ pop}$	
Other indicators:		
■ Mortality rate due to CKD (ICD-10 codes: N17, N18, N19, N28.9)	$M_{\text{CKD}} = \frac{\text{CKD deaths from } N_i}{\text{Total population}} \times 100,000 \text{ pop}$	
■ Proportional mortality due to CKD (ICD-10 codes: N17, N18, N19, N28.9) Where $N_i$ is the underlying cause of deaths (N17,N18, N19, or N28.9)	$P_{\text{CKD}} = \frac{\text{CKD deaths from } N_i}{\text{Total deaths}} \times 100 \%$	
Data sources: Dialysis and transplant registries		
Case definitions:		
■ CKD case (KDIGO, 2)		
■ Confirmed case of clinical CKDnT (2)		
Core indicators:		
■ Incidence of CKD cases in renal replacement therapy (CKDrtrt)	$I_{\text{CKDrtrt}} = \frac{\text{New CKDrtrt cases}}{\text{Total population}} \times 1,000,000 \text{ pop}$	
■ Prevalence of CKD cases in renal replacement therapy	$P_{\text{CKDrtrt}} = \frac{\text{New +Old CKDrtrt cases}}{\text{Total population}} \times 1,000,000 \text{ pop}$	
■ Incidence of CKDnT cases in renal replacement therapy	$I_{\text{CKDnTrtrt}} = \frac{\text{New CKDnTrtrt cases}}{\text{Total population}} \times 1,000,000 \text{ pop}$	
■ Prevalence of CKDnT cases in renal replacement therapy	$P_{\text{CKDnTrtrt}} = \frac{\text{New +Old CKDnTrtrt cases}}{(\text{Total population})} \times 1,000,000 \text{ pop}$	
■ Proportion of CKD of unknown etiology (CKDu) among CKDrtrt	$Pr_{\text{CKDu}} = \frac{\text{CKDu cases}}{\text{CKDrtrt cases}} \times 100 \%$	
■ Proportion of CKDnT among CKDu in RRT	$Pr_{\text{CKDnT\_rrt}} = \frac{\text{CKDnT\_rrt cases}}{\text{CKDu\_rrt cases}} \times 100 \%$	
■ Proportion of CKDnT among CKD-RRT	$Pr_{\text{CKDnT\_rrt}} = \frac{\text{CKDnT\_rrt cases}}{\text{CKDrtrt cases}} \times 100 \%$	
Other indicators:		
■ Proportion of treatment modality (dialysis, hemodialysis, transplant) by CKD type (CKD, CKDnT)		
■ Survival rate at 1, 3, 5 year for CKD and CKDnT		
Data sources: Hospital discharges (linked or not to sentinel surveillance)		
Case definitions:		
■ CKD case (KDIGO, 2)		
■ A confirmed clinical case of CKDnT (2)		
Core indicators:		
■ Incidence of CKD cases which etiology is unknown (CKDu)	$I_{\text{CKDu}} = \frac{\text{CKDu cases}}{\text{CKD cases}} \times 100 \%$	
■ Incidence of CKD cases with CKDu confirmed as a clinical case of CKDnT	$I_{\text{CKDnT}} = \frac{\text{CKDnT cases}}{\text{CKDu cases}} \times 100 \%$	
Other indicator:		
Proportion of cases by clinical stages based on CKD definition (KDIGO)	$Pr_{\text{CKDnT\_s}} = \frac{\text{CKDnT cases in stages}}{\text{CKDnT cases}} \times 100 \%$	

Continued on next page

**Table 2.** Recommended Key Metric for CKD and CKDnT Surveillance (continued)

Active Surveillance		
Data sources: Sentinel communities (high/low risk for CKDnT) and workers groups		
Case definitions:		
■ Suspect case of CKDnT (1)		
■ Probable case of CKDnT (1)		
■ A confirmed clinical case of CKDnT (2)		
Core indicators:		
■ Incidence of CKD cases with unknown etiology (CKDu)		$I_{CKDu} = \frac{\text{CKDu cases}}{\text{Total population}} \times 100,000 \text{ pop}$
■ Incidence of CKD cases with unknown etiology confirmed as a clinical cases of CKDnT		$I_{CKDnT} = \frac{\text{CKDnT cases}}{\text{Total population}} \times 100,000 \text{ pop}$
Other indicators:		
■ Proportion of suspected cases of CKDnT who become probable cases of CKDnT		$Pr_{CKDnT\_pc} = \frac{\text{CKDnT probable cases}}{\text{CKDnT suspected cases}} \times 100\%$
■ Proportion of probable cases of CKDnT who become confirmed cases of CKDnT		$Pr_{CKDnT\_cc} = \frac{\text{CKDnT confirmed cases}}{\text{CKDnT probable cases}} \times 100\%$
Surveillance through Repeated Cross-sectional Surveys		
Data sources: Population-based surveys		
Case definition: CKD case (KDIGO, 1)		
Core indicator:		
■ Prevalence of CKD		$P_{CKD} = \frac{\text{CKD cases}}{\text{Sample population size}} \times 100\%$
Core indicators:		
■ Prevalence of clinical stages 1-5 by eGFR		$P_{CKD\_s} = \frac{\text{CKD cases in stages}}{\text{Sample population size}} \times 100\%$
Where s identifies the clinical stage, taking values 1, 2, 3, 4, and 5		
Note: Prevalence calculation from population-based surveys (cross-sectional studies) must be weighted.		
Note: All registrations should have sex, age-group, place of residence, and occupation recorded		

**LEGEND:**

<b>CKD</b>	Cases or deaths from chronic kidney diseases, cause coded as N17, N18, N19, or N28.9
<b>CKDu</b>	Cases of CKD of unknown etiology
<b>CKDnT</b>	Cases of CKD of nontraditional causes
<b>CKDrrt</b>	Cases of CKD in renal replacement therapy
<b>ICD-10</b>	International Statistical Classification of Diseases and Related Health Problems, 10th Revision
<b>KDIGO</b>	Kidney Disease Improving Global Outcomes Clinical Practice Guidelines

# METHODS FOR SURVEILLANCE

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# Passive Surveillance

## Mortality analysis

Mortality analysis, a good example of passive surveillance, is key for an understanding of this epidemic and its trends, distribution, and patterns. Mortality statistics can describe the epidemiological profile of the population using indicators such as general and cause-specific death rates and by examining their relationships with socioeconomic and other conditions.

It is fundamental to assess and monitor the quality of the data provided by mortality information systems. Three indicators can be used to assess the quality of registered deaths:

- 1) Proportion of under-registered deaths.
- 2) Proportion of deaths with underlying causes coded as ill-defined causes of death.
- 3) Proportion of garbage codes which represent those causes unsuitable for epidemiological analysis such as terminal causes of death or those complications that tend to hide the real underlying cause of death. Some examples are sepsis, respiratory failure, and dehydration. A proportion of 10% and lower indicates good quality of data.

Taking into account these three indicators, it is possible to broadly categorize the overall quality of death registration data.

## Data Quality

WHO has defined three broad categories of data quality among countries with at least 50% coverage of deaths:

- High-quality data: >90% completeness and ill-defined codes <10% of registrations;
- Medium-quality data: 70–90% completeness and ill-defined codes 10–20% of registrations; and
- Low-quality data: <70% completeness or ill-defined codes >20% of registrations (68).

In the case of medium- or low-quality data assessments for national vital statistics systems, WHO recommends the following steps to correct incompleteness and inadequacy in recorded deaths from these systems (69):

- 1) Deaths with unknown sex and ages should be corrected. Deaths with unknown sex should be redistributed pro-rata within known sex by stratum, and similarly deaths with unknown ages should be redistributed proportionally within known ages by strata.
- 2) The total number of registered deaths should be corrected to overcome under-registration of deaths.
- 3) Deaths with underlying causes coded to symptoms, signs, and ill-defined conditions should be redistributed proportionally to all non-injury causes of death.

The coverage of the mortality information system can be estimated by dividing the observed general mortality rate by strata of country, year, sex, and age group by the expected death rate in the same stratum based on a life table selected by country. Tabulated deaths by stratum should be corrected by dividing the number of registered deaths by the under-registration estimates. This correction should be applied under the assumption that missing deaths by stratum follow the same distribution of recorded deaths. Deaths with underlying causes coded to symptoms,

signs, and ill-defined conditions should be redistributed proportionally to all non-injury causes of death by stratum (country, year, sex, and age group), under the assumption that these deaths follow the same distribution as recorded deaths from well-defined non-injury causes, and that any deaths coded as an ill-defined condition are not actually due to an injury-related cause of death. Finally, in order to improve the overall quality of mortality data, efforts should be directed to improving countries' capacity to appropriately record the information.

## CKDnT mortality analysis.

The number of deaths with underlying cause of death coded as CKD-N18, a proxy for CKDnT, should be tabulated by country, year, sex, and 5-year age group (from 0–4 to 90–94 and 95+) from the time period of interest. Age-specific mortality rates, per 100,000 population, should be computed for deaths coded as CKD-N18—or where using a provisional ICD code, as recommended by PAHO (3), by country, year, age group, sex, and other variables. Age-standardized mortality rates should be obtained by the direct method of adjustment using the 2000–2015 WHO world standard population (69).

Analyses of frequency, distribution, and trend should be routinely conducted. It is recommended that trend analyses use average annual percent change (AAPC), with calculations, in the case of age-standardized mortality rates, employing software such as the U.S. National Cancer Institute's Joinpoint Trend Analysis (70) or ad-hoc estimation using ordinary least squares regression of the natural log of death rate on year (exponential regression model) [ $\ln(\text{rate}) = \alpha + \beta \times \text{year}$ ]. The rate of AAPC for each country should be derived from the coefficient ( $\beta$ ) (overall and stratified by sex) for the time period of interest, using the formula  $\text{AAPC} = [\text{EXP}(\beta) - 1] \times 100$ .

To improve the identification of CKDnT-related deaths it is also useful to apply a multiple causes of death analysis, used in the analysis of death from NCDs, to complement and enhance more routine analyses of underlying cause of death. It is necessary to register not only the underlying cause of death but also the intervening or contributory causes recorded in the death certificate. WHO recommends that all countries use the WHO death certificate and record all causes at every stage of data management; collection, coding, capturing, and processing.

## Registries

Kidney disease registries, such as registries of dialysis and transplantation, play a vital role in public policy as public health surveillance elements. Registries provide a standardized method to collect data on disease burden, treatment, and outcomes, and they monitor time trends (71).

Registries should be organic, living organisms, with their content, structure, and purposes constantly maturing. They should be simple to use in terms of data entry and extraction, and have options for performing these functions with mobile devices. Storage should ultimately be electronic and confidentiality of data maintained regardless of storage type.

Registries can be based in institutions, communities, regions, states, and countries. There should be sufficient commonalities among condition-specific registries in different jurisdictions that data can be shared, linked, and compared.

**Population-based dialysis and transplant registries (4).** The Latin American Registry for Dialysis and Transplantation (RLADTR, acronym in Spanish) is an example of a population-based registry coordinat-

ed by the Latin American Society of Nephrology and Hypertension (SLANH, acronym in Spanish) with more than 20 years of systematic collection of data for most national registries of Latin American countries. To be useful for surveillance and health planning, a national Dialysis and Transplantation Registry should contain enough quality data to achieve the minimum objective of notifying annually the following indicators outlined in Tables 3 and 4.

Considering that CKD patients may receive various forms of treatment throughout their course and may change dialysis or transplant center, it is recommended that data collection be global (include all modalities) and compulsory, using unique patient identifiers. Table 4 shows the minimum set of variables that should be recorded for each patient (4).

There are few CKD registries worldwide. CKD surveillance is one of the three pillars of the restructured research support program of the International Society of Nephrology. CKD-iNet, the global CKD surveillance network, is a central surveillance program (72). A Latin American member will be an important addition to the CKD-iNet alliance.

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### National renal dialysis and transplant registries in Latin America: How to build and improve them (4)

María Carlota González-Bedat (1), Guillermo Javier Rosa-Díez (1), Juan Manuel Fernández-Cean (1), Pedro Ordunez (2), Alejandro Ferreiro (1), and Walter Douthat (1).

*Representing (1) the Latin American Society of Nephrology and Hypertension (SLANH)/, the Latin American Renal Dialysis and Transplant Registry, (2) Department of Non-Communicable Diseases and Mental Health, Pan American Health Organization.*

**Table 3.** Set of minimal variables per patient for a national registry of dialysis and transplant

Personal data	Renal replacement therapy modality	Situation by December 31st
Gender	Hemodialysis	Alive
Ethnic group	Peritoneal dialysis	Discharged
Date of birth	Transplant	Cause of discharge: death, abandoned, medical indication, functional recovery, left the country
Place of birth		Date of discharge
Date of admission to renal replacement therapy		If patient died: cause of death
Cause of admission (etiology)		
Current address		
Health insurance coverage (public, private, none)		

**Table 4.** Minimum indicators for a dialysis and renal transplant registry

Indicator	Definition	Formula
Prevalence	Quotient between the number of total patients and the country population (expressed per million). The precise prevalence refers to the number of patients alive by December 31st of the corresponding year.	Number of patients alive by December 31st/ country population (expressed in millions)
Incidence rate	Quotient of number of new patients and the country population (expressed per million).	Number of new patients/ country population (expressed in millions)
Mortality rate	Ratio between the number of deaths and the number of patients exposed to risk during the year or the total time of exposure to the risk of the patients in the year.	(100 X number of deaths)/number of patients treated during the year or sum of years of exposure to the risk of all patients treated during the year

## Active Surveillance

Establishing a feasible method for surveillance will be essential for an accurate assessment of the magnitude of the problem—including countries or regions where the epidemic is hidden as a result of insufficiently accurate and agile passive surveillance mechanisms (e.g., poor-quality mortality statistics,

lack of dialysis registries, among others). Active surveillance systems, ethically sound and providing a guarantee of medical follow-up, will be important to compare across regions, to allocate resources, assess trends over time, and provide a basis for studies trying to identify the causes of this multifactorial epidemic.



## Surveillance of high-risk communities

Approaches based on surveillance of high-risk scenarios have the potential to be testing grounds for feasibility as well as to increase understanding of the magnitude and solutions for the epidemic in these particular settings. The inclusion of one or more “control” (i.e., “low-risk”) communities in a “sentinel surveillance” system could be useful for comparisons: these might include communities where electronic hospital records are available. An acceptable population-based alternative is to conduct surveillance in communities selected as representative of different areas within the country. In the selection process, countries should take into account the social determinants of health approach including socioeconomic characteristics (emphasizing the existence of very poor or deprived groups), age distribution, and the local relevance of CKD/CKDnT. The number of communities on which to start surveillance should be left up to each country: some may wish to start on only one community; others may wish to begin with two or more diverse communities. The definition of “community” should also be flexible.

## Laboratory surveillance

Surveillance of CKD markers through regional laboratories can be useful (73, 74). For instance, surveillance of eGFR can begin with review of all creatinine results from a given community, region, or hospital over a recent time period. It can identify previously unsuspected cases, point to communities and regions with high rates of decreased kidney function, and reveal trends over recent years.



Central to a diagnosis of CKDnT currently is an eGFR  $<60$  mL/min/1.73 m<sup>2</sup>. An eGFR estimate is based on a serum creatinine measurement, which is available in most places, usually at a reasonable price, with assays increasingly being standardized around the globe. Despite many limitations to the serum creatinine measurement and its interpretations, creatinine-derived estimates of renal function are very useful. They will provide plenty of suspected and confirmed cases of CKDnT on which to begin surveillance and plan more focused studies. Surveillance of albuminuria is also useful, as increases generally represent deterioration of kidney function. However, proteinuria and albuminuria are not usually markers of early CKDnT. Inspection of urine analyses is potentially useful, and urine sediment abnormalities are sometimes the earliest markers of CKDnT.

## Population-based Surveys

Surveillance in the general population might be conducted through repeated cross-sectional surveys every 3–5 years. Methods recommended by the WHO/PAHO STEPwise approach to NCD risk factor surveillance (STEPS) could be used (75). A CKD module could be added to the STEPS questionnaire already validated in most countries of the region, to include some markers of CKD to explore the prevalence of CKD.

Alternatively, another model may be the Chronic Kidney Disease Surveillance Project of the National Health and Nutrition Examination Survey of the United States (NHANES). The NHANES is a nationally representative, cross-sectional survey that is currently conducted every 2 years by the U.S. National Center for Health Statistics to examine disease prevalence and trends over time with standardized in-home interviews and a physical examination with blood and urine collected at a mobile examination center. For CKD Surveillance Project serum creatinine, albuminuria defined by an albumin-to-creatinine ratio  $>30$  mg/g was utilized as an indicator. Information should be evaluated carefully because it is an estimate of CKD through a proxy (76).

Similarly, at time of press, a newly published proposal is being launched to promote an international collaboration that intends to yield standardized estimates of the distribution of eGFR, and hence the prevalence of reduced renal function: the Disadvantaged Populations eGFR Epidemiology Study (DEGREE). The basic proposal is a simple standardized protocol to estimate the distribution of GFR in low-and-middle-income countries, involving the quantification of renal function in a representative adult population-based sample and a requirement

for standardization of serum creatinine measurements, along with storage of samples for future measurements of cystatin C and ascertainment of estimates of body composition in order to obtain valid comparisons of estimated GFR (eGFR) within and between populations (77).

## Occupational and environmental surveillance

Considering the strong occupational character of CKDnT, occupational surveillance should be included in the surveillance system. This type of surveillance should at least include monitoring of occupational and environmental characteristics, trends, risk factors, and determinants that aggravate or contribute to this epidemic. Surveillance activities or mechanisms could also be designed along the continuum of actions in the agrochemical supply chain, from importation, storage, and distribution to application and disposal activities. Due to the specificity of this type of surveillance, a separate document will be produced in the future.

Environmental health surveillance is the systematic, ongoing collection, integration, analysis, and interpretation of data about environmental hazards, exposure to environmental hazards, and health effects potentially related to exposure to environmental hazards in order to prevent and monitor disease (78). Due to the ample domains of environmental surveillance which include monitoring soil, air, and water, as well as the vast number of chemicals and toxins, there are inherent challenges in implementing environmental surveillance which require specialized treatment beyond the scope of this document.

## Conclusion

Evidently, the operationalization of the surveillance options presented throughout this section requires many efforts and much more detailing of the actual “nuts and bolts” of the processes. This framework surveillance document is solely a precursor to several other documents that will expand on noted topics. It is also important to highlight that many of the preventable chronic diseases are related to one another, like metabolic syndrome, obesity, diabetes, cardiovascular disease, hypertension, CKD, and even chronic lung disease, and that they share risk factors. The ultimate ideal should be an integrated approach to surveillance of all common, prevent-

able conditions of significant social, health, or economic impact. The ability to link to other data sets is desirable, such as registers of birth weights, congenital birth defects, infant growth charts, immunization records, population health screens, other clinical records, diabetes registries, hospital data sets, deaths, and dialysis and transplant registries. One aspiration is that clinical surveillance should ultimately be embedded in routine data collected through an integrated electronic whole-of-life medical record. Such a record could ultimately be co-held by the participant. Although each country may be at a different stage in progression towards these aspirational goals, we can work together within regions to achieve them collectively.

# WAY FORWARD

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The foregoing discussions help frame strategic approaches to CKD/CKDnT surveillance. Surveillance systems using the menu options provided here can shed light on several indicators of CKD and the CKDnT epidemic including prevalence, incidence, distribution, severity, risk factors, and their course under a variety of conditions, range of outcomes, and trends over time. The results from surveillance activities can identify affected individuals, who might benefit from risk factor reduction or treatment or at least be moved out of a noxious environment.

Robust surveillance systems are also critical for collaboration and much will be learned from working with other regions and countries. This includes communications with regional and local governments, regulatory agencies, workers' advocacy groups, and

scientific bodies and health care providers. While being mindful of differences in context, surveillance systems will be useful to compare demographic and clinical features, diet, water sources and water quality, working conditions, energy expenditures, hydration, and environmental exposures, as well as histologic features of kidneys where biopsies or autopsies have been done.

In the future, systematic approaches to biomarker studies seem wise. Improving knowledge of pre-terminal disease and of AKI/CKD interactions are critical. We need to better understand the potential to arrest or retard kidney damage and progression towards renal failure, and the possibility of some renal functional recovery.





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Finally, multi-level interventions aligned with the social determinants of health and workers' health approaches are needed to address the complexity of this epidemic. The "health in all policies" approach should be adopted by governments and inter-sectoral work among health care, industry, and labor sectors needs to be prioritized for a cohesive response to this epidemic. All countries need access to high-quality affordable health service and medicines in the context of the human right to universal health care access. In the work context, better working conditions, such as rest, shade and rehydration, ergonomic efficiencies, rotation of tasks, reassignment to less demanding work, education, and better individual protection equipment, among others, can lessen risk of incidence or progression

of CKDnT and improve health in general, potentially without decreasing productivity. Employers and industry might be willing to participate in such programs. Similarly, proper agrochemical regulation and environmental control may substantially reduce disease appearance or progression with an enormous impact for public health, in general. Hence, they must be implemented, regardless of theories or understanding of causation or mechanisms. The broader issues of multiplicity of causes and the precise nature of other inciting factors can be pursued through public health research programs. However, systematic surveillance needs to be implemented now. Most importantly, it should be carried out with speed and urgency to match the gravity of this epidemic and the human suffering it is causing.

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