THE LANCET

International Society of Nephrology's 0by25 initiative for acute kidney injury (zero preventable deaths by 2025): a human rights case for nephrology

Ravindra L Mehta, Jorge Cerdá*, Emmanuel A Burdmann*, Marcello Tonelli*, Guillermo García-García, Vivekanand Jha, Paweena Susantitaphong, Michael Rocco, Raymond Vanholder, Mehmet Sukru Sever, Dinna Cruz, Bertrand Jaber, Norbert H Lameire, Raúl Lombardi, Andrew Lewington, John Feehally, Fredric Finkelstein, Nathan Levin , Neesh Pannu, Bernadette Thomas, Eliah Aronoff-Spencer, Giuseppe Remuzzi*

Lancet 2015; 385: 2616–43

Published **Online** March 13, 2015 http://dx.doi.org/10.1016/S0140-6736(15)60126-X

See **Comment** page 2551

*Joint first authors

Department of Medicine, University of California San Diego, San Diego, CA, USA (Prof R L Mehta MD, D Cruz MD, E Aronoff-Spencer MD); **Division of Nephrology, Department of Medicine, Albany Medical College, Albany, NY, USA** (Prof J Cerdá MD); **LIM 12, Division of Nephrology, University of Sao Paulo Medical School, São Paulo, Brazil** (Prof E A Burdmann MD); **University of Calgary, Calgary, AB, Canada** (Prof M Tonelli MD); **Nephrology Service, Hospital Civil de Guadalajara, University of Guadalajara Health Sciences Center, Guadalajara, Jalisco, Mexico** (Prof G García-García MD); **The George Institute for Global Health, University of Oxford, Oxford, UK** (Prof V Jha MD); **Division of Nephrology, Department of Medicine, King Chulalongkorn Memorial Hospital, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand** (P Susantitaphong MD); **Tufts University School of Medicine, Boston, MA, USA** (P Susantitaphong, Prof B Jaber MD); **Department of**

Executive summary

Acute kidney injury (AKI) is a major contributor to poor patient outcomes. AKI occurs in about 13·3 million people per year, 85% of whom live in the developing world, and, although no direct link between AKI and death has yet been shown, AKI is thought to contribute to about 1·7 million deaths every year.[1] The course of AKI varies with the setting in which it occurs, and the severity and duration of AKI affects outcomes such as dialysis requirement, renal functional recovery, and survival. Recognition is increasing for the effect of AKI on patients, and the resulting societal burden from its long-term effects, including development of chronic kidney disease and end-stage renal disease needing dialysis or transplantation.[2]

Few systematic efforts to manage (prevent, diagnose, and treat) AKI have been put in place and few resources have been allocated to inform health-care professionals and the public of the importance of AKI as a preventable and treatable disease. Several factors have contributed to the paucity of information. Most importantly, there have been few population-level epidemiological studies in several regions of the world. Difficulties in definition of the incidence of AKI are especially evident in searches for data from low-income and middle-income countries, where more than 85% of the world's population resides. No nationwide data collection systems are available, and data are usually from isolated centres and probably largely underestimate the true extent of AKI because they mostly do not include patients with AKI who were not able to reach a hospital for treatment. A recent meta-analysis that included 312 cohort studies and more than 49 million patients shows a scarcity of data from Africa and large parts of southeast Asia.[3] We did an updated meta-analysis that used the most recent KDIGO (Kidney Disease: Improving Global Outcomes) definitions, which confirms the high incidence and resulting outcomes of AKI, particularly in Africa, Asia, and Latin America, for which data were previously absent. The strong relation between the severity of AKI and consequent mortality is reiterated by our findings and is evident across heterogeneous populations and specific disease cohorts. However, large gaps remain in knowledge about the factors that affect the geographical variation of AKI and poor outcomes. Many differences exist in the aetiology, pathophysiology, and management of AKI across the world. In high-income countries, AKI develops mainly in patients in hospitals. In low-income and middle-income countries, AKI occurs mainly in the community setting in acute illness, usually in association with diarrhoeal states and dehydration, infections such as malaria, and toxins (venoms and poisons). Public health issues (eg, contaminated water, poor sanitation, endemic infections such as malaria and dengue fever, venomous snakes, and toxic traditional medicines) and socioeconomic factors (eg, availability of health-care facilities) affect the epidemiology of AKI. Additionally availability of trained personnel and access to diagnostic tests and dialysis affect practice patterns and impose barriers to care. The extent to which these factors contribute to mortality and non-recovery of renal function has not been quantified.

AKI is potentially preventable and treatable with timely intervention, but there continues to be a high human burden. Which specific factors account for the poor outcomes and to what extent variations in care delivery contribute are unclear. The ability to provide lifesaving treatments for AKI provides a compelling argument to consider therapy for AKI as much of a basic right as it is to give antiretroviral drugs to treat HIV in low-resource regions, especially because care needs only be given for a

short period of time in most patients. These convictions have prompted the International Society of Nephrology (ISN) to put forth the human rights case statement of 0by25—ie, no one should be dying of untreated acute kidney injury in low-resource regions by 2025. ISN's 0by25 initiative aims to eliminate preventable deaths from AKI by 2025 by calling for global strategies that permit timely diagnosis and treatment of potentially reversible AKI for patients and has a particular emphasis of people in lower-income and middle-income countries. The initiative uses a three pronged strategy to address these issues: obtain existing and prospective data to establish AKI as a contributor to the global burden of health loss; raise awareness of AKI in the worldwide community to reduce variations in management; and develop a sustainable infrastructure to enable needs-based approaches for education and training and care delivery, together with studies of appropriate, well thought out interventions and measurable outcomes. In this Commission, we outline a systematic approach to develop the 0by25 initiative by focusing on building the evidence base, creating methods to raise awareness, and standardise AKI management and provide specific measures to monitor progress worldwide.

To provide an evidence base to support this initiative, we have done a meta-analysis to collate and evaluate existing publications and have launched the prospective cohort Global Snapshot of AKI and a subsequent longitudinal AKI cohort study in some centres in lower-income and middle-income counties. As a part of the 0by25 initiative, the ISN has partnered with the Institute of Health Metrics and Evaluation, which coordinates the Global Burden of Disease (GBD) study at the University of Washington in Seattle (WA, USA).[4] AKI will be included in the forthcoming GBD 2014 report (to be published in 2015) and in annual updates thereafter.

To raise awareness of AKI and the 0by25 initiative, we propose a comprehensive approach for the education and training of health-care personnel, general public, and policy makers. Key to this approach is the delineation of AKI under the 5 Rs—risk assessment, recognition, response, renal support, and rehabilitation.[1] These represent the core elements that are required for effective management of AKI and can be used to develop methods to disseminate information, improve knowledge, and facilitate advocacy efforts (figure 1). We anticipate that our use of the 5 Rs in the 0by25 initiative will streamline efforts to establish a formal programme for the prevention and treatment of AKI in low-resource settings.

We have also provided a framework to create a sustainable infrastructure for this initiative. Key elements of our approach include efforts to: increase awareness among decision makers and civil society; focus on horizontal and vertical integration with existing initiatives; build material and human capacity; develop new technologies for the prevention, diagnosis, and treatment of AKI in low-resource settings; and establish and implement an AKI scorecard to foster collaboration and hold governments to account. We propose a focused effort over the next decade to dramatically curtail AKI-associated mortality and to improve health outcomes worldwide, especially in low-resource settings. Partnerships are needed with governments to help them eliminate disparities in access to, and affordability of, health care. This cooperation will require broader vision about how the public and private sector can work together; a greater emphasis on provision and funding of primary care services; and strategies to ensure that all citizens, including poor people, have reliable and affordable access to lifesaving care. Through this multifaceted approach, ISN's 0by25 programme will offer a unique opportunity to tackle the burden of AKI, especially in resource-poor regions, and eventually save many lives.

We recognise that this ambitious initiative will need to address several challenges, including funding for a sustainable effort, implementation of change in low-income areas without competing for scarce health-care resources, and development of viable strategies to support patients who remain dialysis-dependent after AKI. We are confident that these challenges can be met with robust systematic interventions that use existing infrastructure, advances in technology, and human resources across different regions. To this purpose, as a key part of the 0by25 initiative, the ISN has planned to work with Richard Horton, Editor of *The Lancet*, who stressed the need to gather information on an appraisal of nephrology services globally, country by country, detailing the unmet needs of patients around the world. Our ultimate goal is to collect epidemiological data about AKI, its risk factors, management, and outcomes, especially in low-income and middle-income countries, eventually devising recommendations and messages to politicians. We anticipate ongoing projects that provide measurable outcomes within 2–3 year cycles.

Introduction

Acute kidney injury (AKI) is a common disorder worldwide and is associated with high morbidity, mortality, and cost.[5,6] With use of the KDIGO[7,8] (Kidney Disease: Improving Global Outcomes) definition (table 1), one in five adults and one in three children worldwide have AKI during a hospital admission,[3] but the reported incidence of AKI strongly depends on the sampled population.[9] Reports from high-income countries are heavily weighted towards patients in intensive-care units (ICU), where incidence and severity are very high. Reports that include populations with less severe disease describe a lower incidence and variable morbidity and mortality rates. Although 85% of the world's population lives in low-income and middle-income countries (LMICs), systematic prospective studies from those regions are limited by problems with

Internal Medicine, Section of Nephrology, Wake Forest School of Medicine, Winston-Salem, NC, USA (Prof M Rocco MD); **Nephrology Section, Department of Internal Medicine, University Hospital, Ghent, Belgium** (Prof R Vanholder MD, Prof N H Lameire MD); **Department of Nephrology, Istanbul School of Medicine, Istanbul University, Mehmet, Turkey** (Prof M S Sever MD); **St Elizabeth's Medical Center, Boston, MA, USA** (Prof B Jaber); **Department of Critical Care Medicine, SMI, Montevideo, Uruguay** (Prof R Lombardi MD); **Department of Nephrology, Leeds Teaching Hospitals, Leeds, UK** (A Lewington MD); **University of Leicester, Leicester, UK** (Prof J Feehally MD); **Yale University, New Haven, CT, USA** (Prof F Finkelstein MD); **Renal Research Institute, New York, NY, USA** (Prof N Levin MD); **University of Alberta, Edmonton, AB, Canada** (N Pannu MD); **Division of Nephrology, Department of Medicine, University of Washington, Seattle, WA, USA** (B Thomas MD); **IRCCS-Istituto di Ricerche Farmacologiche Mario Negri, Bergamo, Italy** (Prof G Remuzzi MD); **and Department of Medicine, Unit of Nephrology, Dialysis and Transplantation, Azienda Ospedaliera Papa Giovanni XXIII, Bergamo, Italy** (Prof G Remuzzi)

Correspondence to: Prof Ravindra L Mehta, Department of Medicine, University of California San Diego Medical Center, San Diego, CA 92103, USA
rmehta@ucsd.edu

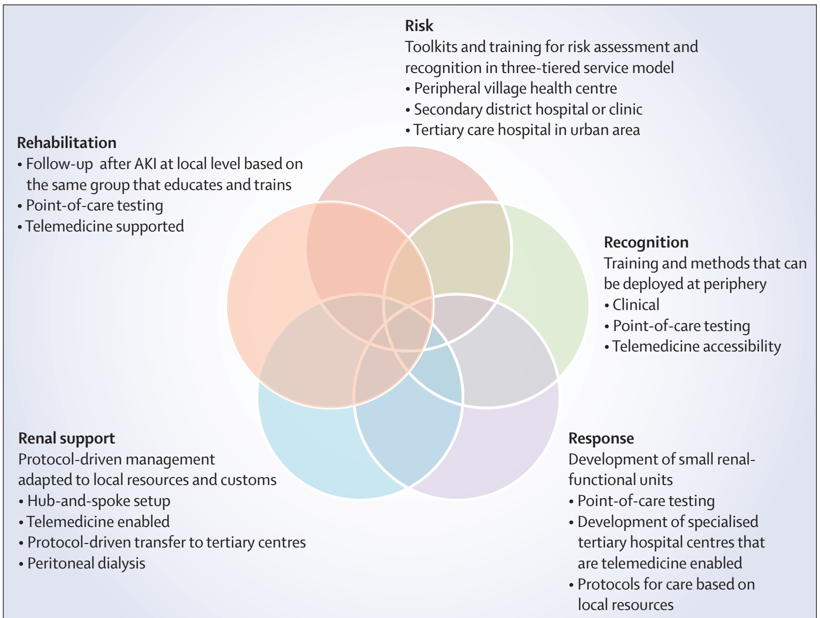

***Figure 1:* International Society for Nephrology's 0by25 initiative: key elements for a sustainable infrastructure to support AKI care based on the 5 Rs**
This framework will be adapted for different regions of the world to account for differences in available resources and infrastructure. AKI=acute kidney injury.

	Creatinine*	Urine output
Stage 1	Rise of ≥26 μmol/L within 48 h or 50–99% rise from baseline within 7 days†	<0·5 mL/kg per h for more than 6 h
Stage 2	100–199% rise from baseline within 7 days†	<0·5 mL/kg per h for more than 12 h
Stage 3	≥200% rise from baseline within 7 days†; or concentration ≥354 μmol/L, with either: rise of ≥26 μmol/L within 48 h or ≥50% rise from baseline within 7 days†; or any requirement for renal replacement therapy	<0·3 mL/kg per h for 24 h or anuria for 12 h

The initial diagnosis or detection of acute kidney injury is based on a patient meeting any of the criteria for stage 1. Staging is carried out retrospectively when the episode is complete. Patients are classified according to the highest possible stage where the criterion is met, either by creatinine rise or by urine output. KDIGO=Kidney Disease Improving Global Outcomes. *SI units rounded to the nearest integer. †Where the rise is known (based on a previous blood test) or presumed (based on the patient history) to have occurred within 7 days.

***Table 1:* The KDIGO classification system[8]**

communication between centres and absence of mechanisms to collect accurate data.[10–13] In several epidemiological studies, increasing severity of AKI is associated with a higher risk of death in patients in both hospital and community settings.[3,14,15] AKI is recognised as an important risk factor for non-recovery of kidney function, incident chronic kidney disease (CKD), and accelerated progression to end-stage renal disease (ESRD), leading to poor quality of life, disability, and high long-term costs.[16–18] Patients with AKI have about a nine-times higher risk of CKD and a two-times higher risk of premature death than do matched patients without AKI.[18] These elements add to the large economic consequences for AKI, as findings of an English study recently showed.[19] The estimated annual cost of AKI care for inpatients was US\$1·72 billion (£1·14 million), slightly more than 1% of the National Health Service (NHS) budget. The lifetime cost of caring for patients with AKI after hospital discharge was \$286 million (£190 million) in 2010–11.[19]

Deaths associated with AKI occur in all countries, but most avoidable deaths occur in LMICs where access to care is poor and children, young adults, and women, are particularly susceptible and are vulnerable to death.[10,11,20] Many cases of AKI lead to death because of build-up of fluid, electrolytes, and toxins, which can be managed with dialysis. However, dialysis is not available for most people in LMICs because universal coverage by national health systems is often absent, and in the lowest-income countries, no care facilities are available to anyone. Absence of infrastructure and resources to diagnose and treat AKI and its complications is a key problem in LMICs. So too are the scarcity of adequately educated health workers and physicians; inadequate diagnostic equipment; long distances and poor transportation hampering access to hospitals; and few hospital resources. However, if managed adequately and in a timely fashion, most cases of AKI are treatable and often reversible.[9]

Another factor in the burden of AKI is poor general knowledge about the role of the kidney in health and the absence of recognition that it is as essential as the brain and heart. Public knowledge of kidney disease is generally linked to CKD from diabetes and hypertension, and its need for chronic dialysis. Risk factors for AKI are not widely known; neither are the facts that it is preventable and treatable with a high likelihood of recovery. AKI is usually first encountered by non-specialised health-care providers, either in communities or hospitals. Since AKI is not associated with any specific symptoms and diagnosis is largely based on measurement of laboratory measurements, it is often unrecognised. Caregivers might not be equipped with the knowledge for early recognition, timely intervention, and effective follow-up. Accordingly, key opportunities to prevent and treat AKI are lost and result in disability and substantial loss of life.

Even when adequate resources are available and accessible, the management of AKI is highly variable. Available guidelines for AKI management are not universally applied and vary by region.[21–25] A key issue is follow-up of patients after AKI. Findings of studies from the USA[26] and the UK[27] show that within 1 year, only 60% of patients are seen by any physician and only 10–15% by a nephrologist, even though involvement by nephrologists improves recovery rates. In low-resource regions, large proportions of the population live in rural areas, remote from tertiary hospital centres with renal units or facilities that are confined to the larger urban centres. This means that major barriers exist for the management and follow-up of patients diagnosed with AKI, leading to increases in morbidity and mortality. Due to the paucity of renal specialists in LMICs, and to the absence of motivation of nephrologists to move to remote rural areas, it is unlikely that these areas will have local access to specialised nephrology care in the foreseeable future.[28]

The main goal of the 0by25 initiative from the International Society of Nephrology (ISN) is to eliminate (or at least reduce) avoidable AKI-related death worldwide by 2025. Two considerations are fundamental to implementation of this initiative: a clear definition of a preventable death from AKI, and a strategy to regionalise any recommendations for AKI care in terms of health-care infrastructure, socioeconomic conditions, and education and training. Generally, preventable deaths from AKI occur at three levels. First, deaths that occur secondary to public health issues such as unclean water and diarrhoea, endemic infections (eg, leptospirosis), and environmental exposures (eg, snakebites)—all of which are complicated by AKI. Second, deaths that occur from absent or delayed recognition of AKI because of inaccesibility of laboratory studies, inadequate response to diagnosis of AKI, or iatrogenic factors that cause additional insults to a failing kidney such as use of non-steroidal anti-inflammatory drugs (NSAIDs), nephrotoxic antibiotics, and exposure to contrast agents. Third, deaths due to the absence of dialysis support to treat life-threatening hyperkalemia, fluid overload, and acidosis.

Documentation of the burden of AKI and the factors that affect AKI-related outcomes in different resource settings is crucial to design and implement initiatives to reduce AKI-related mortality and morbidity. A strategy to reduce the burden of AKI would need to be based on identification of people at risk, implementation of primary and secondary preventive actions, and application of specialised diagnostic methods for prompt treatment of AKI and timely referral for specialist care if needed, in the context of an organised system for the delivery of dialysis. This strategy must be followed by high-quality outpatient care for patients who survive AKI in view of the association of previous injury with long-term development of CKD, need for dialysis or kidney transplantation, cardiovascular disease, and early death.[29,30] Finally, educational and training methods to raise awareness and standardise care of AKI are essential since a nephrologist is not always available to guide prevention and early treatment of AKI,[31] even in developed countries, but especially for patients with a low income.

For the **0by25 website** see www.0by25.org

Because each of these instances needs specific approaches that consider the available resources and infrastructure, we have classified countries into three levels to reflect differences (table 2). We believe that this categorisation establishes a basic framework to assess the epidemiology and management of AKI in comparable regions and to prioritise and tailor the 0by25 interventions. Over time, progress within each specific country could be tracked and benchmarked across levels.

Aim one: establish the burden of AKI

AKI definitions and epidemiological reports

For the past 10 years, AKI has been defined in epidemiological studies through the use of either diagnostic codes (such as International Classification of Diseases [ICD]-9 codes) in national databases, or by defined changes in kidney function such as change in serum creatinine and change in urine output (RIFLE [Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease],[7] AKIN [Acute Kidney Injury Network],[32] and KDIGO[8] criteria; table 1). Whereas in high-income countries, the use of national databases is widespread;[33–35] no comparable databases exist in LMICs, where the use of diagnostic codes is rare or non-existent.[10] Moreover, use of diagnostic codes is thought by some to be inaccurate, for reasons including that they have a lower sensitivity than KDIGO criteria, which might be a source of bias, and can have inaccurate coding.[34,36] In this report, we have focused on studies from 2004 onwards that define AKI on the basis of the RIFLE, AKIN, and KDIGO criteria, because they allow a more accurate ascertainment of the incidence and outcomes of AKI in high-income countries and LMICs. For discussion of our expanded meta-analysis completed for this Commission

	Preventable deaths due to AKI	Health-care system development and accessibility	Dialysis and nephrology services	Implications for 0by25
Level 1	Countries with low incidence of preventable deaths due to AKI	Universal access to goods and services and well developed health-care systems	Most citizens have widely available universal access to dialysis and nephrology services across the country	Generally those countries do not require external assistance for new programmes; internal resources can be leveraged for 0by25
Level 2	Countries with a substantial number of preventable deaths due to AKI	Variable access to goods and services to citizens; health-care systems in various stages of development and accessibility	Dialysis programmes available but with unequal distribution within country; no universal dialysis programmes or nephrology care	These countries would potentially benefit from 0by25 support but some existing resources can be leveraged
Level 3	Countries where most patients who die from AKI die because of insufficient health care	Countries with poor access to goods and services; poorly developed health-care systems	No established dialysis programmes and poor or no access to dialysis or nephrology services to most citizens	These countries might need intervention and provision of resources by 0by25 teams

Universal is defined by services available to everyone. AKI=acute kidney injury.

Table 2: **Country level classifications for 0by25 initiative**

we used KDIGO[8] or a KDIGO-equivalent definition as an inclusion criterion. However, for other studies discussed we used less accurate and more heterogeneous criteria because these data were often the only type available.

As of early 2010, more than 1 million children and adults from the USA, Europe, and Australia have been evaluated with RIFLE, AKIN, and KDIGO criteria in different settings.[37–48] Epidemiological studies of AKI in high-income countries that used RIFLE definitions in ICU patients (reviewed by Hoste and De Corte[48]) show that up to two thirds of ICU patients developed AKI and 4–5% were treated with renal replacement therapy (RRT). The population incidence of less severe AKI was 2000–3000 per 1 million population per year; 200–300 per 1 million population per year had AKI treated with RRT. A 2014 study[46] of a retrospective cohort in the USA of 31 970 hospital admissions showed a rate of 16% of people with use of RIFLE, 17% with use of AKIN, and 18% with use of KDIGO; most patients had KDIGO stage 1 AKI (71%). In this large, single-centre study, one of every six hospital admissions was complicated by AKI. Incidence was highest in patients with sepsis, critical care illness, and cardiovascular surgery. Common findings in all of these studies are the strong associations of AKI with an increased risk of short-term and long-term mortality, which correlates with the stage of AKI. Additionally, AKI has been associated with a higher risk of incident CKD and progression to ESRD and increased resource use across various settings.[2]

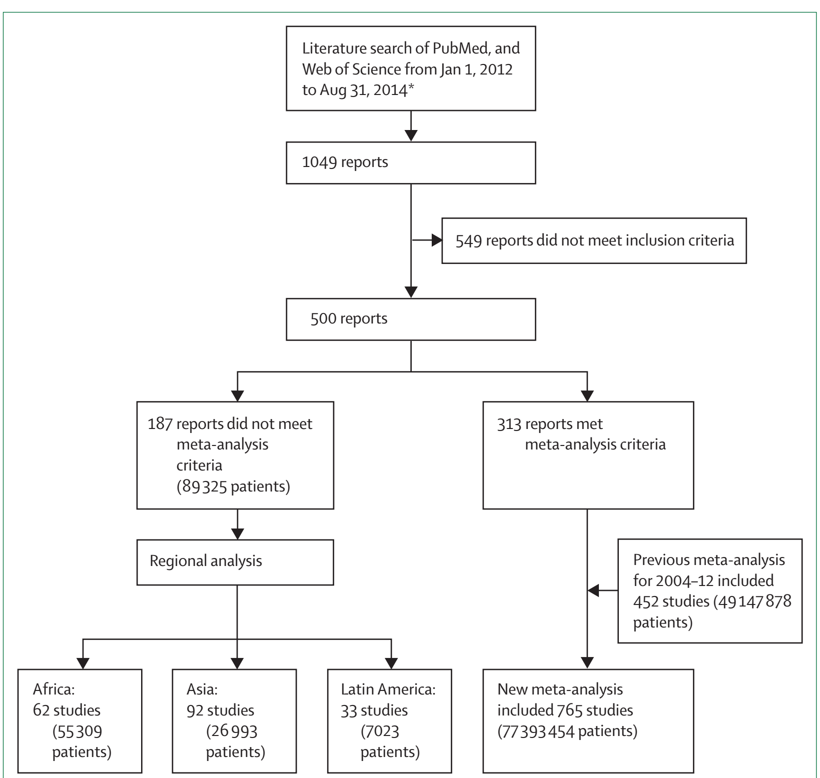

Figure 2: **Description of methods for our meta-analysis**
*Search terms used were identical to Susantitaphong and colleagues.[3] Relevant papers that did not meet the meta-analysis criteria (187 studies, 89 325 patients) were analysed separately and reported by region in table 3.

Recent trends show that the incidence of AKI is increasing. In a large integrated health system in Northern California that used change in serum creatinine as a measure of AKI, between 1996 and 2003, incidence of AKI increased from 3227 per 1 000 000 person-years to 5224 per 1 000 000 person-year, and dialysis requiring AKI increased from 195 per 1 000 000 person-years to 295 per 1 000 000 person-years.[49] In a population-based cohort study[50] in Ontario, Canada, between 1996 to 2010 and limited to dialysis-requiring critically ill patients with AKI, the annual incidence of dialysis-requiring AKI increased from 0·8% in 1996 to 3% in 2010. Mortality declined in the same interval from 50% to 45% of patients, but dialysis dependence after AKI remained high (25%) and unimproved since 1996. Patients who are discharged remain at a high risk of death, rehospitalisation, and progressive CKD and ESRD.[51]

In 2013 Susantitaphong and colleagues[3] described the largest meta-analysis so far, including 49 147 878 patients between 2004 and 2012, mainly in hospitals. Most studies originated from high-income countries (North America, northern Europe, and eastern Asia). In the 154 studies included studies that defined AKI either by KDIGO or KDIGO-equivalent criteria (n=3 585 911), the pooled incidence of AKI was 22% in adults (95% CI 19–24) and 14% in children (95% CI 9–21). As in previous recent studies, mortality decreased over the study period.

Meta-analysis: worldwide epidemiology of AKI

To estimate the worldwide epidemiology of AKI, we updated the meta-analysis by Susantitaphong and colleagues[3] by searching for papers using the same definitions and inclusion and exclusion criteria. We did a systematic search of the literature from Jan 1, 2012, to Aug 31, 2014, which yielded 1049 reports (figure 2). From 500 reports, we included 313 reports that met our criteria—194 that used any definition of AKI and 119 that used KDIGO or KDIGO-equivalent AKI definitions.[9] Added to the reports identified by Susantitaphong and colleagues,[3] we had a new total of 499 reports that used all definitions of AKI and 266 papers that used KDIGO or KDIGO-equivalent AKI definitions. Our addition of the 313 reports increased the sample size from 49 million individuals to more than 77 million individuals (figure 2).

Preliminary analysis of the pooled incidence by KDIGO stage in the 266 studies that use this definition (4 502 158 patients) shows that 21% of hospital admissions were affected, which is in agreement with estimates of actual incidence worldwide.[3,44,52] The overall proportion of patients with AKI who needed dialysis in KDIGO-defined studies was small (2% of hospital admissions; 11% of all AKI), whereas 12% of hospital admissions (80% of all AKI cases) had KDIGO stage 1. Analysis of the geographic distribution of the included

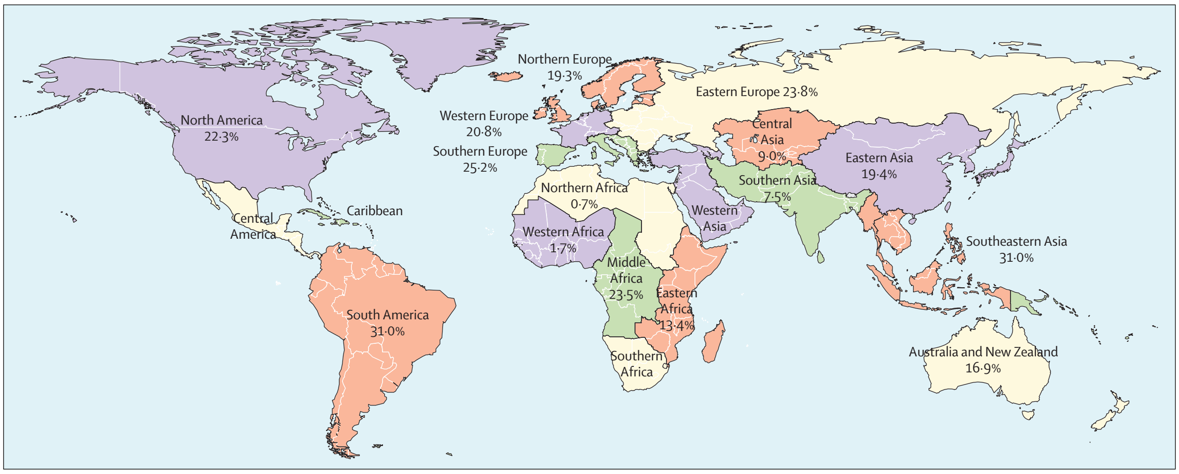

Figure 3: **Pooled incidence of acute kidney injury (AKI) from our meta-analysis**
Shows proportion of people in hospital that had AKI in studies that used Kidney Disease: Improving Global Outcomes (KDIGO) definitions. The colours of the different regions are a depiction of the aggregated regions of each continent (as labelled on the map).

studies shows a change over time in the origin of studies. Whereas in the initial meta-analysis, there were no studies from Africa or southeast Asia and very few from other LMICs, our analysis includes data from several regions of Africa and Asia. These studies not only report on the incidence of broadly defined AKI, but also increasingly use KDIGO or KDIGO-equivalent definitions, thus making the measurement comparable to that in other regions of the world. Additionally, in our analysis, the pooled incidence in LMIC regions seems increasingly close to that of developed countries, by contrast with those of previous reports (figure 3).[10] These two findings are very important because they suggest that over the past 2 years, estimates in LMICs are becoming quantitatively more accurate, and that issues with under-reporting could be decreasing. Furthermore, our results indicate that the use of comparable definitions (KDIGO or KDIGO-equivalent) is already making understanding of AKI in those regions much more reliable. The overall pooled mortality of 21% is probably due to the predominance of mild stages of AKI. However, patients with the more severe KDIGO stage 3 or those who require dialysis had a high mortality (42% and 46%, unadjusted odds ratio 12·5 and 19·7, respectively) in agreement with other studies.

Data from reports that were not included in our meta-analysis because they did not fit the inclusion or exclusion criteria (187 papers, 89 325 patients) are aggregated into three LMIC regions (Africa (62 studies and 55 309 patients), Asia (92 studies and 26 993 patients), and Latin America (33 studies and 7023 patients) and are listed in table 3.[53–60] Analysis of these data show the difficulties in description of the epidemiology of AKI in LMICs. Most reports are not available in mainstream journals and are therefore not readily accessible with the usual search strategies; we acknowledge that we might have missed some in our search. Further, most report a single-centre experience, describing AKI due to a single disease, such as obstetric complications, specific infections (leptospirosis, malaria, tuberculosis, and HIV), or exposure to toxins or traditional remedies, without reference to the underlying population.[61–69] The variation in AKI reporting is not only reflective of variability in distribution of risk factors between the different countries, but might also be attributed to differences in facilities and country characteristics such as diagnostic capacities or accessibility of services. These facts make generalisations about the epidemiology of AKI in LMICs unreliable. Additional limitations in data reporting included a high population-selection bias; all the publications originate from large university hospitals with a nephrology service, but there are almost no data for the incidence of AKI in vast rural areas, making the magnitude and outcome of community acquired AKI virtually unknown.

In Asia, there was much ethnic, socioeconomic, and developmental heterogeneity between countries. Except for in Japan, Korea, Taiwan, Singapore and Hong Kong, care for AKI is not universally available to all patients. The diversity of climate in different parts of Asia has a major effect on the incidence, prevalence, and pattern of AKI in regions. The disease patterns in large parts of south and southeast Asia and the Middle East shows the prevalent tropical ecobiology, whereas the disease pattern in the temperate regions of north and east Asian countries is different.[11] Similarly, in Latin America, there is a knowledge gap in the AKI published work.[70,71] AKI reports in critical-care setting were over-represented. Reports from level 3 countries (Peru, Ecuador, Bolivia, and all countries in Central America), where community acquired AKI is frequent in rural communities, are missing. Overall mortality is higher than in developed nations, perhaps due to the severity of the cases or inadequate care delivery.

	Included studies			Population characteristics			AKI incidence in studies			Outcomes		
	Resource level for countries in regions	Number of papers used	Number of patients overall	Mean sample size of studies	Men and boys (%)	Mean age (years)	Proportion of people in hospital (%)	Incidence (per 1 million population)	Proportion who are children	Deaths (%)	Incomplete recovery (%)	ESRD (%)
Africa	50% level 2, 50% level 3	62	55 309	488 (19–5600)	58% (6–90)	26 (0–96)	50–57%	NA	9·8 per 1 million child population; 1·74% paediatric admissions; 18·4% medical admissions	34–44%	14–18%	8–18%
Asia	95% level 2; 5% level 3	87	26 993	239 (12–2376)	59%	33 (0–73)	<1–2%	275	0·3% paediatric admissions; 25% reported cases	52%	11–19%	7%; 16%
Latin America	10% level 1; 88% level 2; 2% level 3	33	7023	229 (13–879)	59% (44–76)	51 (<1–78)	7–12% ICU admissions	102	0·38% paediatric admissions; 7% reported cases	43%	3%	7%; 18%
High-income countries	100% level 1	Many studies	Many studies	Many studies	55[53]	63·7 (44·9–82·5[53])	20%[3]; 18%[53] 10·7[54]	3000–5000;[30, 31, 34–39, 43, 44, 55] 1811[36]	4·5–82%[56,57]	14–46%[3]	26·3–28·1 patient-years; 10·3% AKI patients[58–60]	3–23

Data are mean (range) unless otherwise indicated. ESRD=end-stage renal disease. NA=not available. ICU=intensive care unit.

Table 3: **Comparison of AKI studies not included in meta-analysis**

	Patients	Mean age (years; SD)	Mean creatinine (μmoles/L)	Mortality (%)
Turkey[72,73]				
Men	321	32·4 (14·4)	433·92	13%
Women	271	30·8 (15·2)	354·83	16%
Pakistan[74]				
Men	50	39·7 (14·1)	837·54	12%
Women	38	30·4 (14·3)	847·24	26%
Haiti[75]				
Men	17	35·7 (11·9)	804·96	12%
Women	10	28·0 (8·6)	1067·43	0

Table 4: **AKI in earthquakes and regional disasters**

Other important sources of knowledge on the global burden of AKI

In addition to studies that use AKI as the primary outcome for specific medical disorders or procedures, AKI is also used as a prespecified secondary outcome in some studies done from a non-nephrology perspective–eg, as a complication of sepsis. Inclusion of these studies makes it possible to develop a much larger database of AKI events. A search in PubMed for articles published between January, 1990, and September, 2014, with the keywords "AKI" and "sepsis" identified 2386 articles, of which 165 met our criteria for inclusion as a renal secondary outcome. Similarly, AKI in the setting of disasters can provide more information about AKI and its course. Table 4 summarises a review of the data collected by the Renal Disaster Relief Task Force of the International Society of Nephrology during the disasters in Marmara, Turkey (1999),[72,73] Kashmir, Pakistan (2005),[74] and Port-au-Prince, Haiti (2010).[75] As with other data obtained in LMICs, the young age of the patients is striking (table 4). In the databases leading to the results displayed in table 4, there is a registration bias towards patients needing RRT, probably because, especially in these conditions, it is difficult to keep track of all non-dialysed people with moderate AKI.

The main findings of these epidemiologic studies (summarised in table 5), show that, in high-income countries, AKI is common, seen in 20% hospital admissions, and affects 3000–5000 per 1 million population per year.[35,43,49,54,76–83] Recent series describe an incidence as high as 15 000 per 1 million population per year.[76] Incidence seems higher than was originally thought, and is possibly increasing.[50,78] There could be several reasons for the increasing incidence: many reports on AKI focus on a critically ill population that is increasingly older and subject to a greater number of invasive surgical and cardiovascular procedures; heightened awareness of AKI has led to increased testing of serum creatinine; and a trend towards earlier initiation of RRT.[50,78] By contrast, AKI incidence in LMICs is unknown, and seems lower than in high-income countries. Under-reporting is probably the most common reason for the discrepancy: it is difficult to accept that the reported incidence of AKI in Latin America of 101·8 per 1 million population per year (G García-García, unpublished) is 30 times lower than in high-income countries. Epidemiological data from LMICs are difficult to interpret because of non-uniform cohorts, heterogeneous methods of reporting, and wide variations in ability to diagnose and treat AKI.

Patterns of AKI are different across the world. In level 1 countries, most patients are older (table 3) and have chronic comorbidities, such as malignancy, diabetes mellitus, cardiovascular disease, and CKD; the most common causes for AKI are ischaemia alone or nephrotoxic drugs, and AKI often develops in association with other acute organ failures.[9] In level 2 and 3 countries, the scenario is complex. In tertiary hospitals, AKI epidemiology is similar to that for developed countries.[84] However, ICUs from these hospitals might have patients with AKI associated with particular situations, such as tropical infectious diseases.[85,86] Conversely, in community-hospitals and rural areas, AKI will often affect young, previously healthy, individuals, and might be secondary to infectious tropical diseases, animal venoms, the use of natural medicines, complications of pregnancy including septic abortion, and infectious diarrhoea.[10,13,87–89] Common to studies from high-income countries and LMICs, strong association exists between AKI and higher mortality and other adverse outcomes. We recognise that there are inherent limitations in drawing conclusions from observational studies and that a causal relationship of AKI to mortality has not been proven; however, the reproducibility of results across multiple studies adds strength to the idea that prevention and treatment of AKI offer opportunities to reduce mortality and improve outcomes.[1]

AKI and the Global Burden of Disease Study

The ISN 0by25 initiative calls for inclusion of AKI in the Global Burden of Disease (GBD) study—a systematic, scientific effort to quantify leading causes of health loss secondary to illness or injury throughout the world.[90] The GBD study categorises such causes of health loss by age, sex, and geography for specific timepoints.[90] Loss of health is calculated with the disability-adjusted life-year (DALY) metric, which quantifies years of life lost to premature death and disability. With use of this metric, GBD 2010 ranked the leading causes of loss of health for the world across the past two decades. Kidney diseases are included among these rankings, the burden of which has been determined through key collaborations with organisations such as the ISN, which helped to assess the burden of CKD. As a part of 0by25's partnership with the Institute of Health Metrics and Evaluation (IHME),[4] AKI will be included in the forthcoming GBD 2014 report (to be published in 2015) and in annual updates thereafter. To do a multi-tiered approach will be necessary to review existing and prospective data for AKI incidence, causes, and outcomes at the population level worldwide. The ultimate goal will be to establish the contribution of AKI to morbidity and mortality for 188 countries throughout the world and across time. Incorporation of AKI into GBD will involve establishing the relationship between causative disorders known to increase the incidence of AKI, and the resultant effect such AKI events have on health outcomes. Modelling AKI as an intermediate event between the initiating cause of AKI and consequent health outcomes has two important ramifications. First, at the country level, it will be possible to establish the leading causes of AKI and portions of the population that are most susceptible to AKI-related health loss, and to establish the causes that lead to the highest AKI mortality and disability, which we anticipate to vary widely among countries. Second, these findings could serve to guide efforts to address preventable deaths among all populations.

Key to the inclusion of AKI in GBD is the requirement of epidemiological data for AKI at the population level. To address the absence of data for LMICs, the 0by25 initiative launched the AKI Global Snapshot, a short prospective observational cohort study done from Sept 29, to Dec 7, 2014, to compare risk factors, aetiologies, diagnosis, management, and outcomes of AKI, with 324 participating centres from 72 countries (as of Dec 7, 2014; for centres see map online). An ancillary aim of this study is to establish the resources available for the non-dialytic and dialytic management and follow-up of patients with AKI in different settings. The results will be reported at the World Congress of Nephrology in Cape Town, South Africa, on March 12–16, 2015. A follow-on longitudinal AKI Cohort Study is planned to start the second quarter of 2015 in selected centers across the world, based on the results of the Global Snapshot data. The data are being collected from participating centres with a dedicated online platform, KEEP, run by ISN's technology partner, Distributed Health Laboratories (University of California San Diego, CA, USA). KEEP is a web and mobile application for patient-centric health studies, which grew from the need for simple yet robust data collection in resource-poor settings and can be reached via smartphones, tablets, and other informatic instruments that are now widely available, even in poor countries. The system has now been used in nearly 100 countries worldwide and allows rapid and robust deployment of health data-gathering studies and many settings. These two studies will provide novel information on the growing burden of AKI as well as how it is identified, managed,

For the **interactive map** see http://keep.0by25.org/isn/lancet_paper

For **KEEP** see keep.distributedhealth.org

	AKI in high-income countries	AKI in low-income and middle-income countries
Pattern of occurrence	Occurs predominantly in intensive care units	Occurs in health centres and hospitals in rural areas and large hospitals and intensive care units in large cities
Disease patterns	Associated with multiple organ failure	Often caused by a single disease; multiple organ failure less common
Associations	Associated with sepsis and complex surgery (major trauma, cardiovascular surgery)	Frequently associated with specific disease (eg, diarrhoea) and specific infection (eg, malaria)
Mortality	High mortality	Same or lower mortality than in high-income countries
Populations affected	A disease of elderly populations	A disease of young, otherwise healthy people
Prevalence	Could be increasingly prevalent	Could be increasingly prevalent?
Sufficiency of reporting	Accurately reported	Severely under-reported
Preventable status	Difficult to prevent	Preventable
Expense	Very expensive to treat	Very inexpensive to treat at early stages, too costly for most at severe stages

Table 5: **Typical characteristics of acute kidney injury (AKI) in high-income and low-income countries**

and treated in these different settings and should provide the evidence base for inclusion of AKI in the GBD study.[90] The inclusion of AKI in GBD offers several benefits for the 0by25 initiative. It will be the first attempt of its kind to characterise AKI burden across such a range of geography, time, and lifespan. This effort will enrich understanding of the relative contributions of the leading causes of AKI, a crucial step towards guiding necessary efforts of early detection and possible interventions. The effort to characterise causes of AKI that are specific to world regions will provide critical information to governments charged with the difficult task of health-care resource allocation. Identification of world regions with the highest death toll from AKI because of insufficient access to acute dialysis will guide efforts to address such resource limitations and ultimately, save lives.

Aim two: raise awareness and reduce variations in care delivery for AKI

Targeting change in AKI management

The large variation in AKI management worldwide suggests that there is still a dearth of understanding of the disorder among physicians, allied personnel, and the general public. The absence of globally accepted standards for prevention, recognition, treatment, and follow-up of AKI contribute to the substantial differences in care delivery. The recently released KDIGO guidelines[25] for AKI suggest specific approaches for stage-based management of AKI, but we have little data for their application. Studies to assess the quality of care in AKI report that prompt diagnosis of AKI is frequently inadequate and too slow. The advisers from the UK National Confidential Enquiry into Patient Outcome and Death (NCEPOD) study reported that 43% of the patients had an improper delay in diagnosis for post-hospitalisation AKI.[91] An assessment of the quality of care given to a cohort of patients with AKI in Western Infirmary (Glasgow, UK) found that AKI was not recognised in 24% of patients.[92] One key finding from published studies is the wide variation in use of RRT to treat AKI, particularly in level 2 and 3 countries. Even when RRT is available, socioeconomic factors can prevent patients from getting dialysis and, even if offered, the dose (duration and frequency) might be curtailed for economic reasons.

These findings focus attention on one of the three key objectives of the 0by25 initiative: to raise awareness and thereby reduce the variation in care for AKI that contributes to preventable deaths. Management of AKI can be considered under the 5 Rs—risk assessment, recognition, response, renal support and rehabilitation (figure 1).[1] These five parameters form the core of the management strategy of AKI that need to be addressed to improve care (table 6). The 0by25 initiative focuses on these five domains to optimise the management of AKI worldwide. There is a general scarcity of information on the 5 Rs for AKI in all countries and almost no information from level 2 and 3 countries. We anticipate that there will be differences in the 5 Rs based on differences in the geographic area and available health-care resources, and that the clinical pattern of AKI will be substantially different depending on the country.

To tackle this issue we recognise that a multifaceted approach will be necessary, encompassing education, training, and ongoing research coupled with a systematic process to disseminate information. Awareness about AKI needs to improve in all the levels of the health-care system. Individuals responsible for the health planning (governmental and private) must recognise the burden of mortality, disability, and cost associated with AKI.[19] In level 1 and developed areas of level 2 countries, educational campaigns about the importance of AKI must occur in cooperation with the public health administration, private health insurance companies, and medical societies. They must send a straightforward message about AKI detection and care to specialists, general practitioners, nurses, and medical allied personnel. In less developed areas of level 2 and in level 3 countries, these campaigns should be tailored to reach all non-specialist medical practitioners, nurses, and allied personnel working in health care, with use of messages and media appropriated to those particular settings. Educational material directed to community healers might be useful in these areas. Awareness of potential short-term and long-term consequences of AKI should be offered to people in all countries.

These targeted approaches will need to be coupled with a plan to educate and train health-care providers on the best tactics to recognise, treat, and follow up patients

	Area of focus
Risk	
Susceptibility	Genetic, risk scores
Surveillance	Electronic (e-) alerts, drug dosage modification
Primary prevention	High-risk patients and exposures
Recognition	
Diagnosis	Urine output, serum creatinine, new biomarkers
Staging	RIFLE, AKIN, KDIGO, AKI duration
Response	
Reversible factors	Hydration, haemodynamics, haematocrit, oxygenation, and relieve urinary obstruction
Nephrotoxins	Halt or correct drug dose for renal function
Referral therapy	Early nephrology consultation, if feasible
Renal support	
RRT modalities	Dosing, duration, timing, initiation, and withdraw
Rehabilitation	
Follow-up	Team approach (general practitioner, specialist, nurse, social worker, and family)
Recovery	Targeted interventions (eg, hypertension control)
Functional assessment	Quality of life

AKI=acute kidney injury. RIFLE=Risk, Injury, Failure, Loss, End-Stage Renal Disease. AKIN=Acute Kidney Injury Network. KDIGO=Kidney Disease: Improving Global Outcomes. RRT=renal replacement therapy.

Table 6: **Focus areas for the 5 Rs approach to intervention in patients with AKI[1]**

with AKI. We propose a systematic approach anchored on the 5 R principles (figure 1). We have embedded the 5 R framework in the prospective Global Snapshot and AKI Cohort Study. Specific approaches should be developed for individuals at high risk for AKI, those submitted to exposures that can cause AKI, and those with established (diagnosed) AKI.[8] The keystone of any intervention plan for AKI is the concept that many episodes of AKI are preventable, are amenable to early detection, and are treatable.[1,8] Data obtained will be used to define key elements that affect outcomes and that can be targeted to reduce variation and improve survival (table 7).

Areas in which knowledge should be transferred between experienced and less experienced centres include identification of high-risk patients, exposures that can cause AKI, diagnostic testing to confirm AKI, interventions to correct reversible factors, recognition of need for renal support, and referral for nephrology care. Instruction and training in these areas would need to be adapted for different regions, taking into account the availability of health-care resources, personnel, and infrastructure. A key element is the availability of inexpensive point-of-care diagnostic tests—eg, urea and serum creatinine and urinalysis. At the community level, particularly in level 2 and 3 countries, a key goal is to set up and develop a regional network of trained village health-care workers, who become experts in sanitation, immunisation, recognising high-risk settings for AKI, detection of disease, rehydration, and triage. At the secondary level of health care, the health-care teams need to be trained in protocol-oriented diagnosis and non-dialytic treatment of AKI and in the use of acute peritoneal dialysis to treat patients with dialysis-dependent AKI. In tertiary level hospitals, health-care teams should be trained in the adequate assessment of risk factors and exposures leading to AKI, timely prevention and initial treatment of AKI, non-dialytic AKI treatment, and need for early involvement of nephrologists where possible. In addition, the care delivery team (often not including a nephrologist) will need to be trained to choose the appropriate dialysis modality that is best suited to the patient's individual circumstances. Several excellent resources to educate patients and providers are available that could be leveraged to develop specific toolkits for patients with AKI.[93,94]

There is great need for additional research on AKI in LMICs. Risk factors for AKI in these countries are not well defined. Research leading to implementation of point-of-care techniques might allow for timely identification of high-risk patients and diagnosis of AKI, and thus might reduce AKI's incidence, severity, morbidity, and mortality. In addition, treatment protocols for specific causes of AKI in LMICs, such as those for

	Type 1: high-risk settings	Type 2: missed or delayed recognition, inadequate response, or iatrogenic AKI	Type 3: inadequate access to dialysis
Risk	Establish risk for development of AKI (diarrhoea, infection, sanitation, envenomation, trauma, obstetrical complications, and drug nephrotoxicity); vaccinations; prophylaxis	Risk assessment for severity and progression	Risk scores for need for dialysis; RRT availability; factors preventing access to care
Recognition	Special attention and surveillance of high-risk populations (volume contraction, obstetrics, sepsis, major surgery, trauma, and pre-existing comorbidity)	Point-of-care testing for serum creatinine, urine output; development of renal-care guidelines that are customised for region	Point-of-care testing for serum creatinine, potassium, and bicarbonate
Response	Primary prevention	Secondary prevention: treating underlying disorder; correction of volume and electrolyte depletion to improve haemodynamics; avoidance of nephrotoxins; and ensuring of appropriate drug dosing	Timely intervention; managing complications of AKI hyperkalemia, acidosis; referral–counter-referral RRT system
Renal support	..	..	Access to RRT; catheters and supplies; environment (electricity, solar power, and water purification); measurements to monitor safety of dialysis delivered—eg, water testing for purity and absence of bacterial growth; RRT according to complexity of patient (eg, PD for non-ICU patients; dialysis or continuous RRT for ICU patients)
Rehabilitation	Follow-up to document renal recovery, with appropriate treatment as needed.	Follow-up to document renal recovery, with appropriate treatment as needed.	Follow up to document renal recovery, with appropriate treatment as needed.
Education and methods	Risk recognition and assessment; surveillance; training of first-contact health-care providers (non-nephrologist and non-intensivist staff)	Initial management and monitoring	Dialysis-related training and infrastructure

RRT=renal replacement therapy. ICU=intensive care unit. PD=peritoneal dialysis.

***Table 7:* Strategies to reduce preventable deaths from acute kidney injury (AKI) through the 5 Rs**

obstetrical complications, infections, and animal venoms, should be defined and implemented. General and specific research questions for all the three levels of countries are shown in panel 1. Answers to these questions will help to reduce the burden of untreatable AKI—the main goal of ASN's 0by25 initiative.

5 Rs—risk: identifying high-risk individuals

Timely identification of patients who are at increased risk of development of AKI is pivotal for preventive strategies. Researchers have identified several risk factors (panel 2); however, most of this research was done with patients from hospitals in level 1 countries. Some risk factors are potentially modifiable, others, such as comorbid medical disorders or demographic factors, are not.[8,95,96] The myriad of different exposures that contribute to AKI in different settings make development of a single method for risk assessment difficult (panel 3).[10,13,84–89,97] Individuals exposed to these insults should be assessed carefully for AKI risk factors, and when possible, the exposure should be avoided or postponed.

The identification of high-risk patients is particularly relevant in hospitals and would allow clinicians to act on modifiable risk factors and to avoid or tailor potential kidney injury exposures. Nevertheless, this pre-emptive strategy does not seem to be standard practice, as shown by results of the UK NCEPOD study. The authors of the enquiry found a poor assessment of risk factors for AKI, both in individuals admitted into hospital with established AKI and in those who developed it in hospital.[91] Showing how identification can lower rates of AKI, Cho and colleagues[98] reported on a computerised alert programme that warned the physician (and recommended prophylactic measures) when an investigation using contrast was ordered for patients at high risk of AKI. This increased the use of prophylaxis and lowered the incidence of contrast nephropathy (3% *vs* 10%).[98]

General practitioners, emergency department physicians, and allied health personnel are frequently the first practitioners to interact with patients at high risk of AKI, so assessment of patients at risk of AKI needs to be done not only by nephrologists and by intensivists, but by all health providers. Patients with a high risk for AKI must have early and sequential assessment of serum creatinine and urinary output, at a frequency consistent with their risk and the presence of potential exposures, including environment-linked and infrastructure-linked risk factors (panel 3).[7] This approach is achievable in most situations, but a serum creatinine measurement might be difficult to do in resource-poor countries or in some rural settings. In those situations, the importance of decreases in urinary output and increases in bodyweight due to fluid overload must be strongly stressed to the local health-care teams.

Environmental and infrastructure conditions (panel 3), such as inadequate sanitation, insufficient clean water, inadequate control of parasites and infection-carrying vectors, and poor transportation can increase the risk of AKI. In a health budget, other pressing problems compete for resources, including maternal health, undernutrition, and disease epidemics. Measures to correct these factors are more dependent on political stability, increasing of the population's educational level, better health, and transport infrastructure than on medical interventions alone. In regions where one physician can serve 2–3 million people, it will be necessary to plan an alternative care system relying on non-physician resources to deliver basic care, and recognise modifiable situations of high-risk AKI.

The development and validation of risk scores that assess the probability of AKI is highly desirable.[7] Specific risk scores for the development of AKI have already been proposed,[27–34] aiding the decision-making process when a patient at risk of AKI faces an event that could cause AKI. The scores also allow comparison of AKI incidence for specific settings while correcting for comorbidities. As with research for risk factors, most of the available risk scores were created with data from patients in level 1 countries. Their effectiveness is not known in individuals in whom different demographic, comorbid, and socioeconomic conditions might exist and for whom causes might have been under-represented in the population studied, such as crush injuries in the rhabdomyolysis prediction score.[99] There is a need to

Panel 1: **Key points to consider on the research agenda for acute kidney injury**

General
- How can we best educate people and raise awareness about acute kidney injury (AKI)?
- Do broad-based educational campaigns about AKI importance and recognition, directed at non-nephrology health professionals and the public, modify AKI frequency and burden?
- Epidemiological data accumulation
- Development of a global risk score for AKI.
- What is the role of telemedicine in AKI care, especially in remote areas of level 2 and in level 3 countries?
- What will be the role of point-of-care testing for renal function in prevention and early AKI treatment?
- Development of general best practices suited for AKI care in all settings.
- How to provide renal replacement therapy (RRT) in areas with a fragile health infrastructure?
- How to change the prognosis of patients who survive AKI, preserving renal function and decreasing late mortality?

Specific
- Would the implementation of electronic systems to detect AKI change its in-hospital morbidity and mortality?
- What is the role of the new biomarkers in the diagnosis, treatment, and prognosis of AKI?
- Is fluid overload a biomarker for AKI?
- When should RRT be started in non-life threatening situations?
- When should RRT be discontinued in a patient who is beginning to recover from dialysis-dependent AKI?

develop a general risk score for AKI that could be assessed in populations worldwide. This score would greatly enhance identification of high-risk patients and allow preventive strategies.

5 Rs—recognition: prompt diagnosis

The key concept for management of AKI is that it is a dynamic process—ie, further insults will cause further injury and progression of the disease, which is associated with deleterious outcomes, including death.[52,100] The timely diagnosis of AKI is essential to allow the health team to intervene to minimise further renal injury. In level 2 and 3 countries, delays in recognition of AKI might be caused by inadequate access to health care due to poor infrastructure or financial constraints, and point-of-care tests by physicians or by other health-care professionals might be particularly useful to identify AKI quickly. As yet, point-of-care tests for urea have not been validated in human beings, and creatinine tests require electricity and expensive manufacturer-specific consumables.[101]

In addition, definitions for AKI also have limitations. Although there is strong evidence that the diagnostic and staging criteria of AKI (serum creatinine and urine output) are associated with adverse outcomes, including mortality, a causal relationship has not been established. They also do not take into account the circumstance in which individuals present to the health-care system with a high serum creatinine, which subsequently decreases or returns to baseline (retrospectively classified as AKI). Another limitation is the short time window during which AKI is diagnosed by changes in serum creatinine or urine output or both—7 days using RIFLE, 48 h using AKIN, and either 7 days or 48 h with KDIGO. However, some patients in hospital develop increases in serum creatinine concentration over a period longer than 7 days but shorter than 90 days (the period used to diagnose CKD). This circumstance, sometimes called acute kidney disease or subacute AKI, is associated with higher in-hospital mortality compared with those without AKI.[45,102] The identification of patients with acute kidney disease or subacute AKI is of particular importance in community settings. This diagnosis is frequently missed because the patient presents to a health facility with a raised serum creatinine concentration but a recent previous concentration is not available. These patients are at increased risk for further progression of AKI while in hospital so their renal status should be monitored closely.

Findings after introductions of in-hospital electronic alerting systems for AKI confirm the importance of early AKI diagnosis. In a Belgian hospital, the implementation of an electronic AKI alert system covering all ICU beds was associated with a shorter time to therapeutic intervention and a more frequent normalisation of serum creatinine concentrations.[103] A real-time alert for the detection of in-hospital AKI (serum creatinine changes) in the UK identified 22 754 episodes of AKI in

Panel 2: Main risk factors for acute kidney injury

Patient

Modifiable

- Dehydration
- Intravascular volume depletion
- Hypotension
- Anaemia
- Hypoxia
- Use of nephrotoxic drugs and agents (eg, antibiotics, iodinated contrast agents, non-steroidal anti-inflammatory drugs, anticancer drugs, antiretroviral drugs, and calcineurin blockers)

Non-modifiable

Comorbid medical disorders

- Chronic kidney disease
- Diabetes
- Cancer
- Chronic heart disease
- Chronic lung disease
- Chronic gastrointestinal disease

Demographic factors

- Sex
- Older age

Environmental and infrastructure

- Inadequate sanitation
- Insufficient clean water
- Inadequate control of parasites
- Inadequate control of infection-carrying vectors
- Poor transportation
- Inadequate health budget
- Insufficient health-care human resources
- Insufficient health services and hospitals

Panel 3: Main exposures for acute kidney injury

Level 1 and 2 countries

- Sepsis
- Circulatory shock
- Trauma
- Cardiac surgery (especially with cardiopulmonary bypass)
- Major non-cardiac surgery
- Nephrotoxic drugs and agents
- Burns

Level 2 (some areas) and level 3 countries

- Diarrhoea
- Obstetric complications (including septic absorption)
- Infectious diseases (malaria, leptospirosis, dengue fever, cholera, yellow fever, tetanus, and Hantavirus)
- Animal venoms (snakes, bees and wasps, *Loxosceles* spp [recluse] spiders, and *Lonomia* spp caterpillars)
- Natural medicines
- Natural dyes
- Prolonged physically overwhelming work in an unhealthy environment

15 550 patients in a 2 year period (incidence of 11%). About half of the electronic alerts occurred within 24 h of admission, with a median time to alert of 7 h. When the authors assessed only the first alert for the 15 550 patients they observed that about 11% of patients progressed from AKI stage 1 to stages 2 or 3, and 14% progressed from AKI stage 2 to stage 3 during hospital admission.[104] Considering that the above-described electronic alert identified 50% of AKI cases in the first 24 h after hospital admission, this system would allow early adoption of stage-based treatment for AKI, potentially reversing stage 1 AKI in some patients and minimising progression to more severe stages, with a potential result on mortality and economic burden. Although electronic alerting is in its infancy and is used mainly in level 1 countries, with the continued development of wireless technology and access to the internet, access to information might soon be universal. The increasing use of telemedicine could extend these concepts of surveillance for high-risk individuals, even in level 2 and potentially 3 countries. The availability of cellular phones and point-of-care tests could permit health-care workers in remote areas to communicate with physicians in larger regional hospitals to guide management of patients with AKI.

Although several new biomarkers of kidney injury have been tested in the last decade, the goal of a so-called single-shot biomarker for AKI diagnosis has not been achieved. Instead, it is thought that use of a combination of functional (reflecting kidney function) and structural (reflecting damage to the kidney) biomarkers might be helpful in identification of early AKI. The use of these biomarkers might increase the chances of well timed diagnosis of AKI, better planning and earlier institution of protective measures resulting in an improved prognosis for the patient.[105–108] However, the applicability of these new biomarkers assays in resource-poor settings is currently limited by their costs.

Fluid balance is a potential biomarker for AKI. The current thresholds for oliguria are based on arbitrary absolute values. Critically ill patients with normal urinary outputs by current definitions who receive higher volumes of fluid infusion and subsequently develop fluid overload are common in ICUs. Substantial fluid accumulation due to positive fluid balance can dilute the blood and cause a falsely low serum creatinine concentration, delaying diagnosis of AKI.[109] Data have begun to accumulate that suggest that positive fluid balance is associated with increased mortality in patients AKI[110] and might be an early biomarker for AKI development.[111–114]

5 Rs—response: interventions for incipient and established AKI

Acting on modifiable risk factors

Of all the risk factors for AKI, extracellular volume depletion is probably the most recognised and amendable. Indeed, fluid therapy to prevent AKI is well accepted.[115,116] Assessment of the patient's volume condition (comprehensive history, physical examination, and assessment of laboratory findings) is central in prevention of AKI after exposure to nearly any type of potential kidney-injuring situation. The correction of volume depletion must be individually tailored to suit the patient (age, baseline diseases, and cardiac function) and the type of fluid loss and volume depletion. Oral rehydration solutions are quite effective in some situations but intravenous fluids might be needed. The amount and route of fluid replacement is an important consideration and should be based on the setting. For instance, bolus fluids given to children with malaria are associated with a higher mortality, potentially due to fluid overload.[117–119] Many studies have addressed the issue of the timing and type of fluid replacement in situations such as sepsis,[120,121] use of iodinated contrast agents,[122,123] and rhabdomyolysis.[124,125] There is a moderate grade of evidence suggesting that crystalloids should be used in most cases, colloids in some specific situations, and starches should be avoided.[8] The use of balanced-chloride-concentration crystalloids is associated with decreased AKI incidence and lower need for RRT.[126] Hypotonic fluid should be used for dehydration caused by true free-water deficiency. Isotonic fluid should be used to correct reduction of intravascular volume and red blood cells should be considered in cases of reduced intravascular volume caused by bleeding. After successful intravascular fluid resuscitation, patients should be monitored carefully to avoid fluid accumulation, which is associated with higher mortality in patients with AKI.[110] Randomised controlled trials are necessary to assess the optimum goals for volume resuscitation, the role of crystalloids versus albumin, and the effects of saline versus physiological electrolyte solutions.

Haemodynamic optimisation and oxygenation

Hypotension, shock, sepsis, and septic shock frequently co-occur with AKI. Hypertensive patients are more susceptible to hypotensive episodes because of loss of vascular tone and use of antihypertensive drugs so a thorough clinical history is particularly important. Vasopressors should be used in combination with fluids in patients with vasomotor shock who have a high risk for AKI or have established AKI;[127] available data from trials of patients with multiorgan failure or sepsis suggest that norepinephrine and vasopressin are more efficient and safer than is dopamine.[128–130] Adequate oxygen delivery is crucial for kidney function[131] and hypoxaemia is a crucial and modifiable risk factor associated with AKI development.[132] Lower oxygen delivery during cardiopulmonary bypass has been associated with a higher frequency of AKI.[64] KDIGO AKI guidelines[8] suggest protocol-based methods should be used to optimise haemodynamics and oxygenation to prevent or attenuate AKI in high-risk individuals during the perioperative period or in the presence of septic shock.[127,133] These protocols should be adapted for different AKI settings (community acquired *vs* ICU-acquired AKI, high-income countries *vs* LMICs). Guidelines should be interpreted with flexibility, according to the particular aspects of the patient, the medical staff, and the health-care infrastructure, and should be monitored for efficacy and changed accordingly. Randomised trials to compare different vasopressors in AKI and assessment of the parameters to assess haemodynamics are necessary.

Correction of anaemia

Low haematocrit has been associated with AKI development.[134–137] Although no evidence-based data are available, elective procedures to correct low haematocrit levels and prevent AKI might be useful in high-risk patients or in those about to undergo planned interventions that could cause AKI. Detection and correction of anaemia should be a priority for workers in level 2 and 3 countries, in which anaemia might be frequent, especially in children due to parasitosis and malnutrition. Future research on the role of anaemia in AKI and its effect on renal functional recovery is needed.

Non-dialytic therapy for AKI

The same general measures that were mentioned in prevention of AKI section are also applicable in established AKI, and the underlying cause of AKI should first be addressed. After AKI is diagnosed, severity stage should be established with use of KDIGO criteria (table 1). Protective measures to stop AKI from worsening should be started immediately with special attention to ensuring adequate hydration, and maintaining hemodynamic stability and oxygenation as described earlier. Systematic care of patients should include correction and monitoring of fluid balance, haemodynamic optimisation (panel 4). Almost all treatment options for AKI have a low grade of evidence or are based on expert opinion alone.[8] Some of the recommendations rely on the availability of blood chemistry analysers, which might have little or no availability in resource-limited settings, particularly in those in level 2 and 3 countries.

Drugs and nephrotoxins

The avoidance of drugs and nephrotoxins that cause AKI[138,139] and appropriate dose adjustment of renally cleared or protein-bound drugs[140] are essential. Drugs that should be used with caution or avoided include angiotensin-converting-enzyme inhibitors, angiotensin-II receptor blockers, NSAIDs,[141–144] aminoglycosides,[145,146] amphotericin B,[146] contrast media, chemotherapy drugs,[147,148] antiretroviral therapy, and calcineurin blockers. Clinicians should also ascertain the content of any alternative medicines being taken by the patient and ensure that they are not contributing to the event directly or through drug interactions.

Diuretics

Not recommended for the prevention of AKI are diuretics (moderate grade of evidence) and low-dose dopamine (high grade of evidence).[8,130] Data from several studies, including large randomised controlled trials and meta-analysis, show that these drugs are not of benefit, can actually induce AKI, and are associated with other adverse events.[148–154] Despite controversial data about their benefit, a multinational survey on the clinical use of diuretics in AKI concluded that diuretics are often prescribed in this setting (67%) and are most commonly delivered intravenously in bolus.[155] This survey also confirms the need for robust trials of diuretics in AKI.[155] Two RCTs are taking place, but are probably too small to provide a definite answer to this question (NCT00978354).[156] The KDIGO guidelines suggest use of diuretics to treat fluid overload in AKI.

Acidosis and hyperkalemia

Sodium bicarbonate is usually used to correct metabolic acidosis in patients with AKI. However, there is no evidence supporting its use and it can cause fluid overload and hypernatremia. Hyperkalemia is a potentially serious complication of AKI due to the possibility of sudden cardiac death (in severe hyperkalemia, defined as serum potassium ≥6·5 mmol/L, or with increased serum potassium associated with hyperkalemia-related electrocardiographic abnormalities). Hyperkalemia should be prevented in patients with AKI through the avoidance or stopping of potassium supplements and drugs that decrease excretion of urinary potassium (angiotensin-converting enzyme inhibitors, direct renin inhibitors, β-adrenergic receptor antagonists, angiotensin-II receptor blockers, mineralocorticoid receptor antagonists, and sparing potassium diuretics), and by decreases in dietary potassium ingestion. Severe hyperkalemia should be treated by intravenous calcium gluconate infusion (10 mL of 10% solution over 5 min), intravenous polarised solution (regular insulin and dextrose 50%; extreme caution with hypoglycaemia), nebulised salbutamol, and correction of acidosis.

Nutrition and hyperglycaemia

There is a very low grade of evidence to suggest that protein restriction should be avoided and that patients with AKI should receive certain amounts of protein depending of their catabolic state (0·8–1·0 g per kg bodyweight per day of protein in non-catabolic, non-dialysed patients, 1·0–1·5 per kg bodyweight per day in patients on dialysis, and up to a maximum of 1·7 per kg bodyweight per day in patients on continuous RRT and in hypercatabolic patients). There is low grade of evidence that suggests patients should attain a total energy intake of 20–30 kcal per kg bodyweight per day and should use the enteral route preferentially.[8] Randomised controlled trials for the effects of different amounts of protein and

Panel 4: **The ten most important strategies for intervention in acute kidney injury (AKI)**

1. Identify patients at high risk of AKI for prevention (not graded)
2. Identify exposures (not graded)
3. Prompt recognition of AKI by serial urinary output measurements (not graded)
4. Prompt adoption of protective interventions: volume repletion (2B), blood pressure optimisation (1C), haematocrit correction (not graded), maintenance of adequate oxygen saturation (not graded), and avoidance or discontinuation of nephrotoxic drugs (not graded)
5. Avoid furosemide for AKI prevention (1B) or early treatment, except for management of volume overload (2C); avoid low-dose dopamine for AKI prevention or treatment (1A)
6. Early nephrology referral (not graded)
7. If established (diagnosed) AKI: control fluid status (2B) and blood pressure (1C), control acidosis (not rated), control hyperkalemia (not rated), control serum glucose (2C), provide adequate nutrition (2D), and prevent sepsis (not graded)
8. If renal replacement therapy is required, consider transferring the patient to a tertiary care centre (not graded)
9. Consider peritoneal dialysis as a method for renal replacement therapy in AKI (not graded)
10. Provide adequate long-term follow up for patients who survive an AKI episode (not graded)

We classified these strategies according to the Kidney Disease: Improving Global Outcomes (KDIGO) Clinical Practice Guideline for Acute Kidney Injury[8] strength of evidence rating (1=recommended; 2=suggested) and the quality of the supporting evidence (A=high; B=moderate; C=low; D=very low), as judged by the authors. Strategies not subjected to systematic evidence review were classified as not graded.

calories in patients are necessary. There is a low grade of evidence to suggest insulin use to keep plasma glucose between 6·1–8·3 mmol/L. Patients who use intravenous insulin should be carefully monitored for hypoglycaemia.[8]

Nephrology referral

Recognition is increasing for the importance of early nephrological care and intervention in AKI. Delayed or absent nephrology referral have both been associated with a higher mortality, dialysis dependence, and length of hospital stay.[155–160] However, given the worldwide annual burden of new cases of AKI, the number of trained nephrologists available is insufficient to care for this number of patients. In level 3 countries, there is not only a dearth of nephrologists, but also of physicians of any specialty. In many African countries, the density of physicians is 0·02–0·29 per 1000 population, well below the 2·28 professionals per 1000 population recommended by WHO.[161] Furthermore, present numbers of physicians in training is insufficient to maintain even these low levels of access, partially due to the migration of many of these physicians to higher income countries. Training primary care physicians and other health-care givers to raise awareness, share knowledge, and provide practical management of AKI is universally imperative, but of particular importance in level 2 and 3 countries. Nurses and allied health personnel play a key part in building of a work force to manage AKI and are essential members to be included in training. Educational strategies are a pivotal part of the 0by25 initiative.

5 Rs—renal support: RRT

The timing of RRT initiation and the type and dose of RRT are still debated. Available data suggest that earlier initiation of RRT is desirable (although no definitive evidence is available), that there is no clear overall advantage of any type of RRT over others, and that higher doses of RRT do not decrease mortality.[8] Obviously, RRT should be started when life-threatening changes occur in a patient's fluid status, serum electrolyte, and acid-base balance. More subtle indications for RRT, such as increasing fluid overload, should be assessed on a case-by-case and moment-by-moment basis.[8] Wide variations are present in the use of RRT for AKI worldwide[162–166] and there are striking differences in availability, access, and procedures of RRT between level 1 and level 2 and 3 countries. The pattern of RRT in level 2 and 3 countries is extremely complex. Availability and access to RRT is strongly dependent on socioeconomic development and health-system organisation and can vary widely even between different areas of the same country. Resources for equipment and medical supplies and numbers of trained personnel are frequently insufficient. In some regions, especially those in level 2 countries, hospitals with highly sophisticated RRT coexist with hospitals with no RRT accessibility. Even when RRT is available, the universally accepted standards for RRT care and delivery are not always available and modifications to these standards often occur. These include the use of peritoneal dialysis fluid as dialysate for continuous RRT, and inadequate timing and dosing of RRT due to insufficient human resources, equipment, and supplies. In addition, in some regions health insurance is scarce and many patients cannot afford any dialysis or can only pay for dialysis for a short period before their financial resources are exhausted.

Patients who need RRT should be referred to tertiary care centres as soon as possible. The type of RRT used will depend on the patient's characteristics, evolution of AKI, and associated comorbidities, centre availability, and staff experience. RRT should fit the patient and not the other way around. Continuous RRT should be used preferentially for haemodynamically unstable patients and those with either increased intracranial pressure or generalised brain oedema.[8] Intermittent RRT techniques might be an alternative for haemodynamically unstable patients when continuous RRT is not available.[167]

Several reports show that peritoneal dialysis can have a similar effectiveness to extracorporeal blood purification techniques in AKI.[168–171] Peritoneal dialysis is an easy to initiate, safe, and less expensive RRT method and is particularly useful in areas with fragile health infrastructure, but is also associated with peritonitis, mechanical obstruction, protein loss in the dialysate, and systemic glucose increase.[172–175] Intraperitoneal flexible catheters should be used preferentially for acute peritoneal dialysis, but rigid stylet or improvised catheters might be lifesaving in particular situations.[175]

These catheters can be inserted by trained nephrologists, intensivists, or emergency care physicians. The type of dialysate used will depend on patient characteristics. Bicarbonate-buffered dialysate should be used preferentially for patients with shock or hepatic failure. Lactate-buffered solutions are the alternative for other patients or when bicarbonate solutions are not available. Level 3 countries in Africa where RRT availability is very low have launched lifesaving programmes that use peritoneal dialysis for the treatment of dialysis-dependent AKI.[53,176–178]

Because of the low availability of trained personnel and RRT equipment, particularly in low-income countries, a referral and follow-up system is necessary to bring RRT to patients with AKI. This requires a coordinated approach for triaging AKI patients requiring dialysis from community clinics and hospitals without RRT to centres equipped with RRT. When the patient improves they return to the community clinic with information on the care given and follow-up needed. Patients with mild to moderate AKI can be treated in secondary level hospitals; if RRT is indicated, peritoneal dialysis should be considered. Patients with multiorgan dysfunction should be transferred to a tertiary centre. The geographical distribution of the reference centres and its correspondent catchment area should be based in the local epidemiology and demographic variables.

5 Rs—rehabilitation: post-discharge care of patients with AKI

Patients who survive episodes of AKI should be monitored for more than 3 months after discharge and have their serum creatinine concentration routinely measured to assess for recovery of renal function and progression of renal injury. The mental and physical health of these patients should also be monitored since, in patients who survive being critically ill with AKI, late mortality is associated with reports of low quality of life after discharge.[55] However, most patients who survive an AKI episode do not have long-term assessment of kidney function and many do not see a nephrologist at all.[179] This probably affects their chance of recovery and progression to CKD. Inadequate follow-up of patients who have had AKI is probably an even larger problem in level 2 and 3 countries because of poor access to health care and insufficient specialists or general practitioners, where healers or alternative medicine practitioners might be the only available alternative.

Health providers need education and training in caring for patients who have had AKI that takes into account the heterogeneity of available resources in different settings. Educational campaigns for the importance of long-term follow-up of patients with AKI must be planned and presented to health teams (physicians, nurses, and medical allied personal) involved in patient care, based on the level of health organisation (resources available) in the targeted geographical area.

Aim three: create a sustainable infrastructure

Regionalisation of human resources and technology

Several factors need to be considered in development of a sustainable infrastructure to support the 0by25 initiative (figure 4). These include regionalisation of human resources and technology; a referral and follow-up system to appropriately triage patients; appropriate distribution of centres and their catchment areas according to local epidemiology; and a selection of RRT procedures to meet the complexity of a patient's clinical condition (eg, peritoneal dialysis in patients who are not critically ill). Attainment of these factors is the cornerstone to achieve the expected outcomes—avoid (prevent) AKI, reduce the number of cases of both mild and severe AKI, reduce the number of avoidable deaths due to unavailability of RRT, and improve prognosis through a timely consultation with a nephrologist, early RRT, and ICU care, if needed. In this section, we suggest an approach to tackle the ambitious 0by25 goal in LMICs, describing prerequisites for success, proposing metrics for assessing progress, and establishing an accountability framework to assess and compare commitment by governments at national and regional level.

How to frame data for stakeholders

Robust data are central to the establishment of the burden of illness due to AKI, identification of potential solutions, and measurement of progress. However, to maximise the effect and use of data for AKI, it must be framed in a manner that highlights its applicability to relevant stakeholders. First, clear identification of the links between AKI and death related to road safety (trauma), occupational health (workplace accidents), control of malaria, effective management of snake bite, clean water (diarrhoea), or good obstetrical care (eclampsia, post-partum haemorrhage) will help to align the 0by25 initiative with the objectives of current and potential stakeholders—especially for people who do not work in the health sector but are economically and administratively responsible for its development. Opportunities for vertical integration within broader health initiatives and especially the inclusion of AKI within sub-objectives of the Sustainable Development Goal 3 ("ensure healthy lives and promote wellbeing for all at all ages"[180]), should be identified and pursued.

Second, treatment of severe AKI might be viewed as economically impractical for LMICs, and thus out of scope for governments and non-governmental stakeholders. Framing AKI as a problem that disproportionately affects people during their economically productive years, and which can be treated at a reasonable cost (as little as US$150 to save one life[181]), might help persuade such stakeholders of the potential merits of prevention and treatment.

Third, poor people are disproportionately exposed to severe AKI and are more susceptible to its consequences for many reasons, yet they have substantially less access to effective treatment. Framing acute kidney injury as a driver of inequity within and between countries, and the 0by25 initiative as a potential solution, might help to build support among some stakeholders, including governments and charities.

Fourth, framing requisite data in a way that aligns with the broader 0by25 framework will allow understanding and reinforce the overall goals of the initiative. Where possible, the 5 Rs (risk, recognition, response, renal support, and resources) should be used to frame and contextualise data about AKI and its consequences: with use of comparisons between and within regions as well as changes over time to show progress and opportunities.

If repeated regularly, the Global Snapshot will measure progress towards the 0by25 goal, to sustain momentum for the initiative, and to show return on investment. Randomised trials of prevention and treatment strategies, international comparisons, health service integration and education research, and implementation studies will help assess the burden of disease and identify potential solutions.

Finally, partnering with organisations that have expertise in patient-centred research priorities (such as the James Lind Alliance[182]) should help to ensure that future studies fully capture the effect of AKI on patients and their families. This inclusion, in turn, will allow future efforts to engage key stakeholders. Of the existing evidence gaps, better data from trials about how to prevent and treat AKI are most needed.

Making the economic case for the 0by25 goal

Advocacy for dialytic treatment of AKI must include the message that acute dialysis for 1–2 weeks is potentially lifesaving and affordable, even in very low resource settings. Although haemodialysis is often preferred in high-income countries, it is not available or practical in many low-resource settings because of unreliable electricity and water supplies, as well as the costs of equipment and its maintenance. By contrast, acute peritoneal dialysis is technically feasible in nearly all settings because there is no requirement for electricity and water supplies and the fluid-exchange process is gravity driven. However, there is a severe shortage of physicians who are trained to insert catheters or prescribe fluid exchanges for peritoneal dialysis and supplies are relatively expensive and typically produced overseas. The cost of treating an adult in sub-Saharan Africa is currently about $450 if a Tenckhoff catheter and imported fluids are used,[53] although costs would be reduced substantially

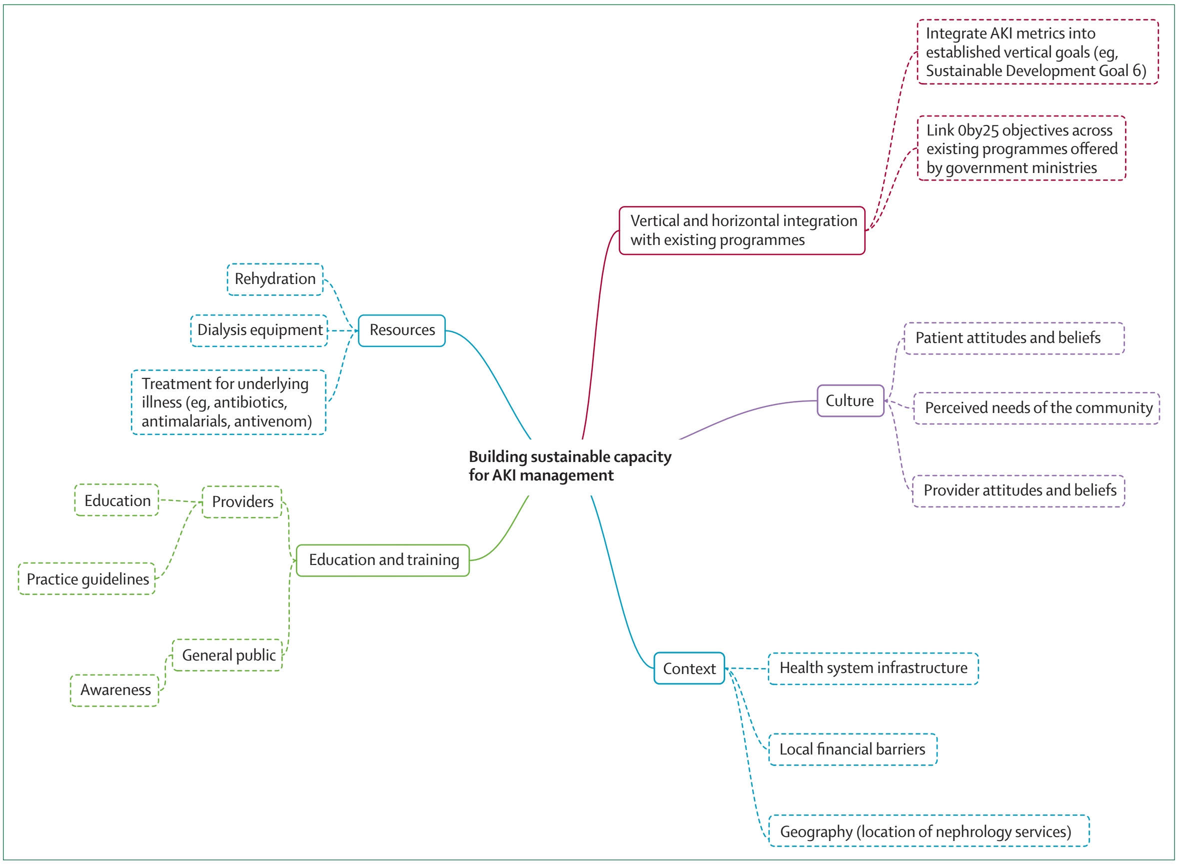

Figure 4: **Considerations relevant to building sustainable capacity for the 0by25 goal**
AKI=acute kidney injury.

with local production of fluids.[175] Increased use of other technical methods to access the peritoneum might reduce costs further; in India, 72 h of potentially lifesaving acute peritoneal dialysis can be provided with stylet-based catheter placement for as little as $150.[181]

The need for knowledge translation

Although necessary for progress, collection of relevant clinical and economic data alone is not sufficient: the information must be accessible and meaningful to key stakeholders. An integrated knowledge translation approach[183] will maximise the chance of success through integration of key stakeholders in all phases of work—from generating questions to dissemination of results. For AKI, this should establish a collaborative framework for problem solving between the ISN initiative and decision makers, with feedback from observational and implementation studies to design and assess the next steps. For instance the information gleaned from the Global Snapshot will inform the design and sites for implementation of longitudinal cohort studies. We will use this information to develop appropriate methods to disseminate information to policy makers and the public based on the existing health-care resources and knowledge of the environmental factors that are prevalent in the region. Methods used to communicate key messages should be customised for each setting. Knowledge learned from each implementation project would similarly guide subsequent steps.

Identification, engagement, and connection of a network of stakeholders

As for most complex health objectives, the 0by25 goal cannot be achieved by health ministries alone. Experience from fighting other diseases such as childhood diarrhoea, pneumonia, malaria, and malnutrition[184–186] shows that a concerted multisectoral effort to tackle AKI could lead to tremendous health gains, especially for the most disadvantaged people. Many partners will be needed to ensure the success of this initiative; some of which have already been identified. In addition to nephrologists, strong links with primary care providers (who see the majority of affected patients) and allied professionals such as clinical officers and nurses are needed to enhance the timely recognition and management of AKI. Relevant specialties that should be engaged include obstetrics, traumatology, intensive care, and infectious disease physicians. A key challenge will be to expand the number of centres able to provide high-quality AKI care. Centres in which there are existing partnerships between developed countries and LMICs might be useful to show proof of concept, but lessons learned need to be scaled up rapidly for broader adoption at regional and national levels.

Besides health professionals, strong links to government and non-government players are necessary to increase the chance of success. Within government, both vertical collaboration (ie, federal governments working with provincial and local counterparts) and horizontal collaboration (ie, between different ministries) will be essential. To help horizontal collaboration, relationships must be built between elected and non-elected officials to establish champions within government who see the value of prevention and treatment of AKI. A key facilitator for vertical collaboration will be to communicate the links between AKI and other aspects of the post-2015 development agenda such as Sustainable Development Goal 6 (ensure availability and sustainable management of water and sanitation for all[180]) and then to build links with non-governmental organisations and charities interested in achievement of these broader objectives.[187–189]

Finally, organisations of patients and citizens will be especially effective partners because patients' accounts of their experiences (often viewed by politicians as voters' experiences) are potentially powerful to influence policy and secure funds.[190] These personal accounts are an important supplement to the presentation of hard data and are crucial for appreciation of complex medical issues in civil society. The efforts to build and maintain connections between these diverse stakeholders, and to keep them engaged, will need to be sustained over time. Although this task is daunting, experience related to the control of HIV and non-communicable diseases show that such alliances are feasible and productive.[191,192]

Adapting initiatives to the local context

Besides financial capital, considerable additional human effort will be needed for the initiative. A key challenge in LMICs will be to support local health-care providers in planning and coordinating the care of patients with AKI in settings with widely varying health-care services, laboratory support, and educational organisations (figure 4). Achievement of the 0by25 goal will also require consideration of educational, cultural, and financial factors in the context of patient expectations and beliefs—adapting the services offered to the wishes and preferences of the medical community and civil society in each local community. Many educational guidelines for the management of AKI have been developed or are being developed, mainly for use in high-resource settings.[193] These guidelines must be put in the context of the educational and cultural background of health-care providers in villages and regional health clinics and in the context of what treatment options are available. Laboratory facilities are often unavailable in village health centres, and might not be consistently available even in referral centres. Implementation will demand consideration of specific local financial circumstances. Even if very cost effective by global standards, AKI prevention and treatment strategies might cause substantial financial hardship for patients and their families. Implementation of 0by25 at the local level must explicitly address this issue by ensuring that there is no incentive to sacrifice the financial security of individuals in pursuit of targets (eg, by providing dialysis to patients who will not benefit simply to improve performance on a particular metric). Third, it will be important to set realistic expectations about clinical outcomes among patients treated for AKI: families need to understand that death can occur even with the best of treatment and that not all people with AKI will recover kidney function, even with optimum treatment.

Building capacity

There are not enough nephrologists practising in LMICs to address the present incidence of AKI.[194] Management of severe AKI in LMICs is usually available only in large referral hospitals. Building of capacity for prevention and treatment of AKI in local communities will be crucial for the success of 0by25. Key early goals include: strengthening and supporting the ability of primary care physicians and other health professionals to recognise and manage AKI; empowering non-physician providers to work to their full scope of practice; facilitating prevention and initial treatment in local communities; and enabling appropriate referral to centres of excellence that can provide advanced AKI care. Many acute disorders are routinely managed by oral or intravenous rehydration and so there is already much capacity for prevention of AKI in LMICs. The widespread use of oral rehydration salts for management of acute diarrhoea is an example of a treatment that can be rapidly scaled up to achieve tremendous health benefits.

A second solution to the workforce gap is the education and training of non-physicians such as nurses or clinical officers, as was done for communicable illnesses such as HIV and tuberculosis. With appropriate training, such individuals could manage patients with AKI in their local communities, especially if telemedicine support was available. Since these providers give such a large proportion of clinical care in LMICs, it will be particularly important to educate them about the potential value of serum creatinine measurements in patients at risk for AKI so that kidney injury is more frequently recognised and managed before dialysis is needed. In addition to provision of direct patient care, non-physician providers could build capacity through education of physician and non-physician colleagues who have not had nephrology training. Several institutions in Europe, Africa, and South America have initiated such programmes, with encouraging early results.[195] Scaling up such initiatives is a potentially important mechanism for increasing capacity to prevent and manage AKI.

A third potential solution would be to train non-health professionals to recognise and manage uncomplicated urine output, including the clinical significance of sustained oliguria or anuria. Successful but disparate models for village health-care workers have been developed in several countries and have been used to manage a wide range of communicable and non-communicable diseases. There might be scope to integrate information about AKI into existing training schemes for providers.

Irrespective of whether efforts to build capacity are targeted at health professionals, the general public, or both, once trained individuals must be linked with providers who can provide advanced AKI care, including dialysis if needed. Therefore, teaching providers to recognise patients who need transfer for specialised care will be a core objective of capacity-building efforts (panel 5).

Asim Tanveer/Reuters/Corbis

The 0by25 goal will require cooperation between multiple government ministries such as education (provider training), public works and the environment (sanitation; clean water), and transport (road construction and safety). The ISN and other stakeholders will help to drive the horizontal integration of AKI into the objectives of these ministries across affected countries—as well as engaging charities, regional offices of the WHO, and other non-governmental organisations, as mentioned above.

Metrics for assessing progress

The ultimate goal of the 0by25 initiative is to eliminate preventable deaths from AKI. Progress towards this goal can be assessed in terms of metrics that are aligned with the 5 Rs (table 8). These metrics must be objective, measurable in low-resource settings, and should minimise the risk of unintended consequences while being sensitive to true progress towards the 0by25 goal. Some metrics can be assessed at the national level, whereas others will need targeted surveys in selected centres (table 8).

Knowledge and training are a prerequisite to assess the risk of AKI and identify clinical scenarios in which AKI is likely. Unfortunately, assessing changes in knowledge among providers across countries is not practical; a suitable but indirect surrogate is the proportion of medical schools that include a teaching encounter (lecture, small group session, and case study) focused on AKI (table 8).

Identification of AKI cases that might benefit from intervention not only needs risk assessment but also the availability of serum creatinine assays and timely measurement of kidney function in patients at risk. Many district hospitals in low-resource settings offer blood tests such as haemoglobin concentration or serum electrolytes but do not have consistent access to serum creatinine testing. This suggests that the proportion of health facilities that routinely offer serum creatinine testing would be a suitable metric for the 0by25 initiative, provided that the denominator is restricted to facilities that already offer blood-based laboratory testing (table 8).

Availability of tests is necessary but not sufficient: the assays must be used if they are to detect cases, but overly broad use of serum creatinine tests in low-risk patients would waste resources. Therefore the proportion of high-risk patients in whom serum creatinine is measured at least once during their hospital stay is another key metric. For very low resource settings where blood testing is not available, regular assessment of urine output could be used instead of serum creatinine assays (table 8). As well as the testing of high-risk patients listed in table 8, it would be desirable to measure the proportion of patients with AKI who received appropriate fluid infusion; who did not receive nephrotoxic medications; who had essential medications dose-adjusted for kidney function, etc. However, it might not be feasible to measure these characteristics in low-resource settings. It would be possible to assess the number of patients with AKI who are transferred to a specialised centre for management, but adoption of this metric might simply increase costs and inconvenience to the patient without improving outcomes. In addition, transfer to a specialised centre will not (on its own) improve outcomes.

Two key current barriers to the 0by25 goal are the poor availability of dialysis and the high cost of dialysis treatment. Therefore, the corresponding metrics we propose are the number of centres in each country that provide acute dialysis during each calendar year; the total number of treatments provided; the in-hospital mortality of patients receiving acute dialysis; and the average out-of-pocket cost associated with 2 weeks of acute dialysis treatment. These metrics should be provided separately for children (table 8). To differentiate between industry-driven and government-driven out-of-pocket costs, consideration should be given to also reporting the tariffs associated with importing dialysis fluids and other equipment.[196]

In high-income countries, a substantial proportion of the total human and financial burden of AKI is due to incomplete renal recovery with subsequent CKD. Patients with incomplete renal recovery might benefit from treatments that delay or avert progressive loss of kidney function, which in turn might be lifesaving. The key metric is the proportion of patients in whom serum creatinine is measured within 6 months of discharge from an AKI-related hospital admission, stratified by receipt of dialysis (table 8).

Ultimately, the key metric will be the number of deaths from AKI that occur every year, stratified by age and country. Together with data for the frequency of CKD in people who have had AKI, this information will assist inclusion of AKI in GBD,[79] which will help to achieve the

Panel 5: Skills required by non-physician care providers of acute kidney injury (AKI)

- Ability to impart basic information about risk factors for AKI to individuals in villages and small towns
- Assuming an adequate supply chain, ability to maintain an adequate stock of items (such as packaged electrolytes and antivenom) necessary in the prevention and basic treatment of illness leading to AKI
- Ability to use available diagnostic method (urine output, serum creatinine, and point-of-care testing) to identify AKI among patients at risk
- Management of patients with uncomplicated AKI: ensuring of adequate volume status, withdrawing of common toxins (drugs; traditional remedies), and monitoring for clinical deterioration
- Recognition of patients who require urgent acute dialysis for AKI
- (Optional): capacity to insert catheters for peritoneal dialysis in children and adults

	Comments
Overall	
Annual deaths from AKI, per 1 million population	Will be compared with existing incidence of AKI-related deaths in high-income countries; stratified by age (<16 *vs* ≥16 years)
Risk	
Proportion of medical schools that include a teaching encounter (lecture, small group session or case study) focused on AKI	..
Recognition	
Availability of serum creatinine assays among facilities where blood-based laboratory testing is already available	Systematic assessment of urine output might be an alternative for very low resource settings
Measurement of serum creatinine at least once in patients at high risk* of AKI	Stratified by age (<16 *vs* ≥16 years)
Response and renal support	
Number of centres that provided acute dialysis during each calendar year, with and without standardisation per 1 million population	Stratified by dialysis modality (peritoneal dialysis *vs* intermittent or continuous haemodialysis)
Total number of patients who need acute dialysis treated	Stratified by age (<16 *vs* ≥16 years)
In-hospital mortality among patients receiving acute dialysis	Stratified by age (<16 *vs* ≥16 years)
Average out-of-pocket cost associated with 2 weeks of acute dialysis	
Government tariffs associated with supplies needed for 2 weeks of acute dialysis	
Rehabilitation	
Proportion of patients in whom serum creatinine is measured within 6 months of discharge from an AKI-related hospital admission	Stratified by receipt of dialysis and age (<16 *vs* ≥16 years)

AKI=acute kidney injury. *Patients with severe diarrhoea (needing admission into hospital), those with trauma or post-partum haemorrhage needing blood transfusion, those admitted for urgent or emergent surgery, and anyone admitted to an intensive care or high-dependency unit.

Table 8: **Potential metrics for an AKI scorecard**

0by25 goal by increasing awareness and supporting attempts at vertical and horizontal integration.

Establishing an accountability framework for AKI

Together with other key stakeholders, such as the International Federation of Kidney Foundations and national nephrology societies from around the world, the ISN will lead the development and coordination of an independent mechanism to hold governments to account for the performance of their health systems in terms of AKI management, using the AKI scorecard.[197,198] Given that dialysis fluids and catheters are essential to the scaling up of acute dialysis, a secondary objective of the framework will be to hold to account industry and government for the cost and availability of these materials. This work will be led by an ISN standing committee (the ISN Global AKI Coordinating Committee), which reports to ISN Executive (figure 5).

The scorecard will serve three key purposes. First, publishing of information on health-system performance on AKI will help to raise awareness about the potentially preventable nature of AKI-related deaths. Rather than punishing or shaming countries with lower scores, the scorecard will aim to show opportunities for collaboration within and across sectors, which could lead to better outcomes.[199] Second, the AKI scorecard should help to identify countries in which appropriately regulated partnerships with industry would be especially valuable—eg, to provide low-cost diagnostics or to reduce the cost of dialysis supplies.[200] Third, comparisons between countries could show positive deviants:[197] settings in which better-than-expected performance can help otherwise similar neighbours to improve.

Effective use of the results of the scorecard will need cooperation between multiple government ministries. Because customs, labour, and licensure regulations in certain countries seem to be a substantial barrier to the cross-border movement of potentially lifesaving materials (eg, dialysis fluid and catheters) and personnel (eg, trained physicians and nurses), ministries responsible for regulating customs duties and provider training should also be involved. The ISN and other stakeholders will help to drive the horizontal integration of AKI into the objectives of these ministries across affected countries.

As recommended by Beaglehole and colleagues,[198] the framework will be based on the monitor–review–remedy principle, and will be implemented in LMICs where the burden of AKI is high or the need is greatest. As has been done for other diseases,[201] the framework will first be implemented in a pilot cohort of champion countries, and scaled up thereafter. This process will need continuing measurement of the metrics in table 8 nationally by participating LMICs. The principles of monitoring and reviewing concerns and making data available for discussion by stakeholders (including clinicians, academia, decision makers, patient advocates, the public, and industry), implies that the stakeholders will take action on the findings from the review, aiming to improve health-system performance and clinical outcomes.

The ISN will establish a national working group within each participating LMIC to collect data on the requisite metrics, lead country-level review, and spearhead remedial

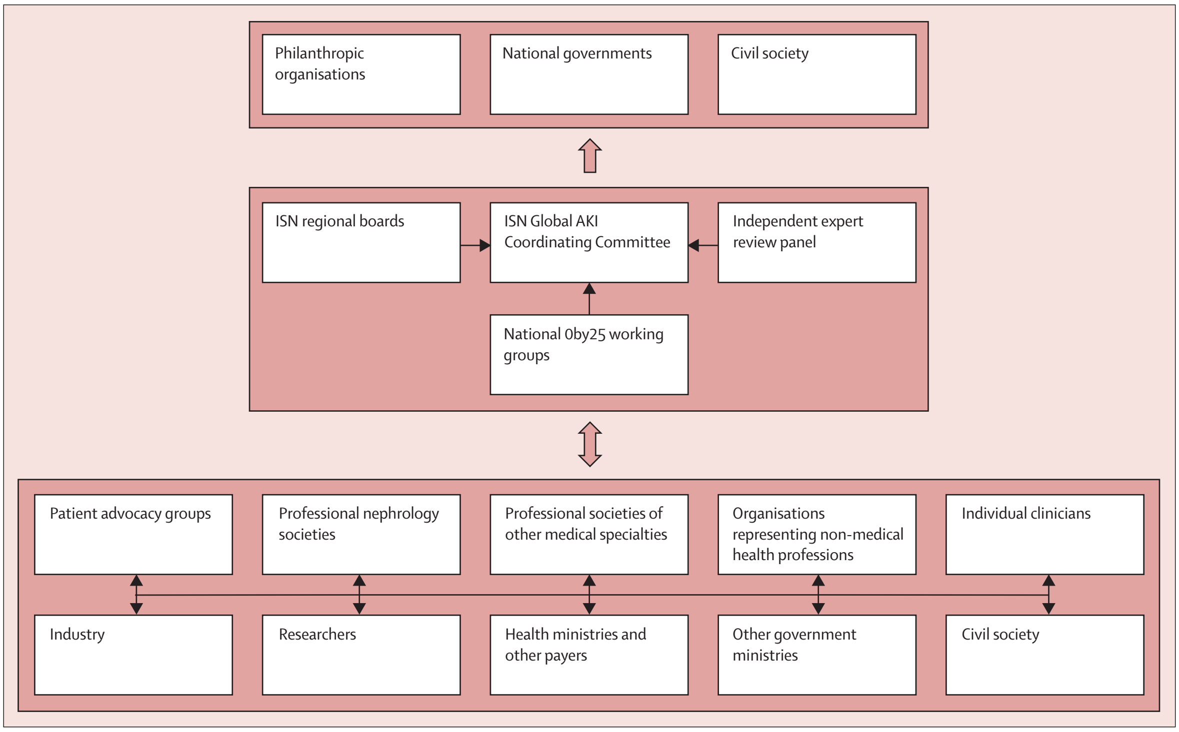

Figure 5: **Accountability framework for the 0by25 initiative**

action (figure 4). Findings from the national working groups will be reported at the World Congress of Nephrology each year and will be simultaneously published online on the 0by25 website, beginning with the 2017 congress in Mexico City. The ISN will also establish an independent expert review group (based on the proposed Expert Review Group for the Global NCD Action Plan),[198] which will evaluate available data (including the national reports and follow-up data from the 0by25 Global Snapshot) and assess progress against the 0by25 goal. Finally, ISN will help the national working groups to disseminate the findings of each biannual review at country-level to relevant stakeholders, as well as directly communicating the findings to leaders from industry, members of the general population, and charitable organisations and non-governmental organisations. An important goal of the interaction between ISN and the national working groups will be to identify opportunities for effective multisectoral action to accelerate progress toward the 0by25 goal.

Anticipated challenges for 0by25 and proposed solutions

The 0by25 project will be viewed by many with scepticism as to its feasibility and likelihood of success given the many complex problems in management of AKI. However, the remarkable accomplishment of the AIDS 3by5 initiative (3 million people with HIV on anti-retroviral treatment by 2005) in low-resource countries provides evidence that concerted efforts can lead to success in reductions in the burden of devastating diseases. We anticipate several challenges for the initiative but we are confident that we have potential solutions for these. Key concerns for the initiative are: to what extent would the improvement in AKI care improve mortality given no direct evidence for a causal relationship; will there be adequate funding and support to develop and sustain the infrastructure for the initiative; will the initiative detract from other more important and beneficial health care initiatives (eg, provision of clean water and eradication of malaria); and would a reduction in mortality for AKI increase the number of patients who need long-term dialysis and add to the societal burden for ESRD management?

For the **website of 0by25** see www.0by25.org

We recognise that despite the consistent findings of many epidemiological studies worldwide that show an association between increased mortality and development of AKI, no direct evidence has been shown for a causal relationship between AKI and death. However, studies report that AKI is a contributory event to adverse outcomes and needs to be addressed as a modifiable factor. Although we might not be able to establish precisely the risk of mortality directly attributable to AKI, we believe that judiciously designed implementation projects will improve mortality.

The demands for health care in low-resource regions, as well as in many low-income countries, are changing. Ensuring of access to clean water and sanitation—basic and essential steps—and battling communicable disease and stemming the tide of preventable deaths, such as those due to AKI, should dominate the attention of those driving the health-care agenda in most countries in

For more on **3by5** see http://www.who.int/3by5/en/

low-resource regions. ISN has developed the 0by25 initiative to catalyse an acceleration of these much needed changes. We strongly believe that concerted efforts to eradicate the most common causes of AKI (infections, environmental risks, and drug toxicity) will be key to reductions in mortality from AKI. We recognise that resource constraints will be important considerations in the prioritisation of targeted interventions for AKI and we will need to ensure that provision of dialysis does not come at the expense of the ability of health-care systems to meet other needs in the region. We will look to partner with existing organisations and governmental agencies to advance the initiative, keeping these points in mind.

Reductions in deaths from AKI will probably lead to an increase in patients who will have CKD and might convert to ESRD, needing chronic dialysis or transplantation.[202–205] Long-term RRT for ESRD will not be an option for patients in most LMICs; however, there is much goodwill in the international nephrology community to assist in the development of AKI programmes for peritoneal dialysis. Lessons learned in Tanzania (Moshi) at the Kilimanjaro Christian Medical Centre,[206] as well as anecdotal initiatives in other sub-Saharan countries and in Asia, show that, in a setting of low resources, good results from peritoneal dialysis are possible and can have favourable outcomes in patients with AKI and also be an affordable dialysis method for patients with ESRD. The 0by25 programme builds on and would implement the Saving Young Lives project a partnership among ISN and the International Paediatric Nephrology Association, International Society of Peritoneal Dialysis, and Sustainable Kidney Care Foundations, already in place and initially funded and supported by the Recanati–Kaplan Foundation. We believe that improved knowledge, coupled with advances in technology and improvements in health care, will provide additional novel approaches for the management of chronic diseases. Some evidence suggests that appropriate management of CKD and its risk factors, to prevent disease progression to ESRD in resource-poor settings, is affordable with the use of cheap drugs and simple organisation.[207] Our proposed strategy will be sustainable because it focuses not only on immediate improvement of care but also on developing education and training programmes for local delivery of care, and enables progress to be measured and challenged.

For the **Saving Young Lives project** see http://www.theisn.org/isn-information/saving-young-lives-in-africa-and-asia/itemid-1050

We have established partnerships with Astute Medical, Danone Nutricia Research, and Bellco as partners with financial support. IHME and the GBD study group have partnered to incorporate AKI in the GBD reports. The 0by25 initiative has been endorsed by more than 20 nephrology societies who are actively engaging their membership in the initiative. In addition, we seek the support and involvement of key stakeholders from multiple arenas who will bring their knowledge, expertise, resources, and network connections to the table.

Future perspective

The effect of AKI on morbidity and mortality will be shaped by advances in methods to detect AKI earlier in the disease course and improvements in epidemiological research to determine the true burden of AKI incidence worldwide, especially in LMICs. However, this will only be feasible if diagnostics are made available at low cost, and, more importantly, if national health authorities can be co-opted to assure the sustainability of AKI programmes. Authorities need to develop health information systems to capture data to better measure the incidence of AKI and track patient outcomes; improve sanitation and health-care provision to prevent or at least reduce the burden of AKI; and provide acute RRT for those in need. ISN's 0by25 initiative offers a great opportunity to help eliminate disparities in access to and affordability of health care for AKI, and, eventually, save many lives.

Contributors

RLM, GR, MT, JC, and EAB conceived of and designed the Commission. JC, MT, GG-G, EAB, RL, BJ, VJ, MSS, NP, AL, BT, RV, PS, and NHL did the literature search. JC, MT, GG-G, EAB, BJ, VJ, MSS, NP, BT, RV, PS, and NHL collected data. RLM, MT, JC, EAB, DC, PS, MR, MP, RL, NHL, and VJ did the analysis. RLM, GR, MT, GG-G, JC, EAB, NL, JF, FF, MR, and NHL interpreted data. RLM, MT, GG-G, JC, EAB, GR, EA-S, BT, MR, and NHL wrote the text. RLM, MT, JC, and EAB created the figures. RLM, GR, MT, JC, and EAB reviewed and revised the final Commission.

Declaration of interests

We declare no competing interests.

Acknowledgments

We thank Arjan van der Tol, Valerie Luyckx, and Noel Gibney for their wonderful work with the RDRTF/ISN (Renal Disaster Relief Task Force of the International Society of Nephrology) for providing the epidemiologic earthquake data; and Sue Lahey and Ann Marie L'Hommedieu from the Schaffer Library, Albany Medical College (NY, USA) for their invaluable help in the literature search. The International Society of Nephrology (ISN) provided funding through unrestricted grants to the 0by25 initiative, gave logistic support for this study, and holds all copyrights on the data obtained through this study. Further support has been provided through unrestricted grants from Astute Medical (San Diego, CA, USA), Danone Nutricia Research (Palaiseau, France) and Bellco (Mirandola, Italy).

References

1 Lewington AJ, Cerdá J, Mehta RL. Raising awareness of acute kidney injury: a global perspective of a silent killer. *Kidney Int* 2013; **84:** 457–67.

2 Chawla LS, Eggers PW, Star RA, Kimmel PL. Acute kidney injury and chronic kidney disease as interconnected syndromes. *N Engl J Med* 2014; **371:** 58–66.

3 Susantitaphong P, Cruz DN, Cerda J, et al, and the Acute Kidney Injury Advisory Group of the American Society of Nephrology. World incidence of AKI: a meta-analysis. *Clin J Am Soc Nephrol* 2013; **8:** 1482–93.

4 Das P, Samarasekera U. The story of GBD 2010: a "super-human" effort. *Lancet* 2012; **380:** 2067–70.

5 Lameire NH, Bagga A, Cruz D, et al. Acute kidney injury: an increasing global concern. *Lancet* 2013; **382:** 170–79.

6 Cerdá J, Lameire N, Eggers P, et al. Epidemiology of acute kidney injury. *Clin J Am Soc Nephrol* 2008; **3:** 881–86.

7 Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P, for the Acute Dialysis Quality Initiative workgroup. Acute renal failure - definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis Quality Initiative (ADQI) Group. *Crit Care* 2004; **8:** R204–12.

8 Group KAW. KDIGO clinical practice guideline for acute kidney injury. *Kidney Int* 2012; **2** (suppl)**:** 1–138.

9 Rewa O, Bagshaw SM. Acute kidney injury–epidemiology, outcomes and economics. *Nat Rev Nephrol* 2014; **10:** 193–207.

10 Cerdá J, Bagga A, Kher V, Chakravarthi RM. The contrasting characteristics of acute kidney injury in developed and developing countries. *Nat Clin Pract Nephrol* 2008; **4:** 138–53.

11 Jha V, Parameswaran S. Community-acquired acute kidney injury in tropical countries. *Nat Rev Nephrol* 2013; **9:** 278–90.

12 Naicker S, Aboud O, Gharbi MB. Epidemiology of acute kidney injury in Africa. *Semin Nephrol* 2008; **28:** 348–53.

13 Lombardi R, Yu L, Younes-Ibrahim M, Schor N, Burdmann EA. Epidemiology of acute kidney injury in Latin America. *Semin Nephrol* 2008; **28:** 320–29.

14 Coca SG, Yusuf B, Shlipak MG, Garg AX, Parikh CR. Long-term risk of mortality and other adverse outcomes after acute kidney injury: a systematic review and meta-analysis. *Am J Kidney Dis* 2009; **53:** 961–73.

15 Daher EF, Silva Junior GB, Santos SQ, et al. Differences in community, hospital and intensive care unit-acquired acute kidney injury: observational study in a nephrology service of a developing country. *Clin Nephrol* 2012; **78:** 449–55.

16 Chawla LS, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. *Kidney Int* 2012; **82:** 516–24.

17 Coca SG. Long-term outcomes of acute kidney injury. *Curr Opin Nephrol Hypertens* 2010; **19:** 266–72.

18 Coca SG, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int* 2012; **81:** 442–48.

19 Kerr M, Bedford M, Matthews B, O'Donoghue D. The economic impact of acute kidney injury in England. *Nephrol Dial Transplant* 2014; **29:** 1362–68.

20 Ujah IA, Aisien OA, Mutihir JT, Vanderjagt DJ, Glew RH, Uguru VE. Factors contributing to maternal mortality in north-central Nigeria: a seventeen-year review. *Afr J Reprod Health* 2005; **9:** 27–40.

21 Fliser D, Laville M, Covic A, et al, for the Ad-hoc working group of ERBP. A European Renal Best Practice (ERBP) position statement on the Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines on acute kidney injury: part 1: definitions, conservative management and contrast-induced nephropathy. *Nephrol Dial Transplant* 2012; **27:** 4263–72.

22 James M, Bouchard J, Ho J, et al. Canadian Society of Nephrology commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. *Am J Kidney Dis* 2013; **61:** 673–85.

23 Okusa MD, Davenport A. Reading between the (guide)lines--the KDIGO practice guideline on acute kidney injury in the individual patient. *Kidney Int* 2014; **85:** 39–48.

24 Palevsky PM, Liu KD, Brophy PD, et al. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for acute kidney injury. *Am J Kidney Dis* 2013; **61:** 649–72.

25 Thomas ME, Blaine C, Dawnay A, et al. The definition of acute kidney injury and its use in practice. *Kidney Int* 2015; **87:** 62–73.

26 Goldstein SL, Jaber BL, Faubel S, Chawla LS, for the Acute Kidney Injury Advisory Group of American Society of Nephrology. AKI transition of care: a potential opportunity to detect and prevent CKD. *Clin J Am Soc Nephrol* 2013; **8:** 476–83.

27 Thomas ME, Sitch A, Baharani J, Dowswell G. Earlier intervention for acute kidney injury: evaluation of an outreach service and a long-term follow-up. *Nephrol Dial Transplant* 2015; **30:** 239–44.

28 Swanepoel CR, Wearne N, Okpechi IG. Nephrology in Africa–not yet uhuru. *Nat Rev Nephrol* 2013; **9:** 610–22.

29 Chawla LS, Amdur RL, Shaw AD, Faselis C, Palant CE, Kimmel PL. Association between AKI and long-term renal and cardiovascular outcomes in United States veterans. *Clin J Am Soc Nephrol* 2014; **9:** 448–56.

30 Leung KC, Tonelli M, James MT. Chronic kidney disease following acute kidney injury-risk and outcomes. *Nat Rev Nephrol* 2013; **9:** 77–85.

31 Li PK, Burdmann EA, Mehta RL, for the World Kidney Day Steering Committee 2013. Acute kidney injury: global health alert. *Kidney Int* 2013; **83:** 372–76.

32 Mehta RL, Kellum JA, Shah SV, et al, for the Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. *Crit Care* 2007; **11:** R31.

33 Waikar SS, Liu KD, Chertow GM. The incidence and prognostic significance of acute kidney injury. *Curr Opin Nephrol Hypertens* 2007; **16:** 227–36.

34 Waikar SS, Wald R, Chertow GM, et al. Validity of International Classification of Diseases, ninth revision, clinical modification codes for acute renal failure. *J Am Soc Nephrol* 2006; **17:** 1688–94.

35 Xue JL, Daniels F, Star RA, et al. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. *J Am Soc Nephrol* 2006; **17:** 1135–42.

36 Grams ME, Waikar SS, MacMahon B, Whelton S, Ballew SH, Coresh J. Performance and limitations of administrative data in the identification of AKI. *Clin J Am Soc Nephrol* 2014; **9:** 682–89.

37 Bagshaw SM, George C, Dinu I, Bellomo R. A multi-centre evaluation of the RIFLE criteria for early acute kidney injury in critically ill patients. *Nephrol Dial Transplant* 2008; **23:** 1203–10.

38 Kellum JA, Bellomo R, Ronco C. Classification of acute kidney injury using RIFLE: What's the purpose? *Crit Care Med* 2007; **35:** 1983–84.

39 Ricci Z, Cruz D, Ronco C. The RIFLE criteria and mortality in acute kidney injury: a systematic review. *Kidney Int* 2008; **73:** 538–46.

40 Thakar CV, Christianson A, Freyberg R, Almenoff P, Render ML. Incidence and outcomes of acute kidney injury in intensive care units: a Veterans Administration study. *Crit Care Med* 2009; **37:** 2552–58.

41 Joannidis M, Metnitz B, Bauer P, et al. Acute kidney injury in critically ill patients classified by AKIN versus RIFLE using the SAPS 3 database. *Intensive Care Med* 2009; **35:** 1692–702.

42 Ostermann M, Chang RW. Acute kidney injury in the intensive care unit according to RIFLE. *Crit Care Med* 2007; **35:** 1837–43, quiz 1852.

43 Ali T, Khan I, Simpson W, et al. Incidence and outcomes in acute kidney injury: a comprehensive population-based study. *J Am Soc Nephrol* 2007; **18:** 1292–98.

44 Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. *Crit Care Med* 2006; **34:** 1913–17.

45 Fujii T, Uchino S, Takinami M, Bellomo R. Subacute kidney injury in hospitalized patients. *Clin J Am Soc Nephrol* 2014; **9:** 457–61.

46 Zeng X, McMahon GM, Brunelli SM, Bates DW, Waikar SS. Incidence, outcomes, and comparisons across definitions of AKI in hospitalized individuals. *Clin J Am Soc Nephrol* 2014; **9:** 12–20.

47 Selewski DT, Cornell TT, Heung M, et al. Validation of the KDIGO acute kidney injury criteria in a pediatric critical care population. *Intensive Care Med* 2014; **40:** 1481–88.

48 Hoste EA, De Corte W. Epidemiology of AKI in the ICU. *Acta Clin Belg Suppl* 2007; **2:** 314–17.

49 Hsu CY, McCulloch CE, Fan D, Ordoñez JD, Chertow GM, Go AS. Community-based incidence of acute renal failure. *Kidney Int* 2007; **72:** 208–12.

50 Wald R, McArthur E, Adhikari NK, et al. Changing incidence and outcomes following dialysis-requiring acute kidney injury among critically ill adults: a population-based cohort study. *Am J Kidney Dis* 2014; published online Dec 17. DOI: 10.1053/j.ajkd.2014.10.017.

51 National Institute of Diabetes and Digestive and Kidney Diseases. United States Renal Data System, 2014 Annual Data Report: epidemiology of kidney disease in the United States. Bethesda: National Institutes of Health, 2014.

52 Porter CJ, Juurlink I, Bisset LH, Bavakunji R, Mehta RL, Devonald MA. A real-time electronic alert to improve detection of acute kidney injury in a large teaching hospital. *Nephrol Dial Transplant* 2014; **29:** 1888–93.

53 Callegari J, Antwi S, Wystrychowski G, Zukowska-Szczechowska E, Levin NW, Carter M. Peritoneal dialysis as a mode of treatment for acute kidney injury in sub-Saharan Africa. *Blood Purif* 2013; **36:** 226–30.

54 Waikar SS, Curhan GC, Wald R, McCarthy EP, Chertow GM. Declining mortality in patients with acute renal failure, 1988 to 2002. *J Am Soc Nephrol* 2006; **17:** 1143–50.

55 Joyce VR, Smith MW, Johansen KL, et al, for the Veteran Affairs/National Institutes of Health Acute Renal Failure Trial Network. Health-related quality of life as a predictor of mortality among survivors of AKI. *Clin J Am Soc Nephrol* 2012; **7:** 1063–70.

56 Akcan-Arikan A, Zappitelli M, Loftis LL, Washburn KK, Jefferson LS, Goldstein SL. Modified RIFLE criteria in critically ill children with acute kidney injury. *Kidney Int* 2007; **71:** 1028–35.

57 Bailey D, Phan V, Litalien C, et al. Risk factors of acute renal failure in critically ill children: A prospective descriptive epidemiological study. *Pediatr Crit Care Med* 2007; **8:** 29–35.

58 Wald R, Quinn RR, Luo J, et al, for the University of Toronto Acute Kidney Injury Research Group. Chronic dialysis and death among survivors of acute kidney injury requiring dialysis. *JAMA* 2009; **302:** 1179–85.

59 Bucaloiu ID, Kirchner HL, Norfolk ER, Hartle JE 2nd, Perkins RM. Increased risk of death and de novo chronic kidney disease following reversible acute kidney injury. *Kidney Int* 2012; **81:** 477–85.

60 Jones J, Holmen J, De Graauw J, Jovanovich A, Thornton S, Chonchol M. Association of complete recovery from acute kidney injury with incident CKD stage 3 and all-cause mortality. *Am J Kidney Dis* 2012; **60:** 402–08.

61 William T, Menon J, Rajahram G, et al. Severe *Plasmodium knowlesi* malaria in a tertiary care hospital, Sabah, Malaysia. *Emerg Infect Dis* 2011; **17:** 1248–55.

62 Wasnik PN, Manohar TP, Humaney NR, Salkar HR. Study of clinical profile of falciparum malaria in a tertiary referral centre in Central India. *J Assoc Physicians India* 2012; **60:** 33–36.

63 Vikrant S, Dheer SK, Parashar A, et al. Scrub typhus associated acute kidney injury--a study from a tertiary care hospital from western Himalayan State of India. *Ren Fail* 2013; **35:** 1338–43.

64 Suchithra N, Pappachan JM, Sujathan P. Snakebite envenoming in Kerala, South India: clinical profile and factors involved in adverse outcomes. *Emerg Med J* 2008; **25:** 200–04.

65 Rizwan N, Uddin SF. Obstetrical acute renal failure: a challenging medical complication. *J Ayub Med Coll Abbottabad* 2011; **23:** 66–68.

66 Prakash J, Niwas SS, Parekh A, et al. Acute kidney injury in late pregnancy in developing countries. *Ren Fail* 2010; **32:** 309–13.

67 Najar MS, Shah AR, Wani IA, et al. Pregnancy related acute kidney injury: a single center experience from the Kashmir Valley. *Indian J Nephrol* 2008; **18:** 159–61.

68 Herath NJ, Kularatne SA, Weerakoon KG, Wazil A, Subasinghe N, Ratnatunga NV. Long term outcome of acute kidney injury due to leptospirosis? A longitudinal study in Sri Lanka. *BMC Res Notes* 2014; **7:** 398.

69 Vachiat AIME, Wadee S, Naicker S. Renal failure in HIV-positive patients - a South African experience. *Clin Kidney J* 2013; **6:** 584–89.

70 Santacruz F, Barreto S, Mayor MM, Cabrera W, Breuer N. Mortality in elderly patients with acute renal failure. *Ren Fail* 1996; **18:** 601–05.

71 Lombardi R, Zampedri L, Rodriguez I, Alegre S, Ursu M, Di Fabio M. Prognosis in acute renal failure of septic origin: a multivariate analysis. *Ren Fail* 1998; **20:** 725–32.

72 Vanholder R, Sever MS, De Smet M, Erek E, Lameire N. Intervention of the Renal Disaster Relief Task Force in the 1999 Marmara, Turkey earthquake. *Kidney Int* 2001; **59:** 783–91.

73 Sever MS, Erek E, Vanholder R, Lameire N. Effect of gender on various parameters of crush syndrome victims of the Marmara earthquake. *J Nephrol* 2004; **17:** 399–404

74 Vanholder R, Borniche D, Claus S, et al. When the earth trembles in the Americas: the experience of Haiti and Chile 2010. *Nephron Clin Pract* 2011; 117: c184–97.

75 Vanholder R, van der Tol A, De Smet M, et al. Earthquakes and crush syndrome casualties: lessons learned from the Kashmir disaster. *Kidney Int* 2007; **71:** 17–23.

76 Bedford M, Stevens PE, Wheeler TW, Farmer CK. What is the real impact of acute kidney injury? *BMC Nephrol* 2014; **15:** 95.

77 Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. *Am J Med* 1983; **74:** 243–48.

78 Hsu RK, McCulloch CE, Dudley RA, Lo LJ, Hsu CY. Temporal changes in incidence of dialysis-requiring AKI. *J Am Soc Nephrol* 2013; **24:** 37–42.

79 Hwang YJ, Shariff SZ, Gandhi S, et al. Validity of the International Classification of Diseases, Tenth Revision code for acute kidney injury in elderly patients at presentation to the emergency department and at hospital admission. *BMJ Open* 2012; published online Nov 29. DOI: 10.1136/bmjopen-2012-001821.

80 Liangos O, Wald R, O'Bell JW, Price L, Pereira BJ, Jaber BL. Epidemiology and outcomes of acute renal failure in hospitalized patients: a national survey. *Clin J Am Soc Nephrol* 2006; **1:** 43–51.

81 Nash K, Hafeez A, Hou S. Hospital-acquired renal insufficiency. *Am J Kidney Dis* 2002; **39:** 930–36.

82 Siddiqui NF, Coca SG, Devereaux PJ, et al. Secular trends in acute dialysis after elective major surgery—1995 to 2009. *CMAJ* 2012; **184:** 1237–45.

83 Swaminathan M, Shaw AD, Phillips-Bute BG, et al. Trends in acute renal failure associated with coronary artery bypass graft surgery in the United States. *Crit Care Med* 2007; **35:** 2286–91.

84 Santos WJ, Zanetta DM, Pires AC, Lobo SM, Lima EQ, Burdmann EA. Patients with ischaemic, mixed and nephrotoxic acute tubular necrosis in the intensive care unit--a homogeneous population? *Crit Care* 2006; **10:** R68.

85 Daher EF, Junior Silva GB, Vieira AP, et al. Acute kidney injury in a tropical country: a cohort study of 253 patients in an infectious diseases intensive care unit. *Rev Soc Bras Med Trop* 2014; **47:** 86–89.

86 Saravu K, Rishikesh K, Parikh CR. Risk factors and outcomes stratified by severity of acute kidney injury in malaria. *PLoS One* 2014; **9:** e90419.

87 Esezobor CI, Ladapo TA, Osinaike B, Lesi FE. Paediatric acute kidney injury in a tertiary hospital in Nigeria: prevalence, causes and mortality rate. *PLoS One* 2012; **7:** e51229.

88 Mathew AJ, George J. Acute kidney injury in the tropics. *Ann Saudi Med* 2011; **31:** 451–56.

89 Lombardi R, Rosa-Diez G, Ferreiro A, et al, for the Acute Kidney Injury Committee of the Latin American Society of Nephrology and Hypertension Working Group. Acute kidney injury in Latin America: a view on renal replacement therapy resources. *Nephrol Dial Transplant* 2014; **29:** 1369–76.

90 Murray CJ, Ezzati M, Flaxman AD, et al. GBD 2010: design, definitions, and metrics. *Lancet* 2012; **380:** 2063–66.

91 Stewart J, Findlay G, Smith N, Kelly K, Mason M. Adding insult to injury: a review of the care of patients who died in hospital with a primary diagnosis of acute kidney injury (acute renal failure). London: National Confidential Enquiry into Patient Outcome and Death, 2009.

92 Aitken E, Carruthers C, Gall L, Kerr L, Geddes C, Kingsmore D. Acute kidney injury: outcomes and quality of care. *QJM* 2013; **106:** 323–32.

93 Basoor A, Doshi NC, Cotant JF, et al. Decreased readmissions and improved quality of care with the use of an inexpensive checklist in heart failure. *Congest Heart Fail* 2013; **19:** 200–06.

94 Xu G, Baines R, Westacott R, Selby N, Carr S. An educational approach to improve outcomes in acute kidney injury (AKI): report of a quality improvement project. *BMJ Open* 2014; **4:** e004388.

95 Finlay S, Bray B, Lewington AJ, et al. Identification of risk factors associated with acute kidney injury in patients admitted to acute medical units. *Clin Med* 2013; **13:** 233–38.

96 Huang TM, Wu VC, Young GH, et al, for the National Taiwan University Hospital Study Group of Acute Renal Failure. Preoperative proteinuria predicts adverse renal outcomes after coronary artery bypass grafting. *J Am Soc Nephrol* 2011; **22:** 156–63.

97 Paula Santos U, Zanetta DM, Terra-Filho M, Burdmann EA. Burnt sugarcane harvesting is associated with acute renal dysfunction. *Kidney Int* 2014; published online Sep 17. DOI: 10.1038/ki.2014.306.

98 Cho A, Lee JE, Yoon JY, et al. Effect of an electronic alert on risk of contrast-induced acute kidney injury in hospitalized patients undergoing computed tomography. *Am J Kidney Dis* 2012; **60:** 74–81.

99 McMahon GM ZX, Waikar SS. A risk prediction score for kidney failure or mortality in rhabdomyolysis. *JAMA Intern Med*. 2013; **173:** 1821–28.

100 Palmieri T, Lavrentieva A, Greenhalgh DG. Acute kidney injury in critically ill burn patients. Risk factors, progression and impact on mortality. *Burns* 2010; **36:** 205–11.

101 Shephard MD. Point-of-Care testing and creatinine measurement. *Clin Biochem Rev* 2011; **32:** 109–14.

102 Bedford M, Farmer C, Levin A, Ali T, Stevens P. Acute kidney injury and CKD: chicken or egg? *Am J Kidney Dis* 2012; **59:** 485–91.

103 Colpaert K, Hoste EA, Steurbaut K, et al. Impact of real-time electronic alerting of acute kidney injury on therapeutic intervention and progression of RIFLE class. *Crit Care Med* 2012; **40:** 1164–70.

104 Porter CJ, Juurlink I, Bisset LH, Bavakunji R, Mehta RL, Devonald MA. A real-time electronic alert to improve detection of acute kidney injury in a large teaching hospital. *Nephrol Dial Transplant* 2014; **29:** 1888–93.

105 Cruz DNMR, Mehta RL. Acute kidney injury in 2013: breaking barriers for biomarkers in AKI–progress at last. *Nat Rev Nephrol* 2014; **10:** 74–76.

106 Arthur JM, Hill EG, Alge JL, et al, for the SAKInet Investigators. Evaluation of 32 urine biomarkers to predict the progression of acute kidney injury after cardiac surgery. *Kidney Int* 2014; **85:** 431–38.

107 Kerr KF, Meisner A, Thiessen-Philbrook H, Coca SG, Parikh CR. Developing risk prediction models for kidney injury and assessing incremental value for novel biomarkers. *Clin J Am Soc Nephrol* 2014; **9:** 1488–96.

108 Murray PT, Mehta RL, Shaw A, et al, for the ADQI 10 workgroup. Potential use of biomarkers in acute kidney injury: report and summary of recommendations from the 10th Acute Dialysis Quality Initiative consensus conference. *Kidney Int* 2014; **85:** 513–21.

109 Macedo E, Bouchard J, Soroko SH, et al, for the Program to Improve Care in Acute Renal Disease Study. Fluid accumulation, recognition and staging of acute kidney injury in critically-ill patients. *Crit Care* 2010; **14:** R82.

110 Bouchard J, Soroko SB, Chertow GM, et al, for the Program to Improve Care in Acute Renal Disease (PICARD) Study Group. Fluid accumulation, survival and recovery of kidney function in critically ill patients with acute kidney injury. *Kidney Int* 2009; **76:** 422–27.

111 Bagshaw SM, Brophy PD, Cruz D, Ronco C. Fluid balance as a biomarker: impact of fluid overload on outcome in critically ill patients with acute kidney injury. *Crit Care* 2008; **12:** 169.

112 Dass B, Shimada M, Kambhampati G, Ejaz NI, Arif AA, Ejaz AA. Fluid balance as an early indicator of acute kidney injury in CV surgery. *Clin Nephrol* 2012; **77:** 438–44.

113 Kambhampati G, Ross EA, Alsabbagh MM, et al. Perioperative fluid balance and acute kidney injury. *Clin Exp Nephrol* 2012; **16:** 730–38.

114 Hassinger AB, Wald EL, Goodman DM. Early postoperative fluid overload precedes acute kidney injury and is associated with higher morbidity in pediatric cardiac surgery patients. *Pediatr Crit Care Med* 2014; **15:** 131–38.

115 Kellum JACJ, Cerda J, Kaplan LJ, Nadim MK, Palevsky PM. Fluids for prevention and management of acute kidney injury. *Int J Artif Organs* 2008; **31:** 96–110.

116 Venkataraman R, Kellum JA. Prevention of acute renal failure. *Chest* 2007; **131:** 300–08.

117 Kiguli S, Akech SO, Mtove G, et al. WHO guidelines on fluid resuscitation in children: missing the FEAST data. *BMJ* 2014; **348:** f7003.

118 Maitland K, George EC, Evans JA, et al, for the FEAST trial group. Exploring mechanisms of excess mortality with early fluid resuscitation: insights from the FEAST trial. *BMC Med* 2013; **11:** 68.

119 Maitland K, Kiguli S, Opoka RO, et al, for the FEAST Trial Group. Mortality after fluid bolus in African children with severe infection. *N Engl J Med* 2011; **364:** 2483–95.

120 Serpa Neto A, Veelo DP, Peireira VG, et al. Fluid resuscitation with hydroxyethyl starches in patients with sepsis is associated with an increased incidence of acute kidney injury and use of renal replacement therapy: a systematic review and meta-analysis of the literature. *J Crit Care* 2014; **29:** e1–7.

121 Caironi P, Tognoni G, Masson S, et al, for the ALBIOS Study Investigators. Albumin replacement in patients with severe sepsis or septic shock. *N Engl J Med* 2014; **370:** 1412–21.

122 McCullough PA. Contrast-induced acute kidney injury. *J Am Coll Cardiol* 2008; **51:** 1419–28.

123 Kelly AM, Dwamena B, Cronin P, Bernstein SJ, Carlos RC. Meta-analysis: effectiveness of drugs for preventing contrast-induced nephropathy. *Ann Intern Med* 2008; **148:** 284–94.

124 Gunal AI, Celiker H, Dogukan A, et al. Early and vigorous fluid resuscitation prevents acute renal failure in the crush victims of catastrophic earthquakes. *J Am Soc Nephrol* 2004; **15:** 1862–67.

125 Sever MSVR, Vanholder R, Lameire N. Management of crush-related injuries after disasters. *N Engl J Med* 2006; **354:** 1052–63.

126 Yunos NM, Bellomo R, Hegarty C, Story D, Ho L, Bailey M. Association between a chloride-liberal vs chloride-restrictive intravenous fluid administration strategy and kidney injury in critically ill adults. *JAMA* 2012; **308:** 1566–72.

127 Brienza N, Giglio MT, Marucci M, Fiore T. Does perioperative hemodynamic optimization protect renal function in surgical patients? A meta-analytic study. *Crit Care Med* 2009; **37:** 2079–90.

128 De Backer D, Biston P, Devriendt J, et al, and the SOAP II Investigators. Comparison of dopamine and norepinephrine in the treatment of shock. *N Engl J Med* 2010; **362:** 779–89.

129 Gordon AC, Russell JA, Walley KR, et al. The effects of vasopressin on acute kidney injury in septic shock. *Intensive Care Med* 2010; **36:** 83–91.

130 Dellinger RP, Levy MM, Rhodes A, et al, for the Surviving Sepsis Campaign Guidelines Committee including the Pediatric Subgroup. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med* 2013; **41:** 580–637.

131 Evans RGGB, Gardiner BS, Smith DW, O'Connor PM. Intrarenal oxygenation: unique challenges and the biophysical basis of homeostasis. *Am J Physiol Renal Physiol* 2008; **295:** F1259–70.

132 Li H, Qian Z, Liu Z, Liu X, Han X, Kang H. Risk factors and outcome of acute renal failure in patients with severe acute pancreatitis. *J Crit Care* 2010; **25:** 225–29.

133 Lin SMHC, Huang CD, Lin HC, Liu CY, Wang CH, Kuo HP. A modified goal-directed protocol improves clinical outcomes in intensive care unit patients with septic shock: a randomized controlled trial. *Shock* 2006; **26:** 551–57.

134 Ng RRCS, Chew ST, Liu W, Shen L, Ti LK. Identification of modifiable risk factors for acute kidney injury after coronary artery bypass graft surgery in an Asian population. *J Thorac Cardiovasc Surg* 2014; **147:** 1356–61.

135 Murakami R, Kumita S, Hayashi H, et al. Anemia and the risk of contrast-induced nephropathy in patients with renal insufficiency undergoing contrast-enhanced MDCT. *Eur J Radiol* 2013; **82:** e521–24.

136 Karkouti K, Wijeysundera DN, Yau TM, et al. Influence of erythrocyte transfusion on the risk of acute kidney injury after cardiac surgery differs in anemic and nonanemic patients. *Anesthesiology* 2011; **115:** 523–30.

137 Khan UA, Coca SG, Hong K, et al. Blood transfusions are associated with urinary biomarkers of kidney injury in cardiac surgery. *J Thorac Cardiovasc Surg* 2014; **148:** 726–32.

138 Pannu N, Nadim MK. An overview of drug-induced acute kidney injury. *Crit Care Med* 2008; **36** (suppl)**:** S216–23.

139 Evenepoel P. Acute toxic renal failure. *Best Pract Res Clin Anaesthesiol* 2004; **18:** 37–52.

140 Philips BJLK, Lane K, Dixon J, Macphee I. The effects of acute renal failure on drug metabolism. *Expert Opin Drug Metab Toxicol* 2014; **10:** 11–23.

141 Nielson E, Hennrikus E, Lehman E, Mets B. Angiotensin axis blockade, hypotension, and acute kidney injury in elective major orthopedic surgery. *J Hosp Med* 2014; **9:** 283–88.

142 Arora P, Rajagopalam S, Ranjan R, et al. Preoperative use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers is associated with increased risk for acute kidney injury after cardiovascular surgery. *Clin J Am Soc Nephrol* 2008; **3:** 1266–73.

143 Fournier JP, Sommet A, Durrieu G, Poutrain JC, Lapeyre-Mestre M, Montastruc JL, for the French Network of Regional Pharmacovigilance Centres. More on the "Triple Whammy": antihypertensive drugs, non-steroidal anti-inflammatory agents and acute kidney injury - a case/non-case study in the French pharmacovigilance database. *Ren Fail* 2014; **36:** 1166–68.

144 Lapi F, Azoulay L, Yin H, Nessim SJ, Suissa S. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. *BMJ* 2013; **346:** e8525.

145 Boyer A, Gruson D, Bouchet S, et al. Aminoglycosides in septic shock: an overview, with specific consideration given to their nephrotoxic risk. *Drug Saf* 2013; **36:** 217–30.

146 Safdar A, Ma J, Saliba F, et al. Drug-induced nephrotoxicity caused by amphotericin B lipid complex and liposomal amphotericin B: a review and meta-analysis. *Medicine (Baltimore)* 2010; **89:** 236–44.

147 Seeliger E, Sendeski M, Rihal CS, Persson PB. Contrast-induced kidney injury: mechanisms, risk factors, and prevention. *Eur Heart J* 2012; **33:** 2007–15.

148 Lameire NH, Flombaum CD, Moreau D, Ronco C. Acute renal failure in cancer patients. *Ann Med* 2005; **37:** 13–25.

149 Lombardi R, Ferreiro A, Servetto C. Renal function after cardiac surgery: adverse effect of furosemide. *Ren Fail* 2003; **25:** 775–86.

150 Ho KM, Sheridan DJ. Meta-analysis of frusemide to prevent or treat acute renal failure. *BMJ* 2006; **333:** 420.

151 Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J, for the Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. *Lancet* 2000; **356:** 2139–43.

152 Kellum JA, Decker MJ. Use of dopamine in acute renal failure: a meta-analysis. *Crit Care Med* 2001; **29:** 1526–31.

153 Friedrich JO, Adhikari N, Herridge MS, Beyene J. Meta-analysis: low-dose dopamine increases urine output but does not prevent renal dysfunction or death. *Ann Intern Med* 2005; **142:** 510–24.

154 Levi TM, Rocha MS, Almeida DN, et al. Furosemide is associated with acute kidney injury in critically ill patients. *Braz J Med Biol Res* 2012; **45:** 827–33.

155 Bagshaw SM, Delaney A, Jones D, Ronco C, Bellomo R. Diuretics in the management of acute kidney injury: a multinational survey. *Contrib Nephrol* 2007; **156:** 236–49.

156 Bagshaw SM, Gibney RT, McAlister FA, Bellomo R. The SPARK Study: a phase II randomized blinded controlled trial of the effect of furosemide in critically ill patients with early acute kidney injury. *Trials* 2010; **11:** 50.

157 Mehta RL, McDonald B, Gabbai F, et al. Nephrology consultation in acute renal failure: does timing matter? *Am J Med* 2002; **113:** 456–61.

158 Costa e Silva VT, Liaño F, Muriel A, Díez R, de Castro I, Yu L. Nephrology referral and outcomes in critically ill acute kidney injury patients. *PLoS One* 2013; **8:** e70482.

159 Ponce D, Zorzenon CP, dos Santos NY, Balbi AL. Early nephrology consultation can have an impact on outcome of acute kidney injury patients. *Nephrol Dial Transplant* 2011; **26:** 3202–06.

160 Meier P, Bonfils RM, Vogt B, Burnand B, Burnier M. Referral patterns and outcomes in noncritically ill patients with hospital-acquired acute kidney injury. *Clin J Am Soc Nephrol* 2011; **6:** 2215–25.

161 Kinfu Y, Dal Poz MR, Mercer H, Evans DB. The health worker shortage in Africa: are enough physicians and nurses being trained? *Bull World Health Organ* 2009; **87:** 225–30.

162 Overberger P, Pesacreta M, Palevsky PM, for the VA/NIH Acute Renal Failure Trial Network. Management of renal replacement therapy in acute kidney injury: a survey of practitioner prescribing practices. *Clin J Am Soc Nephrol* 2007; **2:** 623–30.

163 RENAL Study Investigators. Renal replacement therapy for acute kidney injury in Australian and New Zealand intensive care units: a practice survey. *Crit Care Resusc* 2008; **10:** 225–30.

164 Basso F, Ricci Z, Cruz D, Ronco C. International survey on the management of acute kidney injury in critically ill patients: year 2007. *Blood Purif* 2010; **30:** 214–20.

165 Legrand M, Darmon M, Joannidis M, Payen D. Management of renal replacement therapy in ICU patients: an international survey. *Intensive Care Med* 2013; **39:** 101–08.

166 Jamal JAM, Mat-Nor MB, Mohamad-Nor FS, Udy AA, Lipman J, Roberts JA. A national survey of renal replacement therapy prescribing practice for acute kidney injury in Malaysian intensive care units. *Nephrology (Carlton)* 2014; **19:** 507–12.

167 Lima EQ Sr, Silva RG, Donadi EL, et al. Prevention of intradialytic hypotension in patients with acute kidney injury submitted to sustained low-efficiency dialysis. *Ren Fail* 2012; **34:** 1238–43.

168 Gabriel DPCJ, Caramori JT, Martim LC, Barretti P, Balbi AL. High volume peritoneal dialysis vs daily hemodialysis: a randomized, controlled trial in patients with acute kidney injury. *Kidney Int Suppl* 2008; **108:** S87–93.

169 Ponce D, Berbel MN, Regina de Goes C, Almeida CT, Balbi AL. High-volume peritoneal dialysis in acute kidney injury: indications and limitations. *Clin J Am Soc Nephrol* 2012; **7:** 887–94.

170 Ponce D, Berbel MN, Abrão JM, Goes CR, Balbi AL. A randomized clinical trial of high volume peritoneal dialysis versus extended daily hemodialysis for acute kidney injury patients. *Int Urol Nephrol* 2013; **45:** 869–78.

171 Bonilla-Félix M. Peritoneal dialysis in the pediatric intensive care unit setting: techniques, quantitations and outcomes. *Blood Purif* 2013; **35:** 77–80.

172 Burdmann EA, Chakravarthi R. Peritoneal dialysis in acute kidney injury: lessons learned and applied. *Semin Dial* 2011; **24:** 149–56.

173 Chionh CY, Soni SS, Finkelstein FO, Ronco C, Cruz DN. Use of peritoneal dialysis in AKI: a systematic review. *Clin J Am Soc Nephrol* 2013; **8:** 1649–60.

174 Obiagwu PN, Abdu A. Peritoneal dialysis vs. haemodialysis in the management of paediatric acute kidney injury in Kano, Nigeria: a cost analysis. *Trop Med Int Health* 2015; **20:** 2–7.

175 Cullis B, Abdelraheem M, Abrahams G, et al. Peritoneal dialysis for acute kidney injury. *Perit Dial Int* 2014; **34:** 494–517.

176 Kilonzo KG, Ghosh S, Temu SA, et al. Outcome of acute peritoneal dialysis in northern Tanzania. *Perit Dial Int* 2012; **32:** 261–66.

177 Kilonzo KMA, Croome A. Establishment of an acute peritoneal dialysis program in Tanzania. *Kidney Int Suppl* 2013; **3:** 186–89.

178 Ademola AD, Asinobi AO, Ogunkunle OO, Yusuf BN, Ojo OE. Peritoneal dialysis in childhood acute kidney injury: experience in southwest Nigeria. *Perit Dial Int* 2012; **32:** 267–72.

179 Department of Health and Human Services. USRDS Annual Report 2007. United States Renal Data System (USRDS) (NIH publication no 07-3176). Washington, DC: Department of Health and Human Services, 2007: 240–41.

180 United Nations Department of Economic and Social Affairs. Division for Sustainable Development. Sustainable Development Goals. 2014. http://sustainabledevelopment.un.org/?menu=1300 (accessed Oct 28, 2014).

181 Prabhu MV, Subhramanyam SV, Sinoj KA, Nayak KS. Manual acute PD with rigid catheters–a relook. *Open Urology and Nephrology* 2015, **8:** 31–38.

182 Petit-Zeman S, Firkins L, Scadding JW. The James Lind Alliance: tackling research mismatches. *Lancet* 2010; **376:** 667–69.

183 CIHR. More About Knowledge Translation at CIHR. 2014. http://wwwcihr-irscgcca/e/39033html (accessed Oct 31 2014).

184 UNDP. Roll Back Malaria. Multisectoral Action Framework for Malaria. New York: United Nations Development Programme, 2013.

185 Gillespie S, Haddad L, Mannar V, Menon P, Nisbett N, for the Maternal and Child Nutrition Study Group. The politics of reducing malnutrition: building commitment and accelerating progress. *Lancet* 2013; **382:** 552–69.

186 Bhutta ZA, Das JK, Walker N, et al, for the *Lancet* Diarrhoea and Pneumonia Interventions Study Group. Interventions to address deaths from childhood pneumonia and diarrhoea equitably: what works and at what cost? *Lancet* 2013; **381:** 1417–29.

187 Gopalakrishnan A. Can Modi deliver a clean India? *India Today*. Oct 13, 2014.

188 Tiwari R. The case of the missing toilets. *India Today*. Oct 13, 2014. 2014.

189 Coffey D, Spears D. To end open defecation, make Indians want to. *India Today*. Oct 13, 2014.

190 Tonelli M, Agarwal S, Cass A, et al. How to advocate for the inclusion of chronic kidney disease in a national noncommunicable chronic disease program. *Kidney Int* 2014; **85:** 1269–74.

191 Global Fund to Fight AIDS, Tuberculosis, and Malaria. The harmonization of global fund programs and donor coordination: four case studies with a focus on HIV/AIDS. Geneva: Global Fund to Fight AIDS, 2005.

192 Alliance NCD. The NCD Alliance Report 2013–14: Putting non-communicable diseases on the global agenda. Oct 13, 2014.

193 Ftouh S, Lewington A, for the Acute Kidney Injury Guideline Development Group convened by the National Clinical Guidelines Centre and commissioned by the National Institute for Health and Care Excellence, in association with The Royal College of Physicians. Prevention, detection and management of acute kidney injury: concise guideline. *Clin Med* 2014; **14:** 61–65.

194 Kenyunko K. Tanzania has low kidney experts. Aug 24, 2014. http://www.ippmedia.com/frontend/?l=71353 (accessed Oct 21, 2014).

195 Dahl R, Chapman KR, Rudolf M, et al. Safety and efficacy of dual bronchodilation with QVA149 in COPD patients: the ENLIGHTEN study. *Respir Med* 2013; **107:** 1558–67.

196 African Leaders Malaria Alliance. The ALMA Scorecard For Accountability and Action; 2011. http://www.fightingmalaria.org/event.aspx?id=1689 (accessed Sept 19, 2011).

197 Rosinski AA, Narine S, Yamey G. Developing a scorecard to assess global progress in scaling up diarrhea control tools: a qualitative study of academic leaders and implementers. *PLoS One* 2013; **8:** e67320.

198 Beaglehole R, Bonita R, Horton R. Independent global accountability for NCDs. *Lancet* 2013; **381:** 602–05.

199 Bergh G, Foresti M, Menocal AR, Wild L. Building governance into a post-2015 framework: exploring transparency and accountability as an entry point. London: Overseas Development Institute, 2012.

200 Save the Children. Nutrition in the first 1,000 days: state of the world's mothers 2012. http://www.savethechildren.org/atf/cf/%7B9def2ebe-10ae-432c-9bd0-df91d2eba74a%7D/STATEOFTHEWORLDSMOTHERSREPORT2012.PDF (accessed Feb 3, 2015).

201 International Diabetes Federation. The diabetes scorecard – tracking progress for action: informal advisory group terms of reference. Brussels: International Diabetes Federation, 2013.

202 Swaminathan M, Hudson CC, Phillips-Bute BG, et al. Impact of early renal recovery on survival after cardiac surgery-associated acute kidney injury. *Ann Thorac Surg* 2010; **89:** 1098–104.

203 Mammen C, Al Abbas A, Skippen P, et al. Long-term risk of CKD in children surviving episodes of acute kidney injury in the intensive care unit: a prospective cohort study. *Am J Kidney Dis* 2012; **59:** 523–30.

204 Heung M, Chawla LS. Predicting progression to chronic kidney disease after recovery from acute kidney injury. *Curr Opin Nephrol Hypertens* 2012; **21:** 628–34.

205 Macedo E, Bouchard J, Mehta RL. Renal recovery following acute kidney injury. *Curr Opin Crit Care* 2008; **14:** 660–65.

206 Kilonzo KMA, Croome AJ. Establishment of an acute peritoneal dialysis program in Tanzania. *Kidney Int* 2013; **3** (suppl)**:** 186–89.

207 Sharma SK, Ghimire A, Carminati S, Remuzzi G, Perico N. Management of chronic kidney disease and its risk factors in eastern Nepal. *Lancet Glob Health* 2014; **2:** e506–07.