

# Chronic kidney disease in low-income to middle-income countries: the case for increased screening

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## ABSTRACT

Chronic kidney disease (CKD) is fast becoming a major public health issue, disproportionately burdening low-income to middle-income countries, where detection rates remain low. We critically assessed the extant literature on CKD screening in low-income to middle-income countries. We performed a PubMed search, up to September 2016, for studies on CKD screening in low-income to middle-income countries. Relevant studies were summarised through key questions derived from the Wilson and Jungner criteria. We found that low-income to middle-income countries are ill-equipped to deal with the devastating consequences of CKD, particularly the late stages of the disease. There are acceptable and relatively simple tools that can aid CKD screening in these countries. Screening should primarily include high-risk individuals (those with hypertension, type 2 diabetes, HIV infection or aged >60 years), but also extend to those with suboptimal levels of risk (eg, prediabetes and prehypertension). Since screening for hypertension, type 2 diabetes and HIV infection is already included in clinical practice guidelines in resource-poor settings, it is conceivable to couple this with simple CKD screening tests. Effective implementation of CKD screening remains a challenge, and the cost-effectiveness of such an undertaking largely remains to be explored. In conclusion, for many compelling reasons, screening for CKD should be a policy priority in low-income to middle-income countries, as early intervention is likely to be effective in reducing the high burden of morbidity and mortality from CKD. This will help health systems to achieve cost-effective prevention.

## INTRODUCTION

Chronic kidney disease (CKD) is an increasing global public health issue,<sup>1</sup> with an estimated overall prevalence of 8%–16%.<sup>2</sup> This corresponds to nearly 500 million affected individuals, of whom 78% (387.5 million) reside in low-income to middle-income countries (LMICs).<sup>3</sup> Between 1990 and 2010, deaths attributable to CKD nearly doubled, and was ranked the 18th leading cause of death in 2012.<sup>4</sup> Although the exact burden of CKD in LMICs has yet to be fully elucidated, it is estimated that the incidence rates might be up to four times higher than those observed

## Key questions

### What is already known about this topic?

- ▶ Chronic kidney disease (CKD) is increasingly common in low-income to middle-income countries due to the significant increase in non-infectious disease (particularly type 2 diabetes and hypertension) and infectious conditions such as HIV, combined with ill-equipped healthcare systems.
- ▶ As kidney disease progresses, it may lead to kidney failure (end-stage renal disease (ESRD)), and since most people in low-income to middle-income countries have no health insurance and limited access to healthcare, diagnosis of ESRD is thus essentially a death sentence.
- ▶ Early detection of CKD is essential because therapeutic interventions are likely to be effective if implemented early in the course of the disease.

### What are the new findings?

- ▶ This review critically evaluated the available research evidence to support CKD screening in low-income to middle-income countries through a series of key questions derived from the Wilson and Jungner criteria for disease screening, and concluded that screening for CKD should be a policy priority in these resource-poor settings, as early interventions are likely to be effective in reducing the high burden of CKD morbidity and mortality.

### Recommendations for policy

- ▶ Designing policies for CKD screening offers a unique opportunity to scale up CKD care and by so doing strengthen the healthcare system of low-income to middle-income countries, and thus potentially limiting future healthcare costs.

in developed countries.<sup>5 6</sup> In addition, in sub-Saharan Africa, CKD more commonly affects individuals aged between 20 and 50 years,<sup>7 8</sup> and the age of onset of end-stage renal disease (ESRD) is 20 years earlier in populations of African descent compared with other ethnic groups in Western countries (45 years vs 63 years).<sup>7 9</sup> These statistics highlight the need for early and accurate detection of CKD

**Table 1** Wilson and Jungner criteria for disease screening

1	The condition sought should be an important health problem.
2	There should be an accepted treatment for patients with recognised disease.
3	Facilities for diagnosis and treatment should be available.
4	There should be a latent or early symptomatic stage.
5	There should be a suitable test or examination.
6	The test should be acceptable to the population.
7	The natural history of the condition, including development from latent to declared disease, should be adequately understood.
8	There should be an agreed policy on who to treat as patients.
9	The cost of case finding (including diagnosis and treatment of patients diagnosed) should be economically balanced in relation to possible expenditure on medical care as a whole.
10	Case finding should be a continuing process and not a 'once and for all' project.

Adapted from the WHO.<sup>15</sup>

in LMICS, as well as establish the mechanisms for appropriate management for screen-detected individuals.

The global increase in the incidence and prevalence of CKD is mainly driven by the rise in the prevalence of type 2 diabetes mellitus (T2D), hypertension, obesity and ageing,<sup>10</sup> but also by the high prevalence of infectious diseases, especially HIV in sub-Saharan Africa.<sup>11 12</sup> ESRD requires renal replacement therapy (RRT) or kidney transplant, both of which are costly to the individual and the society, imposing a major burden on health systems. Currently, about 2.6 million individuals worldwide are estimated to be receiving RRT, with 93% of these individuals residing in high-income or high-middle-income countries.<sup>13</sup> Awareness of CKD remains limited in most LMICs, where a large proportion of individuals with CKD go undetected.<sup>14</sup> There is a need for early detection of CKD in LMICs in order to reduce the related morbidity, mortality and economic costs. Studies suggest that early detection and treatment of CKD is feasible in low-resource settings<sup>9</sup>; however, recommendations on CKD screening are largely based on data from developed nations and may not necessarily apply to LMICs.

The main purpose of this review is to critically evaluate the available research evidence to support CKD screening in LMICs through a series of key questions derived from the Wilson and Jungner criteria for disease screening<sup>15</sup> (table 1), rather than it being a traditional systematic review.

We searched Medline via PubMed for observational studies, randomised controlled trials or reviews pertaining to CKD screening among adults in LMICs, using relevant key terms like 'screening', 'chronic kidney (or renal) disease', 'kidney (or renal) dysfunction',

'decreased kidney (renal) function', 'end-stage renal disease', 'glomerular filtration rate', 'albuminuria', 'developing countries', 'low income countries', 'low-to-middle income countries', 'Cockcroft-Gault equation', 'Modification of Diet in Renal Disease equation', 'CKD Epidemiology Collaboration equation', 'prevalence', 'incidence', 'type 2 diabetes', 'hypertension', 'HIV/AIDS' and 'cardiovascular disease'. Additional searches included handsearch of reference list of relevant articles, and search of websites including those of the WHO and major global and regional professional organisations in the area of nephrology and cardiometabolic diseases. Identified entries were evaluated, irrespective of date or country of publication, to retain the most relevant in the judgement of the authors for the current review.

## WHAT ARE THE ARGUMENTS FOR CKD SCREENING IN LMICS?

### The burden of CKD

A recent study on CKD, which included 12 LMICs, reported a CKD prevalence of 14.3% in the general population and 36.1% in the high-risk population.<sup>16</sup> These findings are consistent with those of a previous meta-analysis of 21 studies in LMICs, in which 13.9% of the general population had CKD,<sup>5</sup> with estimates of CKD prevalence ranging from 2% in Cote d'Ivoire to 30% in Zimbabwe.<sup>5</sup> However, given the heterogeneity of the CKD definition (based on different equations to estimate glomerular filtration rate (GFR)) used in these studies, these figures could be an inaccurate estimation. Certainly, a number of these studies used the Cockcroft-Gault equation, which may not be suitable for use among individuals of black ancestry, and some of these studies did not include a nationally representative population-based sample. Therefore, in many LMICs or regions within these countries, data on the burden of CKD are still lacking, mainly due to an absence of quality resources and inadequate data collection methods.<sup>5 6</sup>

The major CKD risk factors include T2D, hypertension, obesity, ageing and black ethnicity.<sup>10 17</sup> LMICs, in particular those in Africa, are experiencing an accelerated increase in non-infectious disease, mainly hypertension and T2D, which contributed to >15% of CKD cases.<sup>18</sup> Furthermore, infectious diseases, such as HIV, schistosomiasis and leishmaniasis, which also contribute to CKD, are highly prevalent in LMICs.<sup>11</sup> In sub-Saharan Africa more than 22 million individuals have HIV, accounting for more than 70% of the global burden of infection,<sup>19</sup> with HIV-associated nephropathy (HIVAN) fast becoming an important cause of morbidity and mortality related to kidney disease.<sup>12 20</sup> Moreover, individuals of African descent have a higher prevalence of CKD compared with individuals from European descent, suggesting a possible genetic predisposition in African populations.<sup>21 22</sup> Apolipoprotein L1 (*APOLI*), which is fairly common throughout Africa,<sup>23</sup> accounts for much of the excess genetic risk of CKD among individuals of African ancestry.<sup>8 11 21 22 24</sup> This is particularly evident in

individuals with two risk alleles,<sup>11 23</sup> as they experience a more rapid progression to ESRD.<sup>21</sup>

In LMICs, awareness of CKD remains low,<sup>25–27</sup> particularly during the early asymptomatic stages of the disease. Jha *et al*<sup>2</sup> estimated that only one-third of people with CKD are diagnosed. These findings are corroborated by other studies also reporting very low rates of detection, such as in Northern Tanzania, where in a sample of 606 participants from 431 urban and rural households, only 10% of individuals with CKD were aware of their condition.<sup>6</sup> Similarly, 23% of an adult population living in Northern Senegal, 3.5% in Taiwan<sup>28</sup> and 9.7% in China<sup>29</sup> were aware of their disease before intervention.<sup>30</sup> In a more recent cross-sectional study in LMICs, it was documented that 6% of the general population and about 10% of high-risk individuals were aware they had CKD.<sup>16</sup> These low rates of CKD awareness result in a large number of people progressing from CKD to ESRD,<sup>14 27</sup> which is in most cases fatal, particularly in LMICs where treatment is unavailable and unaffordable. According to the Global Burden of Disease (GBD) Study, 956 200 deaths worldwide were directly attributable to CKD in 2013, mainly due to lack of access to treatment.<sup>31</sup> Currently, only 20 per million population (pmp) and 68 pmp in low-income countries and LMICs, respectively, receive dialysis treatment, versus 273 pmp and 1064 pmp in upper-middle-income to high-income countries.<sup>13</sup>

The economic burden of CKD has seldom been evaluated in LMICs; however, it is estimated to be significantly higher than observed in developed countries.<sup>2</sup> In LMICs, the majority of patients present to hospital at late stages of CKD (ESRD), when dialysis is required,<sup>32</sup> adding to treatment costs. Most people in LMICs have no health insurance and limited access to healthcare, which makes treatment for ESRD unaffordable and diagnosis of ESRD essentially a death sentence.<sup>4 33 34</sup> In settings where limited renal care is available, patients with ESRD seldom have access to RRT, due to the high cost.<sup>35 36</sup> Globally, only about 7% of patients receiving RRT in 2010 were from LMICs.<sup>14</sup> In India and Pakistan, for example, only about 5% of all patients with ESRD receive RRT.<sup>37</sup> In North Africa (Egypt, Libya, Tunisia, Algeria, Morocco), less than 5% of patients with ESRD receive renal transplantation.<sup>38</sup> It has been estimated that one session of dialysis costs US\$100 in Nigeria<sup>10</sup> and between US\$20 and US\$60 in India.<sup>33</sup> In China, the annual cost of dialysis is estimated at US\$14 300 per patient,<sup>39</sup> and in Africa the estimated annual cost of dialysis ranges between US\$8000 and US\$12 000 per patient.<sup>10</sup>

Some governments have introduced the subsidisation of treatment, by instituting insurance schemes for the poor. For instance, in Nigeria, after several years of discussion and dialogue through the local nephrology association, the federal government has recently agreed to provide cover for the first six sessions of dialysis, with the possibility of extension to the first 3 months.<sup>40</sup> The Chinese government has also implemented insurance schemes for the poor; however, patients in rural areas are still responsible

for paying 35%–45% of the total cost, which is unaffordable for most.<sup>39</sup> In India, certain states have started schemes to provide free RRT to the poor; however, coverage is limited.<sup>41</sup> Although this is not nearly enough, it is a positive step in the right direction that will benefit patients and their families with access to RRT. Overall, given the high prevalence of CKD and the high costs of treatment during the advanced stages of the disease, the accessibility to treatment in LMICs remains low compared with developed countries. Whether the various schemes adopted by governments to facilitate access to RRT would be effectively implemented and translate into outcomes improvement remains to be established.

### Natural history of CKD among populations in LMICs

The natural history of CKD is relatively well understood. CKD, which is defined as a reduced GFR ( $<60\text{ mL/min/1.73 m}^2$  for  $\geq 3$  months) and/or increased urinary albumin excretion ( $\geq 30\text{ mg/24 hours}$ ), is classified into five stages, based on the estimated GFR (eGFR). Stages 1–3 are considered the early stages of CKD and nearly always asymptomatic.<sup>42</sup> Stages 4 and 5 are classified as ESRD and are characterised by multiple complications.<sup>42</sup> Once CKD is established, the natural expectation is that of disease progression, with each subsequent stage representing a deterioration from the previous stage, until ESRD is reached and ultimately death in the absence of intervention. The pace of CKD progression is variable and is a function of the underlying aetiological factors, comorbidities and the management thereof, and other factors operating specifically in the milieu of established CKD.<sup>10 17</sup> The interval from onset of CKD stage 3 to kidney failure is around 12 years,<sup>43</sup> but the course of CKD progression can be halted at any time due to mortality from competing risk, particularly cardiovascular diseases (CVD).

The GBD expert group estimated that in 2013, reduced GFR accounted for 4% of deaths worldwide, with over 50% of these related to CVD and the remaining to ESRD.<sup>44</sup> In this study, mortality from CVD in people with reduced GFR was slightly higher in LMICs than in developed countries.<sup>44</sup> Furthermore, the mortality rate declined by 9% from 1990 in developed countries, while a 44% decline occurred in developing countries within the same time window.<sup>44</sup> The presence of CKD is independently associated with increased rates of CVD, and the risk of death due to CVD linearly increases with decreasing eGFRs below  $75\text{ mL/min/1.73 m}^2$ .<sup>45 46</sup> Thus, a small proportion of patients actually reach the terminal phase of CKD, as most die as a result of CVD prior to reaching ESRD. Accordingly, the prevalence rate (expressed as number of patients per million population) of ESRD in LMICs is much less than that observed in developed countries.<sup>47</sup> For example, in Japan more than 2000/million people have ESRD, 1500/million people in the USA and roughly 800/million in Europe. Conversely, in LMICs such as South Asia ESRD affects between 100/million people and 200/million people, and less than 100/million people in sub-Saharan Africa and India.<sup>48 49</sup>



In LMICs, various factors contribute to the high risk of progression to ESRD.<sup>14 27 43</sup> First, there is a lack of optimal blood pressure control in patients with hypertension, where more than 90% of hypertension cases are uncontrolled in these settings.<sup>50 51</sup> Furthermore, uncontrolled T2D is of great concern in LMICs, with diabetic nephropathy being the leading cause of ESRD and affecting one in three patients with diabetes.<sup>52</sup> HIV/AIDS is also known to accelerate CKD progression and is very prevalent in LMICs. This is particularly concerning as nearly 70% of HIV-infected individuals are concentrated in LMICs, and of those infected only 38% are currently receiving antiretroviral therapy (ART).<sup>19</sup> In the absence of effective ART, approximately 50% of patients with HIVAN progress to ESRD within 2 years.<sup>53</sup> ART is known to decrease the risk of renal disease in patients with HIV by 46% compared with naïve patients; however, some ART treatments (such as tenofovir disoproxil fumarate, ritonavir-boosted atazanavir and ritonavir-boosted lopinavir) have been associated with renal impairment.<sup>54 55</sup> The use of herbal medicines, which is common in rural populations in Africa and Asia,<sup>56–58</sup> can also act as nephrotoxins, thus increasing the risk of CKD progression.

### WHICH SCREENING TESTS TO USE IN LMICs?

The first line of screening tools could consist of risk scores and questionnaires to determine risk of CKD, which are followed by biochemical tests, comprising eGFR and albuminuria tests. These tests may be used alone or in combination for detecting the specific stages of the diseases.<sup>59</sup> Based on their advantages and limitations, some of the screening tests may be suitable for use in LMIC setting.

#### Risk scores and questionnaires

Various estimation/prediction models have been developed to be used as screening methods for the prevalence of CKD and its progression.<sup>60</sup> These risk models are potentially ideal tools for large-scale CKD risk screening; however, risk models tend to be population-specific.<sup>60</sup> More so, the participants used to develop CKD prediction models are more often of European origin. This is problematic because a homogeneous population does not allow for accurate determination of variability in CKD risk, and black ethnicity is particularly prone to CKD.

A systematic review of CKD risk prediction tools found that the discriminative performance of these models is generally acceptable-to-good in the population in which it was developed<sup>60</sup> and modest-to-acceptable if tested in another population.<sup>60–62</sup> However, only a few of the existing CKD risk algorithms have been validated in different populations and seldom in populations of LMICs.<sup>63–67</sup> Among all the models, the cross-sectional population-based survey Screening for Occult Renal Disease (SCORED) appears to be a fairly reliable model for CKD risk prediction, as it has been validated various times, in mixed

ethnic groups and with reasonable discrimination.<sup>63 68</sup> However, in resource-poor settings, a simple prediction model that does not incorporate laboratory-based predictors is essential as it will keep costs low and reduce the screening burden. Therefore, a possible drawback to the use of the SCORED model is the cost attached to determining the presence of anaemia and T2D. To diagnose anaemia, a full blood count is needed, and to more accurately diagnose T2D particularly in black populations a 2-hour glucose tolerance test is advocated.<sup>69</sup> Even so, the SCORED model is a possible candidate to be used in LMICs; however, the model needs to be validated and calibrated for populations in these settings.<sup>63 70 71</sup>

#### Biochemical tests

Currently the key markers used to detect CKD include a persistent reduction in the eGFR ( $<60 \text{ mL/min/1.73 m}^2$  for  $\geq 3$  months) and abnormal urine albumin levels ( $\geq 30 \text{ mg/day}$ ).<sup>1</sup> Several biochemical screening tests, with various practical advantages and limitations, have been evaluated for CKD screening and can potentially be used in LMICs.

#### Glomerular filtration rate

GFR is measured indirectly by assessing the rate of clearance of markers such as inulin, iothalamate, iohexol, ethylenediaminetetraacetic acid or diethylenetriaminepentaacetic acid.<sup>72</sup> However, these methods are expensive, cumbersome and time-consuming and not useful in general population screening or in routine clinical practice.

Therefore, the eGFR using prediction equations has been adopted as a routine measure of renal function. The most popular equations use serum creatinine level, although cystatin C-based equations have also been developed to estimate kidney function<sup>73 74</sup> and have been reported to better predict all-cause mortality and cardiovascular events in older people, and all-cause mortality and ESRD in the general adult population.<sup>75</sup> However, in LMICs the use of creatinine would be favoured above the use of cystatin C, as serum creatinine determination is a simple and less expensive and it is an internationally standardised test.<sup>76</sup>

The three commonly used creatinine-based estimators of GFR for adults include the Cockcroft-Gault,<sup>77</sup> the Modification of Diet in Renal Disease (MDRD)<sup>78</sup> and the CKD Epidemiology Collaboration (CKD-EPI) equations.<sup>79</sup> The latter two equations contain a correction factor for ethnicity. However, the addition of a correction factor for ethnicity may result in misdiagnosis of CKD and is not a valid approach in all settings.<sup>8 80 81</sup> Various studies have compared the prevalence of CKD based on the different eGFR equations,<sup>8 82–87</sup> and results show that CKD prevalence differs depending on which equation is used and on which population the equation is based.<sup>8 80 81</sup> For example, in studies conducted in populations in sub-Saharan Africa<sup>8 82</sup> and predominant Caucasian populations,<sup>86</sup> the MDRD equation had an advantage over the CKD-EPI equation. These studies are

however limited by the fact that the reference standard for estimating GFR was not used. Conversely, studies conducted in Asian populations favour the use of the CKD-EPI equation above MDRD equation.<sup>83 84 87</sup> Even though these equations have not been validated for use in LMICs, there is a need to include eGFR (either MDRD or CKD-EPI) in routine practice, as this would give an indication for the presence of kidney disease and could lead to early referral and intervention.<sup>88</sup>

### Albuminuria

Albuminuria is also a frequently used index of kidney function.<sup>72</sup> The 24-hour urinary albumin concentration (UAC) is considered to be the reference standard. This method entails urine collection commencing immediately after discarding first morning urine and collecting all urine in the same container (including final voided urine next morning) until completion of 24 hours.<sup>89</sup> This method is time-consuming and cumbersome as sample collection errors may occur and patient compliance is usually low. To avoid these limitations, random urine samples can be used for quantification of albuminuria, by calculating the urinary albumin to creatinine ratio (ACR).<sup>72</sup> Here, midstream urines are collected for a random urine sample.<sup>89</sup> It is important that during the 24 hours and spot urine collection period, no heavy muscular work should be done as this will influence the serum creatinine concentration. The ACR has been found to correlate well with 24-hour UAC,<sup>89-91</sup> with a high sensitivity (ranging between 79% and 87.6%) and specificity (ranging between 87.5% and 95.5%) to detect microalbuminuria.

### WHICH THERAPIES ARE AVAILABLE FOR SCREEN-DETECTED PATIENTS, AND HOW CAN THESE BE IMPLEMENTED IN LMIC SETTINGS?

Interventions, if implemented timely, can slow the progression of CKD and subsequently reduce the risk of death due to CVD or ESRD.<sup>2</sup> During CKD stages 1 and 2, the general focus should be on aggressively treating the comorbid conditions, including elevated blood pressure and glucose levels and infectious diseases. The Joint National Committee for the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure recommends a lower blood pressure goal for patients with decreased kidney function (<130/85 mm Hg if urine protein excretion is <1 g/day, and <125/75 mm Hg if urine protein excretion is >1 g/day).<sup>92</sup> Various studies have shown that antihypertensive regimens containing ACE inhibitors or angiotensin receptor blockers are effective in delaying the progression of CKD, independent of blood pressure effects,<sup>93-97</sup> by a sixth for every 5 mm Hg reduction.<sup>98</sup> Intensive blood pressure lowering has also been shown to reduce the relative risk of ESRD by 11% and produce a 10% reduction in the risk of albuminuria.<sup>99</sup> Large clinical trials have also provided strong evidence that intensive glycaemic control (haemoglobin A1c target ≤6.5%) in patients with diabetes reduces the risk of ESRD by 65%,

and reduces the relative risk of developing microalbuminuria by 9%<sup>100</sup> and macroalbuminuria by 33%.<sup>101 102</sup> CKD is a frequent complication of HIV infection and the use of ART is known to decrease the risk of CKD progression; however, meta-analytic results showed a significantly increased CKD risk in patients treated with tenofovir disoproxil fumarate-containing ARTs as compared with those receiving other regimens.<sup>54</sup> Thus, the choice of ART is an extremely important decision in terms of managing HIV-infected patients, particularly those at high risk of CKD.

During stage 3 of CKD, in addition to continuing with the measures described above, the focus should shift to evaluating and treating the complications of CKD. During the advanced stages of CKD, patients are particularly at risk for developing anaemia, which occurs in about 90% of patients receiving RRT,<sup>103</sup> the predominant cause being failure of the kidneys to produce enough endogenous erythropoietin (EPO), accompanying the fall in GFR. Even though EPO is the standard treatment of anaemia in CKD and associated with improved CVD outcome,<sup>104</sup> the use thereof is limited in LMICs, due to the cost associated with this treatment.<sup>104-107</sup> Bone and mineral metabolism is also compromised during CKD, with patients having an exceptionally high rate of severe vitamin D deficiency, which is further exacerbated by the reduced ability to convert 25-(OH) vitamin D into the active form, 1,25 di-hydroxy vitamin D.<sup>108</sup> Vitamin D deficiency results in low calcium levels and hyperparathyroidism, a common complication in patients with CKD. Use of vitamin D and calcium supplements in these instances is feasible in LMICs. In addition to the decline in kidney function, the kidney becomes less efficient in excreting excess phosphate, resulting in phosphate build-up,<sup>108</sup> a condition that can also be addressed irrespective of the setting.

By stage 4, referral to a nephrologist for RRT preparation, including dialysis, transplantation or both, should start. The death rate at the early stage of starting RRT in LMICs is very high, due essentially to the fact that most people with ESRD are referred at a very late stage and never get prepared on time for the start of long-term dialysis.<sup>109 110</sup> Early referral to a nephrologist has been found to decrease the chance of developing fatal complications associated with CKD substantially.<sup>111</sup>

### HOW FEASIBLE, EFFECTIVE AND COST-EFFECTIVE WILL SCREENING BE FOR CKD IN LMICs?

A number of CKD screening programmes have been implemented in LMICs, of which the programme set up by the BP Koirala Institute of Health Science in Dharan, Nepal, in collaboration with International Society of Nephrology (ISN) and the Clinical Research Center of the Mario Negri Institute in Bergamo, Italy, is an example.<sup>112</sup> In this study, 20 811 individuals aged >18 years were screened, and data on family and personal medical history of disease (CKD, hypertension, T2D and

CVD), treatments received for these conditions, demographic data, diet, smoking habit, alcohol consumption, physical activity, height, weight and blood pressure were collected. A spot urine protein, fasting blood glucose and serum creatinine concentrations were also assessed. Of the individuals screened, 4471 individuals had high blood pressure, high fasting glucose, proteinuria and impaired renal function. These high-risk individuals were followed up annually for 3 years and prescribed low-cost antihypertensives, antidiabetic or renoprotective medication, depending on the need. After the 3-year follow-up, 63% of the individuals with proteinuria at baseline had normal values and 48% of individuals with mild-to-moderate renal insufficiency at baseline had stable renal function.<sup>112</sup> This study shows the feasibility of a screening and management programme in a low-resource setting, with a potential for population-wide benefit to managing CKD.

Often, a strong argument against screening or early detection is the cost-effectiveness of such an undertaking.<sup>113</sup> Implementing screening for CKD in resource-poor settings can be very challenging logistically, time-consuming and expensive. However, whether the cost of screening followed by treatment outweighs the huge burden of this disease on the individual and the health system is still unknown. More economic research is needed in LMICs in order for health policymakers to prioritise CKD screening. Once policy is in place, an effective screening system can be implemented; however, the healthcare system would need to redirect existing resources as country budgets are most often limited. Cost-effectiveness of CKD screening needs to be assessed and evaluated against other health interventions. Studies from developed countries have demonstrated the feasibility of early detection and treatment of CKD.<sup>2</sup> In particular, these studies showed that screening for CKD would be beneficial and cost-effective, when screening is geared more towards high-risk groups (hypertension, T2D and the elderly) compared with that of the general population, and screening followed by lifestyle modifications or treatment offers better cost-effective ratios.<sup>14 59 114</sup>

Currently, there are limited data on the cost-effectiveness of CKD screening in LMICs. In a systematic review of 10 studies (8 studies of proteinuria and 2 studies of eGFR), the cost-effectiveness ratios for proteinuria ranged from \$14 063–\$160 018/quality-adjusted life years (QALY) in the general population, \$5298–\$54 943/QALY in the diabetic population and \$23 028–\$73 939/QALY in the hypertensive population.<sup>113</sup> Additionally, the cost-effectiveness ratios for eGFR screening were \$23 680/QALY in the diabetic population and \$100 253–\$109 912/QALY in the general population. For both eGFR and proteinuria, the cost of screening for CKD in the general population was higher than screening only the high-risk populations, which include those individuals with known hypertension and T2D. Another study found that compared with no screening, screening for CKD in the general population was associated with a cost of \$C104 900/QALY.<sup>115</sup> In subgroups of people with T2D and hypertension, the cost

per QALY gained was \$C22 600 and \$C334 000, respectively.<sup>115</sup> The current data on cost-effectiveness models are however from developed countries, which have a much higher per-person gross domestic product (GDP) and thus cost-effectiveness threshold. According to the WHO Commission of Macroeconomics and Health, the cost-effectiveness of an intervention depends on the local GDP.<sup>2</sup> Therefore cost-effectiveness studies should be done in all regions.

### WHICH SCREENING STRATEGY TO ADOPT IN LMICS?

Screening may be population-based or conducted in the context of healthcare (opportunistic screening). Population-based screening attempts to screen the entire population at risk, and opportunistic screening involves screening individuals as part of a routine medical visit for other purposes.<sup>116</sup> Both these screening methods have merit, but neither meets the screening needs in all circumstances.

Screening high-risk individuals for CKD, such as those with hypertension, T2D, HIV infection and >60 years of age, is already included in clinical practice guidelines in several countries around the world,<sup>117–119</sup> and would be a viable option when mass campaigns are not possible or resources are limited. However, in LMICs a very large proportion of patients at high risk remain undiagnosed,<sup>16 50 120</sup> mainly because they do not have access to healthcare. A recent systematic review showed that only 18% of the adult African population with hypertension were aware of their condition.<sup>50</sup> However, even among populations already in regular contact with healthcare systems, hypertension remains unrecognised, with 70% of patients with HIV<sup>121</sup> and more than 10% of patients with diabetes in Africa not being aware of their comorbid hypertension.<sup>122</sup>

However, the use of the presence of major risk factors as a starting point for CKD screening in clinical settings has relevance for a number of purposes: (1) The yield of screening is likely to be high and for low investment considering the high prevalence or incidence of CKD in the presence of those risk factors; (2) treatment routinely used to control those factors on their own can in turn prevent the onset or slow the progression of CKD; and (3) the presence of CKD can however invite the intensification of treatments targeting those risk factors, to maximise their beneficial effects on CKD prevention and/or the modification of those treatments to introduce compounds that are safer for the kidney or have better renal protection properties. In the absence of strategies to improve the detection of those risk factors, targeting only populations with levels defining high-risk status for CKD screening will have a limited impact on the burden of undiagnosed CKD in general in LMICs. A large proportion of people with CKD is likely made up of people with a combination of non-optimal levels of risk factors, but below the threshold for defining disease states (such as prediabetes or prehypertension), and therefore not targeted for CKD screening in routine practice.



Screening for CKD in high-risk individuals would be based on eGFR and urinary albumin excretion. This may not be widely achievable in primary care setting particularly the underserved rural ones in LMICs, where laboratory investigations may not always be routinely available. The approach will also become expensive in routine care setting when considering expanding CKD screening to those with a combination of non-optimal level of risk factors. Parameters included in prevalent CKD risk models, not requiring laboratory tests, such as history of diseases and treatment, blood pressure level, age, gender and others, are routinely collected in clinical settings in LMICs. Therefore, in addition to targeting high-risk individuals for CKD screening (using eGFR and/or urinary albumin excretion where available), validated CKD risk models could be used in routine practice in LMICs. This could aid in identifying individuals at high risk in settings where laboratory investigations are not available. These individuals can then be referred or prescribed laboratory test for CKD screening. Furthermore, among those eventually diagnosed with CKD, validated CKD progression models can be used to identify those patients who are more likely to progress to ESRD, and thus need interventions to slow CKD progression. Risk prediction models are (or can be made) available in formats easily applicable (smartphone versions for instance) in routine settings with little extra effort, facilitated by lay health workers.

Across LMICs, there is a lack of access to healthcare services where opportunistic screening for CKD and risk factors can occur. In South Africa for instance, the country with the most developed healthcare system in sub-Saharan Africa, less than 20% of the population has continuous contact with the health system. Therefore, using only hospital-based strategies is unlikely to achieve significant reduction in the burden of undiagnosed CKD, necessitating further strategies to identify those beyond the traditional healthcare setting.

Lessons learnt from preventing and controlling infectious diseases suggest that community-based outreach activities play a major role in improving access to health interventions. Access to immunisation has been achieved in Africa for instance, among others, through community-based vaccination campaigns by nurses and community health workers. Interestingly, some of these community-based activities have been successfully adapted for chronic infectious conditions like HIV/AIDS and tuberculosis. There is therefore already an opportunity to implement community-based CKD screening as a by-product of existing programmes for chronic infectious diseases, or to use such programmes to inform those of CKD. For community-based screening of CKD to be attractive and useful, it should not be considered in isolation, but rather in the context of coscreening for major risk factors such as hypertension and T2D. The availability of affordable electronic blood pressure measuring devices and point-of-care glucose monitors makes community-based screening for those factors achievable. A simple and practical strategy could consist of using

community-based hypertension status assessment as an entry point, followed by the implementation of non-laboratory-based risk scores to identify high-risk individuals for CKD and T2D. Those with prevalent hypertension, T2D and/or high risk of CKD or T2D then get referred to the healthcare facilities for confirmation and further screening via laboratory tests.

The course of action following screening is likely setting-specific. In health facility-based settings, those diagnosed with a CKD should benefit from additional screening to identify modifiable risk and aetiological factors, and receive optimal risk factor control and renoprotective interventions to prevent/slow the progression of the disease, bearing in mind that these interventions could be less accessible or affordable in some settings. Patients diagnosed with advanced/progressing (in spite of appropriate interventions) CKD should be referred to nephrologists or relevant specialists where additional aetiological investigations and refined treatments could be implemented, or timely preparation started for patients who would ultimately need RRT. Ideally, community-based screening should occur in the context of health promotion activities targeting reductions in the overall population risk of CKD and major risk factors.

While the limited coping capacity has been cited as a deterrent to CKD and non-communicable diseases (NCD) screening in LMICs, there are possible strategies to overcome some of these limitations. Risk screening for CKD and NCDs at large can be implemented both in health facilities and at community level using trained lay health workers, simplified clinical pathways and taking advantages of existing technologies. With little additional training, low-level health workers can efficiently prescribe and tailor most treatments needed to mitigate CKD risk.<sup>123</sup> Their availability also increases the prospect of implementing community-based high-risk approach to CVD (and by extension CKD) risk reduction, using for instance trained community health workers and simplified algorithms.

## CONCLUSION

Extant evidence suggests that CKD screening should receive attention in LMICs. CKD is increasingly common in these settings, due to the significant increase in non-infectious disease (particularly T2D and hypertension), as well as infectious conditions such as HIV. To decrease the high mortality and morbidity associated with CKD, early detection is essential because therapeutic interventions are likely to be effective if implemented early in the course of the disease. Additional research is needed on screening programmes in LMICs as most available studies were conducted in developed countries. It should however be emphasised that the implementation of these interventions in real-world settings of LMICs can pose a challenge to the already burdened health systems, which currently deliver suboptimal care. Furthermore, cost-effectiveness of screening for CKD should be investigated

extensively in LMICs, as one cannot infer cost-effectiveness across countries. Designing policies for CKD screening offers a unique opportunity to scale up CKD care and by so doing strengthen the healthcare system of LMICs, and thus potentially limiting future healthcare costs.

**Correction notice** This paper has been amended since it was published Online First. Owing to a scripting error, some of the publisher names in the references were replaced with 'BMJ Publishing Group'. This only affected the full text version, not the PDF. We have since corrected these errors and the correct publishers have been inserted into the references.

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